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(54) PRODUCTION OF QUINOXALINE-DI-N-OXIDES AND
 BENZIMIDAZOLE MONO- AND DI-N-OXIDES

(71) We, RESEARCH CORPORATION, a corporation of the State of New York, United States of America, having a place of business at 405 Lexington Avenue, New York, New York, 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 a novel synthetic procedure and, more particularly, to a novel method for the preparation of quinoxaline-di-N-oxides and related compounds such as benzimidazole-di-N-oxides and 1-hydroxy benzimidazole-3-oxides.

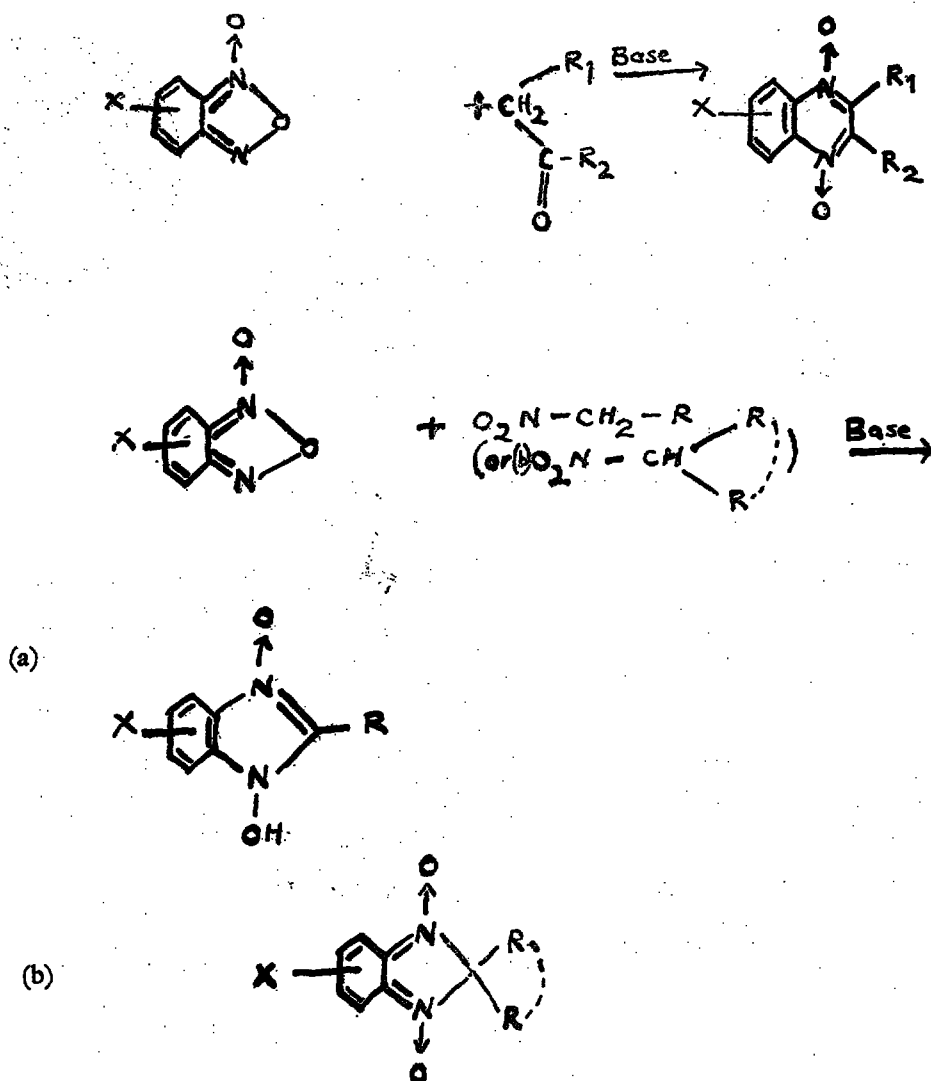
The compounds prepared by the novel subject process are useful in the control of various pathogenic microorganisms. Also, as shown in U.S. Patent 3,047,579, such oxides are generally prepared by processes involving the direct oxidation of quinoxaline compounds and usually require the corresponding quinoxaline compound as the starting material. Oxidation reactions are generally known to be somewhat non-selective and may give rise to low yields of the desired product together with one or more difficult to separate by-products.

The gram-negative antibacterial activity of several quinoxaline-di-N-oxides bearing 2-alkyl or 2,3-dialkyl groups has been described by Lundquist et al, U.S. Patent 2,626,259, issued January 20, 1953, and by Wiedling, Acta Pathol, et Microbiol. Scand. 22, 379—91 (1945). McIlwain, J. Chem. Soc. 322 (1943) and King et al, J. Chem. Soc. 3012 (1949), disclose the antibacterial activity of 2-methyl-3-n-amyloquinoxaline-di-N-oxide and of several 6-substituted quinoxaline-di-N-oxides, respectively. Hurst et al, Brit. J. Pharmacol. 8, 297 (1953) report on the antiviral properties of quinoxaline-di-N-oxide and various derivatives thereof against the largest viruses of the psittacosis-lymphogranuloma group and note that toxic side reactions preclude their use in man. Hurst et al report that few of the products were active against the virus (lymphogranuloma) in the chick embryo.

In accordance with the present invention, a general organic synthetic method is disclosed for the preparation of the subject compounds which comprises reacting a compound containing a methylene group which is activated by two electron withdrawing groups or a compound containing a methylene group which is activated by one electron withdrawing group, said one electron withdrawing group being a nitro group or a carbonyl group of a ketone or an aldehyde, with an isobenzofuroxan in the presence of a base.

The electron withdrawing groups activating the methylene group having two such groups thereon may be selected from cyano and a carbonyl group of a ketone; ester or amide and the base may be selected from ammonia, organic amines, alkali metal hydroxides and alkali metal alkoxides.

The preparative reaction of the present invention may be summarized as follows:



Reaction I sequence above concerns the reaction between an isobenzofuroxan with a methylene-containing compound activated by electron withdrawing groups to provide a quinoxaline-di-N-oxide. Reaction sequence II above deals with the reaction between an isobenzofuroxan with primary and secondary nitro compounds. As is evident, the primary nitro compounds yield hydroxy benzimidazole-N-oxides whereas the secondary derivatives provide the benzimidazole-di-N-oxides.

With respect to said isobenzofuroxan, also known as benzofuroxan or benzofurazan-N-oxide, it is found that the substituted derivatives will work equally as well as isobenzofuroxan itself. For instance, X on the isobenzofuroxan structure above can be hydrogen and other simple substituents usually found on benzene rings, that is, alkyl, alkoxy, halo, X may be any non-interfering ring substituent and more than one substituent may be present. Thus, isobenzofuroxan or a substituted isobenzofuroxan may be employed in the process of the present invention.

Regarding the methylene-containing reagent in reaction sequence I, it can be either singly or doubly activated by electron withdrawing groups. In the case where it is activated by one electron withdrawing group, the molecule will be either a ketone which is aliphatic or alicyclic, substituted or unsubstituted, or an aldehyde, substituted or unsubstituted. It is obvious from inspection of the formula that R_2 is hydrogen when said compound is an aldehyde. Furthermore, it is possible and within the scope of this invention for R_1 and R_2 to be linked forming a cyclic structure. It must be kept in mind throughout that the subject process is a very fundamental one. Hence, when reference is made to such general terms as aldehydes and ketones, it is meant to

include any and all ketones and aldehydes. This, of course, includes aldehydes and ketones having substituted thereon any moiety which will not interfere with the overall reaction mechanism. In addition to substitution, there may be unsaturation in the carbon chain provided it meets the requirement cited above.

This characteristic of being a fundamental synthetic method applies equally when the methylene-containing compound is activated by two electron withdrawing groups. In fact, the only restriction on this reagent is that one of said electron withdrawing groups must have a carbon atom alpha to said methylene group capable of becoming part of the resulting six-membered di-N-oxide ring. For instance, one of said two electron withdrawing groups may be alkylsulfonyl or aminosulfonyl in combination with any other electron withdrawing group which is capable of providing the second part necessary for formation of the six-membered ring. Therefore, when said methylene-containing compound is doubly activated, typical examples would include β -ketoesters, β -diketones, malonic esters, malononitrile and combinations thereof such as nitrile-esters, β -ketoamides, ester-amides, cyano-amides, keto-sulfonyl compounds and ketosulfonamides.

In the preparation of these quinoxaline-di-N-oxides, particularly with the malonate reactants, a proportion of the corresponding quinoxaline compound is formed along with the quinoxaline-di-N-oxide. The compound of reduced form may be separated by conventional separation techniques, e.g., filtration of the reaction mixture, followed by recovery of the quinoxaline-di-N-oxide from the filtrate.

Reaction sequence II above describes the reaction between an isobenzofuroxan with a nitro compound as indicated. If the nitro compound is of the primary type, that is, where there is a CH_2 group alpha to the nitro group, then the resulting product is a 1-hydroxy-3-oxide illustrated by reaction II (a). Alternatively, if the nitro compound is of the secondary type, that is, where the adjacent methylene has only one hydrogen attached, the resulting product is a benzimidazole-1,3-di-N-oxide. Although the mechanisms involved in reaction sequences I and II are similar, in the latter there is a marked difference in the type of products obtained. As is evident, the quinoxaline-di-N-oxides contain a six-membered B ring whereas the benzimidazoles contain a five-membered B ring. With regard to the substituent R, it can be of any type, for instance, alkyl, alkenyl or alkynyl; it can be substituted, and it can represent a cyclic moiety. Once again, in keeping with the finding that the herein disclosed process is indeed a fundamental one, the term nitro compounds includes any and all such derivatives. Of course, once again the only requirement is that such a reagent must not compete in the overall reaction scheme.

As a necessary element of the herein disclosed novel process, the reaction sequences described above (I and II) must be effected in the presence of a base. Such a base is of a varied character. For instance, it is meant to include such bases as organic amines, ammonia, alkali metal hydroxides and alkali metal alkoxides. Once again, since the herein disclosed novel process is a fundamental one, the term base is typified by the above illustrated examples. However, there is no need to be restricted to this group. Furthermore, it has been found that it is more preferable to use certain bases for each of the possible methylene-containing compound reagents. For instance, it is found that when said methylene-containing compound is a ketone, that the preferred base to use is an organic amine or ammonia. Similarly, for aldehydes and the nitro compounds, the same bases are preferred. When said activated methylene-containing compound is a β -diketone or a β -ketoester, the preferred bases are alkali metal hydroxides and alkali metal alkoxides. When the reagent is a malonic ester the preferred base is an alkali metal alkoxide.

The amount of base used in any of the reactions discussed herein is not critical. That is to say, a catalytic amount of base in most instances will work as effectively or as efficiently as an equimolar amount. Of course, there will be instances where the preferred amount of base utilized will be more than a catalytic amount. Such a finding will derive solely from experimental determination.

As for the inclusion of a solvent in the basic process of this invention, this will not be a critical factor and its desirability will depend on many factors. For instance, if a sizable amount of liquid basic amine is used, there may not be any need to use a solvent. If, however, the reactants when combined produce a viscous system, it is highly desirable to include an appropriate solvent. For purposes of this invention, an appropriate solvent is any solvent which does not react in an undesired way with either the reactants or the final products. One of the advantages in including a solvent is that when certain reflux temperatures are desired, by choosing the appropriate solvent, the desired elevated reaction temperature can be attained.

With regard to the isolation of the desired products of this invention, it is found

in many instances that in the course of or upon completion of reaction the product precipitates out in crystalline form. In such cases, all that is required is filtration, washing and drying. If, on the other hand, the product does not completely precipitate or if it remains in solution, the reaction workup consists of evaporating the mixture almost to dryness and then filtering the product. If the sodium salt of the product forms, as it does on certain instances, the general procedure consists of filtering said salt, dissolving it in water, acidifying the solution and subsequently filtering the product which forms. All of the above techniques are well known to trained technicians working in the organic laboratory.

Chemical and physical evidence confirms the di-N-oxide structure of products obtained from reaction scheme I. For example, the infrared spectrum of the product of the reaction of dibenzoylmethane and isobenzofuroxan, assigned the structure 2-phenyl-3-benzoylquinoxaline-di-N-oxide, displayed strong bands at cm^{-1} 1670 (conjugated carbonyl), 1335 (N-oxide), 770 (orthosubstituted phenyl), and 690 (monosubstituted phenyl). Reduction with sodium dithionite gave a product identical (mixed melting point and infrared spectrum) with a sample of 2-phenyl-3-benzoylquinoxaline prepared according to the method of Brandt et al. Am. 688, 189 (1965).

The product from isobenzofuroxan and acetylacetone was assigned the structure 2-methyl-3-acetylquinoxaline-di-N-oxide. Its n.m.r. spectrum showed singlets at τ 7.55 (2H) and 7.34 (2H), and two multiplets centered at 2.24 (3H) and 1.52 (3H) respectively, and its infrared spectrum showed intense bands at cm^{-1} 1700 (carbonyl), 1330 (N-oxide), and 770 (ortho-substituted phenyl). These data are consistent with the assigned structure.

The following examples are provided by way of illustration and should not be interpreted as limiting the invention, many variations of which are possible without departing from the spirit or scope thereof.

EXAMPLE I

2-Methylquinoxaline-di-N-oxide

A mixture containing isobenzofuroxan (6.8 g., 0.05 moles), acetone (20 ml.) and acetonitrile (20 ml.) is heated to reflux and pyrrolidine (1.0 ml., 0.012 moles) is added and the resulting reaction mixture is refluxed for about 15 minutes and then allowed to cool. After sitting at room temperature overnight, the product which precipitates is filtered, washed and dried to give a 68% yield, M.P. 172—174°C.

EXAMPLE II

2,3-Dimethylquinoxaline-di-N-oxide

The procedure of Example I is repeated to prepare this product wherein methyl-ethyl ketone and morpholine are used in stoichiometric equivalent amounts, in place of acetone and pyrrolidine, respectively and similar results are obtained. The product is recrystallized from a chloroform-hexane (1:1) mixture, M.P. 190—192°C.

EXAMPLE III

2-Ethyl-3-methylquinoxaline-di-N-oxide

The procedure of Example I is repeated to prepare this product wherein 3-pentanone and morpholine are used, in stoichiometric equivalent amounts, in place of acetone and pyrrolidine, respectively, and similar results are obtained. The product is recrystallized from a chloroform-hexane (1:1) mixture, M.P. 143—146°C.

EXAMPLE IV

The procedure of Example I is repeated to prepare the following products wherein the listed reagents (ketone, base) are used in place of acetone and pyrrolidine, in stoichiometric equivalent amounts, to yield substantial amounts of products shown.

Ketone	Base	Product
heptanone-4	morpholine	2-ethyl-3-propylquinoxaline-di-N-oxide
hexanone-2	morpholine	2-methyl-3-propylquinoxaline-di-N-oxide

EXAMPLE V

1,2,3,4-Tetrahydrophenazine-5,10-dioxide

A mixture containing isobenzofuran (6.8 g., 0.05 moles), cyclohexanone (5.9 g., 0.06 moles), morpholine (4.3 g.) and benzene (300 ml.) is refluxed for two hours, allowed to cool and then evaporated almost to dryness. The solid material (product)

is triturated with an acetone-ether (1:1) mixture and then filtered to give 5.0 g. of product, M.P. 158—168°C. dec. Recrystallization from benzene gives product, M.P. 170—175°C. dec.

EXAMPLE VI

2,3-Dimethylenequinoxaline-di-N-oxide

The procedure of Example V is repeated to prepare the subject product wherein a stoichiometric equivalent amount of cyclobutanone is used in lieu of cyclohexanone and comparable results are obtained. Recrystallization from a chloroform-hexane (1:1) mixture gives a product, M.P. 213.5—214.5°C. dec.

Analysis: Calc'd. for $C_{10}H_8O_2N_2$: %C, 63.82; %H, 4.28; %N, 14.89
Found: %C, 63.85; %H, 4.29; %N, 14.86

EXAMPLE VII

2,3-Trimethylenequinoxaline-Di-N-oxide

The procedure of Example V is repeated to prepare the above product wherein a stoichiometric equivalent amount of cyclopentanone is used in place of cyclohexanone with comparable results. The product is recrystallized from a chloroform-hexane (1:1) mixture, M.P. 174—177°C.

EXAMPLE VIII

The procedure of Example V is repeated to prepare the products derived from the list of cyclic ketones shown below wherein a stoichiometric equivalent amount of each of said cyclic ketones is used in place of cyclohexanone and a stoichiometric equivalent amount of the amine shown is used in place of morpholine with comparable results.

	Product	Ketone	amine	Melting Point	
25	1-methyl-1,2,3,4-tetrahydro-phenazine-4,10-dioxide	α -methyl-cyclohexanone	morpholine	138—140°C.	25
30	2,3-decamethylenequinoxaline-di-N-oxide	cyclodecanone	morpholine	139.5—142°C.	30
	2,3-tridecamethylenequinoxaline-di-N-oxide	cyclopentadecanone	morpholine	—	
35	1,2,3,4-tetrahydro-1,4-methanophenazine-5,10-dioxide	Norcamphor	pyrrolidine	202—203°C	35

EXAMPLE IX

2-Hydroxymethyl-3-Methylquinoxaline-Di-N-Oxide

A mixture of isobenzofuroxan (0.1 moles), 4-hydroxy-2-butanone (0.15 moles), pyrrolidine (0.025 moles) and dimethylformamide (20 moles) is stirred at room temperature for about 2—3 hours. The solid which precipitates is filtered off, washed with acetonitrile and dried to provide 11 g. (54%) of product, M.P. 180—183°C.

EXAMPLE X

2-Carboethoxymethyl-3-Methylquinoxaline-Di-N-Oxide

A mixture of isobenzofuroxan (0.01 moles) ethyl laevulinate (0.1 moles), morpholine (8.7 g.) and chloroform (50 ml.) is refluxed for about 4 hours. The resulting mixture is then evaporated almost to dryness and filtered. The solid precipitate is recrystallized from acetone-hexane (1:1) to give good yield of product, M.P. 150—152°C.

Analysis: Calc'd. for $C_{13}H_{14}N_2O_4$: %C, 59.56; %H, 5.35; %N, 10.67
Found: %C, 59.61; %H, 5.46; %N, 10.72

EXAMPLE XI

A. 2-Phenyl-3-benzoylquinoxaline-di-N-oxide.

Benzofuroxan (3.4 g.) and dibenzoylmethane (5.6 g.) were dissolved in warm triethylamine (25 ml.) and allowed to stand at room temperature for 24 hours. The

resulting yellow precipitate was thinned with triethylamine and collected by filtration. The filtrate was allowed to stand for 30 hours, and a second crop of crystals collected. The total yield of 2-phenyl-3-benzoylquinoxaline-di-N-oxide was 3.6 g. or 42% of the theoretical. Recrystallization from methanol gave thin yellow needles melting at 234°C.

Infrared: 1670, 1335, 1250, 1090, 900, 870, 770, 690 cm^{-1} .

Analysis: Calc'd. for $\text{C}_{21}\text{H}_{14}\text{N}_2\text{O}_3$: C, 73.67; H, 7.12; N, 8.18.

Found: C, 73.88; H, 4.06; N, 8.36.

Melting points of most di-N-oxides vary slightly with the rate of heating and are uncorrected. Infrared spectra were run in Nujol mulls on a Perkin-Elmer Model No. 137 spectrophotometer.

B. 2-Phenyl-3-benzoylquinoxaline (included to assist in confirming the structure of Example XI A.)

2-Phenyl-3-benzoylquinoxaline-di-N-oxide (0.5 g.) was dissolved in hot methanol (150 ml.). The solution was cooled to room temperature and concentrated hydrochloric acid added (1 ml.). A solution of sodium dithionite (1 g. in 5 ml. of warm water) was added slowly to the stirred solution. A black coloration developed and disappeared to give a colorless solution. Water was added (200 ml.) and the solution was stirred for ten minutes. The resulting yellowish solid was collected, washed with water, and recrystallized from methanol after charcoal treatment to give 0.42 g. of shiny prisms melting at 150°C.

Infrared: 1670, 1018, 925, 770, 740, 715, 700, 690 cm^{-1} .

The product was identical (mixture melting point and superimposable infrared spectra) with an authentic sample of 2-phenyl-3-benzoylquinoxaline.

C. 2-Phenylquinoxaline-di-N-oxide.

2-Phenyl-3-benzylquinoxaline-di-N-oxide (1 g.) was suspended in 2% methanolic potassium hydroxide (45 ml.). The mixture was heated until the solid dissolved and then cooled with stirring. The resultant precipitate was collected and washed thoroughly with methanol. The yield was 0.65 g. of 2-phenylquinoxaline-di-N-oxide as yellow needles melting at 205–206°C. This compound has been reported by J. K. Landquist, J. Chem. Soc., 2822 (1953).

The mother liquor was allowed to stand overnight and filtered. The filtrate was acidified with dilute hydrochloric acid and extracted with water. The ether extract was dried and evaporated to leave 0.2 g. of benzoic acid as the residue.

EXAMPLE XII

2-Methyl-3-acetylquinoxaline-di-N-oxide

Benzofuroxan (5.4 g.) and acetylacetone (4.5 g.) were dissolved in triethylamine (10 ml.), and the solution allowed to stand at room temperature for 18 hours. The yellow precipitate was collected, washed with chilled methanol, and dried to afford 5.45 g. of product. The mother liquor, after standing overnight, gave a second crop of product. The total yield of 2-methyl-3-acetylquinoxaline-di-N-oxide melting at 152°C. was 6.88 g. or 78%. Recrystallization from methanol raised the melting point to 153–154°C.

The n.m.r. spectrum showed singlets at τ 7.55 (3H) and 7.34 (3H), and multiplets centered at 2.24 (2H) and 1.52 (2H) in deuterated chloroform with TMS as internal reference set at 10 (Varian A-60 spectrometer).

Infrared: 1700, 1510, 1330, 1270, 1100, 1050, 830, 770 cm^{-1} .

Analysis: Calc'd. for $\text{C}_{11}\text{H}_{10}\text{O}_3\text{N}_2$: C, 60.54; H, 4.62; N, 12.84.

Found: C, 60.48; H, 4.70; N, 12.33.

EXAMPLE XIII

2-Methyl-3-carboethoxyquinoxaline-di-N-oxide

A solution of benzofuroxan (3.4 g.) and ethylacetoacetate (3.3 g.) in triethylamine (25 ml.) was allowed to stand at room temperature for 30 hours. The mother liquor was decanted and the resultant solid washed with water and recrystallized from acetone-water. The yield was 1.1 g. of yellow prisms melting at 132–133°C. Another crop of product was obtained from the mother liquor after 18 hours. The total yield of 2-methyl-3-carboethoxyquinoxaline-di-N-oxide melting at 132–133°C. was 1.4 g. or 22%.

Infrared: 1730, 1510, 1330, 1275, 1240, 1050, 1010—1000, 770 cm^{-1} .

Analysis: Calc'd. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_4$: C, 58.06; H, 4.87; N, 11.29.
Found: C, 58.27; H, 4.74; N, 10.98.

EXAMPLE XIV

Quinoxaline-Di-N-Oxide

A mixture of isobenzofuroxan (2.5 g.), acetaldehyde (2.5 ml.) and triethylamine (20 ml.) is allowed to stand at room temperature for 24 hours. The solid material which precipitates is filtered and dried to give product, M.P. 223—224°C. dec.

EXAMPLE XV

2-Methylquinoxaline-Di-N-Oxide

A mixture of isobenzofuroxan (8.7 g.), propionaldehyde (13.6 g.) and diethylamine (60 ml.) is allowed to stand at room temperature for 24 hours. The solid material which precipitates is filtered and dried to give 8.0 g. of product. Recrystallization from a chloroform-acetone (1:1) mixture gives product having a M.P. 176—178°C.

EXAMPLE XVI

The procedure of Example XV is repeated wherein stoichiometric equivalent amounts of butyraldehyde and valeraldehyde are used in lieu of propionaldehyde and corresponding products, 2-ethylquinoxaline-di-N-oxide and 2-propylquinoxaline-di-N-oxide, respectively, are obtained in good yields.

EXAMPLE XVII

1-Hydroxybenzimidazole-3-Oxide

To a mixture containing nitromethane (7.4 g., 0.12 moles), isobenzofuroxan (13.6 g., 0.10 moles) and tetrahydrofuran (50 ml.) is slowly added dimethyl pyrimidine (11.3 g.) dropwise. The heat of reaction causes the reaction temperature to rise sharply, therefore, an ice-bath is used to maintain a steady rate of reflux. Upon completion of addition, the resulting mixture is allowed to cool to room temperature whereupon the solid product which precipitates is filtered, washed with water, dried and recrystallized from a $\text{MeOH}:\text{NaOCH}_3$ mixture which is subsequently acidified. The crystalline product has a M.P. 213°C. dec.

Analysis: Calc'd. for $\text{C}_7\text{H}_6\text{O}_2\text{N}_2$: %C, 56.00; %H, 4.03; %N, 18.66.

Found: %C, 56.13; %H, 4.06; %N, 18.77.

EXAMPLE XVIII

1-Hydroxy-2-Methylbenzimidazole-3-Oxide

To a mixture containing nitroethane (9.0 g., 0.12 moles), isobenzofuroxan (13.6 g., 0.10 moles) and tetrahydrofuran (50 ml.) is added dropwise diethylamine (8.7 g., 0.12 moles). The reaction temperature rises almost to reflux upon addition. Upon completion, the mixture is allowed to cool and then set overnight.

The solid product which precipitates is filtered, washed with tetrahydrofuran and then dried. The filter cake is recrystallized from acetic acid to give 9.6 g. (45%) of product, M.P. 204—205°C. dec.

Analysis: Calc'd. for $\text{C}_8\text{H}_8\text{O}_2\text{N}_2$: %C, 58.53; %H, 4.91; %N, 17.07.

Found: %C, 58.38; %H, 4.95; %N, 16.70.

EXAMPLE XIX

1-Hydroxy-2-Ethylbenzimidazole-3-Oxide

To a mixture containing 1-nitropropane (10.7 g., 0.12 moles), isobenzofuroxan 13.6 g. (0.10 moles) and tetrahydrofuran (50 ml.) is added dropwise diethylamine (8.7 g., 0.12 moles). The reaction temperature rises almost to reflux on addition of amine. Upon completion, the mixture is allowed to cool and then sit overnight.

The solid product which precipitates is filtered, washed with tetrahydrofuran and then dried. The dried filter cake is recrystallized from acetic acid to give 10.95 g. (49%) of product, m.p. 194—196°C. dec.

Analysis: Calc'd. for $\text{C}_9\text{H}_{10}\text{O}_2\text{N}_2$: %C, 60.66; %H, 5.66; %N, 15.72.

Found: %C, 60.46; %H, 5.70; %N, 15.91.

EXAMPLE XX

1-Hydroxy-2-Propylbenzimidazole-3-Oxide

The procedure of Example XIX is repeated for the preparation of the subject compound wherein a stoichiometric equivalent amount of 1-nitrobutane is used in place of 1-nitropropane with comparative results.

EXAMPLE XXI

1-Hydroxy-2-Benzimidazole Propionamide-3-Oxide

To a mixture containing gamma nitro butyric acid amide (15.8 g., 0.12 moles), isobenzofuroxan (13.6 g., 0.10 moles) and dimethyl formamide (75 ml.) is added dropwise diethylamine (8.7 g., 0.12 moles). The reaction temperature rises and is maintained at 55°C. with an ice-bath. Upon completion of addition, the mixture is allowed to cool and then sit overnight.

The solid product is filtered and a second crop is obtained by adding acetone to the filtrate. The two crops are combined, washed, dried and recrystallized from an acetone-acetic acid (1:1) mixture to give 12.5 g. (43%) of product, m.p. 215°C. dec.

Analysis: Calc'd. for $C_{10}H_{11}O_3N_3$: %C, 54.29; %H, 5.01; %N, 19.00.
Found: %C, 54.56; %H, 5.09; %N, 19.00.

EXAMPLE XXII

1-Hydroxy-2-Carboethoxybenzimidazole-3-Oxide

A solution containing ethyl nitro acetate (4.22 g., 0.0317 moles), tetrahydrofuran (5 ml.) and triethylamine (5 ml.) is added to a solution of isobenzofuroxan (4.30 g., 0.0317 moles) in tetrahydrofuran (10 ml.) containing 10 ml. of triethylamine. Upon completion of addition, the reaction mixture was allowed to sit at room temperature for about 4 hours whereupon the yellow precipitated solid is filtered, washed and dried. Recrystallization from ether/acetone gives 1.1 g. (13%) of product, m.p. 154.5°C—156.5°C. dec.

Analysis: Calc'd. for $C_{10}H_{10}O_4N_2$: %C, 54.05; %H, 4.54; %N, 12.61.
Found: %C, 54.03; %H, 4.46; %N, 12.60.

EXAMPLE XXIII

2,2-Dimethyl-2H-Benzimidazole-1,3-Dioxide

To a mixture containing 2-nitropropane (10.7 g., 0.12 moles), isobenzofuroxan (13.6 g., 0.10 moles) and tetrahydrofuran (50 ml.) is added dropwise diethylamine (8.7 g., 0.12 moles). The reaction temperature rises during addition. Upon completion of addition, the reaction mixture is allowed to sit overnight at room temperature.

The solid product which precipitates is filtered, washed and dried to give 8.0 g. (33%) of product, m.p. 132—134°C. dec.

Analysis: Calc'd. for $C_9H_{10}O_2N_2$: %C, 60.66; %H, 5.66; %N, 15.72.
Found: %C, 60.67; %H, 5.64; %N, 15.98.

EXAMPLE XXIV

2,2-Methyl, Ethyl-2H-Benzimidazole-1,3-Dioxide

To a mixture containing 2-nitrobutane (6.2 g., 0.06 moles), isobenzofuroxan (6.8 g., 0.05 moles) and tetrahydrofuran (25 ml.) is added dropwise diethylamine (4.4 g., 0.06 moles). The reaction is exothermic. Upon completion of addition, the reaction mixture is allowed to sit for about 4 hours at room temperature. The resulting solution is evaporated almost to dryness, the solids filtered, washed, dried and recrystallized from an acetone/hexane mixture to give a good yield of product.

EXAMPLE XXV

2,2-Pentamethylene-2H-Benzimidazole-1,3-Dioxide

To a mixture containing nitrocyclohexane (15.5 g., 0.12 moles) isobenzofuroxan (13.6 g., 0.10 moles) and tetrahydrofuran (50 ml.) is added dropwise 1,5-diazabicyclo-[4,3,0]-5-nonane (0.10 moles). The reaction is exothermic and is cooled with an ice-bath to prevent temperature above 50°C.

Upon completion the reaction mixture is cooled and the filtrate allowed to sit overnight. After this time the filtrate is filtered again and then evaporated almost to dryness. The oil crystallizes on standing and is filtered, washed and dried to give a good yield of product, m.p. 112°—115°C.

Analysis: Calc'd. for $C_{12}H_{14}O_2N_2$: %C, 66.03; %H, 6.47; %N, 12.84.
Found: %C, 65.95; %H, 6.59; %N, 12.95.

EXAMPLE XXVI

2-Cyano-3-Aminoquinoxaline-Di-N-Oxide

A mixture of malononitrile (20.0 g., 0.3 moles), isobenzofuroxan (34.0 g., 0.25 moles), triethylamine (10 ml.) and tetrahydrofuran (200 ml.) is stirred at room temperature. After approximately 30 minutes, the reaction mixture becomes violently exothermic and must be controlled with an ice-bath. After a while the ice-bath is removed and the mixture allowed to stand for about 24 hours. The material which precipitates is filtered and dried. Recrystallization from methanol gives product, M.P. 239°C. dec.

Analysis Calc'd. for $C_8H_6O_2N_4$: %C, 53.46; %H, 2.99; %N, 27.72.
Found: %C, 53.52; %H, 3.47; %N, 27.42.

EXAMPLE XXVII

2-Carbomethoxymethyl-3-Carbomethoxyquinoxaline-Di-N-Oxide

A mixture of isobenzofuroxan (13.6 g.) dimethylacetonedicarboxylate (50 ml.) and morpholine (5 ml.) is allowed to stir for about 2—3 hours (exothermic) and is then thinned out by adding 200 ml. of benzene. The material which precipitates is filtered, dried and recrystallized from acetonitrile, M.P. 152.5—153.5°C.

Analysis: Calc'd. for $C_{13}H_{12}O_6N_2$: %C, 53.42; %H, 4.14; %N, 9.59.
Found: %C, 53.37; %H, 4.27; %N, 9.74.

EXAMPLE XXVIII

2-(2'-Pyrrolidylethylene)Quinoxaline-Di-N-Oxide

A solution of isobenzofuroxan (13.6 g., 0.1 mole) and 2-keto-4-dimethoxybutane (13.2 g., 0.1 mole) in tetrahydrofuran (150 ml.) is treated with pyrrolidine (14.2 g., 0.2 mole) and the reaction mixture is allowed to stand for 3 days at room temperature. It is then poured over excess crushed ice and the product extracted with chloroform. The extract is stripped of chloroform and the resulting crude product purified by recrystallization from chloroform-hexane.

EXAMPLE XXIX

2-N-Phenylcarbamyl-3-Methylquinoxaline-Di-N-Oxide

A mixture of isobenzofuroxan (13.6 g.), acetoacetanilide (17.7 g.), morpholine (10 ml.) and tetrahydrofuran (100 ml.) is allowed to stand for about 2 hours. The material which precipitates is filtered, dried and recrystallized from a chloroform-methanol (1:1) mixture, M.P. 226—227°C. dec.

Analysis: Calc'd. for $C_{18}H_{13}O_3N_3$: %C, 65.08; %H, 4.44; %N, 14.23.
Found: %C, 65.01; %H, 4.58; %N, 14.14.

EXAMPLE XXX

2-N-(p-Methylphenyl)carbamyl-3-Methylquinoxaline-Di-N-Oxide

The procedure of Example XXIX is repeated except a stoichiometric equivalent amount of *p*-acetoacetotoluidide is used in place of acetoacetanilide. Good yields of product are obtained, M.P. 196—198°C.

Analysis: Calc'd for $C_{17}H_{15}O_3N_3$: %C, 66.01; %H, 4.89; %N, 13.59.
Found: %C, 66.24; %H, 4.89; %N, 13.40.

EXAMPLE XXXI

2-N-(o-Methoxyphenyl)carbamoyl-3-Methylquinoxaline-Di-N-Oxide

The procedure of Example XXIX is repeated except a stoichiometric equivalent amount of *o*-acetoacetanisidide is used instead of acetoacetanilide. Good yields of product are obtained, M.P. 197—199°C.

Analysis: Calc'd for $C_{17}H_{13}O_4N_3$: %C, 62.76; %H, 4.65; %N, 12.92.
Found: %C, 62.93; %H, 4.66; %N, 12.68.

EXAMPLE XXXII

2-N-Cyclohexylcarbonyl-3-Methylquinoxaline-Di-N-Oxide

The procedure of Example XXIX is repeated except a stoichiometric equivalent amount of acetoacetocyclohexylamide is used in place of acetoacetanilide. Substantial yields of product are obtained, M.P. 204.5—206°C.

Analysis: Calc'd for $C_{15}H_{18}O_3N_2$: %C, 63.98; %H, 6.04; %N, 13.99
Found: %C, 63.68; %H, 6.49; %N, 13.93.

EXAMPLE XXXIII

2-[-N-2-(6-Ethoxybenzothiazole)carbonyl]-3-Methylquinoxaline-Di-N-Oxide

The procedure of Example XXIX is repeated except a stoichiometric equivalent amount of 2-acetoacetamido-6-ethoxybenzothiazole is used in place of acetoacetanilide. Substantial yields of product are obtained, M.P. 235—237°C. dec.

Analysis:

Calc'd for $C_{19}H_{18}O_5N_2S$: %C, 57.60; %H, 4.07; %N, 14.14; %S, 8.08
Found: %C, 57.67; %H, 4.19; %N, 14.20; %S, 8.07

EXAMPLE XXXIV

2-N-(*t*-butyl)carbonyl-3-Methylquinoxaline-Di-N-Oxide

The procedure of Example XXIX is repeated except a stoichiometric equivalent amount of N-*t*-butylacetoacetamide is used in lieu of acetoacetanilide. Substantial yields of product are obtained, M.P. 224.5—225.5°C. dec.

Analysis: Calc'd. for $C_{14}H_{17}O_3N_2$: %C, 61.08; %H, 6.22; %N, 15.26
Found: %C, 60.84; %H, 6.30; %N, 15.10.

EXAMPLE XXXV

2-N-Piperidinocarbonyl-3-Methylquinoxaline-Di-N-Oxide

The procedure of Example XXIX is repeated wherein stoichiometric equivalent amounts of acetoacetopiperidide and piperidine are used in place of acetoacetanilide and morpholine, respectively, and substantial yields of product are obtained, M.P. 174—176°C.

Analysis: Calc'd for $C_{15}H_{17}O_3N_2$: %C, 62.70; %H, 5.96; %N, 14.63
Found: %C, 62.92; %H, 6.13; %N, 14.41.

EXAMPLE XXXVI

2-Methyl-3-Carboethoxyquinoxaline-Di-N-Oxide

Sodium metal pellets (2.3 g., 0.1 moles) are dissolved in 800 ml. of ethanol. To this resulting sodium ethoxide solution is added ethylacetoacetate (13.4 g., 0.1 moles) and then isobenzofuroxan (13.6 g., 0.1 moles) and the mixture is allowed to stand overnight. The material which precipitates is filtered, dried and recrystallized from ethanol to give good yields of product, M.P. 133—134°C.

Analysis: Calc'd. for $C_{12}H_{12}N_2O_4$: %C, 58.06; %H, 4.87; %N, 11.29
Found: %C, 58.15; %H, 4.84; %N, 11.16.

This product is the same as that prepared by the method of Example XIII.

This procedure of Example XXXVI is repeated wherein a stoichiometric equivalent amount of potassium hydroxide is used in place of sodium ethoxide with comparable results.

EXAMPLE XXXVII

2-Carbomethoxy-3-Hydroxyquinoxaline-Di-N-Oxide

A mixture of dimethylmalonate (14.5 g., 0.11 mole), isobenzofuroxan (13.6 g., 0.1 mole), sodium methoxide (5.4 g., 0.1 mole) and methanol (300 ml.) is allowed to stand overnight. The precipitated sodium salt of 2-carbomethoxy-3-hydroxyquinoxaline is separated by filtration and the product is isolated by acidification of the filtrate with 2N hydrochloric acid followed by extraction with chloroform. Evaporation of the solvent from the extract yields the crude product, which is purified by crystallization from chloroform-hexane.

EXAMPLE XXXVIII

2-Carboethoxy-3-Hydroxyquinoxaline-Di-N-Oxide

This product is prepared in the same manner as that of the preceding example, substituting sodium ethoxide in ethanol for the sodium methoxide in methanol and diethylmalonate for dimethylmalonate.

EXAMPLE XXXIX

2-Formyl-Quinoxaline-Di-N-Oxide

Method A

13.6 g. isobenzofuroxan (0.1 mole) 11.8 g. pyruvaldehyde dimethylacetal (0.1 mole) 100 ml. acetonitrile.

To the above mixture is added 0.05 mole pyrrolidine and the reaction mixture is allowed to stand overnight at room temperature. The solvent is stripped *in vacuo* and the residue is dissolved in 25 ml. conc. hydrochloric acid. The solution is diluted with water and extracted with chloroform. The extract is stripped of chloroform to obtain crude 2-formylquinoxaline-di-N-oxide, which is purified by crystallization from chloroform-hexane.

Method B

The reaction procedure of Method A is repeated, substituting 21.8 g. γ,γ -diethoxy ethylacetoacetate (0.1 mole) for the pyruvaldehyde dimethylacetal. After standing overnight at room temperature, the reaction mixture is stripped *in vacuo* and the concentrate is heated on the steam-bath for 15–30 minutes, cooled, and diluted with water. The product is recovered and purified as before by chloroform extraction and chloroform-hexane crystallization.

Method C

The reaction procedure of Method B is repeated, substituting 0.1 mole sodium ethoxide for the pyrrolidine, and substituting ethanol for the acetonitrile reaction medium. The reaction mixture is heated at reflux temperature for 3 hours and concentrated *in vacuo*. The residue is dissolved in 50 ml. concentrated hydrochloric acid, heated 15–30 minutes on the steam-bath, cooled and diluted with water. Chloroform extraction and chloroform-hexane crystallization as before yields the product.

EXAMPLE XL

2,3,5-Trimethylquinoxaline-Di-N-Oxide

A mixture of 5-methylisobenzofuroxan (1.5 g., 0.01 moles), methyl ethyl ketone (7 ml.) and pyrrolidine (2 drops) is stirred at room temperature overnight. The product which precipitates is filtered and recrystallized from an acetone-methanol (1:1) mixture, M.P. 193–194°C.

Analysis: Calc'd. for $C_{11}H_{12}N_2O_2$: %C, 64.69; %H, 5.93; %N, 13.72
Found: %C, 64.77; %H, 5.78; %N, 13.69.

EXAMPLE XLI

2,3-Dimethyl, 5-Methoxyquinoxaline-Di-N-Oxide

The procedure of Example XL is repeated wherein a stoichiometric equivalent amount of 5-methoxy-isobenzofuroxan is used in lieu of 5-methylisobenzofuroxan with comparable results. The product is recrystallized from an acetone-methanol (1:1) mixture, M.P. 209–210°C. dec.

Analysis: Calc'd for $C_{11}H_{12}N_2O_3$: %C, 59.99; %H, 5.49; %N, 12.72
Found: %C, 60.38; %H, 5.51; %N, 12.63.

EXAMPLE XLII

2-Acetyl-3-Methyl-5-Methoxyquinoxaline-Di-N-Oxide

5-Methoxy-isobenzofuroxan (8.3 g., 0.05 mole) and 2,4-pentanedione (5 g., 0.05 mole) are added to 100 ml. of a 0.5 molar solution of sodium methoxide in methanol and the mixture is heated at reflux temperature for 3 hours. After cooling in an ice-salt bath, the reaction mixture is filtered to recover the product.

EXAMPLE XLIII

2-Acetyl-3,4-Dimethylquinoxaline-Di-N-Oxide

The procedure of Example XLII is repeated with substitution of 7.5 g. (0.05

mole) of 4-methylisobenzofuroxan for the 5-methoxy-isobenzofuroxan, and the product is recovered as before.

EXAMPLE XLIV

2-Acetyl-3,5,6-Trimethylquinoxaline-Di-N-Oxide

The procedure of Examples XLII is repeated, this time substituting 8.2 g. (0.05 mole) of 5,6-dimethylisobenzofuroxan for the isobenzofuroxan of that example and the product is recovered as before.

EXAMPLE XLV

6-Acetyl-1,2,3,4-Tetrahydrophenazine-Di-N-Oxide

A mixture containing 5-acetylisobenzofuroxan (8.2 g., 0.05 mole) cyclohexanone (5.9 g., 0.06 mole), morpholine (4.3 g.) in 300 ml. benzene is refluxed for two hours, allowed to cool and then evaporated almost to dryness. The solid product is triturated with 1:1 acetone:ether and the purified solid product recovered by filtration.

EXAMPLE XLVI

6-Chloro-1,2,3,4-Tetrahydrophenazine-Di-N-Oxide

This product is prepared by the procedure of Example XLV with substitution of 8.6 g. (0.05 mole) of 5-chloro-isobenzofuroxan for the 5-acetyl-isobenzofuroxan of that example and the product is recovered as before.

EXAMPLE XLVII

2-Carbethoxy-3-formyldiethylacetal-quinoxaline-di-N-oxide

Ethyl-γ-diethoxyacetoacetate (10.8 g., 0.05 mole) and isobenzofuroxan (6.8 g., 0.05 mole) are added to 50 ml. of a 0.005 molar solution of sodium ethoxide in ethanol, with stirring under nitrogen. The reaction mixture is stirred for three hours at room temperature and then heated at reflux temperature for three additional hours. After cooling to room temperature, the reaction mixture is stirred overnight and concentrated on the steam bath to a viscous oil. Upon cooling, the oil solidifies and the resulting solid is slurried with ethanol, broken up, and the purified solid recovered by filtration. 9.8 Grams of yellow solid are obtained and purified by crystallization from acetone-hexane, with activated carbon treatment, to yield 8.3 grams, melting at 120—123°C. Recrystallization from acetone-hexane gives 7.19 grams, melting at 120.5—123.5°C. Analysis, calculated for $C_{16}H_{20}O_6N_2$: carbon, 57.14; hydrogen, 5.95; and nitrogen, 8.33%; found: carbon, 57.38; hydrogen, 6.06; and nitrogen 8.35%.

EXAMPLE XLVIII

2-Methyl-Quinoxaline-di-N-oxide

Method A

The mixture employed in Method A is again prepared, this time substituting for the propylamine 6.21 grams of 1,5-diazo-bicyclo[4.3.0]-5-nonene (0.05 mole). This mixture is stirred overnight at room temperature and the resulting yellow solid is separated by filtration, washed with ether and dried to yield 1.12 gram of product, melting at 135—143°C. It is further purified by recrystallization from chloroform-hexane.

Method B

A mixture of isobenzofuroxan and propionaldehyde in tetrahydrofuran in the same proportions as before is treated with 3.24 ml. ammonium hydroxide (29.5% NH_3) and stirred at room temperature for 4 1/2 days. The resulting slurry is filtered to yield 1.55 gram of product melting at 163—165°C.

EXAMPLE XLIX

2-Formyl-dimethylacetal-quinoxaline-di-N-oxide

A series of preparations is conducted, in each case dissolving isobenzofuroxan (13.6 g., 0.1 mole) and pyruvaldehyde dimethylacetal (11.8 g., 0.1 mole) in the indicated volume of solvent, with addition of base as indicated in the table below. Where ammonia gas is the chosen base, it is introduced into the solution through a dispersion tube over a 10 minute period. Where pyrrolidine is the base selected, 2 ml. are added to the solution. In each run, the reaction mixture is permitted to stand overnight at room temperature and the product then recovered by evaporation under

vacuum to dryness followed by ether trituration and separation of the resulting solid product by filtration. The individual runs are summarized in the table.

	Solvent	Base	Yield % of Theory	Product Melt Point	
5	1. 50 ml. chloroform	pyrrolidine	61%	128—130°C.	5
	2. 100 ml. diethyl ether	"	71%	140—141°C.	
	3. 100 ml. methanol	"	39%	128—134°C.	
	4. 50 ml. tetrahydrofuran	"	51%	127—131°C.	
	5. 50 ml. acetonitrile	"	68%	120—128°C.	

- 10 The product of run 2, above, is recrystallized from benzene to yield a purified sample melting at 142—143°C. Analysis, calculated for $C_{11}H_{12}N_2O_4$: carbon, 55.93; hydrogen, 5.12; nitrogen, 11.86 and oxygen, 27.09%; found: carbon, 56.22; hydrogen, 5.15 and nitrogen, 11.78%. 10

EXAMPLE L

- 15 2-Methyl-3-(2'-pyrrolidyl)-n-propyl-quinoxaline-di-N-oxide 15
- To a solution of isobenzofuroxan (6.8 g., 0.05 mole) and allylacetone (4.9 g., 0.05 mole) in 100 ml. tetrahydrofuran is added 7.1 g. pyrrolidine with cooling in an ice bath. The reaction mixture is stirred overnight at room temperature and concentrated to remove the tetrahydrofuran. The resulting concentrate is fractionated by chromatography in benzene on a 30×4 cm. cylindrical column of "Florisil" 20 Registered Trade Mark (an activated magnesium silicate available from the Floridin Co., of Tallahassee, Florida). The chromatogram is developed with benzene, as 150—200 ml. effluent fractions are collected. Each fraction is evaporated and the product residues are selected on the basis of ultraviolet absorption in methanol solution (those having $\lambda_{max}=378\text{ m}\mu$). The product fractions are combined and purified by re-crystallization from ether to yield 297 mg. of product melting at 99—101°C. Analysis, 25 calculated for $C_{16}H_{21}O_2N_3$: carbon, 66.87; hydrogen, 7.37 and nitrogen, 14.62%; found: carbon, 66.83; hydrogen, 7.29 and nitrogen, 14.48%. 25

EXAMPLE LI

- 30 2-(2'-diethylaminoethylene)-quinoxaline-di-N-oxide 30
- A solution of isobenzofuroxan (1.36 g., 0.01 mole), crotonaldehyde (2.0 g.) and diethylamine (3.0 g.) in 20 ml. tetrahydrofuran is stirred at room temperature overnight. The resulting slurry is filtered to recover 650 mg. of orange-red solid, which is purified by recrystallization from chloroform-hexane. The resulting 0.5 g. of product melts at 188—190.5°C. with decomposition. Analysis, calculated for $C_{14}H_{17}O_2N_3$: 35 carbon, 64.86; hydrogen 6.56 and nitrogen, 16.22%; found: carbon, 64.67; hydrogen, 6.99 and nitrogen, 16.11%. 35

EXAMPLE LII

- 40 2-Methyl-3-cyclopentyl-quinoxaline-di-N-oxide 40
- A mixture of cyclopentyl acetone (12.6 g., 0.1 mole), isobenzofuroxan (13.6 g., 0.1 mole) and pyrrolidine (1.57 g., 0.025 mole) in 100 ml. tetrahydrofuran is stirred at room temperature overnight. The reaction mixture is then combined with an equal volume of 2N hydrochloric acid and extracted with chloroform. The chloroform extract is dried over anhydrous sodium sulfate, treated with activated carbon and filtered. The filtrate is evaporated to dryness and the resulting solid residue 45 is triturated with ether and the slurry filtered. The resulting 4 grams of yellow-green solid is dissolved in chloroform and treated with activated carbon. The slurry is filtered and the filtrate crystallized by addition of chloroform-hexane. 2.73 Grams of dark yellow crystalline solid melting at 156—158°C. is separated by filtration. Analysis, calculated for $C_{14}H_{16}O_2N_2$: carbon, 68.83; hydrogen, 6.60 and nitrogen 50 11.47%; found: carbon, 68.91; hydrogen, 6.50 and nitrogen, 11.26%. 50

EXAMPLE LIII

- 55 2-Carboethoxy-1,2,3,4-tetrahydrophenazine-quinoxaline-di-N-oxide 55
- To a solution of isobenzofuroxan (13.6 g., 0.1 mole) and 4-carboethoxy cyclohexanone (15 g.) in 100 ml. acetonitrile is added 2 ml. pyrrolidine. After about 15 minutes, an exothermic reaction ensues. The reaction mixture is stored overnight at room temperature and evaporated under vacuum to a semi-solid, which is triturated with ether to yield 8.55 grams of solid product melting at 140—150°C. Purification by recrystallization gives a product melting at 156—160°C.

EXAMPLE LIV

2-Acetyl-3-Methyl-6-Trifluoromethylquinoxaline-Di-N-Oxide and
2-Acetyl-3-Methyl-7-Trifluoromethylquinoxaline-Di-N-Oxide

A. A solution of 20.4 grams (0.1 mole) of 5-trifluoromethylisobenzofuroxan, 12.0 grams (0.12 moles) of 2,4-pentanedione, 100 ml. of anhydrous ethanol and 1.0 ml. of 10N sodium hydroxide is stirred and a spontaneous temperature rise to 46° is observed initially. After a few hours the temperature drops to 25°C. After stirring overnight at room temperature the reaction mixture is evaporated under reduced pressure and the oily residue is triturated under ether. After cooling in an ice-bath crystals are slowly formed; yield 5.3 grams, M.P. 137—140°C. This product is recrystallized from 2-propanol to afford 1.8 grams of material, M.P. 153—154°C. A further recrystallization from chloroform/hexane afforded 0.7 grams of 2-acetyl-3-methyl-6-trifluoromethylquinoxaline-di-N-oxide, M.P. 167—168°C.

Anal. Calc'd. for $C_{12}H_9F_3N_2O_3$: %C, 50.35; %H, 3.17; %N, 9.79
Found: %C, 50.52; %H, 3.16; %N, 9.66.

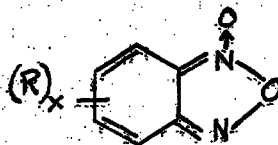
From the initial ether filtrate a second crude product is obtained, Yield: 6.5 grams, M.P. 117—121°C. This is recrystallized three times from 2-propanol to furnish pure 2-acetyl-3-methyl-7-trifluoromethylquinoxaline-di-N-oxide, Yield: 1.5 grams, M.P. 152—153°C. Mixed melting points of the isomeric trifluoromethyl compounds is 141—142°C.

Anal. Calc'd. for $C_{12}H_9F_3N_2O_3$: %C, 50.35; %H, 3.17; %N, 9.79
Found: %C, 50.56; %H, 3.30; %N, 9.80

B. Preparation of 5-Trifluoromethylisobenzofuroxan Starting Material

A solution of 103 grams (0.5 moles) of 4-amino-3-nitro-benzotrifluoride, 750 ml. of acetic acid and 385 ml. of concentrated sulfuric acid is cooled in an ice-bath with sufficient stirring. Sodium nitrite (38 grams, 0.55 moles) is added portionwise at such a rate that the reaction temperature does not exceed 5°C. After addition is complete, 38 grams of urea is added, and with vigorous stirring 32.5 grams of sodium azide is then added. Stirring is continued for 20 minutes, then the reaction mixture is poured into 4 liters of ice and water. The crude product, 4-azido-3-nitrobenzotrifluoride is extracted from the aqueous mixture with chloroform. The extract is dried over anhydrous sulfate, filtered and evaporated under reduced pressure to furnish an oily residue which is taken up 800 ml. of toluene. The toluene solution is heated under reflux for 18 hours behind a shatter-proof shield. After cooling to room temperature, the solvent is evaporated and the residue is distilled under reduced pressure. The fraction boiling at 105—108° (16 ml.) is considered to be sufficiently pure 5-trifluoromethylisobenzofuroxan: Yield 62.3 (61%).

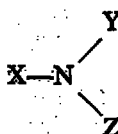
The process claims which follow are not to be construed as including any process for producing quinoxaline di-N-oxides which comprises the following step which is claimed in British Patent No. 1,187,991 namely reacting a compound which contains a ketonic or aldehydic carbonyl group and which has a methylene group in a position adjacent the carbonyl group with at least equimolar quantities of both a benzofuroxane N-oxide of the following general formula:—



in which

x represents 1 or 2;

R represents a hydrogen or halogen atom, or an alkyl, alkoxy, carbalkoxy or carbaryloxy group or the radical



in which

X denotes $\text{—SO}_2\text{—}$ or —CO— ;

Y denotes a hydrogen atom or an alkyl radical; and

5 Z denotes: (1) a hydrogen atom; (2) an alkyl radical; (3) a cycloalkyl radical having 5 to 8 carbon atoms in the ring system; (4) an aryl radical which may be substituted from one to three times by alkyl or alkoxy radical containing 1 to 6 carbon atoms, or a halogen atom; or (5) a heterocyclic radical; or Y and Z together with the nitrogen atom which links them form a heterocyclic radical; or two radicals R together form a fused benzene ring, and of a primary aliphatic or cycloaliphatic amine or ammonia, or with at least an equimolar quantity of a corresponding Schniff's base which process is carried out in an organic diluent at a temperature of from 20 to 100°C, such process being specifically disclaimed.

Subject to the foregoing disclaimer,

WHAT WE CLAIM IS:—

- 15 1. A process for producing quinoxaline-di-N-oxides and benzimidazole mono- and di-N-oxides which comprises reacting a compound containing a methylene group which is activated by two electron withdrawing groups or a compound containing a methylene group which is activated by one electron withdrawing group, said one electron withdrawing group being a nitro group or a carbonyl group of a ketone or an aldehyde, with an isobenzofuroxan in the presence of a base.
- 20 2. A process according to claim 1 wherein the compound containing a methylene group activated by one electron withdrawing group is a ketone and the base is ammonia or an organic amine.
- 25 3. A process according to claim 2 wherein the ketone is an aliphatic ketone.
4. A process according to claim 2 wherein the ketone is an alicyclic ketone.
5. A process according to claim 3 wherein the ketone is acetone.
6. A process according to claim 3 wherein the ketone is 4-hydroxy-2-butanone.
7. A process according to claim 3 wherein the ketone is pyruvaldehyde dimethyl-acetal.
- 30 8. A process according to claim 3 wherein the ketone is isonitrosoacetone.
9. A process according to claim 1 wherein the compound containing a methylene group activated by one electron withdrawing group is an aldehyde and the base is ammonia or an organic amine.
- 35 10. A process according to claim 1 wherein the compound containing a methylene group activated by one electron withdrawing group is a nitro alkane and the base is ammonia or an organic amine.
11. A process according to claim 10 wherein the nitro alkane is an aliphatic nitro compound.
- 40 12. A process according to claim 10 wherein the nitro alkane is an alicyclic nitro compound.
13. A process according to claim 1 wherein the electron withdrawing groups activating the methylene group in the compound having two such groups thereon are cyano or a carbonyl group of a ketone, ester or amide and the base is ammonia, an organic amine, an alkali metal hydroxide or an alkali metal alkoxide.
- 45 14. A process according to claim 1 wherein the compound containing a methylene group activated by two electron withdrawing groups is a β -diketone and the base is an alkali metal hydroxide or an alkali metal alkoxide.
15. A process according to claim 1 wherein the compound containing a methylene group activated by two electron withdrawing groups is a β -ketoester and the base is an alkali metal hydroxide or an alkali metal alkoxide.
- 50 16. A process according to claim 1 wherein the compound containing a methylene group activated by two electron withdrawing groups is a malonic ester and the base is an alkali metal alkoxide.
17. 2-Cyano-3-aminoquinoxaline-di-N-oxide.
- 55 18. 2-Formyldimethylacetalquinoxaline-di-N-oxide.
19. 2-Carbethoxy-3-formyldiethylacetal-quinoxaline-di-N-oxide.
20. 2-Carbomethoxy-3-hydroxyquinoxaline-di-N-oxide.
21. 2-Carboethoxy-3-hydroxyquinoxaline-di-N-oxide.
22. 2-Carboethoxymethyl-3-methylquinoxaline-di-N-oxide.
- 60 23. 2-Carbomethoxymethyl-3-carbomethoxy-quinoxaline-di-N-oxide.
24. 2-(2'-Diethylaminoethylene)quinoxaline-di-N-oxide.
25. 1-Hydroxy-2-carboethoxybenzimidazole-3-oxide.
26. 1-Hydroxy-2-benzimidazolepropionamide-3-oxide.
27. 2,2-Dimethyl-2H-benzimidazole-1,3-dioxide.



in which

X denotes $-\text{SO}_2-$ or $-\text{CO}-$;

Y denotes a hydrogen atom or an alkyl radical; and

Z denotes (1) a hydrogen atom; (2) an alkyl radical; (3) a cycloalkyl radical having 5 to 8 carbon atoms in the ring system; (4) an aryl radical which may substituted from one to three times by alkyl or alkoxy radical containing 1 to 6 carbon atoms, or a halogen atom; or (5) a heterocyclic radical; or Y and Z together with the nitrogen atom which links them form a heterocyclic radical; or two radicals R together form a fused benzene ring; and of a primary aliphatic or cycloaliphatic amine or ammonia, or with at least an equimolar quantity of a corresponding Schniff's base which process is carried out in an organic diluent at a temperature of from 20 to 100°C, such process being specifically disclaimed.

Subject to the foregoing disclaimer,

WHAT WE CLAIM IS:—

1. A process for producing quinoxaline-di-N-oxides and benzimidazole mono- and di-N-oxides which comprises reacting a compound containing a methylene group which is activated by two electron withdrawing groups or a compound containing a methylene group which is activated by one electron withdrawing group, said one electron withdrawing group being a nitro group or a carbonyl group of a ketone or an aldehyde, with an isobenzofuroxan in the presence of a base.

2. A process according to claim 1 wherein the compound containing a methylene group activated by one electron withdrawing group is a ketone and the base is ammonia or an organic amine.

3. A process according to claim 2 wherein the ketone is an aliphatic ketone.

4. A process according to claim 2 wherein the ketone is an alicyclic ketone.

5. A process according to claim 3 wherein the ketone is acetone.

6. A process according to claim 3 wherein the ketone is 4-hydroxy-2-butanone.

7. A process according to claim 3 wherein the ketone is pyruvaldehyde dimethyl-acetal.

8. A process according to claim 3 wherein the ketone is isonitrosoacetone.

9. A process according to claim 1 wherein the compound containing a methylene group activated by one electron withdrawing group is an aldehyde and the base is ammonia or an organic amine.

10. A process according to claim 1 wherein the compound containing a methylene group activated by one electron withdrawing group is a nitro alkane and the base is ammonia or an organic amine.

11. A process according to claim 10 wherein the nitro alkane is an aliphatic nitro compound.

12. A process according to claim 10 wherein the nitro alkane is an alicyclic nitro compound.

13. A process according to claim 1 wherein the electron withdrawing groups activating the methylene group in the compound having two such groups thereon are cyano or a carbonyl group of a ketone, ester or amide and the base is ammonia, an organic amine, an alkali metal hydroxide or an alkali metal alkoxide.

14. A process according to claim 1 wherein the compound containing a methylene group activated by two electron withdrawing groups is a β -diketone and the base is an alkali metal hydroxide or an alkali metal alkoxide.

15. A process according to claim 1 wherein the compound containing a methylene group activated by two electron withdrawing groups is a β -ketoester and the base is an alkali metal hydroxide or an alkali metal alkoxide.

16. A process according to claim 1 wherein the compound containing a methylene group activated by two electron withdrawing groups is a malonic ester and the base is an alkali metal alkoxide.

17. 2-Cyano-3-aminoquinoxaline-di-N-oxide.

18. 2-Formyldimethylacetalquinoxaline-di-N-oxide.

19. 2-Carboethoxy-3-formyldiethylacetal-quinoxaline-di-N-oxide.

20. 2-Carbomethoxy-3-hydroxyquinoxaline-di-N-oxide.

21. 2-Carboethoxy-3-hydroxyquinoxaline-di-N-oxide.

22. 2-Carboethoxymethyl-3-methylquinoxaline-di-N-oxide.

23. 2-Carbomethoxymethyl-3-carbomethoxy-quinoxaline-di-N-oxide.

24. 2-(2'-Diethylaminoethylene)quinoxaline-di-N-oxide.

25. 1-Hydroxy-2-carboethoxybenzimidazole-3-oxide.

26. 1-Hydroxy-2-benzimidazolepropionamide-3-oxide.

27. 2,2-Dimethyl-2H-benzimidazole-1,3-dioxide.



28. 2,2-Methyl, ethyl-2H-benzimidazole-1,3-dioxide.

29. 2,2-Pentamethylene-2H-benzimidazole-1,3-dioxide.

30. A process for preparing quinoxaline-di-N-oxides and benzimidazole mono- and di-N-oxides substantially as described with reference to any one of the specific examples hereinbefore set forth.

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