122° (27 mm.). The yield was 20%. Its hydrochloride salt melted at 107–108°. This compound is reported[15] to boil at 109° (12 mm.) and its hydrochloride to melt at 108°.

1-Ethyl-3,3-diphenyl-2-piperidone.—In 35 ml. of cold thionyl chloride was dissolved 16 g. (0.05 mole) of δ-diethylamino-α,α-diphenylvaleric acid. This solution was refluxed for thirty minutes while attached to a train described earlier for the trapping of ethyl chloride. Acid chloride formation occurred but no ethyl chloride was evolved. Excess thionyl chloride was removed from the mixture by warming under vacuum and the residual liquid heated gradually to 150° at which point ethyl chloride began to be evolved. When the temperature was then raised to 175° over a period of twenty minutes the reaction appeared complete. Considerable blackening of the mixture occurred. The product was dissolved in ether, and the resulting solution washed with water and dried over potassium carbonate. The solvent was evaporated and the residue dissolved in alcohol, treated twice with charcoal, and recovered from the alcohol by evaporation of this solvent. After recrystallization once from Skelly C and once from a methanol–water mixture, it melted at 119–119.5°. The yield was 4 g. (30%).

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.57; N, 5.01. Found: C, 82.01; H, 7.32; N, 4.88.

3-(γ-Diethylaminopropyl)-1-ethyl-3-phenyl-2-piperidone.—To 50 ml. of cold thionyl chloride was added 25 g. (0.057 mole) of α,α-bis-(γ-diethylaminopropyl)-phenylacetic acid dihydrochloride. The resulting solution was refluxed on a steam-bath for ninety minutes and the excess thionyl chloride removed by distillation on a steam-bath under reduced pressure. The yellow solid acid chloride dihydrochloride residue was heated to 190° before darkening and melting began. At 205–210° ethyl chloride was evolved and the reaction approached completion in thirty minutes. Finally the mixture was heated to 225° for fifteen minutes.

The cooled mixture was dissolved in water, non-basic impurities removed by three ether extractions, the solution made alkaline, and the liberated oil separated by three extractions with ether. The combined extracts were dried over potassium carbonate, the solvent removed, and the product distilled under reduced pressure. It boiled at 150–153° (0.04 mm.), $n^{25}D$ 1.5238. The yield was 13.2 g. (73%).

Anal. Calcd. for $C_{20}H_{32}N_2O$: C, 75.89; H, 10.10; N, 8.84. Found: C, 75.89; H, 9.99; N, 8.78.

Ethyl α,α-bis-(γ-Diethylaminopropyl)-phenylacetate.—To 30 ml. of cold thionyl chloride was added 15 g. (0.041 mole) of α,α-bis-(γ-diethylaminopropyl)-phenylacetic acid. This mixture was refluxed for one hour, the excess thionyl chloride removed on a steam-bath under 10 mm. pressure and the solid residue refluxed with 75 ml. of alcohol for one hour. The alcohol was removed under reduced pressure on a steam-bath, the solid residue dissolved in water, and the solution made alkaline. The liberated oil was diluted with ether, separated, the solution dried over potassium carbonate, the ether evaporated, and the residue fractionated. The yield of ester, b. p. 149–151° (0.05 mm.), $n^{25}D$ 1.4902, was 11.2 g. (70%).

Anal. Calcd. for $C_{24}H_{42}N_2O_2$: N, 7.18. Found: N, N, 7.35. This ester was converted to its dihydrochloride which melted at 220–222° (dec.).

Anal. Calcd. for $C_{24}H_{42}N_2O_2{\cdot}2HCl$: C, 62.17; N, 9.57; Cl, 15.30. Found: C, 62.48; H, 9.72; Cl, 15.45.

Summary

An intramolecular reaction between acid chlorides and tertiary amines, with the simultaneous elimination of a molecular equivalent of alkyl halide, has been noted.

This reaction has been applied to the syntheses of pyrrolidones and piperidones.

A novel method for opening heterocyclic nitrogen rings is presented.

RENSSELAER, NEW YORK RECEIVED FEBRUARY 28, 1949

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[15] C. Räth, *Ann.*, **489**, 107–118 (1931).

[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE]

Pyrolysis of Some Amino Acids

BY ROBERT L. CLARKE AND ARAM MOORADIAN

It has been noted by Le Sueur[1] that pyrolysis of a mixture of ethyl α,α′-dibromoadipate and monoethylaniline at 185–195° produced ethyl 1-phenylpyrrolidine-2,5-dicarboxylate (62.5% yield) and diethylaniline. The intermediate was demonstrated to be ethyl α,α′-bis-(N-ethylanilino)-adipate which then decomposed with evolution of diethylaniline.

With the idea that ethyl α,α-bis-(β-diethylaminoethyl)-α-phenylacetate might be pyrolyzed to produce ethyl 1-ethyl-4-phenylpiperidine-4-carboxylate (the ethyl analog of "Demerol") and triethylamine, Clarke, *et al.*,[2] attempted to make the necessary ester and failed because the acid chloride obtained was transformed into a pyrrolidone.

Since the preparation of ethyl α,α-bis-(β-diethylaminoethyl)-α-phenylacetate was found to be difficult, it seemed of interest to determine whether the acid instead of the ester might be pyrolyzed to give a piperidine carboxylic acid. Pyrolysis of α,α-bis-(β-diethylaminoethyl)-α-phenylacetic acid at 180-200° did not cause separation of any of the expected triethylamine, but gave an excellent yield of diethylamine (91%). From the residue α-diethylaminoethyl-α-phenylbutyrolactone was obtained in 84% yield.

In order to determine whether diethylamine was eliminated in this pyrolysis to produce α-diethylamino-α-vinyl-α-phenylacetic acid which then lactonized or the hydrogen of the carboxyl group was eliminated in the diethylamine, a sample of α,α-bis-(β-diethylaminoethyl)-α-phenyl acetonitrile which contained no carboxyl hydrogen was heated at its boiling point near 300°. There was no evidence of decomposition. In order to exclude the possibility that the decomposition

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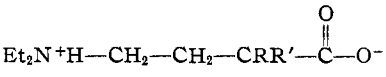
[1] Le Sueur, *J. Chem. Soc.*, **95**, 273 (1909); **97**, 173 (1910).

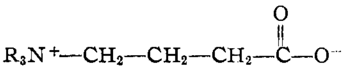
[2] Clarke, Mooradian, Lucas and Slauson, THIS JOURNAL, **71**, 2821 (1949).

was acid catalyzed, a granule of diphenylacetic acid was added to a fresh sample of the nitrile and the mixture heated. Again no decomposition occurred. Apparently it is the form indicated by formula I which undergoes decomposition by attack of the anionoid group upon the nitrogen–γ-carbon bond with simultaneous lactone formation and elimination of diethylamine.



I

$$Et_2N^+H—CH_2—CH_2—CRR'—\overset{\overset{\displaystyle O}{\|}}{C}—O^-$$



II

$$R_3N^+—CH_2—CH_2—CH_2—\overset{\overset{\displaystyle O}{\|}}{C}—O^-$$

A precedent for this reaction is found in the decomposition of betaines of γ-amino acids.[3] These yield trialkylamines and γ-lactones when heated. Formula II indicates the form which is stated to be involved.

The reaction under discussion was first noted with a compound containing two basic groups, but it was shown that two such groups were not necessary since γ-diethylamino-α-phenylbutyric acid was converted into α-phenylbutyrolactone and diethylamine. Even the aryl group was not required as demonstrated by the pyrolysis of γ-diethylaminobutyric acid to give butyrolactone (63%). Here the expected lactone was accompanied by an unidentified basic product.

In order to note the effect of two aryl groups in the α-position, γ-diethylamino-α,α-diphenylacetic acid was heated and found to undergo decarboxylation principally to yield 1-diethylamino-3,3-diphenylpropane[4] (75%) and α,α-diphenylbutyrolactone (15%). The decarboxylation reaction is favored by high temperature. Thus, when this last pyrolysis was accomplished with rapid heating, the yield of the lactone was reduced to 7%.

δ-Diethylamino-α,α-diphenylvaleric acid was subjected to pyrolysis and found to undergo decarboxylation exclusively to give 1-diethylamino-4,4-diphenylbutane.[5] Whether the tendency for lactone formation is overshadowed completely by decarboxylation in this single case involving pyrolysis of a δ-amino acid or this tendency is absent is not known and remains to be investigated with δ-amino acids that have no groups in the α-position which could promote decarboxylation.

Experimental

Pyrolysis of α,α-bis-(β-Diethylaminoethyl)-α-phenylacetic Acid.—α,α-bis-(β-Diethylaminoethyl)-α-phenylacetic acid (50 g., 0.15 mole) was heated in a distillation flask at 210–222° for thirty minutes. The distillate consisted of 10 g. (0.14 mole) of diethylamine; b. p. 55.5–56°; n^{25}_{D} 1.3840. The amine was converted to the hydrochloride which melted at 225–227° (cor.) and contained 32.8% chlorine; calcd. Cl, 32.4.

The residue from the pyrolysis, α-diethylaminoethyl-α-phenylbutyrolactone, boiled at 130–133° (0.05 mm.); n^{25}_{D} 1.5196; yield 33 g. (84%).

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.87; N, 5.36. Found: C, 73.38; H, 8.95; N, 5.31.

Pyrolysis of γ-Diethylaminoethyl-α-phenylbutyric Acid.—The pyrolysis of 30 g. of this acid was accomplished in the manner described above. The α-phenylbutyrolactone boiled at 109–112° (0.25 mm.); n^{25}_{D} 1.5411; yield 15 g. (73%).

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.04; H, 6.21. Found: C, 74.04; H, 6.42.

Pyrolysis of γ-Diethylaminobutyric Acid.—When 17 g. (0.11 mole) of this acid was heated at 225–230° for ninety minutes, 2.8 g. of diethylamine (36%) was collected. When the residue was heated to 250°, 5.8 g. (63%) of γ-butyrolactone distilled; b. p. 210–212° (1 atm.); n^{25}_{D} 1.4372. Continuation of the distillation under reduced pressure yielded 3.2 g. of an impure, unidentified, basic liquid which boiled at 130–133° (7 mm.); n^{25}_{D} 1.4575.

Pyrolysis of γ-Diethylamino-α,α-diphenylbutyric Acid.—Pyrolysis of 15 g. (0.048 mole) of this acid was accomplished as described above. Evolution of carbon dioxide was noted together with a rather small amount of diethylamine. The residue was diluted with ether and a basic fraction extracted with dilute hydrochloric acid. Basification of this extract yielded 9.6 g. (75%) of 1-diethylamino-3,3-diphenylpropane[4] which boiled at 111–113° (0.09 mm.); n^{25}_{D} 1.5438. This compound resulted from decarboxylation of the original acid.

Anal. Calcd. for $C_{19}H_{25}N$: C, 85.34; H, 9.42; N, 5.23. Found: C, 85.13; H, 9.21; N, 5.18.

The ether solution of the pyrolysis residue, after extraction with acid, was dried over potassium carbonate and the ether evaporated. The residue solidified and was recrystallized from Skelly C. This product, which melted at 80–81°, was α,α-diphenylbutyrolactone; 1.8 g. (15%).

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.95; H, 5.66.

Pyrolysis of δ-Diethylamino-α,α-diphenylvaleric Acid.—A 15-g. sample (0.046 mole) of this acid was heated at 200° for one hour and then at 250° for a second hour. No amine, only carbon dioxide was liberated. Fractionation of the residue yielded 9.8 g. (76%) of 1-diethylamino-4,4-diphenylbutane; b. p. 118–120° (0.05 mm.); n^{25}_{D} 1.5398. Marxer[5] found 130–132° (0.08 mm.).

Anal. Calcd. for $C_{20}H_{27}N$: N, 4.98. Found: N, 4.92.

Summary

An initial study of the pyrolysis of γ-N,N-dialkylamino acids has shown that they are converted to γ-lactones with simultaneous elimination of a molecular equivalent of dialkylamine unless decarboxylation becomes the predominating reaction.

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[3] Willstätter and Kahn, *Ber.*, **37**, 1853 (1904).

[4] Eisleb, *ibid.*, **74**, 1433 (1941).

[5] Marxer, *Helv. Chim. Acta*, **24**, 209E (1941).