

PATENT SPECIFICATION

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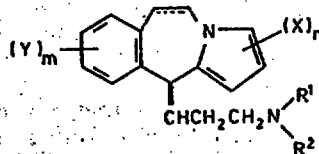
(54) PYRROLO [2,1-b] 3 BENZAZEPINES, METHODS OF
 PREPARING THEM, PHARMACEUTICAL COMPOSITIONS
 CONTAINING THEM, AND THEIR USE FOR TREATMENT
 OF NON-HUMAN ANIMALS

(71) We, MERCK & CO. INC., a corporation duly organized and existing
 under the laws of the State of New Jersey, United States of America, of Rahway,
 New Jersey, United States of America, do hereby declare the invention, for which
 we pray that a patent may be granted to us and the method by which it is to be
 performed, to be particularly described in and by the following statement:—

This invention relates to tricyclic compounds.

Over the past several years several so-called tricyclic compounds such as
 amitriptyline, cyclobenzaprine, nortriptyline and protriptyline have gained
 importance as centrally acting pharmacological agents having skeletal muscle
 relaxant and tranquillizing activity.

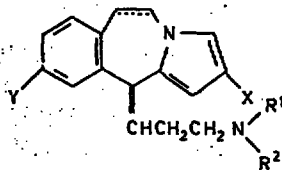
The present invention provides compounds of structural formula:



and their pharmaceutically acceptable salts, in which the dotted line between
 positions 5 and 6 represents saturation or unsaturation; n is 0, (in which case every
 X is hydrogen), 1, 2 or 3; m is 0, (in which case every Y is hydrogen), 1, 2, 3 or 4;
 each of X and Y , which are similar or dissimilar, is

- (1) hydrogen,
- (2) halogen, i.e. chlorine, bromine, fluorine or iodine,
- (3) formyl,

- (4) C₂₋₆ alkanoyl, such as acetyl, pentanoyl, or 2-methylpropanoyl,
 (5) C₁₋₃ alkyl, either straight or branched chain, such as methyl, propyl, or pentyl,
 (6) (C₁₋₃ alkoxy)carbonyl,
 (7) C₁₋₃ hydroxyalkyl,
 (8) C₁₋₃ perhaloalkyl, such as trifluoromethyl,
 (9) C₁₋₃ alkoxy, such as methoxy or propoxy,
 (10) cyano,
 (11) C₁₋₃ perhaloalkylthio, such as trifluoromethylthio,
 (12) C₁₋₃ alkylthio, such as methylthio or propylthio,
 (13) C₁₋₃ alkylsulfonyl, such as methylsulfonyl or isopropylsulfonyl,
 (14) C₁₋₃ perhaloalkylsulfonyl, such as trifluoromethylsulfonyl,
 (15) C₁₋₃ alkylsulfinyl, such as methylsulfinyl,
 (16) C₁₋₃ perhaloalkylsulfinyl, such as trifluoromethylsulfinyl,
 (17) amino,
 (18) C₂₋₆ alkanoylamino, such as acetylamino or pentanoylamino,
 (19) C₁₋₃ alkylamino,
 (20) di(C₁₋₃ alkyl)-amino,
 (21) hydroxy,
 (22) N-(C₁₋₃ alkyl)-carbamoyl,
 (23) N,N-di(C₁₋₃ alkyl)carbamoyl,
 (24) nitro,
 (25) di(C₁₋₃ alkyl)sulfamoyl,
 (26) (C₁₋₃ alkoxy)carbonylamino, or
 (27) N-(C₁₋₃ alkyl)carbamoxyloxy; and
 each of R¹ and R², which are similar or dissimilar, is hydrogen; C₁₋₃ alkyl; C₂₋₃ alkenyl; or C₃₋₆ cycloalkyl; or R¹ and R² are joined to form, together with the nitrogen to which they are attached, a 1-piperidyl, 1-pyrrolidyl, or 4-morpholinyl radical.
- Preferably *n* is 0, 1 or 2 and X, if present, is in the 2 and/or 3 position.
 A particularly preferred group of compounds has the structural formula:



where X and Y are as defined above and R¹ and R² are hydrogen or C₁₋₃ alkyl, especially where one of X and Y is hydrogen, and the other is hydrogen, cyano, formyl, or C₂₋ alkanoyl.

Also contemplated within the scope of the present invention are pharmaceutically acceptable N-acid addition salts of the pyrrolobenzazepines of the present invention. Such pharmaceutically acceptable forms, prepared by conventional means, include the hydrochloride, maleate, sulfate, phosphate, citrate, tartrate and succinate. These pharmaceutically acceptable salts are generally equivalent in potency to the free amino form taking into consideration the stoichiometric quantities involved.

It will be appreciated that the compounds of the present invention exist as *cis-trans* geometrical isomers (also called E and Z isomers in accordance with Blackwood et al, J.A.C.S. 90, 509 (1968)) and are isolable by conventional separation techniques. Such isomers, individually and mixtures thereof, are within the scope of the present invention.

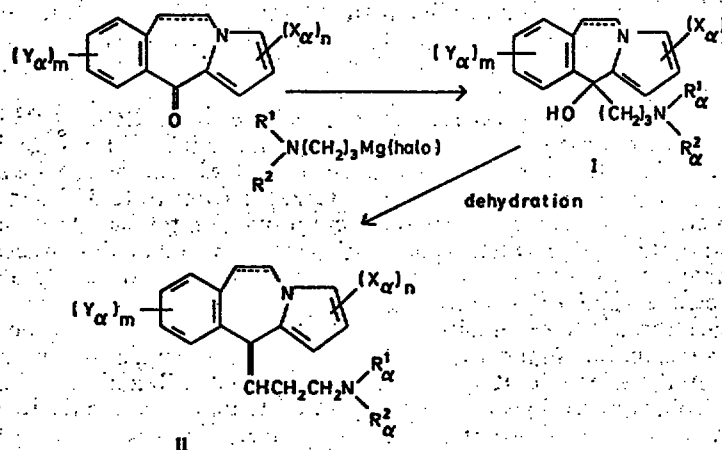
Unexpectedly, it has been discovered that above-described pyrrolobenzazepines of the present invention are useful as skeletal muscle relaxants and can be used for treating muscle spasms and other similar muscle disorders associated with or caused by injury, disease, or arising spontaneously with no known cause. Muscle spasm, spasticity and related clinical disorders involving muscle hyperactivity or increased muscle tone affect a large section of the population. Such clinical disorders involving muscle hyperactivity include the spasticity of cerebral origin which may arise from brain injury or tumor. Another related disorder is cerebral palsy. Other clinical disorders involving tonic skeletal muscle hyperactivity are Parkinson's disease, muscular rigidity, and muscle spasm of traumatic origin including low-back and cervical spine syndromes, many

orthopedic deformities, arthritic states, myositis, whip-lash injuries, fractures, dislocation, cramps, sciatica, and spinal cord injuries. At present, a variety of medicinals are used in an attempt to relieve or correct the clinical disorders involving muscle hyperactivity including muscle spasm, spasticity, and rigidity and pain associated therewith. But administration of these various materials unfortunately is attended by concomitant side effects and toxicity and/or lack of specificity which limit their usefulness. There is an unsatisfied need at the present time for a medication which has a highly specific effect on the muscle hyperactivity associated with various clinical disorders when administered either by the oral or parenteral route which at the same time has a minimum of side effects or contraindications.

In the method of treatment and pharmaceutical composition aspects of the present invention it is to be noted that the precise unit dosage form and dosage level depend upon the case history of the individual being treated and consequently are left to the discretion of the therapist. In general, however, the compounds of the present invention produce the desired effect of skeletal muscle relaxation when given at from about 0.1 to about 30 mg./kg. body weight per day. Any of the usual pharmaceutical forms may be used such as tablets, capsules, elixirs, and aqueous suspensions, and from 0.1 to 300 mg. of the compound of this invention per kilogram body weight should be given daily. Thus for example tablets given 2—4 times per day comprising from 0.5 to 75.0 mg. of the compounds of this invention are suitable; however, the preferred range for the unit dosage level in the form of tablets is from 2.0 to 40.0 mg. of the compounds of the present invention. Sterile solutions for injection comprising from 1 to 30.0 mg. per dose of the compounds of this invention given 2—4 times daily are also a suitable means of delivery.

Compounds of this invention have also been found to possess utility as tranquilizing agents. For this purpose, they may be administered in the same manner and dosage rates described above for the muscle relaxant utility.

In accordance with the present invention, the novel compounds are prepared in accordance with the following reaction scheme:



where X_α and Y_α are as defined for X and Y but exclusive of formyl; and R_α^1 and R_α^2 are as defined for R^1 and R^2 but exclusive of hydrogen. The ketone starting material is treated with a Grignard reagent of formula $R_\alpha^1R_\alpha^2N(CH_2)_3Mg(halo)$ in a solvent such as tetrahydrofuran or ether at a temperature of from $-10^\circ C.$ to reflux for from 10 minutes to 10 hours to provide the 11-hydroxy-11-alkylated intermediate compound, which is then dehydrated by treatment with a suitable reagent, e.g. an acid, such as hydrochloric, oxalic, trifluoroacetic, formic or acetic acid, trifluoroacetic anhydride, trichloroacetic acid, phosphorus oxychloride or a tertiary amine, at a temperature in the range 0 to $100^\circ C.$ for from 5 minutes to 24 hours to provide the final pyrrolobenzazepines. The Grignard reaction and the subsequent dehydration described above are substantially identical to those disclosed in U.S. Patents 3,014,911 (issued December 26, 1961), 2,951,082 (issued August 30, 1960), 3,428,677 (issued February 18, 1969), 3,428,735 (issued February 18, 1969), 3,454,643 (issued July 8, 1969), and 3,499,037 (issued March 3, 1970).

Nitro-pyrrolobenzazepines of this invention are also useful as intermediates in

preparing the corresponding (amino, alkylamino, dialkylamino, or alkanoyl-amino)-pyrrolo-benzazepines.

The amino compounds are prepared by catalytic reduction of the nitro compounds over a noble metal catalyst, preferably palladium on carbon in a C_{1-6} alkanol.

The alkylamino compounds are prepared by heating the corresponding amino compound in a trialkyl orthoformate up to reflux temperature for 2—8 hours, followed by reduction of the product therefrom with an alkali metal borohydride reagent.

The dialkylamino compounds are prepared by reductive alkylation of the corresponding amine with formaldehyde in the presence of a reducing agent such as sodium cyanoborohydride, hydrogen in the presence of a noble metal catalyst, or refluxing formic acid as in the Eschweiler-Clarke reaction.

The alkanoylamino compounds are prepared by treatment of the corresponding amine with an alkanoyl anhydride at 20°—50°C. preferably in the presence of an organic base such as pyridine.

Formylpyrrolobenzazepines may be prepared by reduction of the corresponding cyano compound or its carbinol intermediate compound with nickel-aluminum alloy in formic acid or aqueous formic acid at from 50°C. to reflux temperature for from 30 minutes to 5 hours.

N-Alkylcarbamoyl and N,N-dialkylcarbamoyl compounds may be prepared from the corresponding carboxy compounds by forming the acid chloride therefrom followed by treatment with an alkylamine or a di(alkyl)amine in an inert organic solvent such as methylene chloride at from -20°C. to reflux temperature until the reaction is complete.

Alkoxy-carbonyl compounds may be prepared by heating at 50°C. to reflux for from 1 to 8 hours the corresponding carboxy compound in a C_{1-6} alkanol in the presence of a strong mineral acid, such as hydrogen chloride.

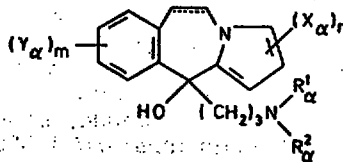
Novel compounds with a trifluoromethylthio or alkylthio substituent in the benzo ring may be prepared by reacting the corresponding iodo- or bromo-compound with trifluoromethylthiocopper (formed by the reaction of copper powder with bis (trifluoromethylthio)mercury) or a cuprous alkylsulfide respectively in a polar organic solvent such as dimethyl-formamide, quinoline, or hexamethylphosphoramide at from 50°C. to 200°C. for from 0.5—24 hours.

Similarly, cyano compounds may be prepared by treating the bromo- or iodo-compounds with cuprous cyanide.

The novel compounds of this invention where one of R^1 and R^2 is hydrogen are prepared by reacting a compound in which one or R^1 and R^2 is alkyl with 2,2,2-trichloroethylchloroformate in an organic solvent such as benzene or toluene at from 50 to 200°C., conveniently at reflux temperature, for from 10 to 24 hours to provide an intermediate N-2,2,2-trichloroethoxycarbonyl compound. This intermediate compound is then subjected to reduction, such as with zinc dust in acetic acid at about ambient temperature for from 10 to 24 hours, to provide a final product in which one of R^1 and R^2 is hydrogen.

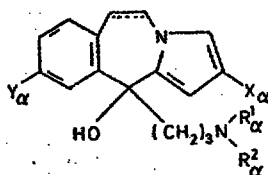
Preparation of the secondary amines of this invention can also be carried out in a conventional manner by reaction of the tertiary amine with cyanogen bromide, as described in R. Adams et al., "Organic Reactions," Vol. VII, pp. 198—262, followed by hydrolysis of the intermediate cyanamide to the desired secondary amine. An alternative well-known route involves heating the tertiary amine with ethyl chloroformate, followed by hydrolysis of the carbamate derivative so formed.

The Grignard reaction product of structural formula:



wherein X_α , Y_α , n , m , R^1_α , R^2_α , and the dotted line are as previously defined forms another embodiment of this invention. Preferably n is 0, 1 or 2 and X_α , if present, is in the 2 and/or 3 position.

A particularly preferred group of such Grignard products have the structural formula:



wherein X_α and Y_α are as defined above and R^1_α and R^2_α are C_{1-3} alkyl, especially when one of X_α and Y_α is hydrogen and the other is hydrogen, cyano or C_{2-6} alkanoyl.

The ketones used as starting materials in novel processes of this invention may be prepared in accordance with the following illustrative Examples 1 to 21 in Group A and Examples 1 to 25 in Group B.

The word "Hasteloy" is a trade mark.

PREPARATION OF STARTING MATERIALS

GROUP A

6,11-Dihydro-5H-pyrrolo[2,1-b][3]benzazepines

Example 1.

6,11-Dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one

Step A: Preparation of 1-(2-phenethyl)-pyrrole-2-carboxylic acid and 1-(2-phenethyl)-4-cyanopyrrole-2-carboxylic acid

Method A: Preparation of 1-(2-phenethyl)pyrrole-2-carboxylic acid

Methyl pyrrole-2-carboxylate (10.0 g.) in 100 ml. of dimethylformamide (DMF) is treated portionwise with sodium hydride (2.21 g.) at 25°C. After evolution of hydrogen has ceased, styrene oxide (11.52 g.) was added and the mixture is heated at 115°C. for 1 hour. The resulting mixture is poured into 600 ml. of ice-water and extracted with ether (2 x 100 ml.). The aqueous phase is acidified to pH 1 with 6N HCl to precipitate the product, which is collected by filtration, washed with water and dried, m.p. 183—185°C.

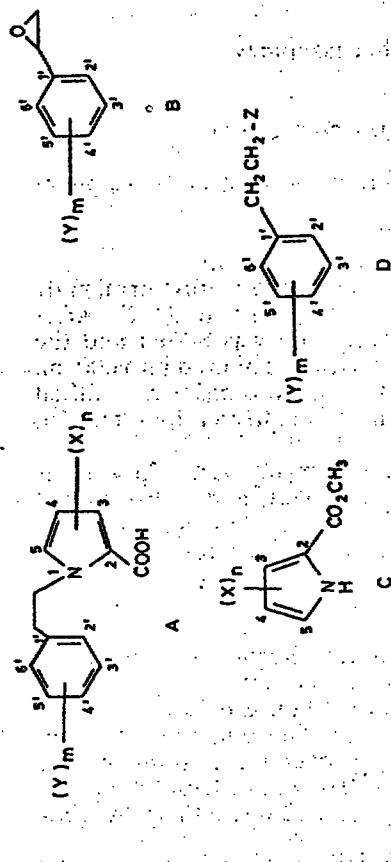
The unsaturated acid, *trans*-1-styrylpyrrole-2-carboxylic acid, 24.4 g, is suspended in 200 ml. ethanol in the presence of 1 g. 10% Pd/C and hydrogenated under 3 atmospheres of hydrogen until uptake of hydrogen has ceased. After removal of the catalyst by filtration, the product, 1-(2-phenethyl)-pyrrole-2-carboxylic acid, is obtained by evaporation of solvent, m.p. 124—125°C.

Method B: Preparation of 1-(2-phenethyl)-4-cyanopyrrole-2-carboxylic acid

To 75 g. of potassium carbonate in 300 ml. of dimethylformamide are added successively 84 g. of 2-phenethyl bromide and 63.5 g. of 2-carbomethoxy-4-cyanopyrrole. The mixture is heated in an oil bath at 85°C. for 4 hours, poured into 1000 ml. of water, and extracted with 3 x 1000 ml. of ether. The combined organic extracts are washed with 2 x 100 ml. of water, dried over magnesium sulfate, filtered and evaporated. The residue is triturated with 500 ml. of fresh ether and the resulting solid filtered to yield 82.8 gm. (77%) of 1-(2-phenethyl)-2-carbomethoxy-4-cyanopyrrole, m.p. 109—110°C.

A mixture of 80.3 g. of 1-(2-phenethyl)-2-carbomethoxy-4-cyanopyrrole, 23.3 g. of potassium hydroxide and 900 ml. of ethanol is heated at 75°C. for 2 hours. The solution is evaporated to dryness, the residue is dissolved in 1000 ml. of water, and the solution is acidified to pH 1 with 6N HCl to cause precipitation of 1-(2-phenethyl)-4-cyanopyrrole-2-carboxylic acid. The product is collected by filtration, washed with water and dried to give 72 g. (95%), m.p. 195—195.5°C.

Following the procedure described in Example 1, Step A, the nuclear substituted 1-(2-phenethyl)-pyrrole-2-carboxylic acids (A) of Table I are obtained when the indicated molar equivalent substitutions for the styrene oxide (B) or 2-(phenethyl) halide (D) and the methylpyrrole-2-carboxylate (C) of Example 1 are made:



where Z is bromide, iodide, tosylate or mesylate

TABLE I.

COMPOUND	PHENYL REACTANT		PYRROLE REACTANT, C		PRODUCT, A		M.P. (°C.)
	(Y) _m	B or D	(X) _n	(Y) _m (X) _n	(Y) _m (X) _n	(Y) _m (X) _n	
1.	H	(B)	4-SO ₂ N(CH ₃) ₂	4-SO ₂ N(CH ₃) ₂	4-SO ₂ N(CH ₃) ₂	4-SO ₂ N(CH ₃) ₂	195—195.5
2.	H	(B)	4-SO ₂ CH ₃	4-SO ₂ CH ₃	4-SO ₂ CH ₃	4-SO ₂ CH ₃	
3.	H	(B)	4-SO ₂ CH(CH ₃) ₂	4-SO ₂ CH(CH ₃) ₂	4-SO ₂ CH(CH ₃) ₂	4-SO ₂ CH(CH ₃) ₂	
4.	H	(B)	4-SO ₂ CF ₃	4-SO ₂ CF ₃	4-SO ₂ CF ₃	4-SO ₂ CF ₃	
5.	H	(D)	4-CN	4-CN	4-CN	4-CN	
6.	H	(B)	4-COOC ₂ H ₅	4-COOC ₂ H ₅	4-COOC ₂ H ₅	4-COOC ₂ H ₅	
7.	H	(D)	4-NO ₂	4-NO ₂	4-NO ₂	4-NO ₂	
8.	H	(B)	4-COCH ₃	4-COCH ₃	4-COCH ₃	4-COCH ₃	
9.	H	(B)	4-CF ₃	4-CF ₃	4-CF ₃	4-CF ₃	

TABLE I (Continued).

COMPOUND	PHENYL REACTANT		B or D	PYRROLE REACTANT, C		PRODUCT, A		M.P. (°C.)
	(Y) _m	(X) _n		(Y) _m	(X) _n	(Y) _m	(X) _n	
6.	H	4-COOCH ₃	(B)	H	4-COOCH ₃	4-COOCH ₃	4-COOCH ₃	
7.	H	4-NO ₂	(D)	H	4-NO ₂	4-NO ₂	4-NO ₂	
8.	H	4-COOCH ₃	(B)	H	4-COOCH ₃	4-COOCH ₃	4-COOCH ₃	
9.	H	4-NO ₂	(B)	H	4-NO ₂	4-NO ₂	4-NO ₂	
10.	4'-O-C(=O)-NHCH ₃	H	(B)	H	4'-OCONHCH ₃	4'-OCONHCH ₃	4'-OCONHCH ₃	
11.	4'-NH-COOCH ₃	H	(B)	H	4'-NHCOOCH ₃	4'-NHCOOCH ₃	4'-NHCOOCH ₃	
12.	4'-CH ₃	H	(B)	H	4'-CH ₃	4'-CH ₃	4'-CH ₃	
13.	H	4,5-Br ₂	(D)	4,5-Br ₂	4,5-Br ₂	4,5-Br ₂	4,5-Br ₂	178—179
14.	H	4-Br	(D)	4-Br	4-Br	4-Br	4-Br	
15.	H	4-Cl	(D)	4-Cl	4-Cl	4-Cl	4-Cl	117—120
16.	H	5-CN	(D)	5-CN	5-CN	5-CN	5-CN	
17.	H	3,4,5-Br ₃	(D)	3,4,5-Br ₃	3,4,5-Br ₃	3,4,5-Br ₃	3,4,5-Br ₃	182—184
18.	H	4-SCF ₃	(B)	4-SCF ₃	4-SCF ₃	4-SCF ₃	4-SCF ₃	123—125
19.	H	4-CON(CH ₃) ₂	(B)	4-CON(CH ₃) ₂	4-CON(CH ₃) ₂	4-CON(CH ₃) ₂	4-CON(CH ₃) ₂	
20.	H	4-CH ₃ -3,5-Br ₂	(D)	4-CH ₃ -3,5-Br ₂	4-CH ₃ -3,5-Br ₂	4-CH ₃ -3,5-Br ₂	4-CH ₃ -3,5-Br ₂	
21.	4'-NH-COOCH ₃	H	(D)	3,4,5-Br ₃	4'-NHCOOCH ₃ -3,4,5-Br ₃	4'-NHCOOCH ₃ -3,4,5-Br ₃	4'-NHCOOCH ₃ -3,4,5-Br ₃	
22.	H	4-CHO	(D)	4-CHO	4-CHO	4-CHO	4-CHO	
23.	4'-CH(CH ₃) ₂	H	(D)	H	4'-CH(CH ₃) ₂	4'-CH(CH ₃) ₂	4'-CH(CH ₃) ₂	
24.	4'-SCH ₃	H	(D)	H	4'-SCH ₃	4'-SCH ₃	4'-SCH ₃	
25.	3',4'-(CH ₃) ₂	4-CN	(D)	4-CN	3',4'-(CH ₃) ₂ -4-CN	3',4'-(CH ₃) ₂ -4-CN	3',4'-(CH ₃) ₂ -4-CN	
26.	4'-OH	4-CN	(D)	4-CN	4'-OH-4-CN	4'-OH-4-CN	4'-OH-4-CN	
27.	4'-OCH ₃	4-CN	(D)	4-CN	4'-OCH ₃ -4-CN	4'-OCH ₃ -4-CN	4'-OCH ₃ -4-CN	

Step B: Preparation of 1-(2-phenethyl)-2,3-dibromopyrrole-5-carboxylic acid chloride

To a solution of 1-(2-phenethyl)pyrrole-2-carboxylic acid (105 g., 0.49 mole) in acetic acid (750 ml.) is added 156 g. of bromine over 30 minutes at 25°C. Formic acid (100 ml.) is added and the reaction chilled in ice, to yield 66 gm. (0.18 mole) of 1-(2-phenethyl)-2,3-dibromopyrrole-5-carboxylic acid after solvent removal. Heating the resulting acid in an excess of thionyl chloride for 1 hour yields the acid chloride in near quantitative yield after removal of solvent by evaporation, washing with petroleum ether and drying in vacuum.

Following the procedure of Example 1, Step B, but using chlorine in place of bromine, there is obtained 1-(2-phenethyl)-2,3-dichloro-5-pyrrole carboxylic acid chloride.

Following the procedure of Example 1, Step B, the mono- and dibrominated acid chlorides depicted in Table II are obtained when an equivalent amount of the appropriate free acid from Table I replaces the 1-(2-phenethyl)-pyrrole-2-carboxylic acid used in Example 1, Step B, and either 1 or 2 equivalents of bromine is reacted therewith.

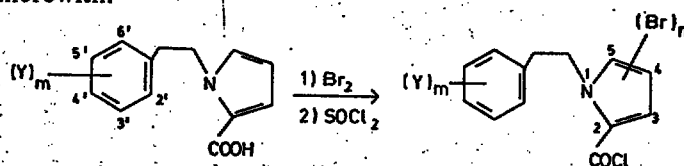


TABLE II.

Starting material from	(Y) _m	Equivalents of Bromine	(Br) _n
Example 1A	H	1	4-Br
Table I(12)	4'-CH ₃	2	4,5-Br ₂
Table I(10)	4'-OCONHCH ₃	2	4,5-Br ₂
Table I(11)	4'-NHCOOCH ₃	2	4,5-Br ₂
Table I(24)	4'-SCH ₃	2	4,5-Br ₂
Table I(23)	4'-CH(CH ₃) ₂	2	4,5-Br ₂

Following the procedure of Example 1, Step B, but omitting the nuclear halogenation step, there are obtained the corresponding acid chlorides when the 1-(2-phenethyl)-pyrrole-2-carboxylic acids of Example 1, Step B, are replaced by an equivalent amount of the free acids enumerated in Table I, respectively.

Step C: Preparation of 2,3-dibromo-6,11-dihydro-5H-pyrrolo-[2,1-b][3]benzazepin-11-one

To a solution of 1-(2-phenethyl)-4,5-dibromo-pyrrole-2-carboxylic acid chloride (40 g., 0.102 mole) in 800 ml. *sym*-tetrachloroethane at 140°C. is added 40 gm. (0.30 mole) of aluminum chloride. After three minutes, the reaction mixture is cooled in ice, poured over 2000 g. of ice, stirred for 10 minutes and filtered, and the organic layer is separated. The aqueous layer is extracted with 2 x 200 ml. of chloroform, which is combined with the first organic layer. The combined organic solution is washed with 3 x 500 ml. of water, dried, and evaporated in vacuum to provide a dark oil (29 g.), which is chromatographed on silica gel using benzene to elute in 50-ml. fractions. Fraction 5-13 are combined and evaporated to yield 20.3 gm. (0.057 mole) of 2,3-dibromo-6,11-dihydro-5H-pyrrolo-[2,1-b][3]-benzazepin-11-one, m.p. 130-132°C.

Following the procedure of Example 1, Step C, but substituting for the 1-(2-phenethyl)-4,5-dibromopyrrole-2-carboxylic acid chloride used therein an equimolecular amount of the acid chlorides prepared in accordance with Example 1, Step B, there are produced, by the following process, the 6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-ones described in Table III:

18

ic acid
mole) in
Formic
mole) of
removal
the aci-
oration,
place of
ylic acid
minated
nt of the
pyrrole-2-
bromine

5

10

15

20

25

30

35

40

nuclear
en the l-
ed by an
y.
nzaepin-
lic acid
added 40
ixture is
red, and
0 ml. of
organic
cuum to
nzene to
to yield
1-b[3]-
the 1-(2-
rein an
Example
dro-5H-

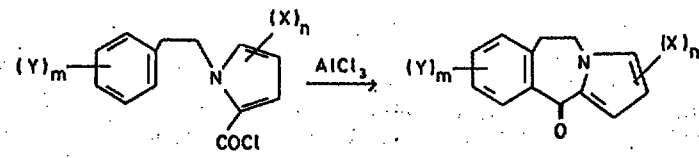


TABLE III.

Compound ^a	(Y) _m	(X) _n	m.p. (°C.)
1	H	2-SO ₂ N(CH ₃) ₂	
2	H	2-SO ₂ CH ₃	
3	H	2-SO ₂ CH(CH ₃) ₂	
4	H	2-SO ₂ CF ₃	
5	H	2-CN	146—147
6	H	2-CO ₂ C ₂ H ₅	
7	H	2-NO ₂	
8	H	2-COCH ₃	
9	H	2-CF ₃	
10 (II 3)	9-OCONHCH ₃	2,3-Br ₂	
11 (II 4)	9-NHCOOCH ₃	2,3-Br ₂	
12 (II 2)	9-CH ₃	2,3-Br ₂	
13	H	2,3-Br ₂	130—132
14 (II 1)	H	2-Br	101—103
15	H	2-Cl	100—105
16	H	3-CN	130—131
17	H	1,2,3-Br ₃	150—155
18	H	2-SCF ₃	
19	H	2-CON(CH ₃) ₂	
20	H	1,3-Br ₂ -2-CH ₃	
21	9-NHCOCH ₃	1,2,3-Br ₃	
22	H	2-CHO	
23 (II 6)	9-CH(CH ₃) ₂	2,3-Br ₂	
24 (II 5)	9-SCH ₃	2,3-Br ₂	
25	8,9-(CH ₃) ₂	2-CN	
26	9-OH	2-CN	
27	9-OCH ₃	2-CN	
28	H	2,3-Cl ₂	

Footnotes to Table III.

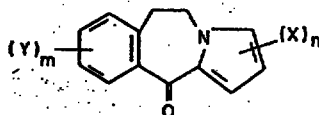
* The numbers of the compounds described in Table III correspond to the numbers of the starting materials described in Table I from which they were prepared, unless otherwise indicated. For example, compound 5 of Table III was prepared from the compound 5 of Table I. Compound 12 was prepared from compound 2 of Table II.

Step D: Preparation of 6,11-dihydro-5H-pyrrolo[2,1-b][3]-benzazepin-11-one

A suspension of 25 g. (0.070 mole) of 2,3-dibromo-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one in 200 ml. ethanol containing 25 ml. of triethylamine and 1 gm. of 10% Pd on charcoal is hydrogenated under 3 atmospheres of hydrogen to yield 6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one, m.p. 54—55°C. after removal of catalyst, recrystallization from petroleum ether and drying under vacuum. The same compound is also obtained by hydrogenolysis of the 2,3-dichloro ketone and the 1,2,3-tribromoketone.

Following the procedure of Example 1, Step D, but substituting for the 2,3-dibromo-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-ones used therein, an equimolecular amount of the halogenated ketones described in Table III, there are produced the ketones described in Table IV.

TABLE IV.



Starting Material			
Table	Compound No.	(Y) _m	(X) _n
III	10	9-OCONHCH ₃	H
III	11	9-NH—COOCH ₃	H
III	12	9-CH ₃	H
III	14	H	H
III	23	9-CH(CH ₃) ₂	H
III	20	H	2-CH ₃
III	21	9-NH—COCH ₃	H
III	24	9-SCH ₃	H

Example 2.

Preparation of 2-cyano-6,11-dihydro-5H-pyrrolo[2,1-b][3]-benzazepine-11-one

To a solution of 73.6 g. of 1-(2-phenethyl)-4-cyanopyrrole-2-carboxylic acid chloride in 850 ml. of tetrachloroethane maintained at 140°C. is added over a period of 2 minutes 114 g. of aluminum chloride. The resulting solution is stirred at 140°C. for 4 minutes and poured over 2000 g. of ice, and the mixture is stirred for 10 minutes. It is then filtered to remove insoluble tarry material and the organic layer is separated. The aqueous layer is extracted with 2 × 500 ml. of chloroform, which is combined with the original organic layer, and washed with 500 ml. of water and with 200-ml. portions of 1N sodium bicarbonate until the aqueous washes remain basic. The organic layer is dried over magnesium sulfate, filtered, and evaporated under vacuum to leave a residue. This residue upon trituration with 300 ml. of ether readily crystallizes. The crystals are filtered and air-dried to yield 57.2 gm. (90%) of 2-cyano-6,11-dihydro-5H-pyrrolo[2,1-b][3]-benzazepine-11-one, m.p. 146—147°C.

Example 3.

Preparation of 2-formyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepine-11-one
2-Cyano-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one (222 mg.) and
222 mg. nickel-aluminum alloy in 2 ml. 75% formic acid is refluxed for 1½ hours.
The solid is filtered off and washed with ethanol. The filtrate is diluted with 50 ml.
water and extracted twice with 50 ml. methylene chloride. The organic layer is
washed with water, 5% sodium bicarbonate and with water; it is then dried over
magnesium sulfate and evaporated to dryness. Addition of ether induces
crystallization and the crystals are filtered and air-dried to yield 125 mg. (56%) of
2-formyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepine-11-one, m.p. 135—136°.

Example 4.

2-Carbamoyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one
2-Cyano-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one (30 g., 0.135
mole) in 100 ml. of concentrated hydrochloric acid and 100 ml. of acetic acid is
refluxed for 2 hours. It is then poured onto 500 ml. of water and continuously
extracted with methylene chloride. The solution, from which crystals are
deposited during the extraction, is left to cool to room temperature and filtered to
afford 2-carbamoyl-6,11-dihydro-11-oxo-5H-pyrrolo[2,1-b][3]benzazepine (27 g.
83%), m.p. 228°C.

Example 5.

6,11-Dihydro-11-oxo-5H-pyrrolo[2,1-b][3]benzazepine-2-carboxylic acid
To 2-carbamoyl-6,11-dihydro-pyrrolo[2,1-b][3]benzazepine-11-one (27 g.,
0.112 moles) in 300 ml. of 50% sulfuric acid maintained at 50°C., is added slowly 25
g. of sodium nitrite in 75 ml. of water. At the end of the addition, the solid is
filtered, washed with water and air-dried to yield 6,11-dihydro-11-oxo-pyrrolo[2,1-
b][3]benzazepine-2-carboxylic acid (24 g., 89%), m.p. 287—290°C.

Example 6.

2-Dimethylcarbamoyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one
Step A: Preparation of 2-chlorocarbonyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benz-
azepin-11-one
6,11-Dihydro-11-oxo-pyrrolo[2,1-b][3]benzazepine-2-carboxylic acid (24 g.,
99 mmoles) in 100 ml. of thionyl chloride is refluxed for 15 minutes. The volatile
materials are removed under vacuum and the residue is triturated in ether.
Filtration and air-drying yield 2-chlorocarbonyl-6,11-dihydro-5H-pyrrolo[2,1-
b][3]benzazepin-11-one (23 g., 89%), m.p. 147—148.5.

Step B: Preparation of 2-dimethylcarbamoyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]-
benzazepine-11-one

Anhydrous dimethylamine is bubbled through a suspension of 2-chloro-
carbonyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one (23 g., 88.5
mmoles) in 100 ml. of methylene chloride. (Note: the introduction of dimethyl-
amine causes the mixture to reflux and this reflux stops when all the acid chloride
has reacted. This takes about 1 hour and complete solution is obtained).

The reaction mixture is washed with water and dried over sodium sulfate. It is
then taken to dryness, triturated in ether, filtered and air-dried to yield 2-dimethyl-
carbamoyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one (20 g., 84%), m.p.
148—149.5°C.

Example 7.

6,11-Dihydro-2-methoxycarbonyl-5H-pyrrolo[2,1-b][3]benzazepin-11-one
6,11-Dihydro-11-oxo-5H-pyrrolo[2,1-b][3]benzazepine-2-carboxylic acid
(25.5 g., 0.11 moles) in 300 ml. of methanol saturated with hydrogen chloride is
refluxed until a homogeneous solution is obtained (4 hours).

The volatile materials are removed under vacuum and the residue is dissolved
in 300 ml. of methylene chloride and washed with dilute sodium hydroxide and
then with water. It was dried over sodium sulfate and concentrated. The residue is
triturated in ether, filtered and air-dried, yielding 6,11-dihydro-2-methoxy-
carbonyl-5H-pyrrolo[2,1-b]-[3]-benzazepin-11-one (23.5 g., 85%), m.p.
125—127°C.

Example 8.

2 - Trifluoromethylthio- and 3 - trifluoromethylthio - 6,11 - dihydro - 5H - pyrrolo-
[2,1-b][3]benzazepin-11-one
6,11-Dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one (9.6 g., 48.7 mmoles),
dissolved in pyridine (20 ml.) and chloroform (50 ml.), is treated with trifluoro-

methysulphenyl chloride (12 g., 86.6 mmoles) in chloroform (50 ml.). The reaction mixture is left at room temperature for 2 hours.

The mixture is washed with water, dried over sodium sulfate and concentrated to 16.2 g. of a black oil.

This oil is adsorbed on 800 g. of silica gel. Elution with petroleum ether-ether 3:1 (v/v) yields 3-trifluoromethylthio-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepine-11-one (8.4 g., 57.7%), m.p. 95—95.5°C.

Elution with ether yields 2-trifluoromethylthio-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepine-11-one (4.2 g., 28.8%), m.p. 77—78°C.

Example 9.

6,11 - Dihydro - 1 - trifluoromethyl - (and - 3 - trifluoromethyl) - 5H - pyrrolo[2,1-b][3]benzazepin-11-one

A mixture of 8.9 g. of 6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepine-11-one, 30 of trifluoromethyl iodide, 20 ml. of pyridine and 300 ml. of acetonitrile is irradiated with a 450-watt lamp for 18 hours. The mixture is evaporated to dryness and the residue is extracted with ether and filtered. The filtrate is evaporated to an oil. The oil is again treated with 25 g. of trifluoromethyl iodide in pyridine/acetonitrile and irradiated for 12 hours. Evaporation to dryness, extraction with ether, filtration and evaporation to dryness give a crystalline residue. The residue is chromatographed on silica gel, by elution with benzene. Fraction 1 from the column provides 3.5 g. of product contaminated with traces of the 2-trifluoromethyl isomer. Fraction 2 provides 900 mg. of pure 6,11-dihydro-3-trifluoromethyl-5H-pyrrolo[2,1-b][3]benzazepin-11-one, m.p. 90—93°C.

Rechromatography of Fractions 3—5 provides pure 6,11-dihydro-1-trifluoromethyl-5H-pyrrolo[2,1-b][3]benzazepin-11-one, m.p. 102—103°C.

Example 10.

6,11-Dihydro-2-pentanoyl-5H-pyrrolo[2,1-b][3]benzazepin-11-one

6,11 - Dihydro - 5H - pyrrolo[2,1-b][3]benzazepin - 11 - one (1.0 g.) is dissolved in 20 ml. of methylene chloride and 2.66 g. of aluminum chloride is added with cooling. At room temperature there is added, little by little, 720 mg. of pentanoyl chloride. Fifteen minutes after the addition is complete the mixture is poured onto ice. The organic phase is separated, filtered, dried and concentrated to dryness. The residue is triturated with ether, collected and dried to give 1.18 g. (85%) of 6,11-dihydro-2-pentanoyl-5H-pyrrolo[2,1-b][3]benzazepin-11-one, m.p. 135—136°C. Chromatography on silica gel by elution with benzene, and 5% (v/v) ethyl acetate in benzene, raises the melting point to 137—138°C.

By the procedure substantially as described in Example 10, but substituting, for the pentanoyl chloride, the acid chlorides described in Table V, there are produced the acyl-pyrrolobenzazepinones also described in Table V by the following procedure:

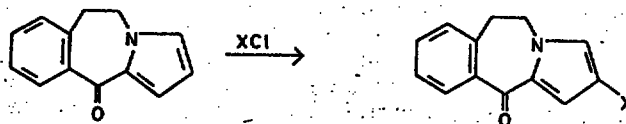


TABLE V.

X	product m.p. (°C.)
—C(=O)CH_3	160—161
$\text{—C(=O)CH(CH}_3)_2$	124—126
$\text{—SO}_2\text{N(CH}_3)_2^a$	134—137

^a reaction conducted in nitromethane at reflux temperature for 20 minutes.

(19)

ml.). The
centrated
ther-ether
2,1-b][3]-
pyrrolo[2,

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Following the procedure of Example 10, but conducting the reaction at 100—130°C. with an excess of alkanoyl chloride as solvent and without the aluminum chloride, there are produced mixtures of 2- and 3- alkanoyl ketones which, upon chromatographic separation on silica gel, provide the alkanoyl ketone products described in Table V and in Example 10 as well as the corresponding 3-pentanoyl-, 3-acetyl-, and 3-isobutyroyl- compounds.

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Example 11.

9-Iodo-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one

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Step A: Preparation of 7-nitro-3,4-dihydro-isocarbostyryl

Fuming nitric acid (17 ml.) is added to 670 ml. of concentrated sulfuric acid at 0°C. 3,4-Dihydro-isocarbostyryl (50 g.) is added portionwise maintaining the temperature below 0°C. After 30 minutes at 0°C., the solution is poured into 8 l. of ice water. The crystalline precipitate is collected, washed with water and air dried to give 62.0 g. (95%) of 7-nitro-3,4-dihydro-isocarbostyryl, m.p. 225—230°C. After recrystallization from acetone it has m.p. 230—232°C.

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Step B: Preparation of 7-amino-3,4-dihydro-isocarbostyryl

The product from Step A (20 g.) is hydrogenated over 2.0 g. of 10% Pd/C in 350 ml. of methanol. The mixture is filtered and the filtrate is evaporated to dryness. The residue is suspended in ether and collected on a filter to give 15.7 g. (93%) of 7-amino-3,4-dihydro-isocarbostyryl, m.p. 123—125°C.

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Step C: Preparation of 7-iodo-3,4-dihydro-isocarbostyryl

A solution of 690 mg. of sodium nitrite in 5 ml. of water is added dropwise to an ice-cold solution of 1.62 g. of 7-amino-3,4-dihydro-isocarbostyryl in 4 ml. of concentrated hydrochloric acid and 12 ml. of water. After about 15 minutes at 0—5°C., a solution of 1.7 g. of potassium iodide in 1 ml. of water is added and the mixture is allowed to warm to room temperature. Acetone (20 ml.) is added and the solution is held at room temperature for 1 hour and at 50—60°C. for 1 hour. The mixture is concentrated to dryness. The residue is taken up in water and extracted with chloroform, and the extract was dried and concentrated to dryness to give 2.0 g. (73%) of 7-iodo-3,4-dihydro-isocarbostyryl.

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Step D: Preparation of 2-aminoethyl-5-iodobenzoic acid hydrochloride.

A mixture of 1.0 g. of 7-iodo compound from Step C and 40 ml. of concentrated hydrochloric acid is heated in a pressure vessel at 145°C. for 30 hours. The solution is concentrated to dryness. The residue is suspended in ether and collected to give 950 mg. (80%) of 2-aminoethyl-5-iodobenzoic acid hydrochloride, m.p. 200—205°C.

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Step E: Preparation of 2-(2-pyrrol-1-yl)ethyl-5-iodobenzoic acid.

A mixture of 12.1 g. of product from Step D, 6.48 g. of 2,5-dimethoxytetrahydrofuran, 180 ml. of water and 30 ml. of acetic acid is stirred at 55°C. for 2 hours and at room temperature overnight. The mixture is diluted with water and extracted with chloroform, and the extract is extracted with 0.5% (w/v) sodium hydroxide solution. The alkaline extract is acidified with 6 N hydrochloric acid and extracted with chloroform. The extract is dried, filtered and concentrated to dryness. The oily residue is triturated with cyclohexane and the solids are collected to give 8.1 g. (58%) of 2-(2-pyrrol-1-yl)ethyl-5-iodobenzoic acid, m.p. 92—95°C.

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Step F: Preparation of 9-iodo-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one

A mixture of 1 g. of the product from Step E and 20 ml. of polyphosphate ester is stirred 1.5 hrs. at room temperature. The mixture is cooled in ice and diluted with 75 ml. of water. The mixture is extracted with benzene and the extract is washed with water, dried and concentrated to dryness to give 500 mg. of 9-iodo-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one, which after recrystallization from cyclohexane has m.p. 120—122°C.

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Following the procedure of Example 11, Steps C, D, E, and F but substituting for the potassium iodide used in Step C thereof an equimolecular amount of cuprous chloride, there is prepared 9-chloro-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one.

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Example 12.

9-Trifluoromethylthio-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one

A mixture of 2.4 g. of iodoketone (from Example 11), 5.14 g. of copper (electrolytic dust), 9.0 g. of bis(trifluoromethylthio)mercury and 20 ml. of dimethyl formamide is stirred and heated on a steam bath for 5 hours. The mixture is cooled in ice, treated with 75 ml. of benzene and treated dropwise with 50 ml. of 10% sodium hydroxide solution. After 1 hour at room temperature the mixture is filtered through diatomaceous earth followed by a benzene wash. The filtrate is extracted with benzene. The combined benzene fractions are washed with water, dried, filtered and concentrated to dryness to give 2.0 g. (90%) of 9-trifluoromethylthio-6,11-dihydro-5H-pyrrolo-[2,1-b][3]benzazepin-11-one, m.p. 81—83°C.

Following the procedure of Example 12, but substituting for the copper dust and the bis(trifluoromethylthio)mercury used therein an equimolecular amount of cuprous methylsulfide or cuprous isopropylsulfide, there are produced 9-methylthio-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one and 9-isopropylthio-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one, respectively.

Example 13.

9-Nitro-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one

Following the procedure of Example 11, Steps D, E, and F, but substituting for the 7-iodo-3,4-dihydroisocarbostyryl used in Step D an equimolecular amount of 7-nitro-3,4-dihydro-isocarbostyryl, there are produced in sequence:

Step A: 2-aminoethyl-5-nitrobenzoic acid, m.p. 230—232°C.;

Step B: 2-(2-pyrrol-1-yl)ethyl-5-nitrobenzoic acid, m.p. 147—149°C.; and

Step C: 9-nitro-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one, m.p. 190—192°C.

Example 14.

9-Amino-6,11-Dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one

Following the procedure of Example 11, Step B, but substituting for the 7-nitro-3,4-dihydro-isocarbostyryl an equimolecular amount of 9-nitro-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one, there is produced 9-amino-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one, m.p. 166—167°C.

Example 15.

9-Methylamino-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one

A solution of 9-amino-6,11-dihydro-5H-pyrrolo-[2,1-b][3]benzazepin-11-one in triethyl orthoformate (2.14 g.; 10 mmoles in 80 ml) is refluxed for 5 hours. The volatile materials are removed under vacuum and the residue is dissolved in 100 ml. of absolute ethanol and stirred in an ice bath while sodium borohydride (0.88 g.; 0.024 moles) is added over a period of 10 minutes. The mixture is stirred for a period of 2 hours. After concentration of the ethanol, the residue is dissolved in ethyl acetate, washed with water, dried over Na₂SO₄ and concentrated to dryness to yield 9-methylamino-6,11-dihydro-5H-pyrrolo-[2,1-b][3]benzazepin-11-one.

Example 16.

9-Dimethylamino-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one

To a solution of 9-amino-6,11-dihydro-5H-pyrrolo-[2,1-b][3]benzazepin-11-one (2.1 g., 10 mmoles) and 4 ml. (50 mmoles) of 37% aqueous formaldehyde in 15 ml. of acetonitrile is added 1 g. (16 mmoles) of sodium cyano borohydride. A vigorous and exothermic reaction takes place and a dark residue separates. The mixture is stirred for 15 minutes and then glacial acetic acid is added dropwise until the solution tests neutral on wet pH paper. Stirring is maintained for an additional 2 hours. The volatile materials are removed under vacuum, and the residue is dissolved in chloroform. The solution is washed with base and with water, dried over sodium sulfate, and concentrated to leave a residue that is purified by chromatography on silica gel. Elution with chloroform yields 9-dimethylamino-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one as a dark brown oil.

Example 17.

9-Cyano-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one

A stirred mixture of 1 gm. of 9-iodo-6,11-dihydro-5H-pyrrolo[2,1-b][3]-

l-one
f copper
dimethyl
is cooled
of 10%
mixture
filtrate is
th water,
trifluoro-
l-83°C.
pper dust
amount of
9-methyl-
opylthio-

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benzazepin-11-one, 1 gm. of cuprous cyanide and 5 ml. of dimethylformamide is heated to reflux for 5 hr. The mixture is then poured into a solution of 4 gm. of ferric chloride hydrate in 25 ml. of 2N hydrochloric acid. After stirring the resulting mixture at 60° for 30 min., it is extracted with 3 x 50 ml. of ethyl acetate and the organic extracts are washed with 3 x 100 ml. of water and dried over Na₂SO₄. Evaporation of the dried solution yields 9-cyano-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one.

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Example 18.

9-Trifluoromethylsulfinyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one

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A solution of 3 gm. of 9-trifluoromethylthio-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one in 25 ml. of acetic acid containing 3 ml. of 50% hydrogen peroxide is stirred at 25°C. for 6 hr. The solvent is evaporated and the residue dissolved in 100 ml. of methylene chloride. The solution is washed with 2 x 25 ml. of 5% Na₂CO₃ solution, dried and evaporated. Chromatography of the residue on silica gel yields 9-trifluoromethylsulfinyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one.

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By the procedure of Example 18, but substituting for the 9-trifluoromethylthio-6,11-dihydro-5H-benzazepin-11-one an equimolecular amount of the corresponding 9-methylthio- or 9-isopropylthio- compound, there is produced respectively 9-methylsulfinyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one or 9-isopropylsulfinyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one.

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Example 19.

9-Trifluoromethylsulfonyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one

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A solution of 2 gm. of 9-trifluoromethylsulfinyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one in 20 ml. of acetic acid containing 5 ml. of 90% hydrogen peroxide is stirred at 25°C. for 4 days. The solvent is evaporated and the residue dissolved in 100 ml. of methylene chloride. After washing the organic solution with 2 x 25 ml. of 1N Na₂CO₃, it is dried and evaporated, and the residue chromatographed on silica gel to yield 9-trifluoromethylsulfonyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one.

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By the procedure of Example 18, but substituting for the 9-trifluoromethylthio-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one an equimolecular amount of the corresponding 9-methylthio- or 9-isopropylthio- compound, there is produced respectively 9-methylsulfonyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one or 9-isopropylsulfonyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one.

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Example 20.

9-Formyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one

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By the procedure of Example 3 but substituting for the 2-cyano compound an equimolecular amount of 9-cyano-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin, there is produced 9-formyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one.

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Example 21.

9-Trifluoromethyl-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one

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A mixture of 5 g. of the 9-iodo ketone from Example 11, 25 g. of trifluoromethyl iodide, 9 g. of precipitated copper and 150 ml. of dimethylformamide is heated in a stainless steel tube with shaking for 12 hours at 140°C. Work-up of the reaction mixture and chromatography yield the desired compound.

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PREPARATION OF STARTING MATERIAL

GROUP B

11H-PYRROLO[2,1-b][3]BENZAZEPINES

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Example 1.

2-Cyano-11H-pyrrolo[2,1-b][3]benzazepin-11-one

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Step A: Preparation of *trans*-2-carboxy-4-cyano-N-styrylpyrrole

A mixture of 5 g. of sodium hydride and 15 g. of methyl 4-cyanopyrrole-2-carboxylate in 75 ml. of dimethyl formamide is stirred until evolution of hydrogen ceases. Styrene oxide (16 g.) is added and heated at 110°C. for 6 hours. The mixture is poured into 300 ml. of water and extracted with 2 x 150 ml. of ether. The

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aqueous phase is purged with nitrogen and acidified with 2 *N* hydrochloric acid. The precipitated solid is collected, washed with water, air dried and washed with ether to give 6.4 g. of pure *trans*-2-carboxy-4-cyano-N-styrylpyrrole, m.p. 195—196°C. (decarboxylation).

The sodium hydride used in the above step can be replaced by an equimolecular amount of potassium *t*-butoxide.

Step B: Preparation of *cis*-2-carboxy-4-cyano-N-styrylpyrrole

A solution of 50 mg. of *trans*-2-carboxy-4-cyano-N-styrylpyrrole in 1 ml. of acetonitrile is irradiated with a 450-watt lamp for 45 minutes. The solution is concentrated to dryness. The residue is triturated with ether and the product is collected and air dried to give 37 mg. of *cis* 2-carboxy-4-cyano-N-styrylpyrrole, m.p. 166—168°C.

Following the procedure substantially as described in Example 1, Steps A and B, but substituting, for the methyl 4-cyanopyrrole-2-carboxylate and styrene oxide used in Step A, equimolecular amounts of the methyl pyrrole carboxylates and styrene oxides, respectively, depicted in Table I, there are produced the *trans*- and *cis*-N-styryl-pyrrole-2-carboxylic acids, also depicted in Table I by the following process.

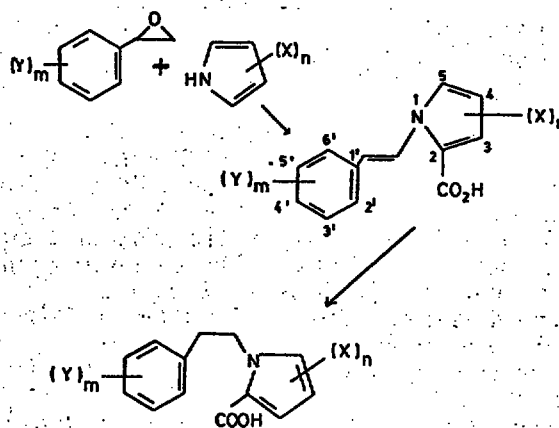


TABLE I.

Compound	(Y) _m	(X) _n
1	H	H
2	H	4-SCF ₃
3	4'-Cl	H
4	4'-SCF ₃	H
5	4'-CN	H
6	H	4-COCH(CH ₃) ₂
7	H	4-SO ₂ N(CH ₃) ₂
8	H	4-SO ₂ CH(CH ₃) ₂
9	H	4-Cl
10	4'-Br	H
11	H	4-NO ₂
12	4'-OCH ₃	H
13	4'-CF ₃	H

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Step C: Preparation of 2-cyano-11H-pyrrolo[2,1-b][3]benzazepin-11-one

A solution of 35 mg. *cis*-2-carboxy-4-cyano-N-styrylpyrrole in 0.5 ml. of dry methylene chloride is treated with 45 μ l. of trifluoroacetic anhydride and stirred for 5 minutes. Stannic chloride (45 μ l.) is added and the mixture stirred for 15 minutes. The mixture is poured into water, neutralized with ammonium hydroxide and extracted twice with chloroform. The extract is washed with water, dried over sodium sulfate, and concentrated to dryness. Trituration of the residue with 0.5 ml. of ethyl acetate and filtering give 2-cyano-11H-pyrrolo[2,1-b][3]benzazepin-11-one, m.p. 197°C.

Following the procedure substantially as described in Example 1, Step C, but substituting for the *cis*-2-carboxy-4-cyano-N-styrylpyrrole, an equimolecular amount of the *cis*-styrylpyrroles from Table I, there are produced the 11H-pyrrolo[2,1-b][3]benzazepin-11-ones described in Table II, by the following process:

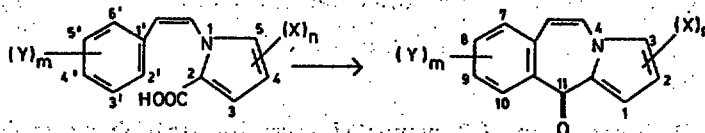


TABLE II.

Compound	Starting material		Product	
	(Y) _m	(X) _n	(Y) _m	(X) _n
1	H	H	H	H ^a
2	H	4-SCF ₃	H	2-SCF ₃
3	4'-Cl	H	9-Cl	H
4	4'-SCF ₃	H	9-SCF ₃	H
5	4'-CN	H	9-CN	H
6	H	4-COCH(CH ₃) ₂	H	2-COCH(CH ₃) ₂
7	H	4-SO ₂ N(CH ₃) ₂	H	2-SO ₂ N(CH ₃) ₂
8	H	4-SO ₂ CH(CH ₃) ₂	H	2-SO ₂ CH(CH ₃) ₂
9	H	4-Cl	H	2-Cl
10	4'-Br	H	9-Br	H
			(m.p. 210—214°C. (dec.))	
11	H	4-NO ₂	H	2-NO ₂
12	4'-OCH ₃	H	9-OCH ₃	H
13	4'-CF ₃	H	9-CF ₃	H

^am.p. 113—114°C.

Example 2.

2-Cyano-11H-pyrrolo[2,1-b][3]benzazepin-11-one

Step A: Preparation of *trans*-4-cyano-N-styrylpyrrole-2-carbonyl chloride

A mixture of 2.4 g. of *trans*-2-carboxy-4-cyano-N-styrylpyrrole (from Example 1) and 10 ml. of thionyl chloride is refluxed for 15 minutes, concentrated to dryness, treated with 10 ml. of toluene and concentrated to dryness to give 2.45 g. (95%) of *trans*-4-cyano-N-styrylpyrrole-2-carbonyl chloride, m.p. 119—121°C.

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Step B: Preparation of 4-cyano-N-(1,2-dichloro-2-phenylethyl)pyrrole-2-carbonyl chloride

A solution of 256.5 mg. of *trans*-4-cyano-N-styrylpyrrole-2-carbonyl chloride in 5 ml. of chloroform is treated with 1 mmole of chlorine dissolved in 1 ml. of carbon tetrachloride. After 15 minutes, it is evaporated to dryness, treated with 5 ml. of carbon tetrachloride, and evaporated to dryness to give 307 mg. (94%) of oily 4-cyano-N-(1,2-dichloro-2-phenylethyl)pyrrole-2-carbonyl chloride.

Step C: Preparation of 2-cyano-5,6-dichloro-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one

Aluminum chloride (231 mg.) is added all at once to a mixture of 160 mg. of 4-cyano-N-(1,2-dichloro-2-phenylethyl)pyrrole-2-carbonyl chloride and 0.5 ml. of tetrachloroethane controlled at 140°C. After 4—5 minutes, the mixture is cooled, 15 ml. of water is added and the mixture is extracted with 4 x 10 ml. of chloroform. The extract is washed with water, dried and chromatographed on 10 g. of silica gel by elution with benzene:ethyl acetate (3:1 v/v). The first fraction provides 47 mg. (33%) of 2-cyano-5,6-dichloro-6,11-dihydro-5H-[2,1-b][3]benzazapin-11-one, m.p. 213—223°C.

Step D: Preparation of 2-cyano-11H-pyrrolo[2,1-b][3]benzazepin-11-one

Chromous chloride prepared under nitrogen from 30 mg. of 100-mesh chromium and 0.1 ml. of concentrated hydrochloric acid in 0.4 ml. of water is added to 20 mg. of 2-cyano-5,6-dichloro-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one in 0.1 ml. of acetone at 70°C. The mixture is poured into 5 ml. of water and extracted with 3 x 3 ml. of chloroform. The chloroform is washed with water, dried and concentrated to dryness to give 13 mg. (86%) of 2-cyano-11H-pyrrolo[2,1-b][3]benzazapin-11-one, m.p. 197°C.

Following the procedure substantially as described in Example 2 steps A, B, C, and D, but substituting for the *trans*-2-carboxy-4-cyano-N-styrylpyrrole used in step A thereof the *trans*-2-carboxy-N-styrylpyrroles described in Table I, there are produced in sequence the carbonyl chlorides, N-(1,2-dichloro-2-phenylethyl)pyrrole carbonyl chlorides, 5,6-dichloro-ketones, and 11H-pyrrolo[2,1-b][3]benzazapin-11-ones described in Table III by the following procedure:

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2,1-b[1]

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100-mesh
of water is
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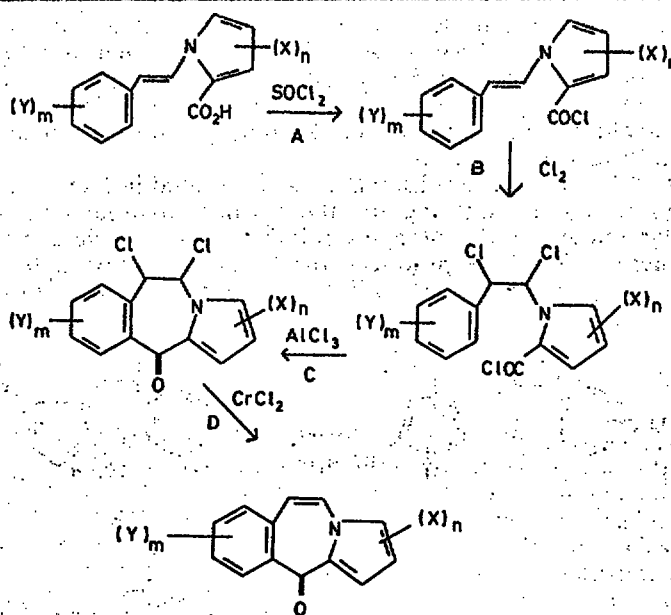


TABLE III.

(Y) _m	(X) _n
H	2-Cl
H	2-SO ₂ N(CH ₃) ₂
H	2-SO ₂ CH(CH ₃) ₂
H	2-NO ₂
H	2-COCH(CH ₃) ₂
H	2-SO ₂ CH ₃

Example 3.

2-Cyano-11H-pyrrolo[2,1-b][3]benzazepin-11-one

Method I.

Step A: Preparation of methyl 4-cyano-N-phenacylpyrrole-2-carboxylate

A mixture of 2 g. of methyl 4-cyanopyrrole-2-carboxylate, 2.7 g. of potassium carbonate, 2.7 g. of phenacylbromide and 15 ml. of dimethyl formamide is heated at 100°C. for 30 minutes. The mixture is poured into 200 ml. of water and extracted twice with ether. The extract is washed with water, dried and concentrated to dryness. The residue was triturated with petroleum ether to give 3 g. (84%) of methyl 4-cyano-N-phenacylpyrrole-2-carboxylate, m.p. 169—172°C.

Step B: Preparation of 4-cyano-N-(2-chloro-2-phenethyl)pyrrole-2-carbonyl chloride

A mixture of 270 mg. of methyl 4-cyano-N-phenacylpyrrole-2-carboxylate, 0.2 ml. of 6N sodium hydroxide solution and 5 ml. of ethanol is refluxed for 1 hour and the mixture is concentrated to a dry residue of 298 mg.

The residue is taken up in 5 ml. of aqueous ethanol (1:1 v/v), treated with 40 mg. of sodium borohydride at room temperature for 30 minutes, and concentrated to dryness.

The residue (351 mg.) is treated with 2 ml. of phosphorus oxychloride and 400 mg. of phosphorus pentachloride and heated at 110°C. for 18 hours. The mixture is

concentrated to dryness and the residue is dissolved in 25 ml. of chloroform. The solution is washed with 2 x 20 ml. of water, dried and concentrated to dryness. The residue is chromatographed on 5 g. of silica gel by elution with benzene: ethyl acetate (1:1 v/v). Concentration of the appropriate eluate provides 277 mg. of oily 4-cyano-N-(2-chloro-2-phenylethyl)pyrrole-2-carbonyl chloride whose nmr and I.R. spectrum confirmed the structure.

Following the procedure substantially as described in Example 3, Method I, Steps A and B, but substituting for the starting material employed therein, equimolecular amounts of the methylpyrrole-2-carboxylates described in Table IV in Step A thereof, there are produced the N-(2-chloro-2-phenylethyl)pyrrole-2-carbonyl chlorides also described in Table IV by the following process.

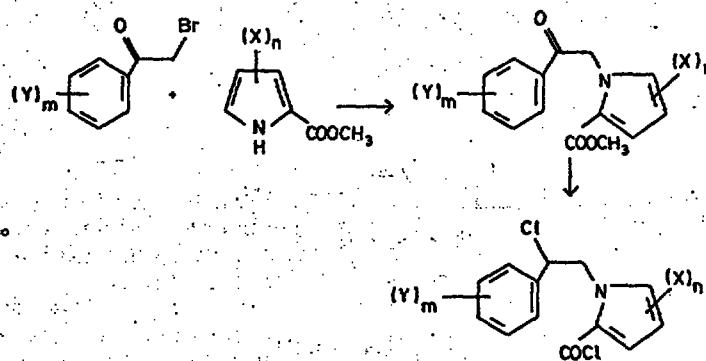


TABLE IV.

(Y) _m	(X) _n
H	4-Cl
H	4-SO ₂ N(CH ₃) ₂
H	4-SO ₂ CH(CH ₃) ₂
H	4-NO ₂
H	4-COCH(CH ₃) ₂

Method II.

Step A: Preparation of 4 - cyano - N - (2 - hydroxy - 2 - phenylethyl)pyrrole - 2 - carboxylic acid lactone

Following the procedure of Example 1, Step A, but substituting for the sodium hydride a catalytic amount of potassium *t*-butoxide, there is produced 4-cyano-N-(2-hydroxy-2-phenylethyl)pyrrole-2-carboxylic acid lactone.

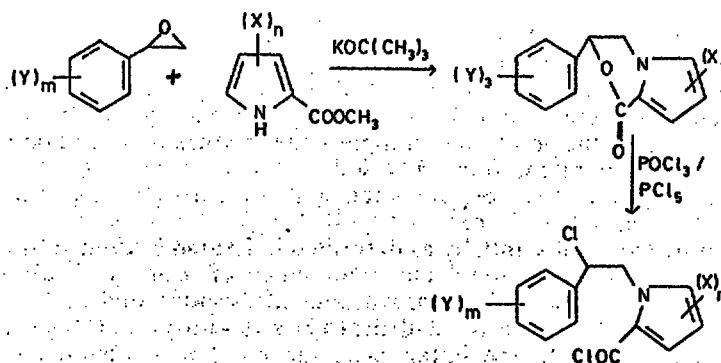
Step B: Preparation of 4 - cyano - N - (2 - chloro - 2 - phenylethyl)pyrrole - 2 - carbonyl chloride

A mixture of 0.54 g. of lactone from Example 3, Method II, Step A, 1 g. of phosphorus pentachloride and 5 ml. of phosphorus oxychloride is refluxed for 36 hours. The volatile materials are removed *in vacuo*, and the residue is flushed three times by vacuum distillation of toluene to give 0.54 g. (93%) of 4-cyano-N-(2-chloro-2-phenylethyl)pyrrole-2-carbonyl chloride.

Following the procedure substantially as described in Example 3, Method B, Steps A and B but substituting for the methyl 4-cyanopyrrole-2-carboxylate used in Step A an equimolecular amount of the methyl pyrrole-2-carboxylates described in Table IV, there are produced the N-(2-chloro-2-phenylethyl)pyrrole-2-carbonyl chlorides also described in Table IV, by the following process:

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Table IV
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Step C: Preparation of 2-cyano-11H-pyrrolo[2,1-b][3]benzazepin-11-one

Following the procedure substantially as described in Example 2, Step C, but substituting for the starting material an equimolecular amount of 4-cyano-N-(2-chloro-2-phenylethyl)pyrrole-2-carbonyl chloride, there is produced 6-chloro-2-cyano-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one. This material is dissolved in 5 ml. of ethanol containing 2 pellets of potassium hydroxide and refluxed for 15 minutes. The ethanol was evaporated. The residue was partitioned between water and chloroform. The chloroform was washed with water, dried and evaporated to dryness to give 109 mg. of crude product. This was chromatographed on 10 g. of silica gel by elution with benzene:ethyl acetate (3:1 v/v) to provide pure 2-cyano-11H-pyrrolo[2,1-b][3]benzazepin-11-one, m.p. 197°C.

Following the procedure of Example 3, Step C, but substituting for the starting material used therein an equimolecular amount of the carbonyl chlorides from Table IV, there are produced the ketones of Table V by the following process:

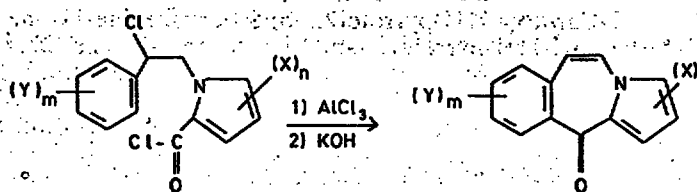


TABLE V.

(Y) _m	(X) _n
H	2-Cl
H	2-SO ₂ N(CH ₃) ₂
H	2-SO ₂ CH(CH ₃) ₂
H	2-NO ₂
H	2-COCH(CH ₃) ₂

Example 4.

3-Trifluoromethylthio-11H-pyrrolo[2,1-b][3]benzazepin-11-one

A mixture of 100 mg. of 11H-pyrrolo[2,1-b][3]benzazepin-11-one, 100 mg. of pyridine, 1.5 ml. of chloroform and 1 meq. of trifluoromethylsulfenyl chloride is kept for 200 minutes at 45°C. and then poured into water. The organic phase is washed with dilute hydrochloric acid and water, dried and concentrated to dryness. The residue on recrystallization from ether gives 124 mg. of 3-trifluoromethylthio-11H-pyrrolo[2,1-b][3]benzazepin-11-one, m.p. 137—137.5°C.

Example 5.

2-Pentanoyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one

11H-Pyrrolo[2,1-b][3]benzazepin-11-one (1.0 g.) is dissolved in 20 ml. of methylene chloride and 2.66 g. of aluminum chloride is added with cooling. At room temperature there is added little by little 720 mg. of pentanoyl chloride. Fifteen minutes after the addition is complete the mixture is poured onto ice. The organic phase is separated, filtered, dried and concentrated to dryness. The residue is triturated with ether, collected and dried to give 2-pentanoyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

By the procedure substantially as described in Example 5, but substituting for the pentanoyl chloride equimolecular amounts of isobutyryl chloride and dimethylsulfamoyl chloride, there are produced 2-isobutyryl-11H-pyrrolo[2,1-b][3]benzazepin-11-one and 2-dimethyl-sulfamoyl-11H-pyrrolo-[2,1-b][3]benzazepin-11-one. In the latter case, the reaction is conducted in nitromethane at reflux temperature.

Following the procedure of Example 5, but conducting the reaction at 100—130°C. with an excess of alkanoyl chloride as solvent and without the aluminum chloride, there are produced mixtures of 2- and 3- alkanoylketones which, upon chromatographic separation on silica gel, provide the alkanoyl ketone products described in Example 5 as well the corresponding 3-pentanoyl- and 3-isobutyryl- compounds.

Example 6.

2-Carbamoyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one

2-Cyano-11H-pyrrolo[2,1-b][3]benzazepin-11-one (30 g., 0.135 mole) in 100 ml. of concentrated hydrochloric acid and 100 ml. of acetic acid is refluxed for 2 hours. It is then poured onto 500 ml. of water and continuously extracted with methylene chloride. The solution is left to cool to room temperature and filtered to afford 2-carbamoyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

Example 7.

2-Carboxy-11H-pyrrolo[2,1-b][3]benzazepine-11-one

To 2-carbamoyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one (27 g., 0.112 moles) in 300 ml. of 50% sulfuric acid maintained at 50°C. is added slowly 25 g. of sodium nitrite in 75 ml. of water. At the end of the addition, the solid is filtered, washed with water and air-dried to yield 2-carboxy-11H-pyrrolo[2,1-b][3]benzazepine-11-one.

Example 8.

2-Dimethylcarbamoyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one

Step A: Preparation of 2-chlorocarbonyl-11H-pyrrolo-[2,1-b][3]benzazepin-11-one
11H-11-oxo-pyrrolo[2,1-b][3]benzazepine-2-carboxylic acid (24 g., 99 mmoles) in 100 ml. of thionyl chloride is refluxed for 15 minutes. The volatile materials are removed under vacuum and the residue is triturated in ether. Filtration and air drying yields 2-chlorocarbonyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

Step B: Preparation of 2-dimethylcarbamoyl-11H-pyrrolo-[2,1-b][3]benzazepine-11-one

Anhydrous dimethylamine is bubbled through a suspension of 2-chlorocarbonyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one (23 g., 88.5 mmoles) in 100 ml. of methylene chloride. (Note: The introduction of dimethyl amine causes the mixture to reflux and this reflux stops when all the acid chloride has reacted.)

The reaction mixture is washed with water and dried over sodium sulfate. It is then taken to dryness, triturated in ether, filtered and air-dried to yield 2-dimethylcarbamoyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

Following the procedure of Example 8, Step B, but substituting for the dimethylamine an equimolecular amount of methylamine, there is produced 2-methylcarbamoyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

Example 9.

2-Methoxycarbonyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one

11-Oxo-11H-pyrrolo[2,1-b][3]benzazepine-2-carboxylic acid (25.5 g., 0.11 moles) in 300 ml. of methanol saturated with hydrogen chloride is refluxed until a homogeneous solution is obtained (4 hours).

The volatile materials are removed under vacuum and the residue is dissolved in 300 ml. of methylene chloride, washed with dilute sodium hydroxide and then with water. It is dried over sodium sulfate and concentrated. The residue is triturated in ether, filtered and air-dried, to yield 2-methoxycarbonyl-11H-pyrrolo[2,1-b][3]benzazepine-11-one.

Example 10.

9-trifluoromethylthio-11H-pyrrolo[2,1-b][3]benzazepine-11-one

A mixture of 42.56 g. of bis(trifluoromethylthio)mercury, 17.27 g. of 9-bromo-11H-pyrrolo[2,1-b][3]benzazepine-11-one, 28 g. of electrolytic copper dust, 98 ml. of quinoline and 84 ml. of pyridine is stirred and heated at 195°C. for 18 hours. The mixture is shaken with 400 ml. of 6N hydrochloric acid and 400 ml. benzene. The organic phase is washed with 5 x 300 ml. of 3N hydrochloric acid and 5 x 300 ml. of water, dried over magnesium sulfate, filtered and concentrated to dryness, to give 9-trifluoromethylthio-11H-pyrrolo[2,1-b][3]benzazepine-11-one.

Example 11.

Preparation of 2-formyl-11H-pyrrolo[2,1-b][3]benzazepine-11-one

2-Cyano-11H-pyrrolo[2,1-b][3]benzazepine-11-one (222 mg.) and 222 mg. of nickel-aluminum alloy in 2 ml. 75% formic acid is refluxed for 1½ hours. The solid is filtered off and washed with ethanol. The filtrate is diluted with 50 ml. of water and extracted twice with 50 ml. of methylene chloride. The organic layer is washed with water, 5% sodium bicarbonate and with water; it is then dried over magnesium sulfate and evaporated to dryness. Addition of ether induces crystallization and the crystals are filtered and air-dried to yield 2-formyl-11H-pyrrolo[2,1-b][3]benzazepine-11-one.

Using substantially the procedure described in Example 11, but starting with 9-cyano-11H-pyrrolo[2,1-b][3]benzazepine-11-one in place of the 2-cyano compound, there is obtained 9-formyl-11H-pyrrolo[2,1-b][3]benzazepine-11-one.

Example 12.

9-Cyano-11H-pyrrolo[2,1-b][3]benzazepine-11-one

A stirred mixture of 1 gm. of 9-bromo-11H-pyrrolo[2,1-b][3]benzazepine-11-one, 1 gm. of cuprous cyanide and 5 ml. of dimethylformamide is heated to reflux for 5 hr. The mixture is then poured into a solution of 4 gm. of ferric chloride hydrate in 25 ml. of 2N hydrochloric acid. The resulting mixture is stirred at 60° for 30 min. and then extracted with 3 x 50 ml. of ethyl acetate. The organic extracts are washed with 3 x 300 ml. of water and dried over Na₂SO₄. Evaporation of the dried solution yields 9-cyano-11H-pyrrolo[2,1-b][3]benzazepine-11-one.

Example 13.

2-Hydroxymethyl-11H-pyrrolo[2,1-b][3]benzazepine-11-one

A solution of 2.23 gm. of 2-formyl-11H-pyrrolo[2,1-b][3]benzazepine-11-one and 95 mg. of sodium borohydride in 20 ml. of ethanol is stirred at 25°C. for 2 hrs. The solvent is evaporated and the residue dissolved in methylene chloride to extract the crude product from inorganic materials. After chromatography on silica gel, there is obtained 2-hydroxymethyl-11H-pyrrolo[2,1-b][3]benzazepine-11-one.

Example 14.

2-Trifluoromethyl-11H-pyrrolo[2,1-b][3]benzazepine-11-one

In a sealed Hasteloy-C lined pressure vessel a mixture of 10 gm. of 2-carboxy-11H-pyrrolo[2,1-b][3]benzazepine-11-one and 15 gm. of sulfur tetrafluoride is heated at 100° for 4 hrs., then at 130° for 4 hrs. The vessel is cooled to room temperature and opened cautiously (toxic fumes!). The contents of the vessel are extracted with 300 ml. of ether and the ethereal solution stirred vigorously with 200 ml. of 1N sodium hydroxide for 6 hrs. The ethereal layer is separated, dried and evaporated and the residue chromatographed over silica gel to yield 2-trifluoromethyl-11H-pyrrolo[2,1-b][3]benzazepine-11-one.

Example 15.

9-Methylthio-11H-pyrrolo[2,1-b][3]benzazepine-11-one

A mixture of 27 gm. of 9-bromo-11H-pyrrolo[2,1-b][3]benzazepine-11-one, 15 gm. of cuprous methylsulfide, 170 ml. of quinoline and 15 ml. of pyridine is stirred under a nitrogen atmosphere for 6 hrs. at a temperature of 195°C. The reaction

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mixture is cooled and poured into 500 ml. of 6N HCl containing 300 gm. of cracked ice. The resulting mixture is extracted with 3 x 200 ml. of benzene which is then filtered to remove some insoluble black material. The benzene extracts are washed with 3N HCl until the aqueous layer remains acidic, then washed with 100 ml. H₂O, dried (Na₂SO₄) and evaporated to yield 9-methylthio-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

Following the above procedure of Example 15 but replacing cuprous methylsulfide by cuprous isopropylsulfide, there is obtained 9-isopropylthio-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

Example 16.

2-Trifluoromethylsulfinyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one
A solution of 3 gm. of 2-trifluoromethylthio-11H-pyrrolo[2,1-b][3]benzazepin-11-one in 25 ml. of acetic acid containing 3 ml. of 50% hydrogen peroxide is stirred at 25°C. for 6 hrs. The solvent is evaporated and the residue dissolved in 100 ml. of methylene chloride. The solution is washed with 2 x 25 ml. of 5% Na₂CO₃ solution, dried and evaporated. Chromatography of the residue on silica gel yields 2-trifluoromethylsulfinyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

Using the procedure of Example 16 but starting with 9-methylthio-11H-pyrrolo[2,1-b][3]benzazepin-11-one, there is obtained 9-methylsulfinyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

Similarly, 9-isopropylthio-11H-pyrrolo[2,1-b][3]benzazepin-11-one, using the procedure of Example 16, produces 9-isopropylsulfinyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

Example 17.

2-Trifluoromethylsulfonyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one
A solution of 2 gm. of 2-trifluoromethylsulfinyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one in 20 ml. of acetic acid containing 5 ml. of 90% hydrogen peroxide is stirred at 25°C. for 4 days. The solvent is evaporated and the residue dissolved in 100 ml. of methylene chloride. After washing with 2 x 25 ml. of 1N Na₂CO₃, the organic solution is dried and evaporated, and the residue is chromatographed on silica gel to yield 2-trifluoromethylsulfonyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

Using the procedure of Example 17 but starting with 9-methylsulfinyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one there is prepared 9-methylsulfonyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

Similarly using the procedure of Example 17 but starting with 9-isopropylsulfinyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one there is obtained 9-isopropylsulfonyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

Example 18.

9-Hydroxy-11H-pyrrolo[2,1-b][3]benzazepin-11-one
Ethanethiol (0.62 g., 10 mmoles), dissolved in dimethyl formamide (10 ml.), is added to a suspension of sodium hydride (0.5 g. of 50% oil dispersion) in dry dimethylformamide (5 ml.). The mixture is stirred until all hydrogen has evolved and 9-methoxy-11H-pyrrolo[2,1-b][3]benzazepin-11-one (2.26 g., 10 mmoles) is added. The solution is refluxed for a period of 3 hours. The cooled reaction mixture is acidified with 0.2N HCl and extracted with chloroform. The organic layer is washed with water, dried over sodium sulfate and concentrated to yield 9-hydroxy-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

Example 19.

9-Carbamoyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one
9-Cyano-11H-pyrrolo[2,1-b][3]benzazepin-11-one (30 g., 0.135 mole) in 100 ml. of concentrated hydrochloric acid and 100 ml. of acetic acid is refluxed for 2 hours. It is then poured onto 500 ml. of water and continuously extracted with methylene chloride. The solution is left to cool to room temperature and filtered to afford 9-carbamoyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

Example 20.

9-Carboxy-11H-pyrrolo[2,1-b][3]benzazepin-11-one
To 9-carbamoyl-11H-pyrrolo[2,1-b][3]benzazepin-11-one (27 g., 0.112 mole) in 300 ml. of 50% sulfuric acid maintained at 50°C. is slowly added 25 g. of sodium nitrite in 75 ml. of water. At the end of the addition, the solid is filtered, washed with water and air-dried to yield 9-carboxy-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

24

25

of cracked
ich is then
are washed
10 ml. H₂O,
[2,1-b][3]-

ous methyl-
H-pyrrolo-

one
[2,1-b][3]-
hydrogen
the residue
2 x 25 ml.
residue on
pin-11-one.
ylthio-11H-
lfinyl-11H-

., using the
pyrrolo[2,1-

one
-b][3]benz-
n peroxide
e dissolved
N Na₂CO₃,
atographed
-11-one.
hysulfinyl-
ifonyl-11H-

-isopropyl-
-isopropyl-

(10 ml.), is
ion) in dry
as evolved
mmoles) is
ed reaction
he organic
d to yield 9-

ole) in 100
luxed for 2
acted with
d filtered to

.112 mole)
. of sodium
ed, washed
zazepin-11-

Example 21.

9-Ethoxycarbonyl amino-11H-pyrrolo[2,1-b][3]benzazepin-11-one

To 9-carboxy-11H-pyrrolo[2,1-b][3]benzazepin-11-one (96 g., 0.4 moles) in 500 ml. ethanol is added successively triethylamine (52 g., 0.52 mole) and diphenylphosphoro azide (112 g., 0.40 mmole). Reflux is maintained for 3 hrs. The mixture is poured onto water, extracted with ethyl acetate, washed with 1N sodium hydroxide and dried over magnesium sulfate to yield after evaporation 1.70 g. of a residue that is chromatographed on silica gel. Elution with methylene chloride yields 9-ethoxycarbonylamino-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

Example 22.

9-Amino-11H-pyrrolo[2,1-b][3]benzazepin-11-one

To 9-ethoxycarbonyl amino-11H-pyrrolo[2,1-b][3]benzazepin-11-one (2.80 g., 10 mmoles) in 100 ml. EtOH is added 10 ml. 2N potassium hydroxide. Reflux is maintained for 42 hrs. The volatile materials are removed under vacuum and the residue is extracted with chloroform, washed with water and dried over magnesium sulfate. Evaporation leaves a dark residue that is purified by chromatography on silica gel. Elution with 10% methanol in chloroform yields 9-amino-11H-pyrrolo[2,1-b][3]benzazepin-11-one that decomposes slowly on standing.

Example 23.

9-Methylamino-11H-pyrrolo[2,1-b][3]benzazepin-11-one

A solution of 9-amino-11H-pyrrolo[2,1-b][3]benzazepin-11-one in triethyl orthoformate (2.17 g., 10 mmoles in 80 ml.) is refluxed for 5 hrs. The volatile materials are removed under vacuum and the residue, dissolved in 100 ml. absolute ethanol, is stirred in an ice bath as sodium borohydride (0.88 g., 0.024 moles) is added over a period of 10 minutes. The mixture is stirred for a period of 2 hrs. After concentration of the ethanol, the residue is dissolved in ethyl acetate, washed with water, dried over Na₂SO₄ and concentrated to dryness to yield 9-methylamino-11H-pyrrolo[2,1-b][3]benzazepin-11-one as a brown amorphous solid.

Example 24.

9-Dimethylamino-11H-pyrrolo[2,1-b][3]benzazepin-11-one

To a solution of 9-amino-11H-pyrrolo[2,1-b][3]benzazepin-11-one (2.1 g., 10 mmoles) and 4 ml. (50 mmoles) of 37% aqueous formaldehyde in 15 ml. of acetonitrile is added 1 g. (16 mmoles) of sodium cyano borohydride. A vigorous and exothermic reaction takes place and a dark residue separates. The mixture is stirred for 15 mins. and then glacial acetic acid is added dropwise until the solution tests neutral on wet pH paper. Stirring is maintained for an additional 2 hrs. The volatiles are removed under vacuum, and the residue is dissolved in chloroform. The solution is washed with base and with water, dried over sodium sulfate, and concentrated to leave a residue that is purified by chromatography on silica gel. Elution with chloroform yields 9-dimethylamino-11H-pyrrolo[2,1-b][3]benzazepin-11-one as a dark brown oil.

Example 25.

9-Acetamido-11H-pyrrolo[2,1-b][3]benzazepin-11-one

9-Amino-11H-pyrrolo[2,1-b][3]benzazepin-11-one (2.1 g., 11.4 mmoles) dissolved in 15 ml. pyridine is treated with acetic anhydride (2 ml.) at room temperature for 19 hours. The volatiles are removed under vacuum and the residue is dissolved in chloroform, and chromatographed on silica gel. Elution with chloroform yields 9-acetamido-11H-pyrrolo[2,1-b][3]benzazepin-11-one.

The following Examples I to XX illustrate the preparation of the 11-(R³R²-aminopropylidene)-pyrrolo[2,1-b][3]benzazepines of this invention and are not meant to limit the invention to the particular processes or novel compounds described therein. Example XXI is illustrative of a pharmaceutical composition in accordance with the invention.

EXAMPLE I.

11-(3-dimethylaminopropylidene)-6,11-dihydro-5H-pyrrolo-[2,1-b][3]benzazepine

Step A: Preparation of 11 - Hydroxy - 11 - (3 - dimethylaminopropyl) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine

To a solution of 16 g. (0.081 mole) of 6,11-dihydro-5H-pyrrolo[2,1-

b][3]benzazepin-11-one in 300 ml. tetrahydrofuran (THF) is added 150 ml. of 1.0*N* solution of 3-dimethylaminopropyl magnesium chloride in THF. After stirring for 40 minutes at ice-bath temperature and for 1.5 hours at 25°C., the bulk of the solvent is distilled below 45°C. under reduced pressure. The residue is dissolved in 500 ml. of methylene chloride and the Grignard adduct is hydrolysed by the dropwise addition of 15 ml. water with cooling in an ice bath. The methylene chloride solution is decanted and the gelatinous precipitate is extracted three times with 80-ml. portions of boiling benzene. The combined organic extracts are washed with water and then evaporated under reduced pressure to yield, after crystallization from ethanol, 11-hydroxy-11-(3-dimethylaminopropyl)-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepine, m.p. 68–70°C.

Step B: Preparation of 11 - (3 - Dimethylaminopropylidene) - 6,11 - dihydro - 5H-pyrrolo[2,1-b][3]benzazepine

Hydrogen chloride gas is bubbled through a solution of 4.8 gm. (0.017 mole) of 11-hydroxy-11-(3 - dimethylaminopropyl) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine in 70 ml. of chloroform at 0°C. for 5 minutes. The resulting dark mixture is stirred for an additional 5 minutes, and then washed with 6*M* NaOH to provide, after evaporation of the chloroform, 4.3 g. of 11-(3-dimethylaminopropylidene)-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepine as an oil. It is converted to a crystalline oxalate by adding a solution of 266 mg. of the free base in 5 ml. of ethanol to a mixture of 90 mg. of oxalic acid and 2 ml. of ethanol and collecting the precipitate by filtration and air drying; m.p. 140–165°C. (dec.).

Following the procedure of Example I, Step B, there may be substituted for the hydrogen chloride-chloroform system (1) used therein trifluoroacetic anhydride-chloroform (2), trifluoroacetic acid (3), oxalic acid in ethanol (4), phosphorus oxychloride and pyridine (5), trichloroacetic acid and ethanol (6), acetic acid (7), or formic acid (8).

Following the procedure of Example I, Steps A and B, but substituting for the 6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepin-11-one used in Step A an equimolecular amount of the ketones described in Table A, there are produced in sequence the 11-hydroxy-11-(3-*R*₁,*R*₂-aminopropyl)-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepines and 11-(3-*R*₁,*R*₂-aminopropylidene)-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepines also described in Table A in accordance with the following process:

ml. of 1.0N
stirring for
bulk of the
dissolve in
used by the
methylene
acted three
extracts are
yield, after
pyl)-6,11-di-

hydro - 5H-

0.17 mole) of
lo[2,1-b][3]-
sulting dark
M NaOH to
ethylamino-
oil. It is
he free base
ethanol and
°C. (dec.).
stituted for
fluoroacetic
ethanol (4),
ethanol (6),

uting for the
A an equi-
produced in
pyrrolo[2,1-
hydro-5H-
ice with the

(33)

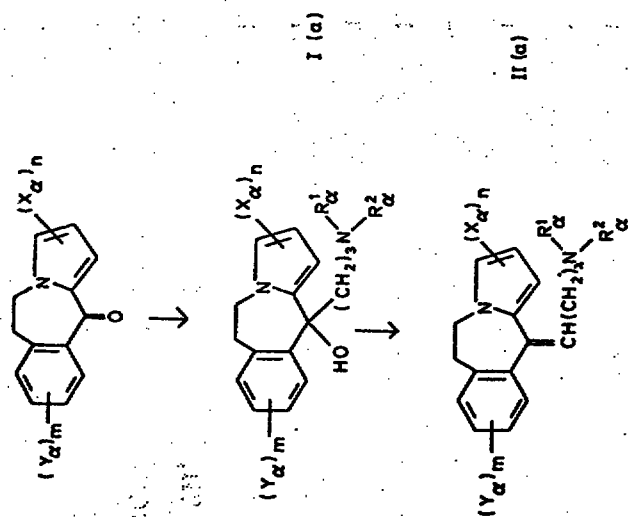


TABLE A.

R ¹ _α	R ² _α	(Y _α) _m	(X _α) _n	DEHYDRATING AGENT	M.P. (°C.) OXALATE SALT OF COMPOUND II(a)
CH ₃	CH ₃	H	2-SO ₂ N(CH ₃) ₂	1	128—136
CH ₃	CH ₃	H	2-CN	1	211—215
CH ₃	CH ₃	H	2-CO ₂ CH ₃	1	115 (dec.)
CH ₃	CH ₃	H	2-Cl	1	142—160
CH ₃	CH ₃	H	2-CO ₂ H	1	223—231 (dec.)*
CH ₃	CH ₃	H	2-CONH ₂	1	190 (dec.)*

*hydrochloride salt

TABLE A (continued).

R_1	R_2	$(Y_n)_m$	$(X_n)_n$	DEHYDRATING AGENT	M.P. (°C.) OXALATE SALT OF COMPOUND II(a)
CH_3	CH_3	H	2- SCF_3	1	161 (dec.)
CH_3	CH_3	H	3- SCF_3	1	174 (dec.)
CH_3	CH_3	H	2- $CON(CH_3)_2$	1	167 (dec.)
CH_3	CH_3	H	3- CF_3	1	155—159
CH_3	CH_3	H	$O=C(CH_3)_2$	1	120—125
CH_3	CH_3	H	$O=C(CH_3)_2$	1	115—132 (dec.)
CH_3	CH_3	H	2- SO_2CH_3	1	
CH_3	CH_3	H	2- $SO_2CH(CH_3)_2$	1	
CH_3	CH_3	H	2- SO_2CF_3	2	
CH_3	CH_3	H	2- $CO_2C_2H_5$	1	
CH_3	CH_3	H	2- NO_2	3	
CH_3	CH_3	H	2- $COCH_3$	1	
CH_3	CH_3	H	2- CF_3	1	
CH_3	CH_3	H	9- $OCONHCH_3$	4	
CH_3	CH_3	H	9- $NHCOOCH_3$	4	
CH_3	CH_3	H	9- CH_3	7	
CH_3	CH_3	H	2,3- Br_2	1	180—185 (dec.)

CH ₃	CH ₃	9-CONHCH ₃	2,3-Br ₂	4	
CH ₃	CH ₃	9-NHCOOCH ₃	2,3-Br ₂	4	
CH ₃	CH ₃	9-CH ₃	2,3-Br ₂	7	
CH ₃	CH ₃	H	2,3-Br ₂	1	180—185 (dec.)

TABLE A (continued).

R ₁	R ₂	(Y _a) _m	(X _a) _n	DEHYDRATING AGENT	M.P. (°C.) OXALATE SALT OF COMPOUND II(a)
CH ₃	CH ₃	H	2-Br	4	
CH ₃	CH ₃	H	3-CN	4	180—185 (dec.)
CH ₃	CH ₃	H	1,2,3-Br ₃	5	
CH ₃	CH ₃	H	1,3-Br ₂ -2-CH ₃	6	
CH ₃	CH ₃	9-NHCOCH ₃	1,2,3-Br ₃	1	
CH ₃	CH ₃	9-CH(CH ₃) ₂	2,3-Br ₂	4	
CH ₃	CH ₃	9-SCH ₃	2,3-Br ₂	4	
CH ₃	CH ₃	8,9-(CH ₃) ₂	2-CN	7	
CH ₃	CH ₃	9-OH	2-CN	4	
CH ₃	CH ₃	9-OCH ₃	2-CN	4	180—185 (dec.)
CH ₃	CH ₃	H	2,3-Cl ₂	5	
CH ₃	CH ₃	9-CONHCH ₃	H	4	
CH ₃	CH ₃	9-NHCOOCH ₃	H	4	
CH ₃	CH ₃	9-CH ₃	H	4	
CH ₃	CH ₃	9-CH(CH ₃) ₂	H	4	
CH ₃	CH ₃	H	2-CH ₃	7	
CH ₃	CH ₃	9-NHCOCH ₃	H	4	
CH ₃	CH ₃	9-SCH ₃	H	4	
CH ₃	CH ₃	9-SCH(CH ₃) ₂	H	4	

(35)

TABLE A (continued).

R^1	R^2	$(Y_n)_m$	$(X_n)_k$	DEHYDRATING AGENT	M.P. (°C.) OXALATE SALT OF COMPOUND II(a)
CH_3	CH_3	H	1-CF ₃	5	
CH_3	CH_3	H	3-CO(CH ₃) ₂ H	1	
CH_3	CH_3	H	3-COCH ₃	1	
CH_3	CH_3	H	3-COCH(CH ₃) ₂	1	
CH_3	CH_3	9-I	H	4	
CH_3	CH_3	9-SCF ₃	H	4	155—165 (dec.)
CH_3	CH_3	9-NO ₂	H	1	
CH_3	CH_3	9-NH ₂	H	1	
CH_3	CH_3	9-NHCH ₃	H	1	
CH_3	CH_3	9-N(CH ₃) ₂	H	1	
CH_3	CH_3	9-CN	H	8	
CH_3	CH_3	9-SOCF ₃	H	4	
CH_3	CH_3	9-SOCH ₃	H	4	
CH_3	CH_3	9-SOCH(CH ₃) ₂	H	4	
CH_3	CH_3	9-SO ₂ CF ₃	H	1	
CH_3	CH_3	9-SO ₂ CH ₃	H	1	
CH_3	CH_3	9-SO ₂ CH(CH ₃) ₂	H	1	
CH_3	CH_3	9-Cl	H	4	

CH ₃	CH ₃	9-SO ₂ CF ₃	H	1
CH ₃	CH ₃	9-SO ₂ CH ₃	H	1
CH ₃	CH ₃	9-SO ₂ CH(CH ₃) ₂	H	1
CH ₃	CH ₃	9-Cl	H	4

TABLE A (continued).

R ₁	R ₂	(Y _a) _n	(X _a) _n	DEHYDRATING AGENT	M.P. (°C.) OXALATE SALT OF COMPOUND II(a)
CH ₃	CH ₃	9-SCH(CH ₃) ₂	H	7	
C ₂ H ₅	CH ₃	H	2-CN	1	
—(CH ₂) ₄ —		H	H	4	
—(CH ₂) ₅ —		H	2-CO(CH ₂) ₃ CH ₃	1	
—(CH ₂) ₂ O(CH ₂) ₂ —		9-CN	H	1	
cyclo-propyl	H	H	2-CN	1	
H —CH=CH ₂		H	2-CN	1	
CH ₃	CH ₃	9-CF ₃	H	1	

EXAMPLE II.

2-Cyano-11-(3-dimethylaminopropylidene)-11H-pyrrolo[2,1-b][3]benzazepine

- 5 Step 4: Preparation of 2-Cyano-11-(3-dimethylaminopropyl)-11-hydroxy-11H-pyrrolo[2,1-b][3]benzazepine

A mixture of 4 g. of 2-cyano-11H-pyrrolo[2,1-b][3]benzazepine-11-one in 50 ml. of tetrahydrofuran is treated dropwise with 20 ml. of tetrahydrofuran containing 28.40 mmole of 3-(dimethylamino)propylmagnesium chloride while maintaining the temperature at 25°C. Ten minutes after the addition is complete, 2 ml. of water is added and the mixture is poured into 200 ml. of methylene chloride, dried over sodium sulfate and filtered. Concentration to dryness provides 3.3 g. (60%) of a solid residue of 2-cyano-11-(3-dimethylaminopropyl)-11-hydroxy-11H-pyrrolo[2,1-b][3]benzazepine, m.p. 123—126°C.

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Step B: Preparation of 2 - Cyano - 11 - (3 - dimethylaminopropylidene) - 11H-pyrrolo[2,1-b][3]benzazepine

A mixture of 2.8 g. of the 11-hydroxy compound in 50 ml. of chloroform is treated with hydrogen chloride gas for 5 minutes while maintaining the temperature at 25°C. The mixture is neutralized with 2N sodium hydroxide and extracted twice with chloroform. The extract is washed with water, dried and concentrated to dryness to give 2.4 g. of oil.

The oil is dissolved in 10 ml. of acetonitrile and treated with 1.0 g. of oxalic acid. After 4 hours at room temperature and overnight in the refrigerator, the solids are collected, washed with ether and air dried to give 2.7 g. of 2-cyano-11-(3-dimethylaminopropylidene)-11H-pyrrolo[2,1-b][3]benzazepine oxalate, m.p. 185-187°C.

Following the procedure of Example II, Step B, there may be substituted for the hydrogen chloride chloroform system (1) used therein, trifluoroacetic anhydride chloroform (2), trifluoroacetic acid (3), oxalic acid in ethanol (4), phosphorus oxychloride pyridine (5), trichloroacetic acid ethanol (6), acetic acid (7), or formic acid (8).

Following the procedure of Example II, Steps A and B, but substituting for the 2-cyano-11H-pyrrolo[2,1-b][3]benzazepin-11-one used in Step A thereof an equimolecular amount of the ketones described in Table B, there are produced in sequence the 11-hydroxy-11-(3-R¹,R²-aminopropyl)-11H-pyrrolo[2,1-b][3]benzazepines and 11-(3-R¹,R²-aminopropylidene)-11H-pyrrolo[2,1-b][3]benzazepines also described in Table B in accordance with the following process:

lene) - 11H-

chloroform is
staining. The
dioxide and
r, dried and

g. of oxalic
generator, the
cyano-11-(3-
late, m.p.

stituted for
fluoroacetic
ol (4), phos-
c acid (7), or

stituting for
thereof an
produced in
lo[2,1-b][3]-
lo[2,1-b][3]-
ing process:

39

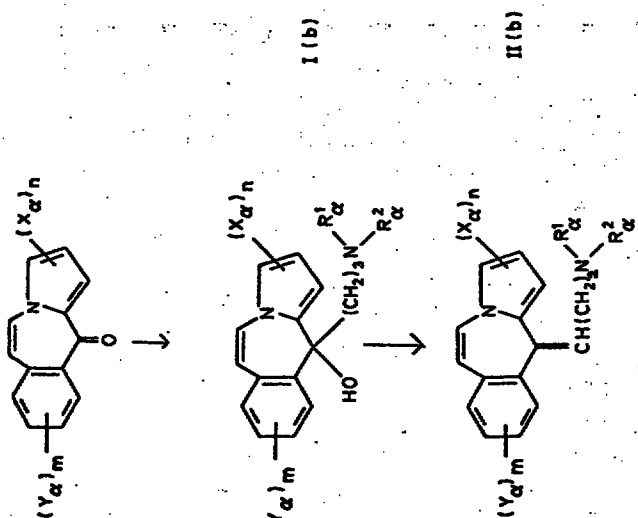


TABLE B.

R ¹	R ²	(Y _α) _m	(X _α) _n		DEHYDRATING AGENT	M.P. (°C.) OXALATE SALT OF COMPOUND II(a)
CH ₃	CH ₃	H	H	H	4	100 (dec.)
CH ₃	CH ₃	H	2-SCF ₃	2-SCF ₃	4	
CH ₃	CH ₃	9-Cl	H	H	4	
CH ₃	CH ₃	9-SCF ₃	H	H	4	110 (dec.)
CH ₃	CH ₃	9-CN	H	H	8	
CH ₃	CH ₃	H	2-COCH(CH ₃) ₂	2-COCH(CH ₃) ₂	1	
CH ₃	CH ₃	H	2-SO ₂ N(CH ₃) ₂	2-SO ₂ N(CH ₃) ₂	1	

TABLE B (continued).

DEHYDRATING AGENT

M.P.(°C.)
OXALATE SALT OF
COMPOUND II(a)

R ¹	R ²	(Y _n) _m	(X _n) _m	DEHYDRATING AGENT	M.P.(°C.) OXALATE SALT OF COMPOUND II(a)
CH ₃	CH ₃	H	2-SO ₂ CH(CH ₃) ₂	1	
CH ₃	CH ₃	H	2-Cl	1	
CH ₃	CH ₃	9-Br	H	4	
CH ₃	CH ₃	H	2-NO ₂	3	
CH ₃	CH ₃	9-OCH ₃	H	4	
CH ₃	CH ₃	H	3-SCF ₃	4	
CH ₃	CH ₃	H	2-CO(CH ₂) ₃ CH ₃	1	
CH ₃	CH ₃	H	3-CO(CH ₂) ₃ CH ₃	1	
CH ₃	CH ₃	H	3-COCH(CH ₃) ₂	1	
CH ₃	CH ₃	H	2-CON(CH ₃) ₂	1	
CH ₃	CH ₃	H	2-COOCH ₃	1	
CH ₃	CH ₃	H	2-CH ₂ OH	7	
CH ₃	CH ₃	H	2-CF ₃	1	
CH ₃	CH ₃	9-SCH ₃	H	4	
CH ₃	CH ₃	9-SCH(CH ₃) ₂	H	4	
CH ₃	CH ₃	H	2-SOCH ₃	4	
CH ₃	CH ₃	9-SOCH ₃	H	4	
CH ₃	CH ₃	9-SOCH(CH ₃) ₂	H	4	
CH ₃	CH ₃	H	2-SO ₂ CF ₃	2	

TABLE B (continued).

R_1	R_2	$(Y_n)_m$	$(X_n)_m$	DEHYDRATING AGENT	M.P. (°C.) OXALATE SALT OF COMPOUND II(a)
CH_3	CH_3	$9-SO_2CH_3$	H	1	
CH_3	CH_3	$9-SO_2CH(CH_3)_2$	H	1	
CH_3	CH_3	9-OH	H	4	
CH_3	CH_3	$9-COOC_2H_5$	H	1	
CH_3	CH_3	9-NH ₂	H	1	
CH_3	CH_3	9-NHCH ₃	H	1	
CH_3	CH_3	$9-N(CH_3)_2$	H	1	
CH_3	CH_3	9-NHCOCH ₃	H	4	
C_2H_5	CH_3	H	2-CN	1	
$-(CH_2)_4-$	$-(CH_2)_4-$	H	H	4	
$-(CH_2)_5-$	$-(CH_2)_5-$	H	2-CO(CH ₂) ₃ CH ₃	1	
$-(CH_2)_2O(CH_2)_2-$	$9-CN$	H	H	8	
CH_3	CH_3	H	2-SO ₂ CH ₃	1	
CH_3	CH_3	O-CF ₃	H	1	

EXAMPLE III.

2 - Formyl - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine

2 - Cyano - 11 - (3 - dimethylaminopropyl) - 11 - hydroxy - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine (0.62 g.) and 6.2 g. Ni—Al 1:1 alloy powder (BDH Chemicals Ltd., Poole, Dorset) in 50 ml. 75% formic acid is refluxed for 1 hr. The dark-red suspension is cooled, filtered to remove the insoluble materials, washed with formic acid and evaporated to dryness. The yield of this red oil is 3.4 g. (57%) and it slowly crystallizes on cooling. The oxalate salt of 2-formyl-11-(3-dimethylaminopropylidene)-6,11-dihydro-5H-pyrrolo[2,1-b][3]-benzazepine is prepared by dissolving the above product in the minimum volume of ethanol and adding dropwise a saturated ethanolic solution of oxalic acid. The resulting crystals are collected by filtration and dried to give 2-formyl-11-(3-dimethylaminopropylidene)-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepine oxalate, m.p. 181°C. (decomp.).

Using 2 - cyano - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine as starting material results in the same product.

By the procedure substantially as described in Example III, but substituting for the starting material an equimolecular amount of 2 - cyano - 11 - (3 - dimethylaminopropyl) - 11 - hydroxy - 11H - pyrrolo[2,1-b][3] - benzazepine or 2-cyano-11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine, there is produced 2 - formyl - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine, which yields a crystalline oxalate salt, m.p. 185°C. (decomp.).

Following the procedure substantially as described in Example III, but substituting for the starting material, an equimolecular amount of 9-cyano-11-(3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine or 9 - cyano - 11 - hydroxy - 11 - (3 - dimethylaminopropyl) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine, there is produced 9 - formyl - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine.

Similarly, by substituting 9-cyano-11-(3-dimethylaminopropylidene)-11H-pyrrolo[2,1-b][3]benzazepine or its intermediate carbinol as starting material, there is produced 9-formyl-11-(3-dimethylaminopropylidene)-11H-pyrrolo[2,1-b][3]benzazepine.

EXAMPLE IV.

9 - Trifluoromethylthio - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine

A mixture of 2.9 g. of 9-iodo-11-(3-dimethylaminopropylidene)-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepine, 5.14 g. of copper (electrolytic dust), 9.0 g. of bis(trifluoromethylthio)mercury and 20 ml. of dimethylformamide was stirred and heated on a steam bath for 5 hours. The mixture was cooled in ice, treated with 75 ml. of benzene and treated dropwise with 50 ml. of 10% sodium hydroxide solution. After 1 hour at room temperature the mixture was filtered through diatomaceous earth followed by a benzene wash. The filtrate was extracted with benzene. The combined benzene fractions were washed with water, dried, filtered and concentrated to dryness to give 9-trifluoromethylthio-11-(3-dimethylaminopropylidene)-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepine.

Following the procedure of Example IV, but substituting for the copper dust and the bis(trifluoromethylthio)mercury an equimolecular amount of cuprous methylsulfide or cuprous isopropylsulfide, there is produced 9 - methylthio - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine or 9 - isopropylthio - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine, respectively.

EXAMPLE V.

9 - Trifluoromethylthio - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine

By the procedure of Example IV, but substituting for the 9-iodo compound an equimolecular amount of 9 - bromo - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine, there is produced 9-trifluoromethylthio-11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine.

By the procedure of Example V, but substituting for the copper dust and bis(trifluoromethylthio) mercury an equimolecular amount of cuprous methylsulfide or cuprous isopropylsulfide, there is produced respectively:

5H - pyrrolo-

5H-powder for 1 hr. The crystals, washed with 3.4 g. (57%) (3-dimethylamino) prepared by adding and adding crystals are methylamino-m.p. 181°C.

5H-dihydro - 5H-product. By substituting (3 - dimethylamino) or 2-cyanopipazine, there is H - pyrrolo-m.p. 185°C.

Example III, but 9-cyano-11-(1-b)[3]benzopyl) - 6,11-formyl - 11-(1-b)[3]benz-

lidene)-11H-ng material, pyrrolo[2,1-b]-

dihydro- 5H-

5,11-dihydro-9.0 g. of is stirred and added with 75 N hydroxide red through racted with ried, filtered methylamino-

the copper t of cuprous 9 - methyl-olo[2,1-b][3]-e) - 6,11 - di-

H - pyrrolo-

o compound ypylidene)-omethylthio-pine. ver dust and ous methyl-

9 - methylthio - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]-benzazepine, or 9 - isopropylthio - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]-benzazepine.

EXAMPLE VI.

9 - Cyano - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine

A stirred mixture of 1 gm. of 9-iodo-11-(3-dimethylaminopropylidene)-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepine, 1 gm. of cuprous cyanide, and 5 ml. of dimethylformamide is heated to reflux for 5 hr. The mixture is then poured into a solution of 4 gm. of ferric chloride hydrate in 25 ml. of 2 N hydrochloric acid. The resulting mixture is stirred at 60° for 30 min. and then extracted with 3 x 50 ml. of ethyl acetate. The aqueous acidic solution is then basified with sodium hydroxide and extracted with 3 x 50 ml. of ether. The combined ethereal extracts are then dried and evaporated to yield 9 - cyano - 11 - (3-dimethylaminopropylidene)-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepine.

By the procedure of Example VI, but substituting for the starting material an equimolecular amount of 9-bromo-11-(3-dimethylaminopropylidene)-11H-pyrrolo[2,1-b][3]benzazepine, there is produced 9 - cyano - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine.

EXAMPLE VII.

9 - Amino - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine

A mixture of 9 - nitro - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro-5H - pyrrolo[2,1-b][3]benzazepine (2.0 g.), 0.2 g. of 10% Pd/C and 350 ml. of methanol is hydrogenated until the theoretical amount of hydrogen has been absorbed. The mixture is filtered and the filtrate is evaporated to dryness to yield 9 - amino - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H-pyrrolo[2,1-b][3]benzazepine.

EXAMPLE VIII.

9 - Ethoxycarbonylamino - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine

To 9 - carboxy - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]-benzazepine (123.2 g., 0.4 mole) in 500 ml. ethanol, is added successively triethylamine (52 g., 0.52 mole) and diphenylphosphoroazide (112 g., 0.40 mmole). Reflux is maintained for 3 hours. The mixture is poured onto water, extracted with ethyl acetate, washed with 1 N sodium hydroxide and dried over magnesium sulfate to yield after evaporation 70 g. of a residue, which is chromatographed on silica gel. Elution with methylene chloride yields 9-ethoxycarbonylamino-11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine.

EXAMPLE IX.

9 - Amino - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]-benzazepine

To 9 - ethoxycarbonylamino - 11 - (3 - dimethylaminopropylidene) - 11H-pyrrolo[2,1-b][3]benzazepine (2.80 g.) in 100 ml. EtOH is added 10 ml. 2 N potassium hydroxide. Reflux is maintained for 42 hours. The volatile materials are removed under vacuum and the residue is extracted with chloroform, washed with water, and dried over magnesium sulfate. Evaporation leaves a dark residue, which is purified by chromatography on silica gel. Elution with 10% methanol in chloroform yields 9 - amino - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine.

EXAMPLE X.

9 - Methylamino - 11 - (3 - dimethylaminopropylidene)- 6,11 - dihydro - 5H-pyrrolo[2,1-b][3]benzazepine

A solution of 9 - amino - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro-5H - pyrrolo[2,1-b][3]benzazepine in triethyl orthoformate (2.8 g.; 10 mmoles in 80 ml.) was refluxed for 5 hours. The volatiles were removed under vacuum and the residue dissolved in 100 ml. of absolute ethanol was stirred in an ice bath as sodium borohydride (0.88 g., 0.024 mole) was added over a period of 10 minutes. The mixture was stirred for a period of 2 hours. After concentration of the ethanol,

the residue was dissolved in ethyl acetate, washed with water, dried over Na_2SO_4 and concentrated to dryness to yield 9 - methylamino - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine.

By the procedure as described in Example X but substituting for the starting material used therein an equimolecular amount of the 9-amino-11-(3-dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine, there is produced 9-methylamino - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine.

EXAMPLE XI.

9 - Dimethylamino - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine.

To a solution of 9 - amino - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine (2.0 g., 10 mmoles) and 4 ml. (50 mmoles) of 37% aqueous formaldehyde in 15 ml. of acetonitrile is added 1 g. (16 mmoles) of sodium cyanoborohydride. A vigorous and exothermic reaction takes place and a dark residue separates. The mixture is stirred for 15 minutes and then glacial acetic acid is added dropwise until the solution tests neutral on wet pH paper. Stirring is maintained for an additional 2 hours. The volatile materials are removed under vacuum, and the residue is dissolved in chloroform. The solution is washed with base and with water, dried over sodium sulfate, and concentrated to leave a residue that is purified by chromatography on silica gel. Elution with chloroform-methanol yields 9 - dimethyl - amino - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine.

By the procedure of Example XI, but substituting for the starting material an equimolecular amount of 9 - amino - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine, there is produced 9 - dimethylamino - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine.

EXAMPLE XII.

9 - Acetamido - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine

9 - Amino - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine (11.4 mmoles) dissolved in 15 ml. pyridine is treated with acetic anhydride (2 ml.) at room temperature for 19 hours. The volatile materials are removed under vacuum and the residue is dissolved in chloroform, and chromatographed on silica gel. Elution with chloroform-methanol yields 9 - acetamido - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine.

By the procedure of Example XII but substituting for the starting material an equimolecular amount of 9 - amino - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine, there is produced 9-acetamido - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine.

EXAMPLE XIII.

2 - Dimethylcarbamoyl - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine

Step A: Preparation of 2 - carbamoyl - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine

2 - Cyano - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine (0.135 mole) in 100 ml. of concentrated hydrochloric acid and 100 ml. of acetic acid is refluxed for 2 hours. It is then poured onto 500 ml. of water and continuously extracted with methylene chloride. The solution is left to cool to room temperature and filtered to afford 2-carbamoyl-11-(3-dimethylaminopropylidene)-11H-pyrrolo[2,1-b][3]benzazepine

Step B: Preparation of 2 - carboxy - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine

To 2 - carbamoyl - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine (0.112 mole) in 300 ml. of 50% sulfuric acid maintained at 50°C. is added slowly 25 g. of sodium nitrite in 75 ml. of water. At the end of the addition, the solid is filtered, washed with water and air-dried to yield 2-carboxy-11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine.

over Na₂SO₄
ethylamino-

the starting
(3-dimethyl-
pyrrolo[2,1-b][3]-

hydro - 5H-

ene) - 6,11-
d 4 ml. (50
added 1 g.
mic reaction
minutes and
utral on wet
ile materials
roform. The
sulfate, and
hy on silica
o - 11 - (3-
benzazepine.
ing material
pyrrolydene)-
lamino - 11-
e.

pyrrolo[2,1-b][3]-

pyrrolo[2,1-b][3]-
with acetic
ile materials
roform, and
anol yields
pyrrolo[2,1-b][3]-

ing material
pyrrolydene)-
acetamido-
pyrrolo[2,1-b][3]-

H - pyrrolo-

dene) - 11H-

pyrrolo[2,1-b][3]-
ic acid and
o 500-ml. of
ion is left to
(3-dimethyl-

ene) - 11H-

H - pyrrolo-
maintained at
e end of the
d 2-carboxy-
epine.

Step C: Preparation of 2 - chlorocarbonyl - 11 - (3 - dimethylaminopropylidene)-
11H - pyrrolo[2,1-b][3]benzazepine

2 - Carboxy - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]-
benzazepine (99 mmoles) in 100 ml. of thionyl chloride is refluxed for 15 minutes.
The volatile materials are removed under vacuum and the residue is triturated
in ether. Filtration and air drying yields 2 - chlorocarbonyl - 11 - (3 - dimethyl-
aminopropylidene) - 11H - pyrrolo[2,1-b][3] - benzazepine.

Step D: Preparation of 2 - dimethylcarbamoyl - 11 - (3 - dimethylaminopropyl-
idene) - 11H - pyrrolo[2,1-b][3]benzazepine

Anhydrous dimethylamine is bubbled through a suspension of 2 - chloro-
carbonyl - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]-
benzazepine (88.5 mmoles) in 100 ml. of methylene chloride. (Note: The intro-
duction of dimethyl amine causes the mixture to reflux and this reflux stops
when all the acid chloride has reacted.)

The reaction mixture is washed with water and dried over sodium sulfate.
It is then taken to dryness, triturated in ether, filtered and air-dried to yield
2 - dimethylcarbamoyl - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b]-
[3]benzazepine.

Following the procedure of Example XIII, Step D, but substituting for
the dimethylamine used therein an equimolecular amount of methylamine,
there is produced 2 - methylcarbamoyl - 11 - (3 - dimethylaminopropylidene)-
11H - pyrrolo[2,1-b][3]benzazepine.

EXAMPLE XIV.

2 - Methoxycarbonyl - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo-
[2,1-b][3]benzazepine

2 - Carboxy - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]-
benzazepine (0.11 mole) in 300 ml. of methanol saturated with hydrogen chloride
is refluxed until a homogeneous solution is obtained (4 hours).

The volatile materials are removed under vacuum and the residue is dissolved
in 300 ml. of methylene chloride. The solution is washed with dilute sodium
hydroxide and then with water, dried over sodium sulfate and evaporated to
yield 2 - methoxycarbonyl - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo-
[2,1-b][3]benzazepine.

EXAMPLE XV.

2 - Cyano - 6,11 - dihydro - 11 - (3 - methylaminopropylidene) - 5H - pyrrolo-
[2,1-b][3]benzazepine oxalate salt

Step A: Preparation of 2 - cyano - 6,11 - dihydro - 11 - (N - 2,2,2 - trichloroethoxy-
carbonyl - 3 - methylaminopropylidene) - 5H - pyrrolo[2,1-b][3]benzazepine

2 - Cyano - 6,11 - dihydro - 11 - (3 - dimethylaminopropylidene) - 5H - pyrrolo-
[2,1-b][3]benzazepine (5 g., 17.2 mmoles) and 2,2,2-trichloroethylchloroformate
(4 g., 18.8 mmoles) in 100 ml. benzene are refluxed for 18 hours. The mixture is
poured onto water, washed with dilute hydrochloric acid and then with water,
dried over sodium sulfate and concentrated under vacuum to yield 7.1 g. of dark
red oil. It is absorbed on 250 g. silica gel and eluted with 2 liters of benzene.
The eluate is discarded.

Elution with 1.2 liters of methylene chloride leaves, after evaporation,
2 - cyano - 6,11 - dihydro - 11 - (N - 2,2,2 - trichloroethoxycarbonyl - 3 - methyl-
aminopropylidene) - 5H - pyrrolo[2,1-b][3]benzazepine as a brown oil (5.0 g.,
63%), R_f 0.6 (benzene:ethyl acetate 3:1, on silica gel TLC).

Step B: Preparation of 2 - cyano - 6,11 - dihydro - 11 - (methylaminopropylidene)-
5H - pyrrolo[2,1-b][3]benzazepine-oxalate salt

2 - Cyano - 6,11 - dihydro - 11 - (N - 2,2,2 - trichloroethoxycarbonyl - 3-
methylaminopropylidene) - 5H - pyrrolo[2,1-b][3]benzazepine (4.0 g., 8.7 mmoles)
and zinc dust (8 g.) in 25 ml. acetic acid are stirred at room temperature for 18
hours. The solid is filtered off and washed with acetic acid. The filtrate is
taken to dryness. The residue is dissolved in dilute hydrochloric acid and
extracted with ethyl acetate. The aqueous phase is then made basic and extracted
with methylene chloride; the organic layer is washed with water, dried over sodium
sulfate and concentrated to yield 2 - cyano - 6,11 - dihydro - 11 - (methylamino-
propylidene) - 5H - pyrrolo[2,1-b][3]benzazepine (2.3 g., 95%) as a brown
oil.

45

This oil is dissolved in 25 ml. ethanol and treated with oxalic acid (1 g.). The oxalate salt is filtered, washed with ethanol and air-dried. The yield is 2.54 g., m.p. 190°C. (dec.).

5 By the procedure of Example XV, Steps A and B, but substituting for the 2 - cyano - 6,11 - dihydro - 11 - (3 - dimethylaminopropylidene) - 5H - pyrrolo-[2,1-b][3]benzazepine used in Step A thereof, an equimolecular amount of any of the 11 - (3 - dialkylaminopropylidene)pyrrolo[2,1-b][3]benzazepines described in Tables A and B and Examples I to XIV, there are produced the corresponding
10 11 - (3 - alkylaminopropylidene)pyrrolo[2,1-b][3]benzazepines such as those depicted in Table C by the following process:

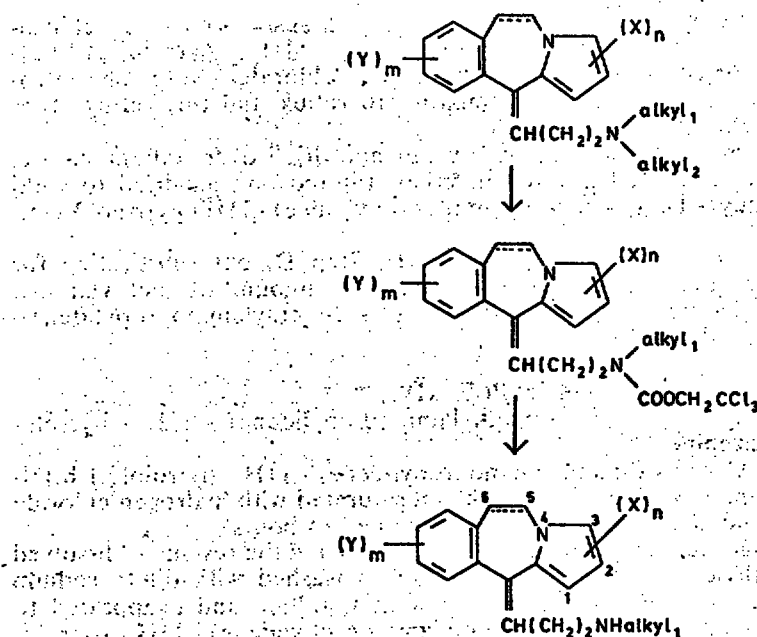


TABLE C.

6—5 positions	(Y) _m	(X) _n	alkyl ₁	alkyl ₂
unsaturated	H	2-CN	CH ₃	CH ₃
saturated	H	2-CHO	CH ₃	CH ₃
unsaturated	H	2-CHO	CH ₃	CH ₃
saturated	H	2-CO(CH ₂) ₄ H	CH ₃	CH ₃
unsaturated	H	2-CO(CH ₂) ₄ H	CH ₃	CH ₃
saturated	H	H	CH ₃	CH ₃
unsaturated	H	H	CH ₃	CH ₃
saturated	9-CN	H	CH ₃	CH ₃
unsaturated	9-CN	H	CH ₃	CH ₃
unsaturated	9-CHO	H	CH ₃	CH ₃
saturated	9-CHO	H	CH ₃	CH ₃
saturated	H	2-CN	C ₂ H ₅	CH ₃
unsaturated	H	2-CN	C ₂ H ₅	CH ₃

acid (1 g.).
The yield is

uting for the
H - pyro-
ount of any
es described
esponding
ch as those

alkyl,

CH₃

CH₃

CH₃

CH₃

CH₃

CH₃

CH₃

CH₃

CH₃

CH₃

CH₃

CH₃

CH₃

EXAMPLE XVI.

Separation of the isomers of 11-(3-dimethylaminopropylidene)-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepine

To a solution of 24 g. (0.0775 mole) of 11-hydroxy-11-(3-dimethylaminopropyl)-6,11-dihydro-5H-pyrrolo-[2,1-b][3]benzazepine in 35 ml. of ethanol is added a solution of 7.8 g. (0.086 mole) of oxalic acid in 90 ml. of ethanol at 25°C. over 20 minutes. The mixture is then stirred for 16 hours at 25°C. and the insoluble oxalate salt removed by filtration to yield 22.7 g. (0.064 moles) of crude oxalate of isomer I. Recrystallization from 150 ml. of hot water gives 15.4 g. of isomer I oxalate, m.p. 188—189°C., unchanged by further recrystallization.

The filtrate from crude isomer I is worked up by basification to yield 4.18 g. (0.016 mole) of crude isomer II as the free base. To a solution of this crude free base in 80 ml. of methanol is added 1.41 g. (0.016 mole) oxalic acid, and the resulting solution is treated with charcoal at reflux for 5 minutes. The solution is filtered and evaporated and the residual oil taken up in 100 ml. of acetonitrile and treated with charcoal at reflux for 5 minutes. This charcoal treatment is repeated twice more, and the solution evaporated to leave a semi-solid which was dissolved in 100 ml. of methanol. The methanol solution is evaporated and the resulting oil dissolved in 20 ml. of acetonitrile, seeded and held at 5°C. The resulting crystals are pulverized, filtered and washed with acetonitrile and finally with ether to give 2.68 gm. (0.0075 mole) of isomer II oxalate, m.p. 110—120°C.

Each isomer is shown to be at least 90% pure by nmr analysis.

EXAMPLE XVII.

Chromatographic separation of the geometrical isomers of 2-formyl-6,11-dihydro-11-(3-dimethylaminopropylidene)-5H-pyrrolo[2,1-b][3]benzazepine

2 - Formyl - 6,11 - dihydro - 11 - (3 - dimethylaminopropylidene) - 5H-pyrrolo[2,1-b][3]benzazepine (3.2 g.) is absorbed on 300 g. silica gel and elution is carried out using 2% methanol in chloroform with fractions of 10 ml. The first isomer comes out between tubes (fractions) 70 and 109; evaporation of the eluent from these fractions yields 0.8 g. of an oil which solidifies on standing. This is isomer I, m.p. 104—105°C. Between tubes 110 and 159, a mixture of the two isomers is obtained (1.62 g.) and finally 0.49 g. of isomer II is obtained by evaporating to dryness tubes 160 to 210.

The difference between the two isomers is best seen by nmr. For the isomer I, the formyl proton absorbs at 0.56 ppm and the N-(CH₃)₂ protons at 2.10 ppm; for the isomer II, the formyl proton is at 9.61 ppm and the N-(CH₃)₂ protons are at 2.20 ppm.

Following the procedure substantially as described in Example XVII, but substituting for the 2-formyl compound an equimolecular amount of any of the pyrrolo[2,1-b][3]benzazepines described in Examples I to XV and XX, and Tables A, B, and C, which appear in Examples I, II and XV respectively, there are produced the corresponding geometric isomers.

For example, the geometric isomers of 9-chloro-6,11-dihydro-11-(3-dimethylaminopropylidene)-5H-pyrrolo[2,1-b][3]benzazepine and 9-chloro-11-(3-dimethylaminopropylidene)-11H-pyrrolo[2,1-b][3]benzazepine, i.e. their (E)- and (Z)- forms, as defined by Blackwood et al. in J. Amer. Chem. Soc. 90, 509 (1968), can be produced by this procedure.

EXAMPLE XVIII.

2 - Cyano - 6,11 - dihydro - 11 - (3 - dimethylaminopropylidene) - 5H - pyrrolo-[2,1-b][3]benzazepine, oxalate salt; isomer I

2 - Formyl - 6,11 - dihydro - 11 - (3 - dimethylaminopropylidene) - 5H-pyrrolo-[2,1-b][3]benzazepine (Isomer I from Example XVIII) (1.4 g., 4.8 mmoles), hydroxylamine hydrochloride (0.7 g., 10 mmoles) and sodium formate (0.85 g., 12.5 mmoles) in 20 ml. ethanol are heated on a steam-bath for 5 minutes. The volatile materials are removed under vacuum; 5% sodium bicarbonate is added to the residue and the solution is extracted with methylene chloride. The organic phase is washed with water, dried over sodium sulfate and concentrated to yield 1.4 g. of oxime.

The oxime in 10 ml. trichloroacetonitrile is heated on a steambath for 15 minutes. The solution is taken to dryness under vacuum, water is added, and the resulting mixture is extracted with methylene chloride to yield, after usual washings and drying, 1.9 g. of crude 2-cyano-6,11-dihydro-11-(3-dimethylaminopropylidene)-5H-pyrrolo[2,1-b][3]benzazepine as a brown oil.

It is adsorbed on 100 g. silica gel and eluted with chloroform to yield tri-chloroacetamide, which was discarded. Elution with 10% methanol in chloroform yields pure 2-cyano-6,11-dihydro-11-(3-dimethylaminopropylidene)-5H-pyrrolo[2,1-b][3]benzazepine as a brown oil (0.84 g., 60%).

When dissolved in 5 ml. of ethanol and treated with 300 mg. of oxalic acid in 0.5 ml. ethanol, the free base yields the oxalate salt (0.85 g., 45%), m.p. 217°C. (dec.).

EXAMPLE XIX.

2- Cyano - 6,11 - dihydro - 11 - (3 - dimethylaminopropylidene) - 5H - pyrrolo[2,1-b][3]benzazepine oxalate salt; Isomer II

By the procedure of Example XVIII but starting with Isomer II of the 2-formyl derivative from Example XVII, there is produced 2-cyano-6,11-dihydro-11-(3-dimethylaminopropylidene)-5H-pyrrolo[2,1-b][3]benzazepine oxalate salt; Isomer II, m.p. 223°C. (dec.).

EXAMPLE XX.

2- Formyl - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine

Step A: Preparation of 6,11 - dihydro - 2 - (2 - dioxolanyl) - 5H - pyrrolo[2,1-b][3]benzazepine - 11 - one

A mixture of 5 gm. of 6,11-dihydro-2-formyl-5H-pyrrolo[2,1-b][3]benzazepine-11-one, 2.5 gm. of ethylene glycol, 0.5 gm. *p*-toluenesulfonic acid and 100 ml. of toluene is refluxed for 16 hr. in an apparatus designed to remove water formed during the reaction (Dean-Stark apparatus). The reaction mixture is cooled to 0°C. and washed rapidly with ice-cold 5% sodium carbonate solution (2 x 50 ml.) and dried over Na₂SO₄. Evaporation of the solvent leaves 6,11-dihydro-2-(2-dioxolanyl)-5H-pyrrolo[2,1-b][3]benzazepine-11-one as an oil which is of sufficient purity for use in the next step.

Step B: Preparation of 6,11 - dihydro - 2 - (2 - dioxolanyl) - 11 - hydroxy - 11 - (3 - dimethylaminopropyl) - 5H - pyrrolo[2,1-b][3]benzazepine

By substantially the procedure of Example I, Step A, but using the ketone acetal from Step A of the present example, there is obtained 6,11-dihydro-2-(2-dioxolanyl) - 11 - hydroxy - 11 - (3 - dimethylaminopropyl) - 5H - pyrrolo[2,1-b][3]benzazepine.

Step C: Preparation of 2 - formyl - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine

To a solution of 3 gm. of 6,11-dihydro-2-(2-dioxolanyl)-11-hydroxy-11-(3-dimethylaminopropyl)-5H-pyrrolo[2,1-b][3]benzazepine in 20 ml. of ethanol containing 1 ml. of water is added 2 gm. of oxalic acid, and the resulting mixture is heated to reflux for 2 hr. Upon cooling to 0°C. for 4 hr., there is obtained the crystalline oxalate of 2-formyl-11-(3-dimethylaminopropylidene)-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepine, m.p. 181°C. (decomp.).

Using substantially the same procedure as in Steps A, B, and C of the present example but starting with 2 - formyl - 11H - pyrrolo[2,1-b][3]benzazepine-11 - one, 6,11 - dihydro - 9 - formyl - 5H - pyrrolo[2,1-b][3]benzazepine - 11 - one, or 9 - formyl - 11H - pyrrolo[2,1-b][3]benzazepine - 11 - one, there is obtained 2-formyl - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine, 9 - formyl - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydro - 5H - pyrrolo[2,1-b][3]benzazepine, or 9 - formyl - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b][3]benzazepine, respectively.

EXAMPLE XXI.

Pharmaceutical Compositions

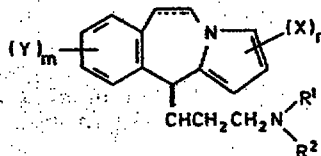
A typical tablet containing 5 mg. of 2-formyl-11-(3-dimethylaminopropylidene)-11H-pyrrolo[2,1-b][3]benzazepine per tablet is prepared by mixing together with the active ingredient calcium phosphate, lactose and starch in the amounts shown in the tables below. After these ingredients have been thoroughly mixed, the dry mixture is blended for an additional three minutes. This mixture is then compressed into tablets weighing approximately 129 mg. each. Similarly prepared are tablets containing 2-formyl-11-(3-dimethylaminopropylidene)-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepine, 11-(3-dimethylaminopropylidene)-6,11-dihydro-5H-pyrrolo[2,1-b][3]benzazepine, or any of the novel compounds of this invention.

Tablet Formula

Ingredient	Mg. per Tablet
2-formyl-11-(3-dimethylaminopropylidene)-11H-pyrrolo-[2,1-b][3]-benzazepine	5 mg.
Calcium phosphate	52 mg.
Lactose	60 mg.
Starch	10 mg.
Magnesium stearate	1 mg.

WHAT WE CLAIM IS:—

1. A compound of structural formula:



or a pharmaceutically acceptable salt thereof, in which the dotted line represents saturation or unsaturation; n is 0, 1, 2 or 3; m is 0, 1, 2, 3 or 4; each of X and Y , which are similar or dissimilar, is

- (1) hydrogen,
- (2) halogen,
- (3) formyl,
- (4) C_{2-2} alkanoyl,
- (5) C_{1-3} alkyl,
- (6) (C_{1-3} alkoxy)carbonyl,
- (7) C_{1-3} hydroxyalkyl,
- (8) C_{1-3} perhaloalkyl,
- (9) C_{1-3} alkoxy,
- (10) cyano,
- (11) C_{1-3} perhaloalkylthio,
- (12) C_{1-3} alkylthio,
- (13) C_{1-3} alkylsulfonyl,
- (14) C_{1-3} perhaloalkylsulfonyl,
- (15) C_{1-3} alkylsulfinyl,
- (16) C_{1-3} perhaloalkylsulfinyl,
- (17) amino,
- (18) C_{2-6} alkanoylamino,
- (19) C_{1-3} alkylamino,
- (20) di(C_{1-3} alkyl)amino,
- (21) hydroxy,
- (22) N -(C_{1-3} alkyl)carbamoyl,
- (23) N,N -di(C_{1-3} alkyl)carbamoyl,
- (24) nitro,
- (25) di(C_{1-3} alkyl)sulfamoyl,
- (26) (C_{1-3} alkoxy)carbonylamino, or
- (27) N -(C_{1-3} alkyl)carbamoyloxy; and each of

R^1 and R^2 , which are similar or dissimilar, is

- (1) hydrogen,
- (2) C_{1-3} alkyl,
- (3) C_{2-3} alkenyl, or
- (4) C_{3-6} cycloalkyl, or



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Tablet Formula

Ingredient

Mg. per Tablet

5 2-formyl-11-(3-dimethylaminopropyl-
idene)-11H-pyrrolo-[2,1-b][3]-
benzazepine

5 mg.

5

Calcium phosphate

52 mg.

Lactose

60 mg.

Starch

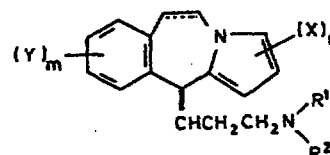
10 mg.

Magnesium stearate

1 mg.

WHAT WE CLAIM IS:—

1. A compound of structural formula:



or a pharmaceutically acceptable salt thereof, in which the dotted line represents saturation or unsaturation; n is 0, 1, 2 or 3; m is 0, 1, 2, 3 or 4; each of X and Y , which are similar or dissimilar, is

- (1) hydrogen,
- (2) halogen,
- (3) formyl,
- (4) C_{2-2} alkanoyl,
- (5) C_{1-3} alkyl,
- (6) (C_{1-3} alkoxy)carbonyl,
- (7) C_{1-3} hydroxyalkyl,
- (8) C_{1-3} perhaloalkyl,
- (9) C_{1-3} alkoxy,
- (10) cyano,
- (11) C_{1-3} perhaloalkylthio,
- (12) C_{1-3} alkylthio,
- (13) C_{1-3} alkylsulfonyl,
- (14) C_{1-3} perhaloalkylsulfonyl,
- (15) C_{1-3} alkylsulfinyl,
- (16) C_{1-3} perhaloalkylsulfinyl,
- (17) amino,
- (18) C_{2-6} alkanoylamino,
- (19) C_{1-3} alkylamino,
- (20) di(C_{1-3} alkyl)amino,
- (21) hydroxy,
- (22) N -(C_{1-3} alkyl)carbamoyl,
- (23) N,N -di(C_{1-3} alkyl)carbamoyl,
- (24) nitro,
- (25) di(C_{1-3} alkyl)sulfamoyl,
- (26) (C_{1-3} alkoxy)carbonylamino, or
- (27) N -(C_{1-3} alkyl)carbamoyloxy; and each of R^1 and R^2 , which are similar or dissimilar, is

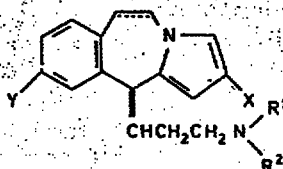
- (1) hydrogen,
- (2) C_{1-3} alkyl,
- (3) C_{2-3} alkenyl, or
- (4) C_{3-6} cycloalkyl, or



R^1 and R^2 are joined to form, together with the nitrogen to which they are attached, a 1-piperidyl, 1-pyrrolidyl, or 4-morpholinyl radical.

2. A compound as claimed in Claim 1, in which n is 2, 1 or 0 and X, if present, is in the 2 and/or 3 position.

3. A compound of the formula:



or a pharmaceutically acceptable salt thereof, in which the dotted line, X and Y are as defined in Claim 1 and R^1 and R^2 are hydrogen or C_{1-3} alkyl.

4. A compound as claimed in Claim 3, in which one of X and Y is hydrogen and the other is hydrogen, cyano, formyl or C_{2-6} alkanoyl.

5. 9 - Chloro - 6,11 - dihydro - 11 - (3 - dimethylaminopropylidene) - 5H-pyrrolo - [2,1-b][3]benzazepine.

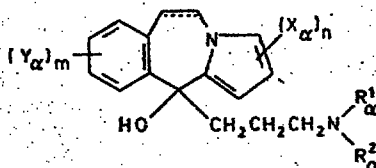
6. 9 - Chloro - 11 - (3 - dimethylaminopropylidene) - 11H - pyrrolo[2,1-b]-[3]benzazepine.

7. The (E) form of the compound claimed in Claim 5.

8. The (E) form of the compound claimed in Claim 6.

9. Every one of the compounds claimed in Claim 1 hereinbefore individually specified, with the exception of those claimed in Claims 5 to 8.

10. A compound of preparing a compound as claimed in Claim 1 that comprises dehydrating a compound of the formula:



in which the dotted line, m and n are as defined in Claim 1, X_α and Y_α are as defined above for X and Y respectively, but excluding formyl, and R^1_α and R^2_α are as defined above for R^1 and R^2 respectively, but excluding hydrogen, with the optional additional step(s) of (a) treating a compound in which X_α and/or Y_α is cyano with nickel-aluminium alloy in formic acid to yield the corresponding compound in which X and/or Y is formyl; and/or (b) dealkylating a compound in which R^1_α and/or R^2_α is alkyl to produce the corresponding compound in which R^1 and/or R^2 is hydrogen.

11. A method as claimed in Claim 10 as applied to the preparation of a compound as defined in Claim 2.

12. A method as claimed in Claim 10 as applied to the preparation of a compound as claimed in Claim 3.

13. A method as claimed in Claim 10 as applied to the preparation of a compound as claimed in Claim 4.

14. A method as claimed in Claim 10, substantially as hereinbefore described in Example I, in Example I with respect to any one of the compounds of Table A, in Example II, in Example II with respect to any one of the compounds of Table B, in Example III or in Example XX.

15. A method of preparing a compound as claimed in Claim 1, substantially as hereinbefore described in any one of Examples IV to XV or in Example XV with respect to any one of the compounds of Table C.

16. A method of preparing a geometric isomer of a compound as claimed in Claim 1, substantially as hereinbefore described in any one of Example XVI to XIX.

17. A compound as claimed in Claim 1 when prepared by a method as claimed in any one of Claims 10 to 16.

18. A pharmaceutical composition containing as active ingredient a compound as claimed in any one of Claims 1 to 9 and 17 and a pharmaceutical carrier.



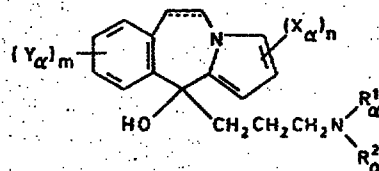
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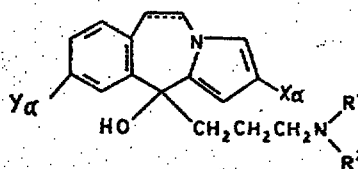
19. A composition as claimed in Claim 18 in the form of a tablet.
20. A composition as claimed in Claim 18 in the form of a capsule, elixir or aqueous suspension.
21. A method of producing a skeletal muscle relaxant and/or tranquilizing effect in a non-human animal in need of such treatment comprising the administration to the animal of an effective amount of a compound as claimed in any one of Claims 1 to 9 and 17.
22. A compound of the formula:



in which the dotted line, m and n are as defined in Claim 1 and X_α , Y_α , R_α^1 and R_α^2 are as defined in Claim 10.

23. A compound as claimed in Claim 22 in which n is 2, 1 or 0 and, if n is 2 or 1, X_α is in the 2 or 3 position.

24. A compound of the formula:



in which the dotted line, X_α , R_α^1 and R_α^2 are the same as in Claim 10.

25. A compound as claimed in Claim 24 in which one of X_α and Y_α is hydrogen and the other is hydrogen, cyano or C_{2-6} alkanoyl.

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