Diastereoisomeric 4-(1-Methyl-1-oxo-3-pyrrolidinylmethylamino)quinazolines

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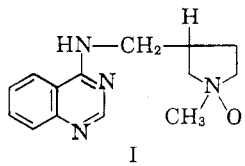
Interest in a series of 4-(1-substituted 3-pyrrolidinylmethylamino)quinazolines[1] prompted the preparation of 4-(1-methyl-1-oxo-3-pyrrolidinylmethylamino)quinazoline (I). A tertiary amine nitrogen oxide containing an asymmetrical nitrogen exists in enantiomorphic forms, Meisenheimer having resolved compounds such as 1-methyl-1,2,3,4-tetrahydroquinoline oxide and methylethylaniline oxide by fractional crystallization of their *d*-bromocamphorsulfonates or *d* and *l*-tartrates.[2] An asymmetrical nitrogen oxide containing a second center of asymmetry such as exists in I should have two racemic modifications, although no such compounds have been reported.



I

Two isomeric products designated A and B were obtained when an acetone solution of 4-(1-methyl-3-pyrrolidinylmethylamino)quinazoline reacted with 30% aqueous hydrogen peroxide. Evidence is presented that both of the isomers are 1-methylpyrrolidine nitrogen oxides; therefore, the isomers are diastereoisomers.

Purified isomer A was obtained in 43% yield and melted at 220–221° dec. after recrystallization from acetonitrile. Purified isomer B was obtained in 41% yield and melted at 200–203° dec. after recrystallization from acetonitrile. A mixed melting point determination gave good depression.

That the 4-(monosubstituted amino)quinazoline moiety had not been altered was shown by the identity of the ultraviolet absorption of both isomers with that of the parent base.

Direct evidence for an *N*-oxide function in each isomer was obtained from their infrared spectra. The infrared spectra of their chloroform solutions were dissimilar (not polymorphic forms), but each showed distinct absorption at 3.41 μ which was not present in their potassium bromide spectra. Such absorption has been attributed as being characteristic of an *N*-oxide function, due to association of the oxygen with the chloroform hydrogen.[3] The parent base did not exhibit this absorption at 3.41 μ.

Tertiary amine oxide character is also shown by the intense water solubility of the two isomers (above 0.5 g./ml.), by their ease of reduction (10% palladium–carbon) to the parent base, and by their high melting points (*cf.*, 112° for parent base).[4] A color reaction for *N*-oxides[5] was positive for both isomers, but negative for the parent base.

The possibility of a rearranged hydroxymethyl or methoxy structure for either isomer is eliminated by infrared absorption and by aqueous titration studies. When an aqueous solution of the parent base was titrated with 0.1 *N* hydrochloric acid, apparent pK'_a's of 9.3 and 5.5 were observed (*cf.*, 10.4 for *N*-methylpyrrolidine and 5.8 for 4-aminoquinazoline).[6] A 0.2% aqueous solution of isomer A had a *p*H of 7.5, while that of isomer B was 6.7; however, when titrated with 0.1 *N* hydrochloric acid, no sharp changes in slope were observed. No sharp change in slope was observed for tribenzylamine oxide[7] and has been attributed to the buffering action of hydrated forms.[4] Failure to observe a sharp point of inflection is attributed to buffering action of *N*-methylpyrrolidine oxide whose pK'_a (*cf.*, 4.65 for trimethylamine oxide)[8] is in the same range as that of 4-aminoquinazoline. Lessened basicities of the isomers compared to the parent base is apparent. An *N*-hydroxymethyl- or *N*-methoxypyrrolidine or a 4-hydroxylaminoquinazoline would be expected to be as basic as the parent base and to titrate similarly. This data also eliminates 1-methyl-?-hydroxypyrrolidine structures.

Experimental[9]

4-(1-Methyl-1-oxo-3-pyrrolidinylmethylamino)quinazolines.—A solution of 24.2 g. (0.1 mole) of 4-(1-methyl-3-pyrrolidinylmethylamino)quinazoline[1] and 12.9 g. (0.114 mole of hydrogen peroxide) of 30% aqueous hydrogen peroxide in 100 ml. of acetone was allowed to stand in an open 250 ml. Erlenmeyer flask for 9 days. The sirupy residue was dissolved in 75 ml. of methyl alcohol and the solution stirred with platinum oxide for 3 hr. and with 10% palladium-on-carbon for 1.5 hr.[10] After removal of catalyst the solution was concentrated under reduced pressure and the residual yellow oil triturated with 150 ml. of acetonitrile during which a white solid separated. The solid was

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(3) (a) R. H. Wiley and S. C. Slaymaker, *J. Am Chem. Soc.*, **79**, 2233 (1957); (b) A. R. Katritzky, J. A. T. Beard, and N. A. Coats, *J. Chem. Soc.*, 3680 (1959).

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(6) A. Albert, "Heterocyclic Chemistry," The Athlone Press, London, 1959, p. 343.

(7) M. M. Davis and H. B. Hetzer, *J. Am. Chem. Soc.*, **76**, 4247 (1954).

(8) P. Nylen, *Tidsskr. Kjemi, og. Bergvesen*, **18**, 48 (1938); ref. 4, p. 92.

(9) All melting points are uncorrected. Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(10) Destruction of excess hydrogen peroxide with platinum oxide has been reported by A. C. Cope and H. H. Lee, *J. Am. Chem. Soc.*, **79**, 964 (1957). A cleaner product was obtained through a subsequent treatment with 10% palladium-on-carbon.

collected and recrystallized from methanolic acetonitrile and from acetonitrile to a constant melting point of 220–221° dec., to furnish 11 g. or 43% of isomer A. There was no loss in weight after drying at 65° at 0.1 mm.

Anal. Calcd. for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 65.15; H, 7.06; N, 21.75.

The acetonitrile liquor from which crude isomer A was obtained was concentrated to 40 ml. and chilled at −20° to furnish a buff solid. The solid was collected and recrystallized twice from acetonitrile to furnish 10.5 g. or 41% of white crystalline isomer B, m.p. 200–203° dec. There was no loss of weight after drying at 65° at 0.1 mm.

Anal. Calcd. for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 65.11; H, 6.82; N, 21.70.

Solutions of either isomer or of the parent base in water or in 0.1 *N* sodium hydroxide exhibited maxima in mμ at 327, 314, 302, 289, 238, and 224 (log ε 3.96, 4.08, 3.99, 4.03, 4.11, and 4.08). Solutions in 0.1 *N* hydrochloric acid exhibited maxima in mμ at 328, 314, 305 (shoulder), 243, and 220 (log ε 4.24, 4.27, 4.08, 4.14, and 4.24).

Chloroform solutions of the isomers showed dissimilar infrared absorption in the 6.1–7-μ region and each showed well developed bands at 3.41, 7.30, and 7.55 μ. Isomer A could be differentiated by well developed maxima at 8.75, 10.30, 10.45, 10.60, and 10.85 μ which were lacking in isomer B. In potassium bromide disks, both compounds possessed poorly differentiated bands in the 3-μ region, with maxima at 2.95 μ.

Reduction of 4-(1-Methyl-1-oxo-3-pyrrolidinylmethylamino)quinazolines to 4-(1-Methyl-3-pyrrolidinylmethylamino)quinazoline.—Solutions of 12.9 g. (0.05 mole) of the oxides in 50 ml. of ethyl alcohol were shaken with 10% palladium-on-carbon under hydrogen in a Parr machine. One equivalent of hydrogen was absorbed in 20 min. after which absorption stopped. After removal of catalyst the solutions were concentrated and the residues recrystallized from acetonitrile to furnish quantitative yields of 4-(1-methyl-3-pyrrolidinylmethylamino)quinazoline. The latter was identified by comparison of melting points (112°) and infrared spectra with authentic material.

Dimethylaniline Color Reaction.[4]—A mixture of 0.1 g. of the oxide, 0.05 ml. of concd. hydrochloric acid, and 0.2 ml. of dimethylaniline was boiled in a test tube for 1 min. An intense blue color was obtained on the addition of ethyl alcohol to the cooled residue.

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Succinamoyl Azide. Preparation and Some Reactions

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For studies on cyclic diacyl diimides,[1] a variety of cyclic diacyl hydrazides were required to serve as precursors in their preparations. Unfortunately, many cyclic diacyl hydrazides are unstable relative to isomeric polymers, and cannot be prepared by interactions of the appropriate diacyl derivatives with hydrazine. For this reason it was of interest to find a general synthetic method in which cyclic diacyl hydrazides would be produced in rate-controlled processes under conditions unfavorable for subsequent isomerizations. In view of recent work on the intermediacy of monovalent azenes in some organic reactions,[2–4] it seemed possible that such a method would be that represented by the sequence of equation 1. The preparation of cyclic succinic hydrazide (1,2,4,5-tetrahydro-3,6-pyridazinedione) appeared a desirable one for testing this possibility, since its properties are known, and it is an example of a cyclic diacyl hydrazide which is unstable relative to isomeric polymers.[5] Unfortunately, when succinamoyl azide (**2**) was subjected to thermal or ultraviolet irradiative decomposition, there was no indication of the formation of cyclic succinic hydrazide; only products of normal Curtius rearrangement were observed. However, the preparation and characterization of the hitherto-unknown succinamoyl azide are of some interest and constitute the subject of this paper.

Succinamoyl azide (**2**) was prepared in 57% yield by the interaction of succinamoyl hydrazide (**1**)[6] with a molar equivalent of nitrosyl chloride

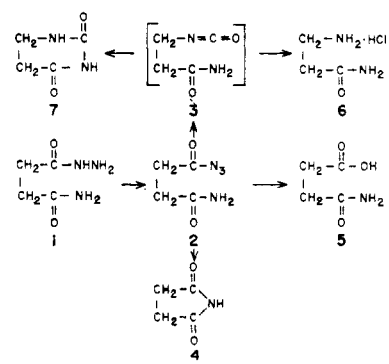

Fig. 1.—Some structures from, and reactions of, succinamoyl azide

in 1,2-dimethoxyethane, as solvent. It is a white crystalline material which, although isolable, is unstable, decomposing slowly at room temperature and almost explosively at *ca.* 70°. In the infrared it exhibited the characteristic azide absorption at 2150 cm.$^{-1}$.

Hydrolysis of succinamoyl azide (**2**) in the presence of two molar equivalents of sodium hydroxide, followed by acidification, produced succinamic acid (**5**) in 80% yield; however, when one molar equivalent of sodium hydroxide was employed, the only isolable product was succini-

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