rapidly and at the same time isomerizes to the levorotatory acid.

All of these data support the formula for the lactone of hydroxytetrahydroabietic acid in which the point of lactonization is at C-4b.

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[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

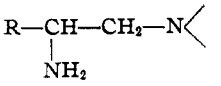
Amino Ketones. II. The Synthesis of α,β-Diamines from α-Amino Ketones*

BY NORMAN H. CROMWELL AND HERMAN HOEKSEMA

In a previous investigation[1] the synthesis of α,γ-diamines from β-amino ketones was reported. It seemed of interest to investigate similar synthesis of α,β-diamines from α-amino ketones to compare the relative yields in the two series.

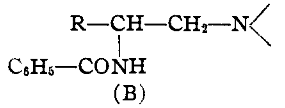
Several investigations[2] by other workers have been concerned with the conversion of α-amino ketones to α-amino alcohols in order that the two series of compounds could be studied for their relative values as pressor agents. A similar comparison of the α-amino ketones with their corresponding α,β-diamino compounds should also prove to be interesting. Furthermore, such α,β-diamino compounds might be converted to the benzamides. It has been shown previously that compounds containing the grouping $-CONH\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-N\langle$ often possess local anesthetic activity.[3]

Thus a series of diamines (A) and the corresponding benzamides (B) might prove to be of considerable interest, pharmacologically.



$$R-\underset{NH_2}{\underset{|}{CH}}-CH_2-N\langle$$

(A)



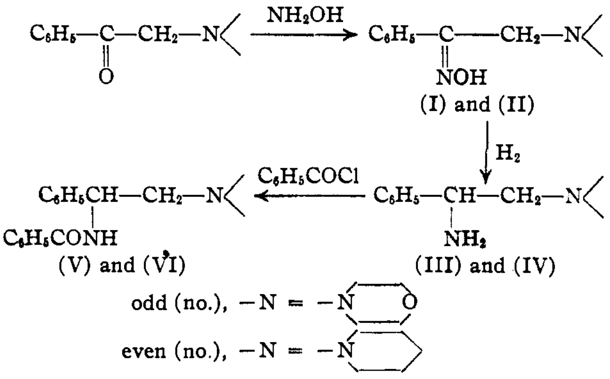
$$R-\underset{C_6H_5-CONH}{\underset{|}{CH}}-CH_2-N\langle$$

(B)

Attempts were made to obtain in good yields the oximes of ω-N-methylbenzylaminoacetophenone,[4] ω-tetrahydroisoquinolinoacetophenone[5] and ω-tetrahydroquinolinoacetophenone,[6] without success.

The oximes of ω-morpholino-[2b] and ω-piperidinoacetophenone[7] were both obtained in good yields. An extensive investigation was made of the reduction of one of these, (I), to the corresponding α,β-diamine. Sodium and alcohol was found to be the most efficient of the reagents tried. It was interesting to find that α-amino ketoximes are reduced to give better yields of the α,β-diamines by catalytic hydrogen, than were the β-amino ketoximes to give α,γ-diamines.[1] In the latter case it was shown that β-amino ketoximes lost the β-amino group on such treatment, probably because of the tendency to form an α,β-unsaturated ketoxime. The absence of such a tendency with α-amino ketoximes accounts for their greater yields of diamines on catalytic reduction.

The general low yields of α,β-diamines experienced even with sodium and alcohol were caused by condensation of the diamine with itself, through loss of ammonia during distillation. This was shown by the detection of ammonia in the forerun of such distillations and by treating the crude diamine ether solution with benzoyl chloride, and determining the yield of benzamide obtained.



The benzamides (V) and (VI) were readily prepared in good yields from the corresponding α,β-diamines (III) and (IV).

These benzamides have been found to be strong local anesthetics. The various compounds reported in this paper are being fully investigated for various pharmacological activities by L. W. Rowe and others of the Parke, Davis and Company Laboratories. A detailed pharmacological report will be published by them in another journal.

Experimental[8]

ω-Morpholinoacetophenone Oxime (I).—A cooled solution of 200 g. (4.35 mole) of potassium hydroxide in one liter of methanol was mixed with a solution of 61 g. (0.88

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(1) Cromwell, Wiles and Schroeder, THIS JOURNAL, **64**, 2432 (1942).

(2) (a) Hartung, *Chem. Rev.*, **9**, 435–437 (1931); (b) Rubin and Day, *J. Org. Chem.*, **5**, 54 (1940).

(3) (a) Wenker, THIS JOURNAL, **60**, 158 (1938); (b) Eisleb, U. S. Patent 2,073,100; *C. A.*, **31**, 3211^{7} (1937).

(4) Cromwell and Witt, THIS JOURNAL, **65**, 311 (1943).

(5) Allewelt and Day, *J. Org. Chem.*, **6**, 384 (1940).

(6) Kunckell, *Ber.*, **30**, 576 (1897).

(7) Rabe and Schneider, *ibid.*, **41**, 874 (1908).

(8) Micro Dumas analyses for nitrogen and semi-micro analyses for carbon and hydrogen by the Analytical Laboratory, Department of Chemistry, University of Nebraska, under the supervision of H. Armin Pagel.

mole) of hydroxylamine hydrochloride in 150 ml. of water at 20°. To this basic solution was added a solution of 46 g. (0.19 mole) of ω-morpholinoacetophenone hydrochloride[2b] in 70 ml. of water at 20°. The well-stoppered mixture was allowed to stand at room temperature for two days. The potassium chloride was filtered from the solution and the methyl alcohol evaporated *in vacuo* until only a sirupy residue remained. This residue was then mixed with 150 ml. of water and the solution neutralized with 300 ml. of 6 *N* hydrochloric acid. The white precipitate so obtained was filtered and washed with cold water until no trace of chloride could be detected in the washings. Recrystallization from methanol and water gave soft, white needles, m. p. 147-149°, weighing 38 g. (91% yield).

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32. Found: C, 65.48; H, 7.42.

This product was soluble in both dilute mineral acids and bases, hot methyl or ethyl alcohol, and warm ether.

ω-Piperidinoacetophenone Oxime (II).—This preparation was carried out in a similar manner to that used for (I), starting with 10 g. (0.043 mole) of ω-piperidinoacetophenone hydrochloride.[7] The white crystalline product weighed 7.9 g. (70% yield), m. p. 111-115°. By fractional crystallization from methyl alcohol, two products were obtained, m. p. 117-118.5° and m. p. 136-138.5°. A mixture of these two isomers melted at 111-115°.

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.40; H, 8.31. Found: m. p. 118°, C, 71.23; H, 8.40; m. p. 138°, C, 71.08; H, 8.37.

Both of these compounds dissolved readily in dilute mineral acids or bases and were soluble in ether and in methyl and ethyl alcohols.

α-Phenyl-β-morpholinoethylamine (III).—This diamine was obtained by the reduction of the corresponding oxime using various procedures.

A. By Catalytic Hydrogenation: (1) Using Raney Nickel.—Five grams (0.023 mole) of (I) was dissolved in 125 ml. of absolute alcohol and shaken with 1.0 g. of Raney nickel for a short time. The catalyst was filtered off and 1.0 g. of Raney nickel again added to the filtrate and the mixture shaken with hydrogen for six hours under a pressure of 50 lb./sq. in. Removal of the catalyst and evaporation *in vacuo* of the alcohol left a yellow oily residue which was dissolved in ether and washed several times with dilute sodium hydroxide and several times with a saturated salt solution. The ether solution was dried over anhydrous sodium sulfate and evaporated to give an oil which was further dried for several days over solid sodium hydroxide. Distillation gave 0.5 g. (10% yield) of a pale yellow oil, b. p. 134° (2 mm.). Considerable residue remained in the distilling flask and ammonia was detected in the forerun.

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.67; H, 8.74; N, 13.58. Found: C, 69.44; H, 8.90; N, 13.43.

When cooled to 0° this diamine solidified. It is slightly soluble in water and very soluble in quite dilute mineral acids.

Reduction of the oxime was inhibited when a similar reduction mixture, to which had been added 0.374 g. of ammonia, was subjected to the same treatment. Almost one-half of the starting oxime was recovered.

(2) **Using Palladium on Charcoal.**—Ten grams (0.046 mole) of (I) was dissolved in 50 ml. of glacial acetic acid and one-half gram of 30% palladium on charcoal added. Isolation of the product as in the previous experiment gave 1.4 g. (15% yield), b. p. 134° (2 mm.) and the product solidified on cooling to 0°. A similar experiment with 5 g. of (I) dissolved in 100 ml. of absolute alcohol to which had been added 3.3 g. of dry hydrogen chloride gas gave 0.5 g. (10% yield) of the diamine (III).

B. With Sodium and Alcohol.—Ten grams (0.046 mole) of (I) was dissolved in 120 ml. of absolute alcohol and 13.5 g. (0.59 mole) of cut sodium added over a period of three hours to the refluxing solution. Water (25 ml.) was added to destroy the sodium ethoxide, the solution neutralized with conc. hydrochloric acid at 0°, and the precipitated sodium chloride filtered off. The filtrate was then acidified and the solvent removed by vacuum distillation. The residue was mixed with 50% sodium hydroxide, with cooling, and the precipitated oil separated, purified and distilled as before, b. p. 150-152° (3 mm.), wt. 2.5 g. (26% yield). This product also solidified on cooling to 0°.

α-Phenyl-β-piperidinoethylamine (IV).—This diamine was prepared by a sodium-alcohol reduction of (II). It was necessary to use carefully dried absolute alcohol as the reduction medium. Because this diamine was somewhat soluble in water and dilute sodium hydroxide, 40% alkali was used in the purification step to remove any unchanged oxime. The product was a light yellow oil obtained in 24% yield, b. p. 128° (3 mm.). Considerable residue remained in the distilling flask and ammonia was detected in the forerun. The diamine became very viscous on cooling to 0° but did not solidify.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.45; H, 9.86; N, 13.70. Found: C, 76.62; H, 10.07; N, 13.54.

α-Phenyl-β-morpholino-N-benzoylethylamine (V) and α-Phenyl-β-piperidino-N-benzoylethylamine (VI).—These benzamides were prepared by treating a dry ether solution of the diamine with an equal molar quantity of benzoyl chloride at 0°. After allowing the mixture to stand at 0° for three hours the white hygroscopic hydrochloride was removed and mixed with dilute sodium bicarbonate and allowed to stand for twelve hours more in the ice-chest. The white gummy precipitate was recrystallized from alcohol and water. A 95% yield of (V), m. p. 143-144°, was obtained.

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.15; N, 9.09. Found: C, 73.79; H, 7.42; N, 9.05.

A 94% yield of (VI), m. p. 135-136°, resulted.

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.87; H, 7.85; N, 9.03. Found: C, 77.99; H, 8.20; N, 9.07.

Both (V) and (VI) were soluble in dilute mineral acids and insoluble in water.

The preparation of (VI) was repeated using an ether solution of the undistilled diamine (IV) (theoretically containing 2.15 g.). A yield of 2.0 g. of (VI), m. p. 135-136°, resulted. Assuming a 94% yield on benzoylation, this indicates a 65% yield of the diamine (IV) from the sodium and alcohol reduction of (II).

Summary

1. The conversion of α-amino ketones to the corresponding diamines via the reduction of the oximes of the amino ketones has been investigated.

2. Some interesting α,β-diamines and their corresponding benzamides have been prepared.

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