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REDUCTION OF QUINOXALINE-N-OXIDES WITH SODIUM BOROHYDRIDE

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ABSTRACT

Sodium borohydride reduction of 2,3-dimethylquinoxaline-di-N-oxide, 2,3-dihydro-1H-cyclopenta-[b]-quinoxaline-4,9-di-N-oxide, 1,2,3,4-tetrahydrophenazine-5,10-di-N-oxide, 7,8,9,10-tetrahydro-6H-cycloheptа-[b]-quinoxaline-5,11-di-N-oxide and 6,7,8,9,10,11-hexahydrocycloocta-[b]-quinoxaline-5,12-di-N-oxide gave cis-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline, cis-1,2,3,4,4a,9,9a-heptahydrocyclopenta-[b]-quinoxaline, cis-1,2,3,4,4a,5,10,10a-octahydrophenazine, cis-5,5a,6,7,8,9,10,11,11a-nonahydrocycloheptа-[b]-quinoxaline and 5,5a,6,7,8,9,10,11,12,12a-decahydrocycloocta-[b]-quinoxaline, respectively, in good yield.

The reaction, which seems to be general and stereospecific, provides a simple route to the above products. A proposed mechanism and possible intermediates for this reduction are presented and discussed.

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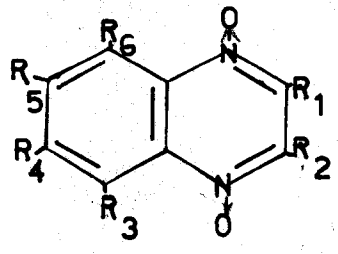
INTRODUCTION

Quinoxaline-di-N-oxides are compounds of the general structure 1.

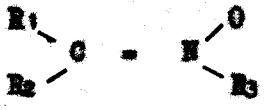


1

These compounds can be conveniently prepared by reactions of enamines[1] or 1,3-diketones[2] with benzofuroxan oxide. This method of synthesis is superior to the classical method which involves oxidation of quinoxaline derivatives with hydrogen peroxide in acetic acid.[3]

Renewed interest in quinoxaline di-N-oxides arose from their promising biological activity as antiviral agents. Some of these oxides were found to suppress the growth of the largest viruses of the psittacosis-lymphogranuloma group in mice[4]; this action was also confirmed in human lymphogranuloma, though toxic side-effects rule out their human use. The quinoxaline di-N-oxides also manifested anti-amoebic and anti-bacterial properties.[5]

The chemical properties of quinoxaline di-N-oxides are related to those of nitrones (2)



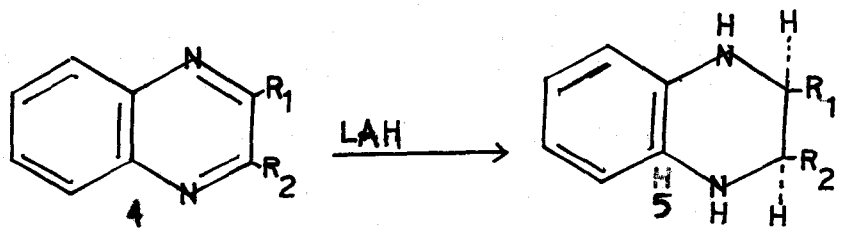
2

The analogy between nitrones and heterocyclic N-oxides was established through various reactions common to both[6], and therefore, quinoxaline di-N-oxides can be considered as bis nitrones.

Nitrones can be converted to N-hydroxylamines either by hydrogenation over platinium black or by treatment with Grignard reagent. Reduction may also be effected by complex metal hydrides (e.g. 2 → 3)[8].

2 3

On the other hand, reduction of quinoxaline (4, $R_1 = R_2 = H$) and 2,3-dimethyl quinoxaline (4, $R_1 = R_2 = CH_3$) with lithium aluminum hydride gave 1,2,3,4-tetrahydroquinoxaline[9] (5, $R_1 = R_2 = H$) and cis-2,3-dimethyl-1,2,3,4-tetrahydro quinoxaline (5, $R_1 = R_2 = CH_3$) respectively.

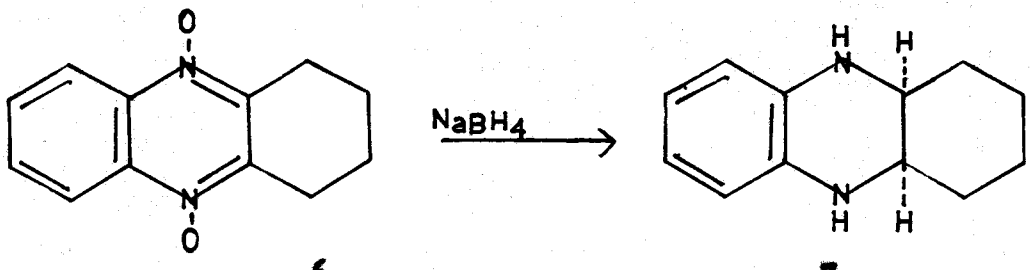


4 5

Furthermore, metallic sodium in absolute alcohol was reported to reduce 1,2,3,4-tetrahydrophenazine into trans-1,2,3,4,4a,5,10,10a-octahydrophenazine (20)[11].

Little is known about the reduction of heterocyclic-N-oxides with complex metal hydrides. Traber, Karrer and Hubman found that isoquinoline-

N-oxide was reduced with lithium aluminum hydride to give 1,2-dihydroisoquinoline.[12] Recently, sodium borohydride was used to reduce 1,2,3,4-tetrahydrophenazine-di-N-oxide (6) to cis-1,2,3,4,4a,5,10,10a-octahydrophenazine (7) as the predominant product.[1]



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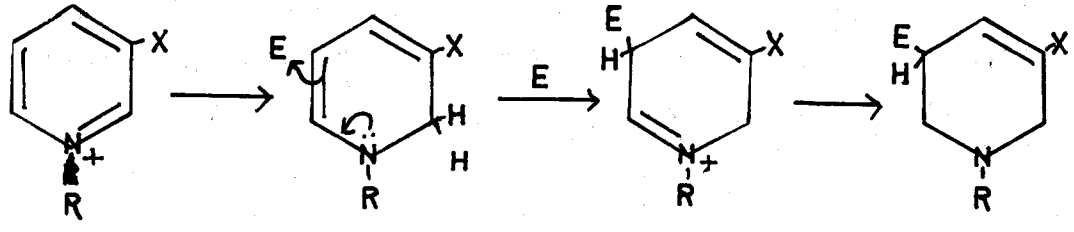
The fact that the main reduction product from 1,2,3,4-tetrahydrophenazine di-N-oxide was diamine (7) and not the N,N'-dihydroxyamine derivative showed a difference in behaviour between nitrones and quinoxaline-di-N-oxides with respect to reduction with sodium borohydride, and hence initiated further interest in this field.

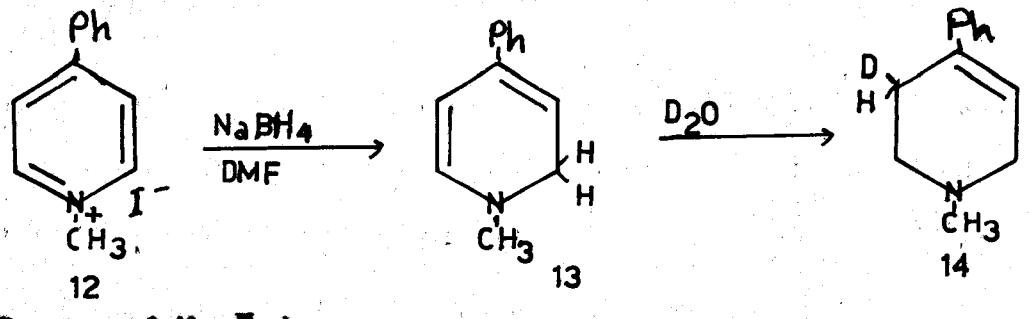
It is noteworthy that the quaternary state of nitrogen in quinoxaline di-N-oxides can be related to that in N-alkylated heterocyclic compounds with complex metal hydrides[13], this reaction is exemplified by the reduction of alkylated pyridinium salts (8) with sodium borohydride to tetrahydropyridine (11).



8 9 10 11

The mechanism for this reduction was viewed by Katritzky[13] to involve a preliminary attack on the carbon atom adjacent to the quaternary nitrogen to give the diemmine system 9. The next step is initiated by the presence, in solution, of an electrophile which is picked up at position 3. Further reduction of the imminium salt (10) yields the tetrahydropyridine 11.

Support for the second step of the mechanism was obtained by reducing 1-methyl-4-phenyl pyridinium iodide with sodium borohydride in dimethyl formamide, in the presence of deuterium oxide as the only source of protons. Nuclear magnetic resonance and mass spectral analysis showed that the product 14 contained one deuterium atom at position 3.[14,15]



12 13 14

Purpose of the Work

The purpose of this work was to study the generality and the stereospecificity of the reaction of sodium borohydride with some quinoxalines-di-N-oxides and to shed some light on the mechanism of the reaction.

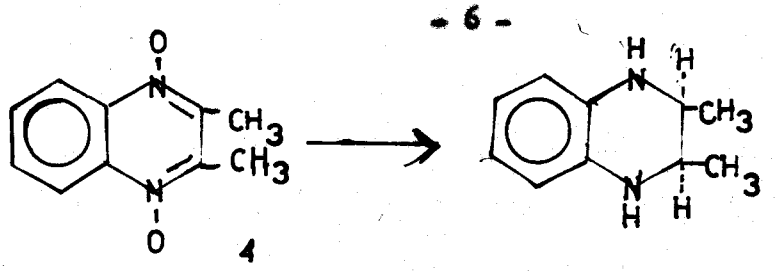
DISCUSSION OF RESULTS

The functional groups in nitrones ($>C-\overset{+}{N}<^{\overset{-}{O}}$) and carbonyl compounds undergo closely related reactions including reduction with complex metal hydrides.[16] The reduction of nitrones is presumed to involve a 1,3-hydride addition to give N-hydroxyamines. Theasing and Sirrenberg[17] reported that Δ^1-pyrroline-N-oxide yielded 1-hydroxypyrolidine when reduced with lithium aluminum hydride.

Quinoxaline di-N-oxides bear a marked resemblance to nitrones, and thus are expected to give N,N'-dihydroxy-1,2,3,4-tetrahydroquinoxalines on reduction with complex metal hydrides. Yet, the reduction of 1,2,3,4-tetrahydrophenazine-di-N-oxide (6) with sodium borohydride afforded mainly cis-1,2,3,4,4a,5,10,10a-octahydrophenazine (7) which gave correct elemental analysis, and showed bands in the infrared at 3300, 3320 (NH) and 1300 cm^{-1} (C-N). Product 7 acquired a blue coloration with iodine vapors, and was identical with an authentic sample prepared according to the method of Clemo and McIlwain.[11]

Treatment of 2,3-dimethyl quinoxaline-di-N-oxide with sodium borohydride yielded cis-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline (5) which was identical with the product obtained by lithium aluminum hydride reduction of 2,3-dimethyl quinoxaline.[10]

Reduction of 2,3-dihydro-1H-cyclopenta [b] -quinoxaline-4,9-di-N-oxide (15), 7,8,9,10-tetrahydro-6H-cycloheptа [b] -quinoxaline-5,11-di-N-oxide (16), and 6,7,8,9,10,11-hexahydrocycloocta [b] -quinoxaline-5,



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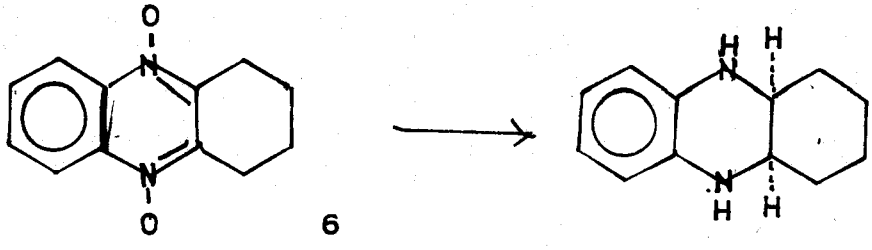

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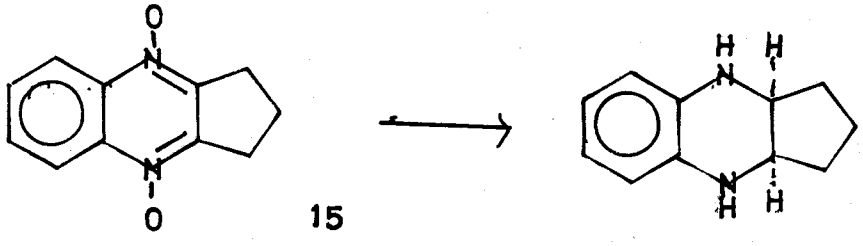

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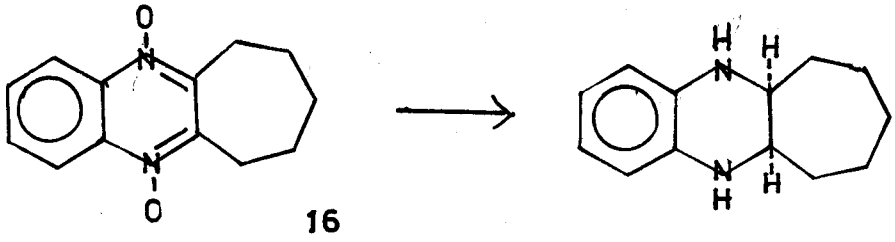

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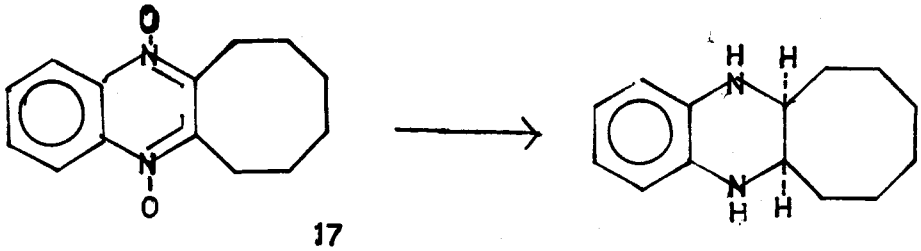

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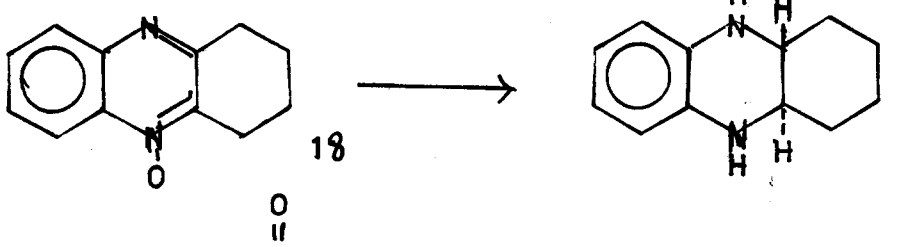
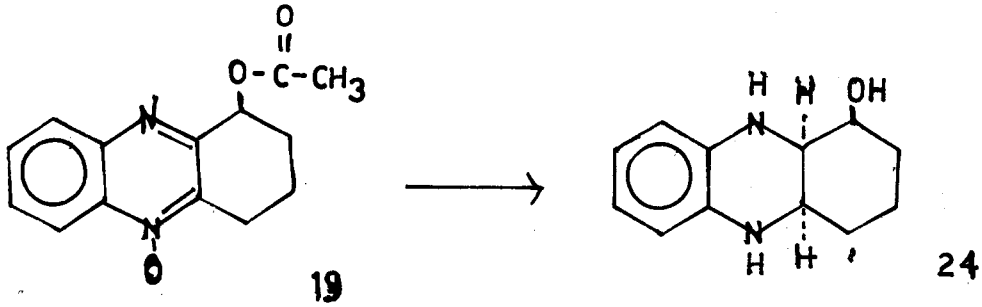


18 20 + 7



19 24 + 7 + 20

12-di-N-oxide (17) with sodium borohydride gave predominantly one product in each case. These products were cis-1,2,3,4,4a,9,9a-heptahydrocyclopenta[b]-quinoxaline (21), cis-5,5a,6,7,8,9,10,11,11a-nonahydro cyclohepta[b]-quinoxaline (22) and cis-5,5a,6,7,8,9,10,11,12,12a-decahydrocyclooctaquinoxaline (23) respectively. All these products (21,22,23) showed N-H absorption in 3300 - 3320 cm^{-1} region, and C-N absorption at 1290 - 1300 cm^{-1}. Compounds 21,22 and 23 were assigned the cis configuration on the assumption that they were formed by the same mechanism that operates in the formation of cis-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline and cis-1,2,3,4,4a,5,10,10a-octahydrophenazine (7).

Another piece of evidence that supports the cis assignment is provided by the ultraviolet spectra (Fig. 1) of the diamide derivatives of products 21, 22, 23 which displayed a shoulder at 258 ± 2 mu and a peak at 227 mu, unlike the ultraviolet spectrum of 5,10-diacetyl-trans-1,2,3,4,4a,5,10,10a-octahydrophenazine (Fig. 1,e) which exhibited a band at 222 mu. Furthermore it was observed that cis-1,2,3,4,4a,5,10,10a-octahydrophenazine (7) and cis-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline on silica gel plates acquired a blue coloration with iodine vapors, whereas trans-1,2,3,4,4a,5,10,10a-octahydrophenazine became brown. This qualitative test was found to be quite effective in detecting mixtures of cis and trans-2,3-disubstituted tetrahydroquinoxalines. Products 21, 22 and 23 gave a a blue color with iodine vapor.

Trans-1,2,3,4,4a,5,10,10a-octahydrophenazine (20) was synthesized by reduction of 1,2,3,4-tetrahydrophenazine with sodium in absolute ethanol.[11] Thin layer chromatography of the crude product revealed only traces of the cis isomer (7). Reduction of 7,8,9,10-tetrahydro-6H-cyclohepta[b]-quinoxaline-5,11-di-N-oxide (16) with metallic sodium in

absolute alcohol, however, failed to give the trans isomer as the main product, but gave about equal amounts of cis and trans-5,5a,6,7,8,9,10,11, 11a-nonahydro cycloheptа[b]-quinoxaline. Separation of this cis-trans mixture by column chromatography was unsuccessful though was evident on thin layer chromatography. Acylation of this mixture with acetic anhydride and pyridine gave a mixture of diamides which melted at 140 - 150°C. The ultraviolet spectrum of this mixture (Fig. 1, g) showed a broad band at 223 - 228 mu with a lower molecular extinction coefficient compared to that of pure 5,11-diacetyl-cis-5,5a,6,7,8,9,10,11,11a-nona-hydrocycloheptа[b]-quinoxaline, m.p. 162°C.

That the reduction of 1,2,3,4-tetrahydrophenazine-5,10-di-N-oxides (6) with sodium borohydride does not proceed via 1,2,3,4-tetrahydro-phenazine is shown by the fact that the latter is recovered unchanged under the conditions of the reaction (6 ⟶ 7) and must therefore be ruled out as an intermediate.

Reduction of 1,2,3,4-tetrahydrophenazine-5-N-oxide (18), prepared by the oxidation of 1,2,3,4-tetrahydroquinoxaline with 40% peracetic acid, yielded a mixture of cis and trans-1,2,3,4,4a,5,10,10a-octahydrophenazine in a 1:1 ratio. The lack of stereospecificity in this case shows that the mono-oxide (18) can not be the main intermediate in the reaction (6 ⟶ 7). A related compound, 1-acetoxy-1,2,3,4-tetrahydrophenazine-5-N-oxide (19), was also reduced to afford a mixture of cis-trans-1,2,3,4,4a,5,10,10a-octahydrophenazine (1:1) and 1 ξ -hydroxy-cis-1,2,3,4,4a,5,10,10a-octa-hydrophenazine (24). The evidence for the cis configuration of the ring junction in this product (24), was not conclusive, yet compound 24 gave a blue coloration with iodine vapor, and the ultraviolet spectrum of

1-acetoxy-5-acetyl-1,2,3,4,4a,5,10,10a-octahydrophenazine was consistent with a cis junction (Fig. 1, d).

A postulated mechanism for the reduction of 1,2,3,4-tetrahydrophenazine-5,10-di-N-oxide is presented in scheme 1. The first step involves a coordination between the boron atom of the borohydride moiety with oxygen in the N-oxide, and a synchronous transfer of a hydride ion to C_{4a}. Transition state 25 eventually leads to intermediate 26 which, upon hydrolysis, yields the N-hydroxy derivative 27. The latter can either lose a molecule of water to give monoxide 18 (route b), or undergo further hydride addition and yield 28 (route a).

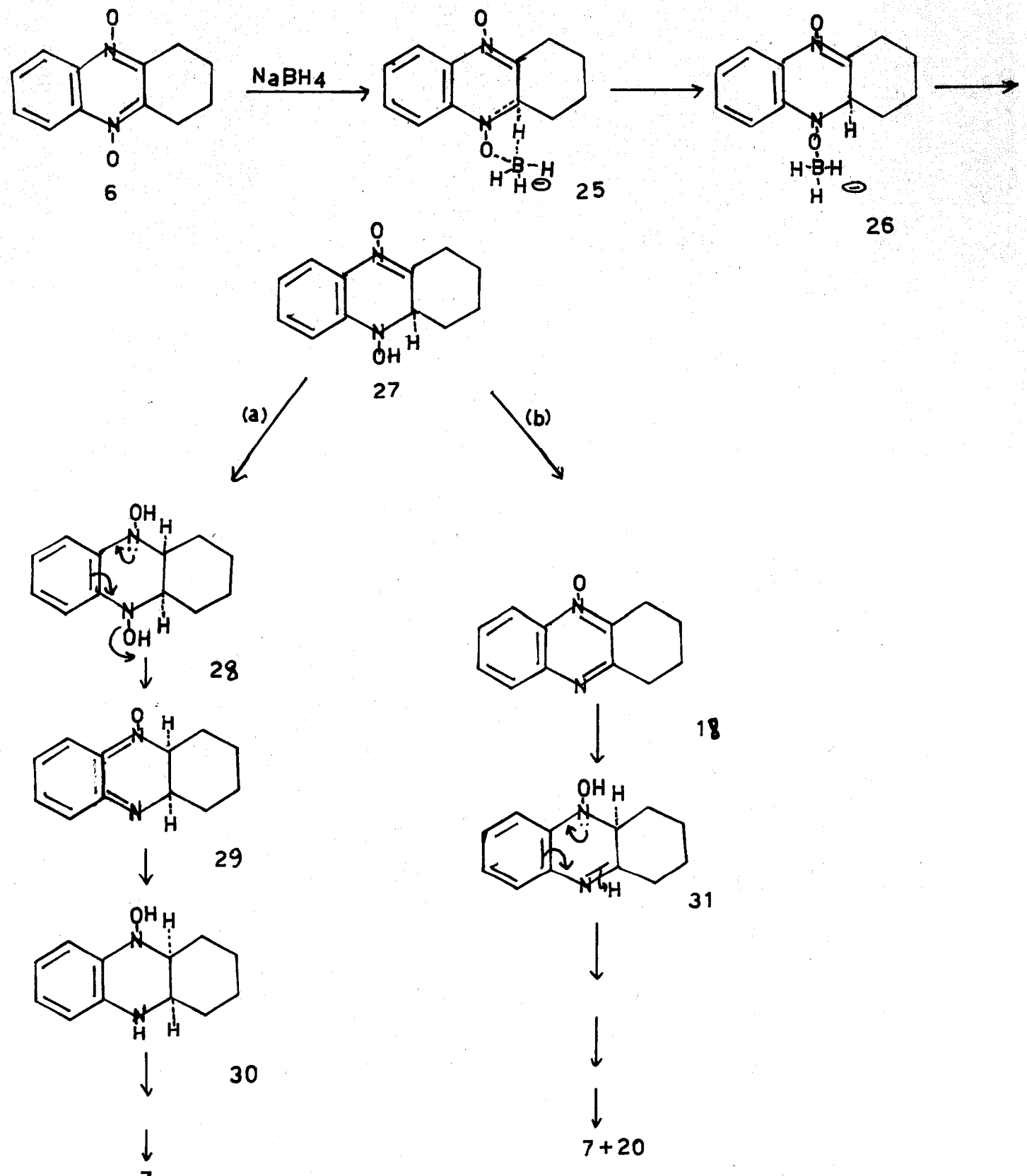
Since the reduction of the monoxide (18) gave a mixture of cis and trans-1,2,3,4,4a,5,10,10a-octahydrophenazine, its formation, if it takes place, can only be considered as a side reaction which possibly accounts for the traces of the trans-1,2,3,4,4a,5,10,10a-octahydrophenazine obtained.

The second hydride addition (route a) through a transition state similar to 25, where the hydride ion for steric reasons, approaches C_{4a} trans to the methylene group at C_{10a}. The subsequent step which gives rise to intermediate 29 is analogous to the formation of azoxybenzene from nitrosobenzene and phenylhydroxyl amine. 1,4-hydride addition to 29 results in 30 which loses a molecule of water (1,4-elimination), and is reduced further to yield cis-1,2,3,4,4a,5,10,10a-octahydrophenazine (7).

The displacement of the hydroxyl groups in 28 by hydride ion to give 7 is unlikely since hydroxyamines are stable to further treatment.[18]

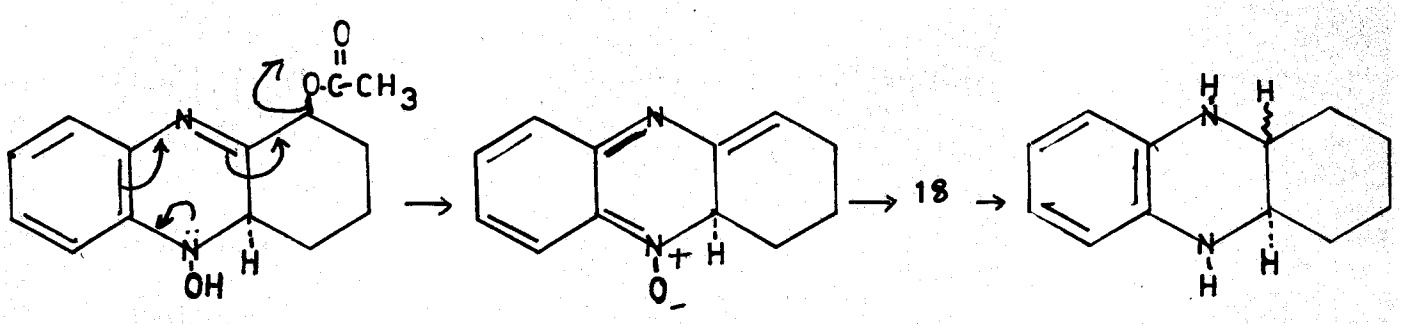
The formation of a 1:1 mixture of cis and trans-1,2,3,4,4a,5,10,10a-octahydrophenazine from 18, can be envisaged to arise from a nonstereospecific reduction of the imine function in intermediate 31, or a

Scheme 1



protonation of the latter (see Scheme 1) at C_{4a} whereby the proton is added from either side of the molecule.

A possible path for the cleavage of the acetate group in 1-acetoxy-1,2,3,4-tetrahydrophenazine-5-N-oxide (19) is depicted in Scheme II.



Scheme II

It is suggested that 1-acetoxy-1,2,3,4-tetrahydrophenazine-5-N-oxide (19) is fragmented to monoxide 18 which leads to 1:1 mixture of 7 and 20. The stereospecificity in the formation of 1-hydroxy-1,2,3,4,4a,5,10,10a-octahydrophenazine (24) as the main product is probably due to the vicinity of the hydroxy group to the sites of the reaction.

In conclusion, sodium borohydride was shown to reduce a number of quinoxaline di-N-oxides selectively. This reaction seems to be general and constitutes a simple method of preparing substituted cis-tetrahydro-quinoxalines.

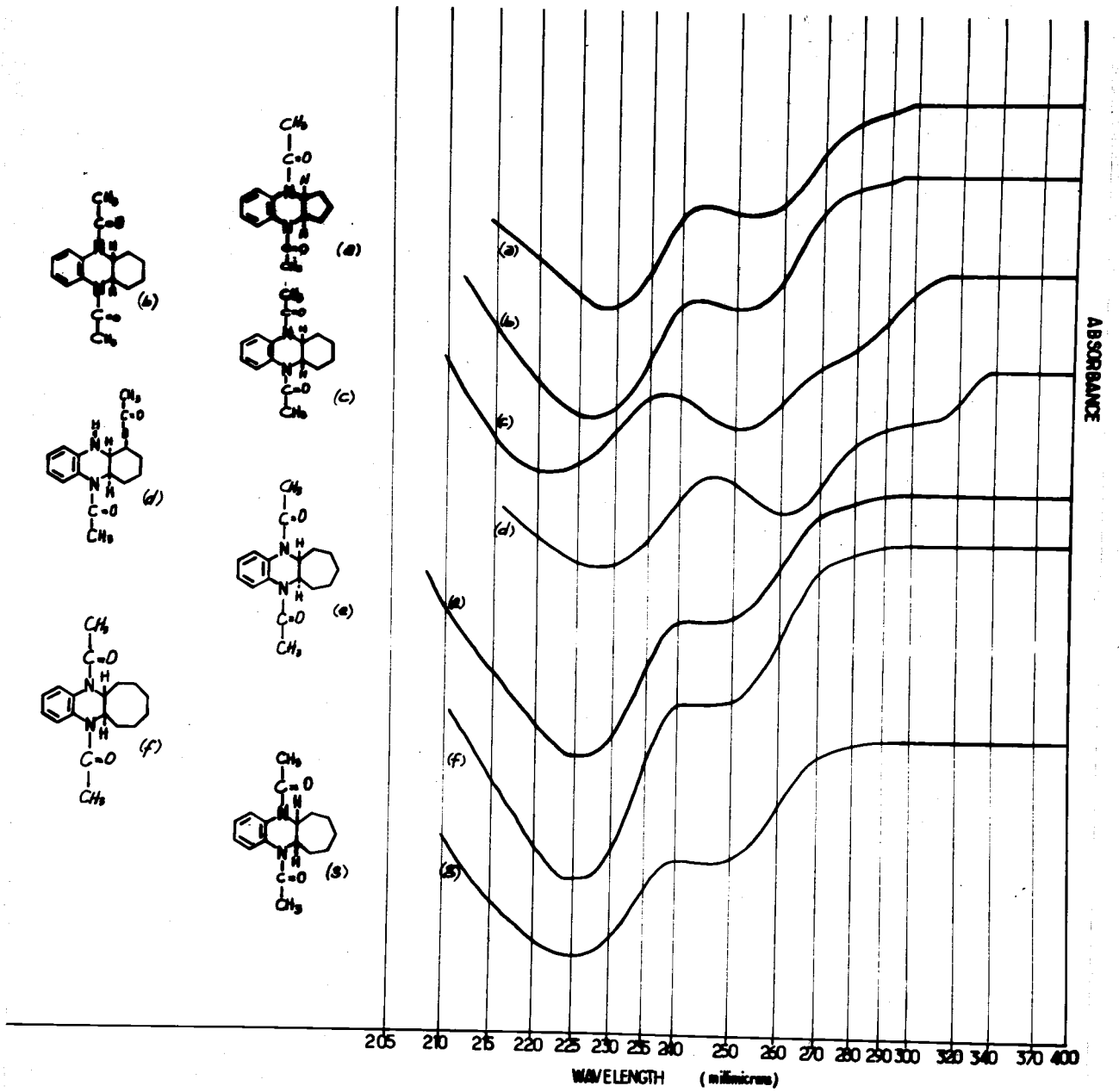
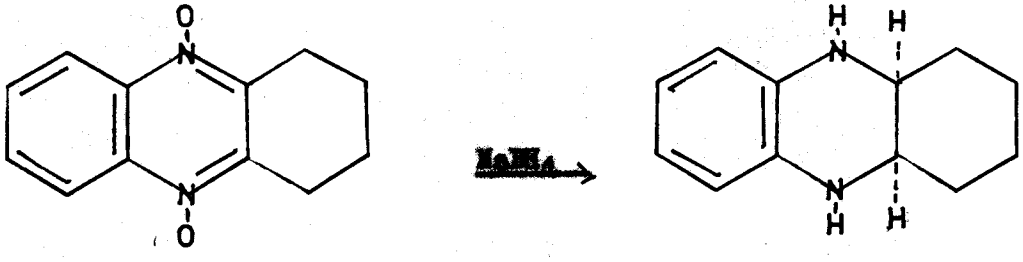

(a)
(b)
(c)
(d)
(e)
(f)
(g)
ABSORBANCE
205 210 215 220 225 230 235 240 250 260 270 280 290 300 320 340 370 400
WAVELENGTH (millimicrons)

Figure 1

EXPERIMENTAL*

Reduction of 1,2,3,4-tetrahydrophenazine di-N-oxide



6 7

1,2,3,4-Tetrahydrophenazine di-N-oxide[1] (1 g) was dissolved in ethanol by warming. An ethanolic suspension of sodium borohydride

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* Melting points are uncorrected. Alumina used for chromatography was neutral, Grade 1 "Woelm" to which 3% water was added. Unless mentioned otherwise, infrared spectra were taken in Nujol using Perkin-Elmer infrared spectrophotometer Model 257. Ultraviolet spectra were determined in methanol solution in a Perkin-Elmer UV-visible-NIR spectrophotometer Model 450, Nuclear Magnetic spectrum was run in deuterated chloroform on a Varian A 60 spectrometer. Elemental analyses were performed by F. Pascher, Bonn, Germany.

(0.5 g) was added in portions with stirring. The mixture was heated for two minutes, during which it developed a purple color which faded into pale yellow. The solution was diluted with water, left to stand for one hour and the resulting product cis-1,2,3,4,4a,5,10,10a-octahydrophenazine was collected (yield 0.48 g) m.p. 140 - 142°. Recrystallization from ethanol or petroleum ether gave colorless plates of product 7 which melted at 147°. The product gave a blue color with ferric chloride (a test characteristic of di-substituted o-phenylenediamines[19]). The product showed a single spot on thin layer chromatography with methanol-benzene (1:100) as eluent. This spot acquired a blue coloration upon complexing with iodine vapors.

Infrared: 3320, 3300 (N-H), 1600, 1370, 1290 (C-N), 1060, 910, 735, 715 cm^{-1}.

Ultraviolet: λ_{max} 250, 315 mu (ε 5 x 10^3, 4.3 x 10^3 respectively).

Nuclear magnetic resonance: τ 3.46 (4H), 6.53 (4H), 8.28, 8.33, 8.37 (8H).

Elemental analysis,

Calcd. for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88

Found: C, 76.71; H, 8.57; N, 14.76.

Extraction of the mother liquor with ether and evaporation of the dried ether gave a residue which upon thin layer chromatography and

development with iodine vapors showed a blue spot due to the cis isomer (7) and a purple one due to the trans-1,2,3,4,4a,5,10,10a-octahydrophenazine (20). The latter was identified and confirmed by comparison with an authentic sample.

The ratio of cis to trans-1,2,3,4,4a,5,10,10a-octahydrophenazine was estimated as 4:1 based on infrared evidence.

The above reaction was conducted using tetrahydrofuran and acetonitrile as solvents. The main product obtained in each case was the cis isomer (7). The mother liquors were extracted, and thin layer chromatography was performed on the extracts which, in addition to the cis isomer, showed traces of the trans-1,2,3,4,4a,5,10,10a-octahydrophenazine.

Preparation of 1,2,3,4-tetrahydrophenazine

32

1,2-Cyclohexanedione (9.0 g) was dissolved in a mixture of acetic acid (20 ml) and ethanol (10 ml). O-Phenylenediamine (10 g) and potassium acetate (8 g) were added to the mixture. The solution was heated to reflux temperature for one hour. After dilution with water, the product was collected and chromatographed over neutral alumina using benzene as

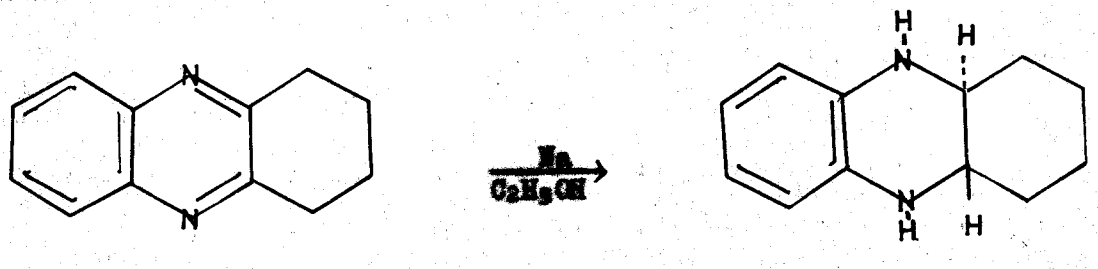
eluent. Evaporation of the benzene fractions yielded 1,2,3,4-tetrahydrophenazine (4 g) m.p. 93-94° (lit.[19] 92.5°).

The method of preparation reported in the literature was unsatisfactory, and only by chromatography a pure colorless (32) was obtained.

Reduction of 1,2,3,4-tetrahydrophenazine

The same procedure for the reduction was carried out using 1,2,3,4-tetrahydrophenazine (0.5 g) which, after the usual work up, was recovered unchanged. (m.m.p. and infrared evidence).

Synthesis of trans-1,2,3,4,4a,5,10,10a-octahydrophenazine (20).



32 20

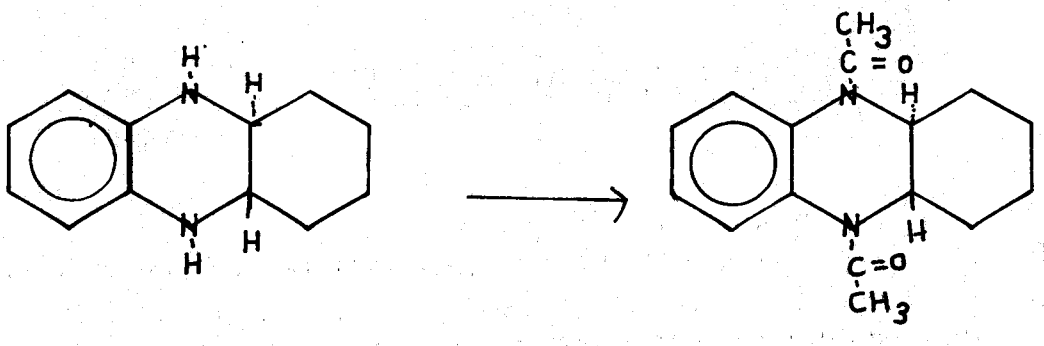
1,2,3,4-Tetrahydrophenazine (0.33 g) was dissolved in absolute alcohol (15 ml). To this solution, metallic sodium (2 g) was added gradually and the mixture was refluxed until it became colorless. After cooling, distilled water (150 ml) was added and the resulting solid was collected by suction filtration, washed with water and dried. Recrystallisation from ethanol afforded trans-1,2,3,4,4a,5,10,10a-octahydrophenazine (0.25 g), m.p. 153 - 155° (lit.[11] 156°).

The product gave a blue color with ferric chloride and a purple spot

on the chromatogram after complexing with iodine vapors.

Infrared: 3325 (doublet N-H), 1605, 1310, 1290 (C-N), 1100, 940, 920, 740 cm^{-1}

Acetylation of trans-1,2,3,4,4a,5,10,10a-octahydrophenazine

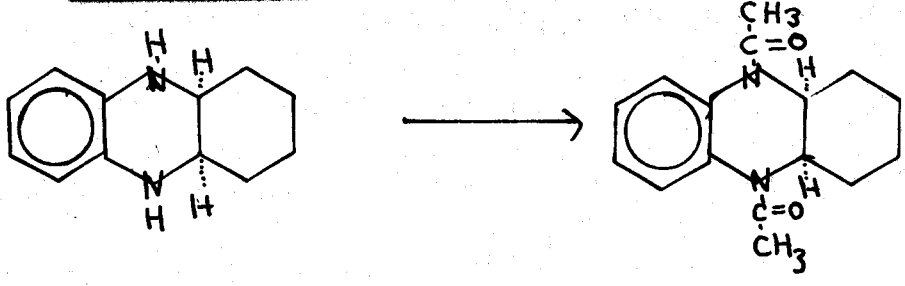


Trans-1,2,3,4,4a,5,10,10a-octahydrophenazine (300 mg) was dissolved in pyridine (1 ml) and acetic anhydride (2 ml). The solution was left to stand at room temperature overnight, and then was poured over crushed ice. The aqueous solution was extracted with ether. Evaporation of the dried ether yielded 5,10-diacetyl-trans-1,2,3,4,4a,5,10,10a-octahydrophenazine (420 mg). Recrystallization from petroleum ether-benzene yielded needles that melted at 182 - 183°.

Infrared: 1670, 1660 (acetate), 1430, 1320, 1300, 1260, 770 cm^{-1}

Ultraviolet λ_{max}: 221, 252 mm (ε 4.1 x 10^4, 3.18 x 10^4 respectively).

Acetylation of cis-1,2,3,4,4a,5,10,10a-octahydrophenazine



The previous procedure was followed for the acetylation of cis-1,2,3,4,4a,5,10,10a-octahydrophenazine (0.3 g). The product 5,10-diacetyl-cis-1,2,3,4,4a,5,10,10a-octahydrophenazine (0.33 g) was recrystallized from petroleum ether-benzene to afford white needles that melted at 147°.

Infrared: 1650 (broad acetate), 1290, 1130, 1035, 980, 775, 765 cm^{-1}

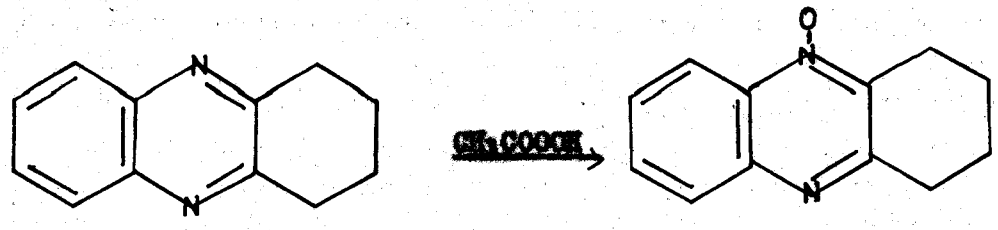
Ultraviolet λ_{max}: 227, 249 mu (ϵ 4.84 x 10^4, 2.69 x 10^4 respectively).

Elemental analysis,

Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29.

Found: C, 70.40; H, 7.20; N, 10.00.

Preparation of 1,2,3,4-tetrahydrophenazine mono N-oxide



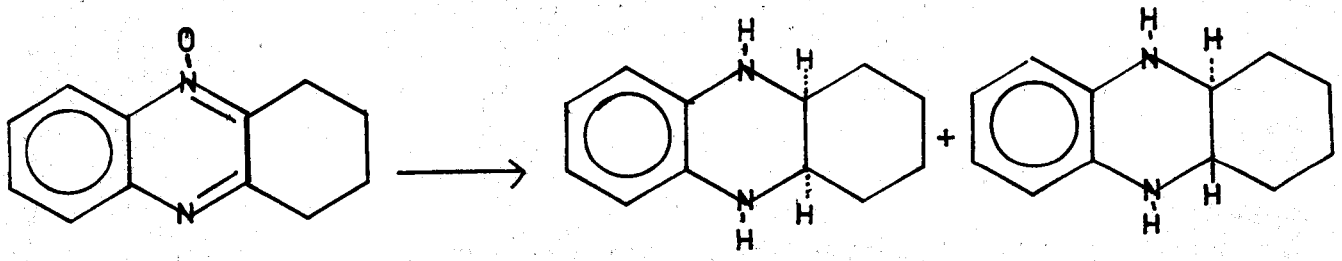
18

A solution of 1,2,3,4-tetrahydrophenazine (3 g) in 40% peracetic acid (10 ml) was warmed gently. As the exothermic reaction started, the solution was diluted immediately with water and left to stand at room temperature overnight. The crystalline solid was collected by suction filtration and washed thoroughly with water and dried (2.33 gm), m.p. 120 - 125°. The product was chromatographed over neutral alumina with

benzene-petroleum ether 1:1; the pure monooxide (1.45 g) was obtained from the first five fractions. m.p. 87 - 96°. The wide range of the melting point and the appearance of a broad hydroxy band in the infrared spectrum indicated that the monooxide crystallises out in its hydrated form. The hygroscopic nature of 1,2,3,4-tetrahydrophenazine monooxide was further confirmed by the loss of the hydroxy band in the infrared spectrum upon azeotroping the water of crystallisation with benzene.

Infrared: 3300 - 3400 (broad OH band), 1580, 1350, 1330 (N-O band), 1310, 1170, 1124, 1105, 1090, 979, 940, 875, 765 cm^{-1}

Reduction of 1,2,3,4-tetrahydrophenazine mono-N-oxide



18 7 20

To an ethanolic solution of 1,2,3,4-tetrahydrophenazine mono-N-oxide (200 mg), sodium borohydride (0.5 g) was added in portions. The mixture was boiled for two minutes. Dilution with water gave 1,2,3,4, 4a,5,10,10a-octahydrophenazine (120 mg), m.p. 120 - 123°.

This was layer chromatography of this product on silica gel with methanol-benzene (1:100) as eluent showed two spots (of the same

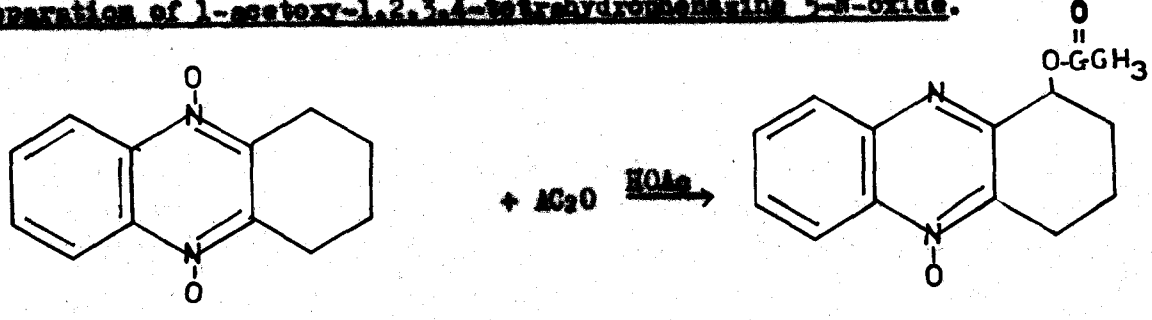
intensity), identical to those shown by a known mixture of cis and trans-1,2,3,4,4a,5,10,10a-octahydrophenazine. The mixture can be separated by careful chromatography on a neutral alumina column with petroleum ether - benzene as eluents.

The infrared spectrum of the product was identical to that of an authentic mixture of cis and trans-1,2,3,4,4a,5,10,10a-octahydrophenazine. The characteristic bands of the cis isomer at 1290 cm^{-1} and that of the trans isomer at 1310 cm^{-1} were of about the same intensity, which indicated that the mixture was approximately in the ratio of 1:1. This conclusion is supported by column chromatography.

Infrared: 3320 (doublet), 3303 (singlet) N-H, 1600, 1510, 1290, 1060, 940, 920, 910, 740 cm^{-1}.

Infrared ($CHCl_3$): 3400, 2935, 1595, 1360, 1300, 1290, 1109 cm^{-1}.

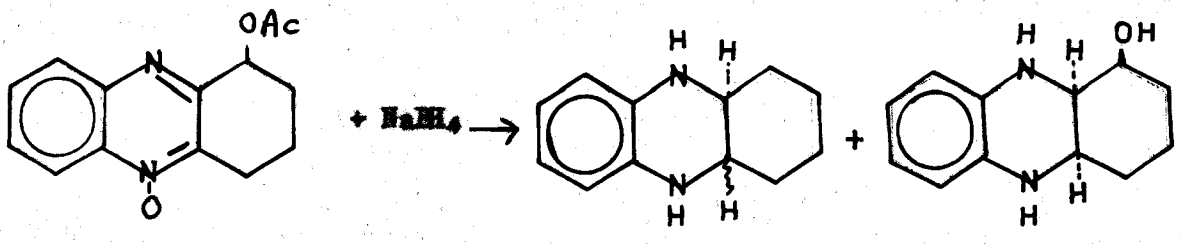
Preparation of 1-acetoxy-1,2,3,4-tetrahydrophenazine 5-N-oxide.[20]



1,2,3,4-Tetrahydrophenazine di-N-oxide (10 g) was dissolved in acetic acid (30 ml) and acetic anhydride (40 ml). The solution was left to stand at room temperature for 48 hours. Then it was poured over crushed ice. The stirred cold aqueous solution was saturated with potassium

acetate to salt out the product. 1-acetoxy-1,2,3,4-tetrahydrophenazine-5-N-oxide (6 g) was collected and crystallized from methanol, m.p. 138 - 139° (lit.[20], 139°).

Reduction of 1-acetoxy-1,2,3,4-tetrahydrophenazine-5-N-oxide



7 + 20 24

1-Acetoxy-1,2,3,4-tetrahydrophenazine-5-N-oxide was dissolved in ethanol. Sodium borohydride (2 g) suspended in ethanol was added gradually. The mixture was heated at 74 - 77° for five minutes. After dilution with water, the resulting mixture was extracted with ether. The ethereal extracts were combined, dried and evaporated under reduced pressure. The brown residue (3 g) obtained was dissolved in benzene and chromatographed over neutral alumina (80 g). Elution with petroleum ether (300 ml), benzene-petroleum ether 1:9 (100 ml); 1.5:8.5 (100 ml), and evaporation of these fractions afforded phenazine. Phenazine is a side product obtained during the preparation of the starting material.[20] Elution with benzene:petroleum ether (1:4, 500 ml; 1:3, 200 ml) and evaporation of the fractions yielded a crystalline solid (0.42 g), m.p.

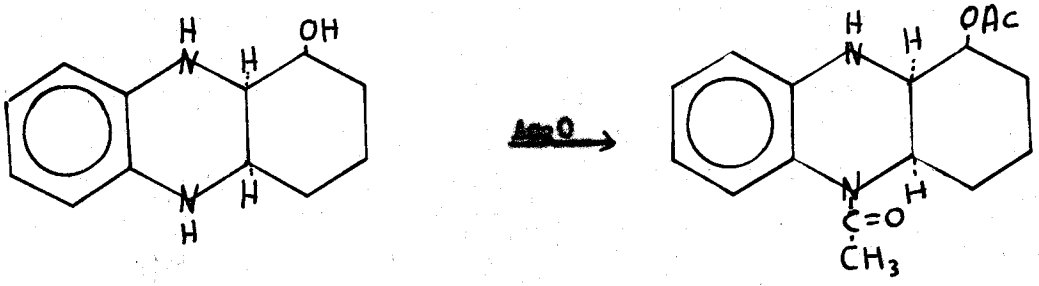
120 - 124°. This product was identified as a mixture of cis and trans-1,2,3,4,4a,5,10,10a-octahydrophenazine.

Thin layer chromatography on different consecutive fractions showed that the cis isomer (7) composed the major product in the earlier fractions. The trans-isomer (20) followed. Evaporation of the fractions eluted with benzene-methanol 100:1 (200 ml); 100:2 (200 ml); gave cis-1-hydroxy-1,2,3,4,4a,5,10,10a-octahydrophenazine (1.5 g). Recrystallisation from petroleum ether furnished crystals that melted at 117 - 120°.

Product 24 gave a positive ferric chloride test and blue colored complexes with iodine vapors.

Infrared: 3510 (OH), 3330, 3310, 1600, 1375, 1300, 1100, 1085, 1050, 1020, 910, 730 cm^{-1}.

<u>Acetylation of 1-hydroxy-1,2,3,4,4a,5,10,10a-octahydrophenazine</u>



1-Hydroxy-1,2,3,4,4a,5,10,10a-octahydrophenazine (100 mg) was dissolved in pyridine (1 ml) and acetic anhydride (1 ml). The solution was left to stand overnight, and poured over crushed ice and stirred.

1-acetoxy-5-acetyl-1,2,3,4,4a,5,10,10a-octahydrophenazine (88 mg) was collected, washed with water, and dried. Needle shaped crystals resulting from recrystallisation from methanol melted at 211 - 213°.

Elemental analysis

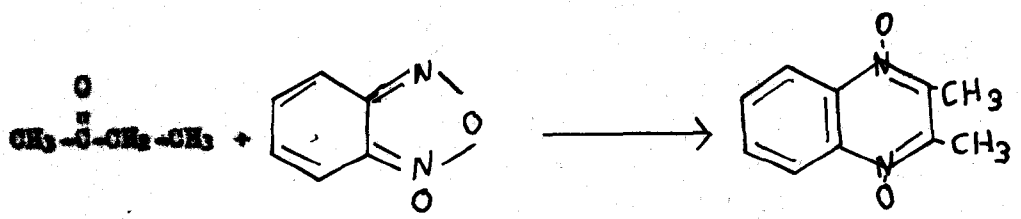
Calcd. for $C_{14}H_{20}O_3N_2$: C, 66.64; H, 6.99; N, 9.72.

Found: C, 66.48; H, 6.82; N, 9.90.

Infrared: 3320 (NH); 1730 (acetate); 1640 (amide), 1600, 1290, 1250, 1035 (C-O); 750 cm^{-1}.

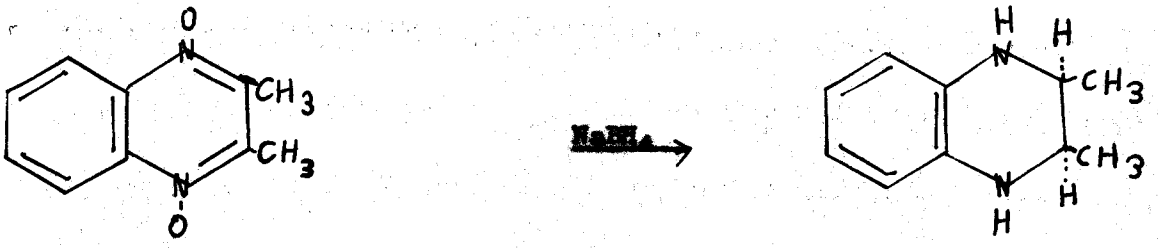
Ultraviolet λ_{max}: 280, 260, 310 mu (ϵ 3.92 x 10^4, 2.84 x 10^4, 1.06 x 10^4 respectively).

Preparation of 2,3-dimethyl quinoxaline-di-N-oxide[21]



Benzofurazan oxide (6.8 g), methyl ethyl ketone (5 g), and morpholine (10 ml) were placed in a round bottomed flask and refluxed for 15 minutes. The solution was allowed to cool, after sitting at room temperature overnight, the precipitated solid was collected by suction filtration. 2,3-dimethyl quinoxaline-di-N-oxide (3.9 g) was recrystallized from acetonitrile. The pure product melted at 190 - 192° (lit.[21] 192°).

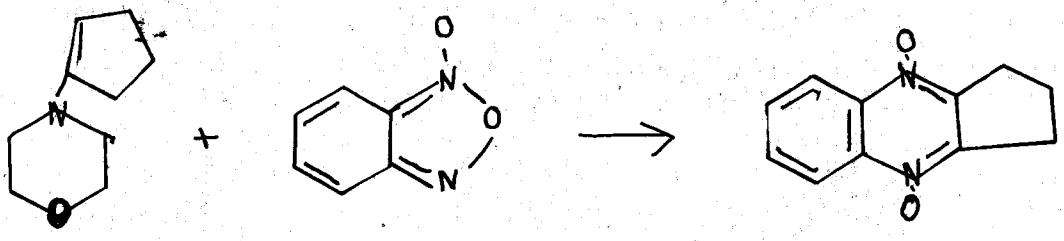
Reduction of 2,3-dimethylquinoxaline-di-N-oxide



Sodium borohydride (0.5 g) was suspended in ethanol and added gradually to an ethanolic solution of 2,3-dimethylquinoxaline-di-N-oxide (0.5 g). After heating for two minutes, the solution was diluted with water. Cis-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline (0.237 g) separated, collected by suction filtration, and recrystallised from petroleum ether m.p. 109 - 111° (lit:[10] 112 - 113°).

Infrared: 3320, 3300 (NH), 1600, 1370, 1290 (C-N), 1010, 920, 740 cm^{-1}.

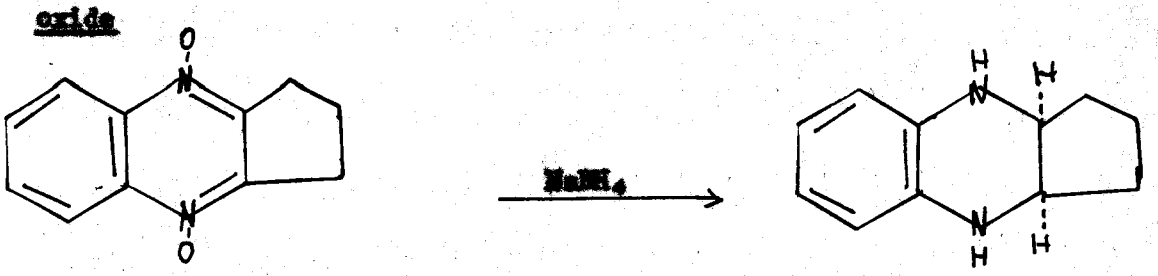
Preparation of 2,3-dihydro-1H-cyclopenta[b]-quinoxaline-4,9-di-N-oxide[1]



1-Morpholino-1-cyclopentene enamine[1] (15 g) was added gradually to a cooled methanolic solution of benzofuroxan oxide (13 g) with stirring. The exothermic reaction resulted in boiling the solvent, and in fifteen minutes slowed down with the appearance of the product. 2,3-Dihydro-1H-cyclopenta[b]quinoxaline-4,9-di-N-oxide (7.7 g) was recrystallised from

from methanol to give tan colored crystals which melted at 180° with decomposition. (lit.[1] 180° dec.).

Reduction of 2,3-dihydro-1H-cyclopenta [b] quinoxaline-4,9-di-N-oxide



15 21

2,3-Dihydro-1H-cyclopenta[b]quinoxaline-4,9-di-N-oxide (2 g) was dissolved in methanol. Sodium borohydride (1 g) was added in portions with stirring. The reaction mixture was warmed at 30 - 45° and then left to stand at room temperature for twelve hours. When the mixture was worked up; 1,2,3,4,4a,9,9a-heptahydrocyclopenta [b] quinoxaline was isolated and crystallised from petroleum ether to give white plates that melted at 104°.

Elemental analysis

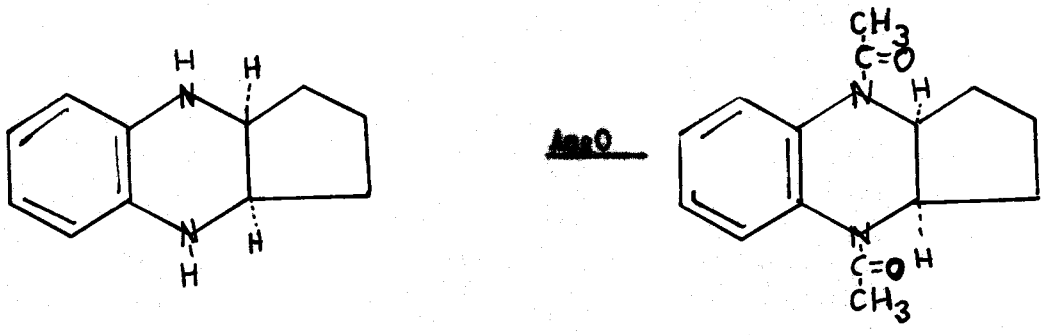
Calcd. for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08.

Found: C, 75.84; H, 8.09; N, 16.27.

Infrared: 3320 (NH), 1600, 1370, 1290, 735 cm^{-1}.

The product and the ethereal extract of the mother liquor revealed a single spot, on thin layer chromatography, corresponding to the cis-1,2,3,4,4a,9,9a-heptahydrocyclopenta-[b]-quinoxaline.

Acetylation of cis-1,2,3,4,4a,9,9a-heptahydrocyclopenta [b] quinoxaline



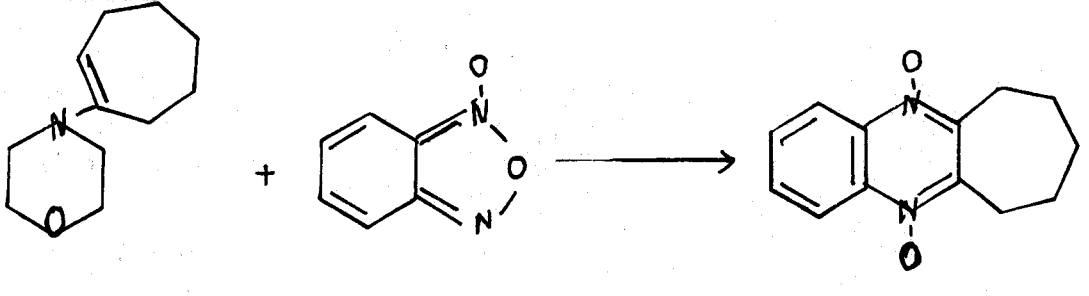
21

A solution of cis-1,2,3,4,4a,9,9a-heptahydrocyclopenta [b] quinoxaline (0.55 g) in pyridine and acetic anhydride (1: 2 ml) was left to stand at room temperature for 16 hours. The solution was poured over crushed ice, the solid collected by suction filtration, washed with water, and dried (0.5 g). Recrystallization from petroleum ether-benzene gave white needles of 5,9-diacetyl-5,5a,6,7,8,9,9a-heptahydro cyclopenta [b] quinoxaline that melted at 150 - 151°.

Infrared: 1640 (amide), 1280, 1100 780 cm^{-1}.

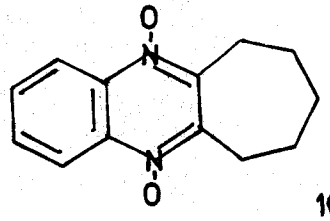
Ultraviolet λ_{max}: 228, 254 mu (ϵ 3.94×10^4, 2.1×10^4 respectively).

Preparation of 7,8,9,10-tetrahydro-6H-cyclohepta [b] quinoxaline-5,11-di-N-oxide



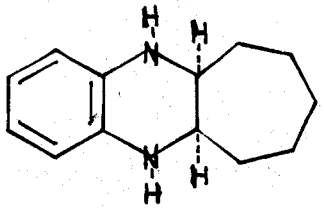
1-Morpholino-1-cycloheptene (20 g)[22] was added to a warm methanolic solution of benzofurazan oxide with stirring. When the exothermic reaction subsided, 7,8,9,10-tetrahydro-6-H-cyclohepta [b] quinoxaline-5,11-di-N-oxide (15 g) precipitated and was collected by suction filtration. Recrystallization from methanol afforded yellow needles, m.p. 172 - 174° (lit.[22] 173 - 175°)

<u>Reduction of 7,8,9,10-tetrahydro-6-H-cyclohepta [b] quinoxaline-5,11-di-N-oxide</u>[22]



16

$NaBH_4$ →



22

The reduction was carried out by adding sodium borohydride (1.5 g) to and ethanolic solution of 7,8,9,10-tetrahydro-6H-cyclohepta [b]-quinoxaline-5,11-di-N-oxide (3 g) which was boiled for three minutes. After cooling and dilution with water, the resulting cis-5,5a,6,7,8,9,10,11,11a-nona-hydrocycloheptа [b] quinoxaline (1.8 g) was collected and crystallized from petroleum ether, m.p. 123 - 124°.

Infrared: 3310, 3290 (NH), 1600, 1300, 1110, 920, 740 cm^{-1}.

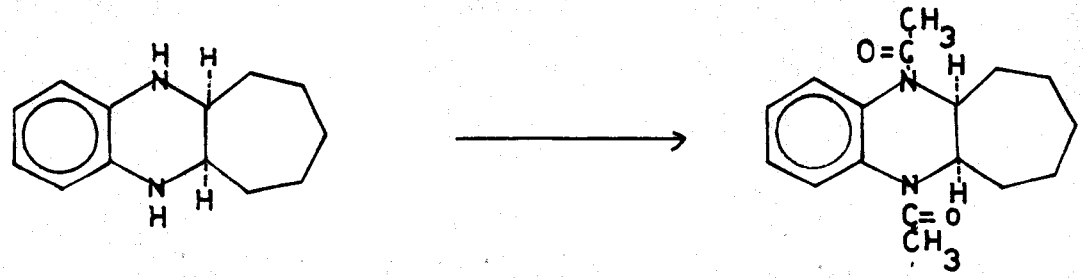
Elemental analysis

Calcd. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85

Found: C, 77.05; H. 8.55; N, 14.01.

A single spot on the thin layer chromatography plate indicated that one isomer (the cis isomer) was obtained.

Acetylation of Cis-5,5a,6,7,8,9,10,11,11a-nonahydrocycloheptal[b]quinoxaline

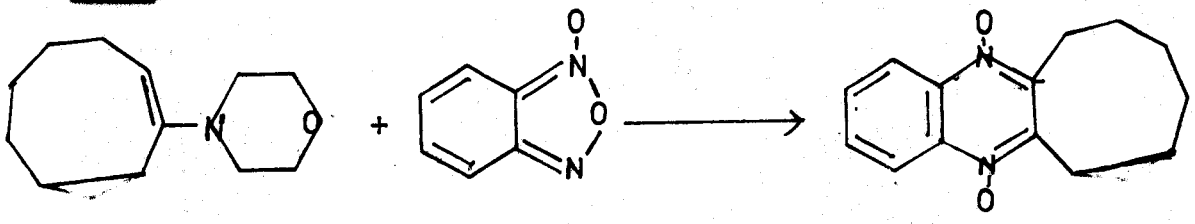


To a pyridine solution (3 ml) of cis-5,5a,6,7,8,9,10,11,11a-nonahydro-cyclohepta[b]quinoxaline (1.2 g), acetic anhydride (6 ml) was added. After standing for 14 hours at room temperature the solution was poured over crushed ice and the product 5,11-diacetyl-5,5a,6,7,8,9,10,11,11a-nonahydrocycloheptal[b]quinoxaline was collected, washed with water, and recrystallised from methanol, m.p. 162 - 163°.

Infrared: 1650 (amide), 1500, 1520, 1290, 785 cm^{-1}.

Ultraviolet λ_{max}: 226, 245 mm (ε 4.8 x 10^4, 2.29 x 10^4 respectively).

Preparation of 6,7,8,9,10,11-hexahydrocycloocta[b]quinoxaline-5,12-di-N-Oxide.

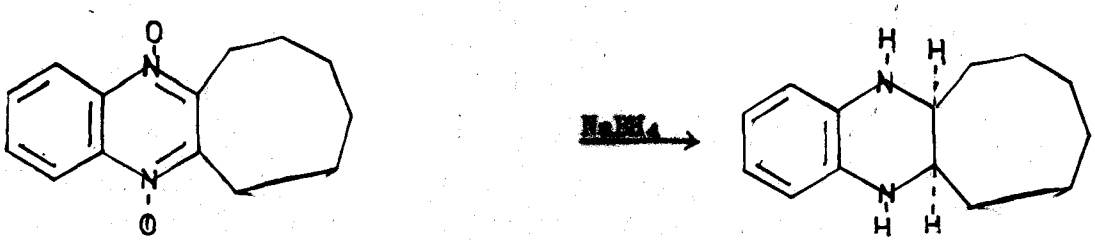


17

1-Morpholino-1-cyclooctene (4.5 g) was prepared from cyclooctanone and morpholine.[22]

The enamine was added to a methanolic solution of benzofurazan oxide. The reaction developed a deep red color with a rise in temperature. Yellow needles of 6,7,8,9,10,11-hexahydrocycloocta-[b]-quinoxaline-5,12-di-N-oxide (2.5 g) precipitated out and were collected by suction filtration. Methanol was used for recrystallization, m.p. 169 - 170°. (lit.[22] 169.5 - 170.5).

Reduction of 6,7,8,9,10,11-hexahydrocycloocta-[b]-quinoxaline-5,12-di-N-oxide



17 23

Treatment of the alcoholic solution of 6,7,8,9,10,11-hexahydrocycloocta-[b]-quinoxaline-5,12-di-N-oxide (2.3 g) with sodium borohydride (1.5 g) at reflux temperature for five minutes and dilution with water yielded a yellow solid (1.4 g). The product was chromatographed over neutral alumina using petroleum ether and benzene as eluents. Evaporation of the first fraction yielded 6,7,8,9,10,11-hexahydrocycloocta-[b]-quinoxaline (74 mg). The identity of this product was confirmed by comparison

with a known product from the deoxygenation of 6,7,8,9,10,11-hexahydrocycloocta-[b]-quinoxaline-5,12-di-N-oxide. The two products displayed identical infrared spectra and showed no depression on a mixture melting point. The rest of the fractions yielded a solid that gave a positive ferric chloride test. The combined fractions yielded cis-5,5a,6,7,8,9,10,11,12,12a-decahydrocycloocta-[b]-quinoxaline (0.4 g). Thin layer chromatograms showed a single spot for each run that acquired a blue color upon development with iodine vapors.

Recrystallization from petroleum ether yielded white plates. The melting point of the analytical sample was 124°.

Infrared: 3310, 3280 (NH), 1600, 1290, 740 cm^{-1}.

Elemental analysis

Calcd. for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95.

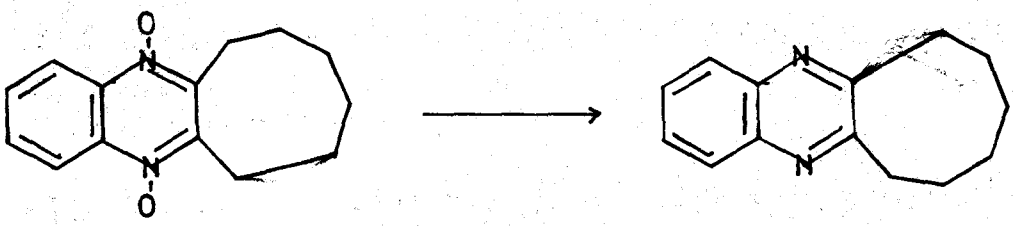
Found: C, 77.71; H, 9.33; N, 12.86.

In another run, 6,7,8,9,10,11-hexahydrocycloocta-[b]-quinoxaline-5,12-di-N-oxide (3 g) was dissolved in ethanol. Sodium borohydride (1.5 g) was added and the temperature was kept at below 40° by cooling when necessary. After 30 minutes an additional amount of sodium borohydride (0.5 g) was added. The solution was left to stand at room temperature for two hours. Dilution with water afforded (2.3 g) of a yellow solid. The product was chromatographed over neutral alumina. The yield of 5,5a,6,7,

8,9,10,11,12,12a-decahydrocycloocta-[b]-quinoxaline was 1.7 g.

The first recrystallization from petroleum ether afforded plates that melted at 114 - 116°.

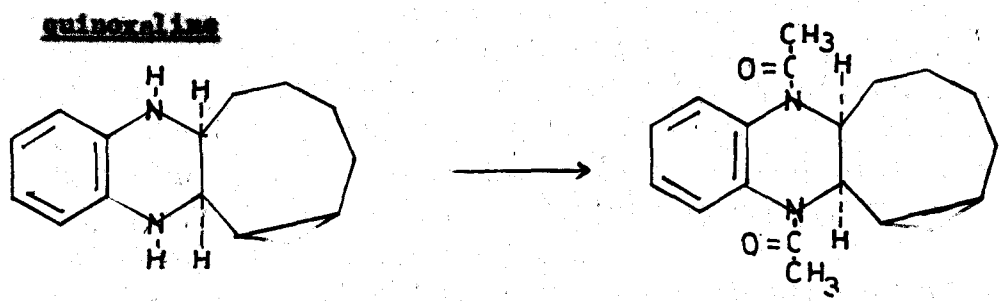
Preparation of 6,7,8,9,10,11-hexahydrocycloocta-[b]-quinoxaline



6,7,8,9,10,11-Hexahydrocycloocta-[b]-quinoxaline-5,12-di-N-oxide (0.2 g) was dissolved in methanol and treated with an aqueous solution of sodium dithionite (0.5 g). The white solid separated after dilution with water was collected and washed with water. The dried product was recrystallized from petroleum ether, m.p. 107 - 110°.

Infrared: 1300, 1160, 1140, 1120, 780 cm^{-1}.

Acetylation of 5,5a,6,7,8,9,10,11,12,12a-decahydrocycloocta-[b]-quinoxaline



Cis-5,5a,6,7,8,9,10,11,12,12a-decahydrocycloocta-[b]-quinoxaline (80 mg) was dissolved in pyridine: acetic anhydride (1:2) and the solution was left to stand at room temperature overnight. The usual work

up (ice-water) yielded 86 mg of 5,12-diacetyl-5,5a,6,7,8,9,10,11,12,12a-decahydrocycloocta-[b]-quinoxaline. Recrystallization from methanol gave prisms that melted at 204 - 206°.

Infrared: 1650 (amide), 1320, 1290, 1250, 1070, 770 cm^{-1}.

Ultraviolet λ_{max}: 226, 248 mu (ε 4.8 x 10^4, 2.3 x 10^4 respectively).

Reduction of 7,8,9,10-tetrahydro-6H-cyclohepta-[b]-quinoxaline-5,11-di-N-oxide

16

To a solution of compound 16 (1 g) in absolute ethanol, metallic sodium (4 g) was added. The solution was refluxed till it became colorless. After dilution with water the product that separated was collected by suction filtration and washed. Thin layer chromatography showed two spots of equal intensity; one of them acquired a blue color and the second acquired a brown color with iodine vapor.

Attempted separation of this mixture by column chromatography failed. Acetylation of cis, trans-5,5a,6,7,8,9,10,11,11a-nonahydrocycloheptа-[b]-quinoxaline (250 mg) gave mixture of diamide derivatives which melted at 146 - 151°.

Ultraviolet λ_{max}: 225 - 228 (ε_{max} 4.2 x 10^4)

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