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PATENT SPECIFICATION

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International Classification:—C07c, d.

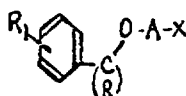
COMPLETE SPECIFICATION

New Basic Ethers and a process for the production thereof

We, C. F. BOEHRINGER & SOEHNE G.M.B.H., a body corporate organised under the laws of Germany, of Mannheim-Waldhof, Germany, 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:—

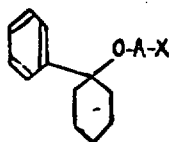
The present invention is concerned with new basic ethers and with a process for the production thereof.

The new ethers according to the present invention may be represented by the general formula:



in which R is an alkylene radical containing 4 to 7 carbon atoms, R₁ is a halogen atom or a C₁—C₃ alkyl, C₁—C₃ alkoxy or C₁—C₃ alkylmercapto radical, A is a straight or branched chain alkylene radical and X is a secondary or tertiary amino radical or a nitrogen-containing heterocyclic radical the nitrogen atom of which is attached to A. The present invention is also concerned with the salts and quaternary ammonium compounds of these basic ethers.

A few compounds of this type are known in which the phenyl radical is unsubstituted. Protiva et al. (Chem. Listy, 42, 175/1948; Chem. Abs., 45, 573h/1951) have produced compounds of the general formula:



in which the substituent —A—X is a β-
[Price 3s. 6d.]

dimethylaminoethyl, a β-diethylaminoethyl or a β-piperidinoethyl radical. These known 1-phenyl-cyclohexanol ethers have no pharmacologically interesting properties; according to the authors, they merely possess a slight anti-histaminic action.

We have now found that by the introduction of suitable substituents into the phenyl radical, compounds are obtained with specific properties which can be used especially in psychiatric pharmacotherapy. In comparison with the above-mentioned known compounds, the new basic ethers show a substantially increased anti-Parkinson effect and, at the same time, a reduction of the cholinergic-mydriatic effect. The new compounds have a relatively low toxicity, possess an outstanding anti-nicotine action, a weak anti-histaminic action and only a slight circulatory effect.

We have also found that compounds which possess a cycloalkyl radical other than a cyclohexyl radical possess interesting pharmacological properties. These new compounds suppress the basic brain motor centres and inhibit the tremorin effect on the central nervous system in a manner similar to known anti-Parkinson compounds, while a peripheral anti-cholinergic effectiveness is only present to a slight degree.

In comparison with known anti-Parkinson agents, such as 1-phenyl-cyclopentane-2-carboxylic acid-β-diethylaminoethyl ester hydrochloride, which, however, are only remotely connected structurally with the new compounds of the present invention, the new basic ethers possess a considerably lower peripheral anti-cholinergic effect; furthermore, several members of the new group of compounds are considerably more effective in the specific anti-tremorin test for anti-Parkinson agents. A large number of the new compounds also show outstanding central nervous system-stimulating properties which the known anti-Parkinson agents, such as 1-phenyl-cyclopentane-2-carboxylic acid-β-diethylaminoethyl ester hydrochloride do

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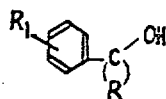
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not shew. Because of the absence of the peripheral anti-cholinergic effect, it can be expected that the usual side-effects associated with the administration of known anti-Parkinson agents to humans will not appear. Some members of the new basic ethers are characterised in animal experiments by a strong isolated central nervous system-stimulating effect while the typical anti-tremorin action of anti-Parkinson agents is, at the same time, absent.

The new basic ethers of the present invention can carry as the basic substituent of the alkyl ether radical a secondary or tertiary amino group, such as an alkyl- or dialkyl-amino radical, or heterocyclic radical, such as an unsubstituted or substituted piperidino, pyrrolidino, morpholino or piperazino radical.

The new compounds can be produced by methods known for the production of basic ethers. The preferred method of production consists of the reaction of substituted 1-phenyl-cyclohexanols of the general formula:



in which R_1 and R_2 have the same meaning as above, with basic substituted alkyl halides of the general formula $\text{Hal}-\text{A}-\text{X}$, in which Hal is a halogen atom and A and X have the same meaning as above, or the salts thereof.

Instead of these aminoalkyl halides, it is also possible to use the corresponding haloalkanols of the general formula $\text{Hal}-\text{A}-\text{OH}$ or the corresponding alkyl dihalides of the general formula $\text{Hal}-\text{A}-\text{Hal}$ and to introduce the basic substituent X subsequently by methods known *per se*.

By way of illustration, the two preferred methods of producing the new basic ethers are described in the following:

METHOD I.

A solution of 0.1 mol of a 1-aryl-cycloalkanol in about 80 cc. toluene or benzene is allowed to drop, with intensive stirring into a suspension of 4.0 g. (0.1 mol) sodamide in 20 cc. toluene at room temperature. The reaction mixture is subsequently heated to 50–60° C. until the evolution of ammonia is ended; if necessary, the reaction mixture can be heated under reflux to complete the reaction.

About 0.11–0.12 mol of an aminoalkyl halide dissolved in an equal amount of toluene or benzene is now added dropwise with stirring at room temperature and the reaction mixture heated for several hours at the boiling point of the solvent used. After cooling, the precipitate is filtered off, the filtrate evaporated *in vacuo* and the residue distilled in a high vacuum.

METHOD II

A solution of 0.1 mol of a 1-aryl-cycloalkanol in about 1000 cc. absolute toluene is added dropwise to a suspension of sodamide (0.2–0.3 mol) in 50 cc. absolute toluene. The reaction mixture is subsequently heated for 1 hour at 50–60° C. and, if necessary, heated under reflux. 0.1 mol of the hydrochloride of an aminoalkyl halide is now introduced at about 50° C. and the reaction mixture heated for 3 hours at boiling point. After cooling, any excess sodamide which may still be present is decomposed by the careful dropwise addition of aqueous alcohol. The toluene layer is shaken up with about 30 cc. water, dried and evaporated *in vacuo*. The oily residue is distilled in a high vacuum.

In general, Methods I and II give the same result; however, in the case of compounds in which R is a butylene radical, it is preferable to use Method II.

The basic ethers obtained can be converted in known manner into their salts, preferably their hydrochlorides, and also into the corresponding quaternary ammonium compounds.

Compounds produced by these two methods are given in the following Table:

Compound	b.p. °C./mm. Hg.	m.p. of the hydrochloride	yield % base
[1-(<i>p</i> -chlorophenyl)-cyclohexyl]-[3-dimethylaminoethyl]-ether	140—146/0.4	177—179°	65—70
[1-(<i>p</i> -chlorophenyl)-cyclohexyl]-[3-diethylaminoethyl]-ether	145—152/0.8	145—146°	70—75
[1-(<i>p</i> -chlorophenyl)-cyclohexyl]-[3-triethylaminoethyl]-ether bromide	—	215°	—
[1-(<i>p</i> -chlorophenyl)-cyclohexyl]-[3-dimethylaminopropyl]-ether	135—141/0.1	182—183°	60—65
[1-(<i>p</i> -chlorophenyl)-cyclohexyl]-[2-(1-piperidino)ethyl]-ether	165—175/0.5	181—182°	65—70
[1-(<i>p</i> -chlorophenyl)-cyclohexyl]-[3-(4-morpholino)ethyl]-ether	185—190/0.3	178—179°	55—60
[1-(<i>o</i> -chlorophenyl)-cyclohexyl]-[2-dimethylaminoethyl]-ether	138—143/0.3	146—147°	65—70
[1-(<i>o</i> -tolyl)-cyclohexyl]-[3-dimethylaminoethyl]-ether	125—135/0.5	172—173°	50—55
[1-(<i>o</i> -anisyl)-cyclohexyl]-[3-dimethylaminoethyl]-ether	130—140/0.3	131—133°	70—75
[1-(<i>p</i> -chlorophenyl)-cyclohexyl]-[3-(1-pyrrolidino)ethyl]-ether	145—155/0.2	178—179°	65—70
[1-(<i>p</i> -chlorophenyl)-cyclohexyl]-[3-(4-methyl-piperazinyl-1)-ethyl]-ether	194—196/0.8	215—216° (1 mol H ₂ O)	50
[1-(<i>p</i> -chlorophenyl)-cyclohexyl]-[3-(4-methyl-piperazinyl-1)-propyl]-ether	175—185/0.05	238° (1/2 mol H ₂ O)	55
[1-(<i>o</i> -chlorophenyl)-cyclohexyl]-[3-diethylaminoethyl]-ether	140—150/0.5	117—119°	55—60
[1-(<i>o</i> -chlorophenyl)-cyclohexyl]-[3-(1-piperidino)ethyl]-ether	166—178/0.05	152—154°	50
[1-(<i>o</i> -chlorophenyl)-cyclohexyl]-[3-dimethylaminopropyl]-ether	135—138/0.3	145—146°	60—65



mol

Compound	b.p. °C./mm. Hg.	m.p. of the hydrochloride	yield % base
[1-(<i>p</i> -chlorophenyl)-cyclohexyl]-[γ -diethylamino-propyl]-ether	178—187/0.6	178°	50—55
[1-(<i>p</i> -chlorophenyl)-cyclohexyl]-[γ -(1-piperidino)-propyl]-ether	175—185/0.2	221—222°	60—65
[1-(<i>p</i> -tolyl)-cyclohexyl]-[β -diethylaminoethyl]-ether	125—130/0.15	151°	50—55
[1-(<i>o</i> -tolyl)-cyclohexyl]-[β -(1-piperidino)-ethyl] ether	160—173/0.2	173—174°	55—60
[1-(<i>o</i> -anisyl)-cyclohexyl]-[β -(1-piperidino)-ethyl]-ether	165—168/0.2	138°	55—60
[1-(<i>p</i> -methylmercapto-phenyl)-cyclohexyl]-[β -diethylaminoethyl]-ether	160—170/0.4	116°	60
[1-(<i>p</i> -chlorophenyl)-cyclopentyl]-[β -diethylaminoethyl]-ether	140—145/0.4	138°	50—55
[1-(<i>p</i> -chlorophenyl)-cyclopentyl]-[β -(1-piperidino)-ethyl]-ether	168—180/0.2	176°	65—70
[1-(<i>p</i> -chlorophenyl)-cyclopentyl]-[γ -(4-methyl-piperazinyl-1)-propyl]-ether	190—199/0.3	244° (decomp.)	40—45
[1-(<i>p</i> -tolyl)-cyclopentyl]-[β -diethylaminoethyl]-ether	125—135/0.1	133°	60—70
[1-(<i>p</i> -tolyl)-cyclopentyl]-[β -(1-piperidino)-ethyl]-ether	165—175/0.4	144°	60—65
[1-(<i>p</i> -chlorophenyl)-cycloheptyl]-[β -diethylaminoethyl]-ether	160—180/0.4	129°	50
[1-(<i>p</i> -chlorophenyl)-cyclooctyl]-[β -diethylaminoethyl]-ether	180—190/0.8	132°	70

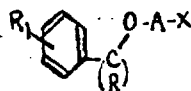
The following compounds used as starting materials are also new: 1 - (*p*-chlorophenyl)-cyclohexanol (m.p. 76—77° C.), 1-(*o*-chlorophenyl) - cyclohexanol (m.p. 56—57° C.), 1 - (*p*-methylmercaptophenyl) - cyclohexanol (m.p. 65—67° C.), 1 - (*p*-chlorophenyl)-cyclopentanol (m.p. 60° C.), 1 - (*o*-anisyl) - cyclopentanol (m.p. 43—44° C.), 1 - (*p*-chlorophenyl) - cycloheptanol (b.p. 157—163/0.4 mm. Hg.) and 1 - (*p*-chlorophenyl)-cyclooctanol (m.p. 41° C.). They can be

produced by a Grignard reaction from cycloalkanes and the corresponding aryl halides in a manner analogous to those used for the production of known 1 - aryl - cyclohexanols; 1 - (*p*-tolyl) - cyclohexanol (Compt. rend., 138, 1322/1904), 1 - (*o*-tolyl) - cyclohexanol (J.C.S., 1932, 1833; J.A.C.S., 75, 3970/1953), 1 - (*p*-anisyl) - cyclohexanol (Rec. trav. chim., 67, 489/1948; J.C.S., 1932, 1934), 1 - (*p*-anisyl) - cyclohexanol (J.C.S., 1951, 516) and 1 - (*p*-tolyl) - cyclopentanol

(Vila and Crespo, Chem. Abs., 1953, 3802 g).

WHAT WE CLAIM IS:—

1. Basic ethers of the general formula:



5 in which R is an alkylene radical containing 4 to 7 carbon atoms, R₁ is a halogen atom or a C₁-C₃ alkyl, C₁-C₃ alkoxy or C₁-C₃ alylmercapto radical, A is a straight or branched chain alkyl radical and X is a

10 secondary or tertiary amino group or a nitrogen-containing heterocyclic radical the nitrogen atom of which is attached to A; and the salts and quaternary ammonium compounds thereof.

15 2. [1 - (p - chlorophenyl) - cyclohexyl] - [β - dimethylaminoethyl] - ether.

3. [1 - (p - chlorophenyl) - cyclohexyl] - [β - diethylaminoethyl] - ether.

4. [1 - (p - chlorophenyl) - cyclohexyl] - [β - dimethylaminopropyl] - ether.

20 5. [1 - (p - chlorophenyl) - cyclohexyl] - [β - piperidino - ethyl] - ether.

6. [1 - (p - chlorophenyl) - cyclohexyl] - [β - (4 - morpholino) - ethyl] - ether.

25 7. [1 - (o - chlorophenyl) - cyclohexyl] - [β - dimethylaminoethyl] - ether.

8. [1 - (o - tolyl) - cyclohexyl] - [β - dimethylaminoethyl] - ether.

9. [1 - (o - anisyl) - cyclohexyl] - [β - dimethylaminoethyl] - ether.

30 10. [1 - (p - chlorophenyl) - cyclohexyl] - [β - (1 - pyrrolidino) - ethyl] - ether.

11. [1 - (p - chlorophenyl) - cyclohexyl] - [β - (4 - methylpiperazinyl-1) - ethyl] - ether.

35 12. [1 - (p - chlorophenyl) - cyclohexyl] - [γ - 4 - methyl - piperazinyl-1) - propyl] - ether.

13. [1 - (o - chlorophenyl) - cyclohexyl] - [β - diethylaminoethyl] - ether.

14. [1 - (o - chlorophenyl) - cyclohexyl] - [β - (1 - piperidino) - ethyl] - ether.

40 15. [1 - (o - chlorophenyl) - cyclohexyl] - [γ - dimethylaminopropyl] - ether.

16. [1 - (p - chlorophenyl) - cyclohexyl] - [γ - diethylaminopropyl] - ether.

17. [1 - (p - chlorophenyl) - cyclohexyl] - [γ - (1 - piperidino) - propyl] - ether.

18. [1 - (p - (tolyl) - cyclohexyl] - [β - (diethylaminoethyl] - ether.

19. [1 - (o - tolyl) - cyclohexyl] - [β - (1 - piperidino) - ethyl] - ether.

20. [1 - (o - anisyl) - cyclohexyl] - [β - (1 - piperidino) - ethyl] - ether.

21. [1 - (p - methylmercaptophenyl) - cyclohexyl] - [β - (diethylaminoethyl) - ether. A

22. [1 - (p - chlorophenyl) - cyclopentyl] - [β - diethylaminoethyl] - ether.

23. [1 - (p - chlorophenyl) - cyclopentyl] - [β - (1 - piperidino) - ethyl] - ether.

24. [1 - (p - chlorophenyl) - cyclopentyl] - [γ - (4 - methylpiperazinyl - 1) - propyl] ether.

25. [1 - (p - tolyl) - cyclopentyl] - [β - diethylaminoethyl] - ether.

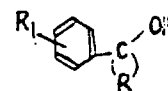
26. [1 - (p - tolyl) - cyclopentyl] - [β - (1 - piperidino) - ethyl] - ether.

27. [1 - (p - chlorophenyl) - cycloheptyl] - [β - diethylaminoethyl] - ether.

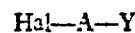
28. [1 - (p - chlorophenyl) - cyclooctyl] - [β - diethylaminoethyl] - ether.

29. [1 - (p - chlorophenyl) - cyclohexyl] - [β - thiethylaminoethyl] - ether bromide.

30. Process for the production of basic ethers of the general formula given in claim 1, wherein a 1-phenylcycloalkanol of the general formula:



in which R₁ and R₂ have the same meaning as above, is reacted with an alkyl halide of the general formula:



in which Hal is a halogen atom, A is a straight or branched chain alkylene radical and Y is the required organic basic radical or a halogen atom or a hydroxyl group, the substituent Y converted, if necessary, into an organic basic radical and the product obtained converted, desired, into its salts or quaternary ammonium compounds.

31. Process according to claim 30, wherein a salt of a basically substituted alkyl halide is used as the alkyl halide reactant.

32. Process for the production of basic ethers of the general formula given in claim 1, substantially as hereinbefore described.

33. Basic ethers of the general formula given in claim 1, whenever produced by the process according to any of claims 30 to 32.

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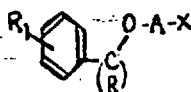
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Chancery Lane, London, W.C.2.

(Vila and Crespo, Chem. Abs., 1953, 3802 g).

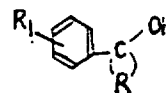
WHAT WE CLAIM IS:—

1. Basic ethers of the general formula:

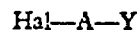


- 5 in which R is an alkylene radical containing 4 to 7 carbon atoms, R₁ is a halogen atom or a C₁—C₃ alkyl, C₁—C₃ alkoxy or C₁—C₃ alylmercapto radical, A is a straight or branched chain alkyl radical and X is a secondary or tertiary amino group or a nitrogen-containing heterocyclic radical the nitrogen atom of which is attached to A; and the salts and quaternary ammonium compounds thereof.
- 10 2. [1 - (p - chlorophenyl) - cyclohexyl] - [β - dimethylaminoethyl] - ether.
- 15 3. [1 - (p - chlorophenyl) - cyclohexyl] - [β - diethylaminoethyl] - ether.
- 20 4. [1 - (p - chlorophenyl) - cyclohexyl] - [β - dimethylaminopropyl] - ether.
- 25 5. [1 - (p - chlorophenyl) - cyclohexyl] - [β - piperidino - ethyl] - ether.
- 30 6. [1 - (p - chlorophenyl) - cyclohexyl] - [β - (4 - morpholino) - ethyl] - ether.
- 35 7. [1 - (o - chlorophenyl) - cyclohexyl] - [β - dimethylaminoethyl] - ether.
- 40 8. [1 - (o - tolyl) - cyclohexyl] - [β - dimethylaminoethyl] - ether.
9. [1 - (o - anisyl) - cyclohexyl] - [β - dimethylaminoethyl] - ether.
10. [1 - (p - chlorophenyl) - cyclohexyl] - [β - (1 - pyrrolidino) - ethyl] - ether.
11. [1 - (p - chlorophenyl) - cyclohexyl] - [β - (4 - methylpiperazinyl-1) - ethyl] - ether.
12. [1 - (p - chlorophenyl) - cyclohexyl] - [γ - 4 - methyl - piperazinyl-1) - propyl] - ether.
13. [1 - (o - chlorophenyl) - cyclohexyl] - [β - diethylaminoethyl] - ether.
14. [1 - (o - chlorophenyl) - cyclohexyl] - [β - (1 - piperidino) - ethyl] - ether.
15. [1 - (o - chlorophenyl) - cyclohexyl] - [γ - dimethylaminopropyl] - ether.
16. [1 - (p - chlorophenyl) - cyclohexyl] - [γ - diethylaminopropyl] - ether.
17. [1 - (p - chlorophenyl) - cyclohexyl] - [γ - (1 - piperidino) - propyl] - ether.
18. [1 - (p - tolyl) - cyclohexyl] - [β - (diethylaminoethyl) - ether.
19. [1 - (o - tolyl) - cyclohexyl] - [β - (1 - piperidino) - ethyl] - ether.
20. [1 - (o - anisyl) - cyclohexyl] - [β - (1 - piperidino) - ethyl] - ether.

21. [1 - (p - methylmercaptophenyl) - cyclohexyl] - [β - (diethylaminoethyl) - ether.
22. [1 - (p - chlorophenyl) - cyclopentyl] - [β - diethylaminoethyl] - ether.
23. [1 - (p - chlorophenyl) - cyclopentyl] - [β - (1 - piperidino) - ethyl] - ether.
24. [1 - (p - chlorophenyl) - cyclopentyl] - [γ - (4 - methylpiperazinyl-1) - propyl] - ether.
25. [1 - (p - tolyl) - cyclopentyl] - [β - diethylaminoethyl] - ether.
26. [1 - (p - tolyl) - cyclopentyl] - [β - (1 - piperidino) - ethyl] - ether.
27. [1 - (p - chlorophenyl) - cycloheptyl] - [β - diethylaminoethyl] - ether.
28. [1 - (p - chlorophenyl) - cyclooctyl] - [β - diethylaminoethyl] - ether.
29. [1 - (p - chlorophenyl) - cyclohexyl] - [β - diethylaminoethyl] - ether bromide.
30. Process for the production of basic ethers of the general formula given in claim 1, wherein a 1-phenylcycloalkanol of the general formula:



in which R₁ and R₂ have the same meaning as above, is reacted with an alkyl halide of the general formula:



in which Hal is a halogen atom, A is a straight or branched chain alkylene radical and Y is the required organic basic radical or a halogen atom or a hydroxyl group, the substituent Y converted, if necessary, into an organic basic radical and the product obtained converted, desired, into its salts or quaternary ammonium compounds.

31. Process according to claim 30, wherein a salt of a basically substituted alkyl halide is used as the alkyl halide reactant.

30. Process for the production of basic ethers of the general formula given in claim 1, substantially as hereinbefore described.

33. Basic ethers of the general formula given in claim 1, whenever produced by the process according to any of claims 30 to 32.

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* C L M S *