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SOME NN'-SUBSTITUTED 1, 2, 3, 4-TETRAHYDROQUINOXALINES AND THE HOFMANN DEGRADATION OF THE QUATERNARY BASE FROM NN'-DIMETHYLTETRAHYDROQUINOXALINE

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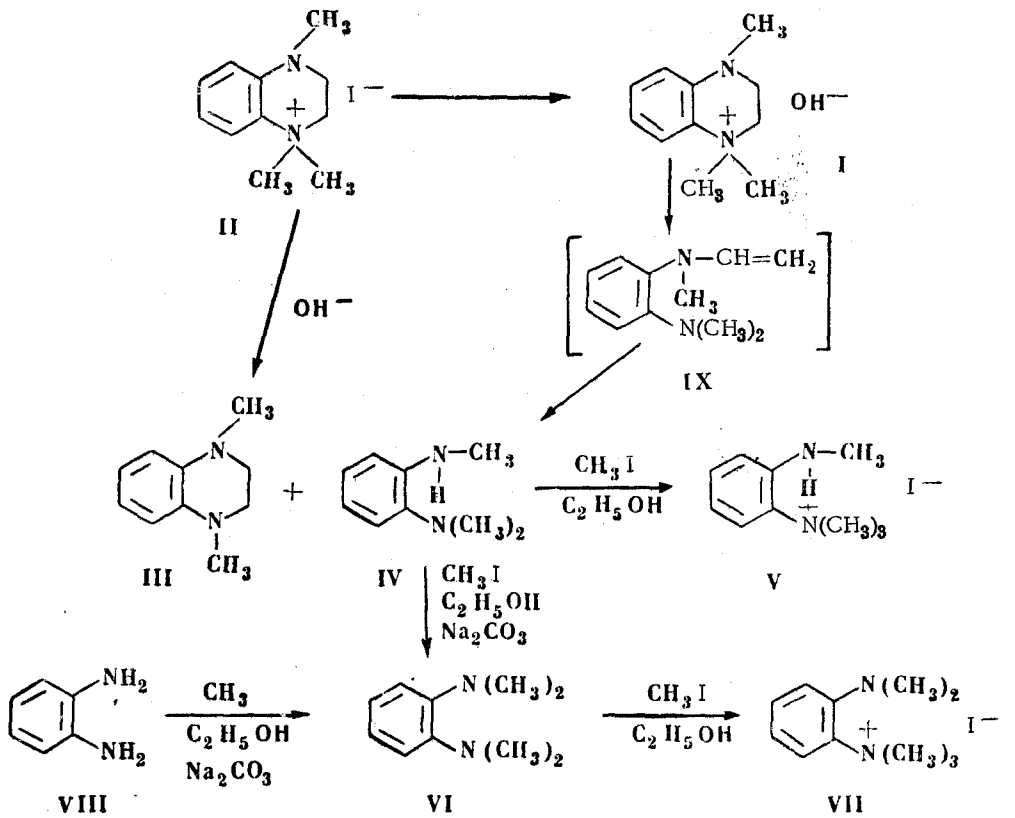
Some N- and NN'-substituted 1, 2, 3, 4-tetrahydroquinoxalines are synthesized. The quaternary base of NN'-dimethyl-1, 2, 3, 4-tetrahydroquinoxaline, obtained from the corresponding methiodide, undergoes the Hofmann degradation reaction. The degradation product, NNN'-trimethyl-o-phenylenediamine, is apparently formed via the intermediate NN-dimethyl-N'-methyl-N'-vinyl-o-phenylenediamine.

It was long believed that the quaternary base from N-methyl-1, 2, 3, 4-tetrahydroquinoline did not undergo the Hofmann degradation, and that the sole product obtained from N-methyltetrahydroquinoline methiodide and its hydroxide under the conditions of the Hofmann degradation was N-methyltetrahydroquinoline [1, 2].

From the stereochemical point of view, however, there is a possibility that the degradation of the quaternary base from N-methyltetrahydroquinoline may be effected, since, by analogy with tetrahydronaphthalene, the half-chair conformation appears to be the most stable one, and in this conformation the requirement for β-elimination (trans-coplanarity of the four centers $\overset{+}{N}—C_{(\alpha)} — C_{(\beta)} — H$ with H equatorial) is satisfied. It was later shown [3] that, on heating N-methyltetrahydroquinoline methiodide in a 40% solution of sodium hydroxide, besides the main reaction product N-methyltetrahydroquinoline, there is also formed a mixture of Hofmann degradation products (o-allyl-NN-dimethylaniline and trans-NN-dimethyl-o-propenylaniline) in 5% yield. This yield was increased to 48% by thermal decomposition of the quaternary base from N-methyltetrahydroquinoline, obtained from the corresponding methiodide.

The probability of successful degradation of the quaternary base from NN'-dimethyl-1, 2, 3, 4-tetrahydroquinoline (I), suggested by these results, is increased by the fact that the inductive effect of the second ring nitrogen atom N' should facilitate the β-elimination reaction. Experimental verification of this hypothesis was provided as follows. By heating the methiodide II with 40% aqueous sodium hydroxide (conditions which, in the case of N-methyltetrahydroquinoline methiodide, afford mainly N-methyltetrahydroquinoline), we obtained NN'-dimethylquinoxaline (III) in 37.7% yield, and the Hofmann degradation product IV in 32.3% yield. The yield of the Hofmann degradation product IV was increased to 56% by thermal decomposition of the quaternary base I.



The provisional structure for IV was based on the following data: elementary formula $C_9H_{14}N_2$; basic properties; the absence of reactions characteristic of an unsaturated carbon chain; and the presence in the IR spectrum of a band in the 3390 cm^{-1} region corresponding to N—H. valency bond stretching. Compound IV was converted to its methiodide V, the analytical figures for which were consistent with the structure NNN'-trimethyl-o-phenylenediamine methiodide, and its IR spectrum showing a marked shift of the N—H band to 2780 cm^{-1}.

In order to confirm the structure of IV, it was exhaustively methylated to give the base VI, and this was converted into the methiodide VII, which proved to be identical with NNN'N'-tetramethyl-o-phenylenediamine, prepared from o-phenylenediamine by known methods [4].

Hofmann degradation of the quaternary base from NN'-dimethyltetrahydroquinoxaline therefore affords, not NN-dimethyl-N'-methyl-N'-vinyl-o-phenylenediamine (IX), but NN-dimethyl-N'-methyl-o-phenylenediamine (IV), which may be formed from IX by hydrolytic removal of the vinyl group as acetaldehyde, or its loss as acetylene. An analogous case of loss of an N-vinyl group during the Hofmann degradation has been described in the case of the quaternary base from bicyclo[2, 2, 2]-1, 4-diaza-octane [5].

In view of the occurrence of compounds of pharmacological interest among piperazine derivatives, substituted on the ring nitrogen atoms by alkyl, aralkyl, and other groups, it was considered of interest to examine the biological activity of the NN'-substituted tetrahydroquinoxalines.

We have synthesized N-acetyl-N'-benzyl-, N'-benzyl-, and N-methyl-N'-benzyl-1, 2, 3, 4-tetrahydroquinoxaline. N-Acetyl-N'-benzyltetrahydroquinoxaline was obtained from N-acetyltetrahydroquinoxaline [6] by treatment with benzyl chloride in anhydrous ethanol in presence of sodium carbonate. In addition to N'-benzylation, a side reaction occurred in which the N-acetyl group was lost and the NN'-dibenzyl derivative of 1, 2, 3, 4-tetrahydroquinoxaline was formed.

The compounds which have been prepared are unsuitable for pharmacological study, since aqueous solutions of their salts decompose rapidly with separation of the insoluble parent bases. They have also been found to possess high toxicity and low antibacterial activity.

EXPERIMENTAL

Reaction of N-acetyl-1, 2, 3, 4-tetrahydroquinoxaline with benzyl chloride. A mixture of 15.87 g of N-acetyl-1, 2, 3, 4-tetrahydroquinoxaline, 19.08 g of anhydrous sodium carbonate and 44.54 g of benzyl chloride in 180 cc of anhydrous ethanol is boiled for 6-1/2 hr, filtered hot, and the filtrate concentrated in vacuo to half its original volume, filtered again to remove inorganic salts and evaporated to dryness. The oily residue is triturated with water, acidified to pH 2 with 2N hydrochloric acid, and extracted with chloroform. The chloroform and excess benzyl chloride are removed by distillation, and the residue redistilled in vacuo to give an oily, partly crystalline reaction product (20.05 g, bp 200-205° at 2 mm), which after repeated crystallization from a mixture of ether and light petroleum afforded 15 g of N-acetyl-N'-benzyltetrahydroquinoxaline as a colorless, crystalline solid, mp 60.5-62.5°. Found: C 76.26; H 6.85; N 10.69%. Calculated for $C_{17}H_{18}N_2O$: C 76.64; H 6.81; N 10.52%.

The oily reaction product, bp 200-205° (2 mm), formed in the benzylation of N-acetyltetrahydroquinoxaline (20 g), is heated with 200 cc of 7.5N hydrochloric acid at 40-50° until it dissolves, then for 1 hr at 95-97°. The solution is cooled, basified with 40% sodium hydroxide solution to pH 8, then extracted with benzene. After removal of the benzene, the residue is distilled in vacuo to give two fractions: 1) 16.15 g, bp 195-205° (2 mm), and 2) 1.53 g, bp 210-230° (2 mm). The first fraction afforded 13 g of N-benzyltetrahydroquinoxaline hydrochloride, mp 170-171° (from ethanol) (found: Cl 13.79%, calculated for $C_{15}H_{17}ClN_2$: Cl 13.60%), and 1.35 g of a compound, mp 92-93°, which gave no depression of melting point on admixture with tetrahydroquinoxaline, mp 96-97°. From the second fraction there was obtained 1 g of NN'-dibenzyltetrahydroquinoxaline hydrochloride, mp 175-177° (from ethanol). Found: C 75.2; H 6.77; Cl 10.47; N 8.08%. Calculated for $C_{22}H_{23}ClN_2$: C 75.24; H 6.60; Cl 10.09; N 7.98%.

N-Benzyl-N'-methyl-1, 2, 3, 4-tetrahydroquinoxaline. To a solution of 1 g of N-benzyltetrahydroquinoxaline in 7 cc of anhydrous ethanol 3 cc of methyl iodide is added, and the mixture boiled for about 9.5 hr. The ethanol and excess methyl iodide are distilled off, and the residue triturated with a small volume of methanol to give 0.6 g of N-benzyl-N'-methyltetrahydroquinoxaline methiodide, mp 175-176° decomp. (from anhydrous ethanol). Found: I 33.54; N 7.28%. Calculated for $C_{17}H_{21}IN_2$: I 33.38; N 7.37%.

Hofmann degradation of the quaternary base from NN'-dimethyltetrahydroquinoxaline (I)

a) NN'-Dimethyltetrahydroquinoxaline methiodide (5 g) dissolved in 30 cc of 40% sodium hydroxide is boiled for 6 hr, then distilled to remove simultaneously water and reaction products (the bath temperature being raised to 250° at the end of the distillation). The distillate is extracted with chloroform, the extract dried over anhydrous sodium sulfate, and the chloroform evaporated. Distillation of the residue yielded two fractions: 1) 0.8 g of NNN'-trimethyl-o-phenylenediamine, bp 62-64° (1 mm), picrate mp 112-113° decomp. (from ethanol). Found: C 48.05; H 4.67; N 18.83%. Calculated for $C_9H_{14}N_2 \cdot C_6H_3N_3O_7$: C 47.63; H 4.52; N 18.46%. Dihydrochloride, mp 165-167° (from anhydrous ethanol).

Found: C 48.48; H 7.19; Cl 31.45; N 12.72%. Calculated for $C_9H_{14}N_2 \cdot 2HCl$: C 48.6; H 7.23; Cl 31.77; N 12.56%, and 2) 1 g of NN'-dimethyl-1, 2, 3, 4-tetrahydroquinoxaline, bp 92-94° (1 mm), picrate mp 122-124° decomp. (from anhydrous ethanol). The mixed melting point with the picrate of NN'-dimethyl-1, 2, 3, 4-tetrahydroquinoxaline obtained by known methods [7] showed no depression.

b) The quaternary base from 5 g of NN'-dimethyl-1, 2, 3, 4-tetrahydroquinoxaline methiodide is heated, the reaction products being allowed to distill. The reaction begins at 130° (bath temp.), the temperature then being gradually raised until it reaches 200°, when the reaction ends, distillation of the products being completed in vacuo. The distillate is extracted with chloroform, the extract dried, and the chloroform removed by distillation. The residue is vacuum-distilled to yield 1.6 g of NNN'-trimethyl-o-phenylenediamine, bp 62-64° (1 mm). The picrate was identical with that obtained above.

NNN'-Trimethyl-o-phenylenediamine methiodide. To 0.34 g of NNN'-trimethyl-o-phenylenediamine, obtained by Hofmann degradation of the quaternary base from NN'-dimethyl-1, 2, 3, 4-tetrahydroquinoxaline, was added 1.52 cc of methyl iodide, and the mixture kept for 24 hr at 20-25°. The reaction mixture was treated with ether, stirred and filtered to afford 0.2 g of NNN'-trimethyl-o-phenylenediamine methiodide, mp 207-208° decomp. (211-212°) (from anhydrous ethanol). The IR spectrum showed a band at 2780 cm^{-1}. Found: C 41.55; H 5.66; I 43.83; N 9.61%. Calculated for $C_{10}H_{17}IN_2$: C 41.10; H 5.86; I 43.43; N 9.59%.

Exhaustive methylation of NNN'-trimethyl-o-phenylenediamine

a) To a solution of 0.51 g of NNN'-trimethyl-o-phenylenediamine (obtained by Hofmann degradation) in 5 cc of anhydrous methanol 0.5 g of sodium carbonate is added, followed by 1 cc of methyl iodide, added slowly with stirring under nitrogen. When the addition is complete, boiling is continued under the same conditions for 10 hr. The excess of sodium carbonate is filtered off, washed with hot methanol, and the methanol solutions evaporated to dryness in vacuo. The residue is worked up with ether, and the ethereal solution dried over KOH. Removal of the ether gives 0.28 g of oily material, to which 0.75 cc of methyl iodide is added, and the mixture is kept for 24 hr at 20-25°. The reaction mixture is worked up with ether, and the NNN'N'-tetramethyl-o-phenylenediamine methiodide (0.19 g) filtered off, mp 219-220° decomp.* (from anhydrous ethanol). Found: C 43.12; H 6.40; I 41.61; N 9.40%. Calculated for $C_{11}H_{19}IN_2$: C 43.2; H 6.26; I 41.5; N 9.15%.

A band characteristic of N–H valency bond stretching occurs in the IR spectrum, together with characteristic bands at 1492, 1460, 948 and 778 cm^{-1}.

b) A specimen of NNN'N'-tetramethyl-o-phenylenediamine methiodide, prepared from o-phenylenediamine by known methods [5], mp 218-219°, gave no depression of melting point with the methiodide described above. The IR spectrum shows the NH valency bond stretching band, and also the characteristic bands at 1493, 1463, 948 and 778 cm^{-1}.**

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REFERENCES

1. A. Feer and W. Koenigs, Ber., 18, 2388, 1885.
2. J. v. Braun, Ber., 40, 3914, 1907.
3. D. A. Archer, H. Booth, P. C. Crisp, and J. Parrick, J. Chem. Soc., 330, 1963.
4. H. C. Brown and K. R. Nelson, J. Am. Chem. Soc., 75, 24, 1953.
5. O. Hromatka and C. Skopalic, Monatsh., 83, 38, 1952.
6. J. S. Morley, J. Chem. Soc., 4002, 1952.
7. H. König and R. Huisgen, Ber., 92, 437, 1959.

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*The melting points of the methiodides of tri- and tetramethyl-o-phenylenediamine vary with the rate of heating and the diameter of the capillary.

**The IR spectra were recorded in the All-Union Chemical-Pharmaceutical Scientific Research Institute physicochemical laboratories (director of spectral group, E. M. Peresleni), and the analyses were carried out in the microanalytical laboratories (director, V. V. Kolpakova).