NOTES

The Preparation of 1-Methyl-4-phenyl-4-cyanopiperidine

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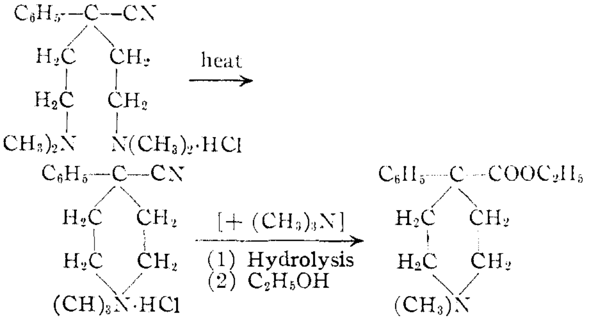
Prior to this investigation we know of no instance in which the direct pyrolysis of an acid salt[1] of a compound which contains two tertiary amino groups has been shown to yield a basic cyclic compound by the elimination of a tertiary amine.

In 1909 Le Sueur[2] heated a mixture of diethyl α,α'-dibromoadipate and monoethylaniline and obtained diethyl 1-phenylpyrrolidine-2,5-dicarboxylate in 62.5% yield. He stated that it is very probable that diethyl α,α'-di-(N-ethylanilino)-adipate was formed first and that this substance lost diethylaniline to form the pyrrolidine.

Le Sueur and Haas,[3] in 1910, heated a mixture of diethyl α,α'-dibromoadipate and diethylaniline and isolated the pyrrolidine mentioned above and ethyl bromide. In this instance we believe that the first reaction product may have been diethyl α,α'-di-(N-ethylanilino)-adipate diethobromide which lost ethyl bromide and then diethylaniline to produce the pyrrolidine. In this event, the reaction is entirely analogous to one which had been carried out a few years earlier by Willstätter[4] in which he found that when the dimethochloride of 1,4-di-(dimethylamino)-butane was heated, methyl chloride and trimethylamine were liberated and 1-methylpyrrolidine was the chief reaction product.

Clarke, *et al.*,[5] hoped to obtain ethyl 1-ethyl-4-phenylpiperidine-4-carboxylate by pyrolytic elimination of triethylamine from ethyl α,α-di-(β-diethylaminoethyl)-α-phenylacetate. However, since they could not obtain the latter ester by the method which they employed, this reaction was not carried out. Clarke and Mooradian[6] then attempted to eliminate triethylamine from α,α-di-(β-diethylaminoethyl)-α-phenylacetic acid. However, instead of triethylamine, diethylamine was evolved and α-diethylaminoethyl-α-phenylbutyrolactone was formed. Finally, they found that when α,α-di-(β-diethylaminoethyl)-α-phenylacetonitrile was heated at its boiling point (about 300°), triethylamine was not eliminated; the nitrile boiled unchanged.

Unaware of the experiments of Clarke, *et al.*, we heated α,α-di-(β-dimethylaminoethyl)-α-phenylacetonitrile at its boiling point in the hope that trimethylamine would be removed with the formation of 1-methyl-4-phenyl-4-cyanopiperidine, a compound which after hydrolysis and esterification with ethanol would yield ethyl 1-methyl-4-phenylpiperidine-4-carboxylate (Demerol). The nitrile remained unchanged at its boiling point but when the solid monohydrochloride was heated to its melting point a vigorous evolution of trimethylamine took place; the residue consisted of the desired nitrile which, after purification, was isolated in 78.5% yield.



It was found that "Demerol nitrile" could also be obtained by pyrolysis of α,α-di-(β-dimethylaminoethyl)-α-phenylacetonitrile dihydrochloride in 55% yield and by pyrolysis of a mixture of equimolecular amounts of the nitrile base and the nitrile dihydrochloride in 71% yield.

Experimental Part

α,α-Di-(β-dimethylaminoethyl)-α-phenylacetonitrile. Mono- and Dihydrochloride.—A solution of 58.5 g. (0.5 mole) of phenylacetonitrile in 50 cc. of benzene was added, dropwise, to a cold (ice-bath), stirred suspension of 43.0 g. (1.1 moles) of pulverized sodamide in 150 cc. of benzene. The mixture was cooled and stirred for one hour, and β-dimethylaminoethyl chloride, obtained from 158.4 g. (1.1 moles) of the basic chloride hydrochloride, dissolved in 150 cc. of benzene was added, in portions, while the temperature was maintained below 40°. After the mixture had been refluxed for 3 hours it was cooled, diluted with 200 cc. of water, the organic layer separated, and the aqueous layer extracted with benzene. The solvent was removed from the combined benzene solutions, and the residue fractionated; b.p. 130–135° (1–2 mm.)[7]; yield 115 g. (89%).

Anal. Calcd. for $C_{16}H_{25}N_3$: N, 16.20. Found: N, 16.05.

The monohydrochloride was obtained when the water was removed, under reduced pressure, from a mixture of 129.3 g. (0.5 mole) of the base, 250 cc. of water and 90.0 g. (0.5 mole) of constant-boiling hydrochloric acid. A sample of the solid residue was dried to constant weight *in vacuo* over phosphorus pentoxide; it melted at 242–243° (dec.) after the bath had been preheated to 220°.

Anal. Calcd for $C_{16}H_{25}N_3 \cdot HCl$: Cl, 12.01. Found: Cl, 12.02.

In the presence of organic solvents the monohydrochloride undergoes transformation into the dihydrochloride. After the monohydrochloride had been ground under absolute ether, the chlorine content rose to 13.60%. The material was then dissolved in hot absolute alcohol, the solution cooled and the gelatinous precipitate filtered. The product then contained 18.43% chlorine and melted at 257–258° (dec.). In another experiment, after the alcohol treatment, the compound contained 21.04% chlorine and melted at 265–266° (dec.).

The dihydrochloride precipitated when an ethereal solution of the base was treated with hydrogen chloride; it melted at 268–269° (dec.) after the bath had been preheated to 260°.

Anal. Calcd. for $C_{16}H_{25}N_3 \cdot 2HCl$: N, 12.65; Cl, 21.41. Found: N, 12.55; Cl, 21.53.

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[1] The term "acid salt" is used to differentiate the compound from a "quaternary salt."

[2] H. R. Le Sueur, *J. Chem. Soc.*, **95**, 273 (1909).

[3] H. R. Le Sueur and P. Haas, *ibid.*, **97**, 173 (1910).

[4] R. Willstätter and W. Huebner, *Ber.*, **40**, 3872 (1907).

[5] R. L. Clarke, A. Mooradian, P. Lucas and T. J. Slauson, This Journal, **71**, 2821 (1949).

[6] R. L. Clarke and A. Mooradian, *ibid.* **71**, 2825 (1949).

[7] P. Lucas, U. S. Patent 2,510,784; *C. A.*, **44**, 8370 (1950).

Pyrolysis of α,α-Di-(β-dimethylaminoethyl)-α-phenylacetonitrile Monohydrochloride.—The monohydrochloride (29.6 g.) was placed in a 300-cc. flask, to which an air condenser was attached, and heated in a metal-bath which was maintained at 270–290°. As soon as the salt melted, trimethylamine was evolved. After about 6 minutes the salt had melted completely, and after ten minutes the evolution of gas had practically stopped. The cold, light brown, glass residue (the material becomes crystalline if rubbed under ether) was dissolved in a warm mixture of 20 cc. of water and 5 cc. of hydrochloric acid. The aqueous, acidic solutions, obtained from three experiments, were combined and the solution was made strongly alkaline. The precipitated nitrile was extracted with ether, the extract dried over magnesium sulfate, the solvent removed and the residue fractionated. The Demerol nitrile boiled at 119–122° (1–2 mm.); yield 47.1 g. (78.5%). The distillate solidified completely; m.p. 53°.[8] The hydrochloride melted at 222–224°[9] after recrystallization from absolute ethanol; mixed m.p. with an authentic sample 222–224°. The picrate melted at 247°[10] after recrystallization from methanol.

The evolved trimethylamine was passed into methyl bromide dissolved in chloroform, and the precipitated tetramethylammonium bromide (77%)[11] was analyzed.

Anal. Calcd. for $C_4H_{12}NBr$: Br, 51.87. Found: Br, 51.84.

Pyrolysis of a Mixture of Molecular Equivalent Amounts of the Base and the Dihydrochloride; Pyrolysis of the Dihydrochloride.—A mixture of 12.9 g. (0.05 mole) of the base and 16.5 g. (0.05 mole) of the dihydrochloride was heated in a bath at 260–280° (bath temperature) for 10 minutes and then at 280–310° for another 10 minutes. After the reaction mixture had been treated in the described manner, 14.2 g. (71%) of pure Demerol nitrile was obtained; m.p. 53°.

The dihydrochloride (22.5 g.) was heated in the manner described above. There was obtained 7.5 g. (55%) of Demerol nitrile. The hydrochloride melted at 222–224°.

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[8] O. Eisleb (*Ber.*, **74**, 1433 (1941)), m.p. 53°.

[9] Reference 8, m.p. 221–222°.

[10] F. Bergel, A. L. Morrison and H. Rinderknecht (*J. Chem. Soc.*, 265 (1944)), m.p. 249–250°.

[11] A small amount of trimethylamine escaped from the solution.

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RECEIVED DECEMBER 14, 1951

Wien Effect in Polyelectrolytes

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RECEIVED NOVEMBER 24, 1951

If polyvinylpyridine is quarternized by the addition of butyl bromide, a typical polyelectrolyte is obtained. The statistical coil characteristic of the neutral polymer is distended by the intramolecular repulsion among the built-in cations; this is, however, partially screened by the counter ions which are held in the volume of the coil by the total cationic field. The equilibrium between free and associated counter ions is, of course, a dynamic one. (Here, we define free counter ions as those in the solvent between the polyions, and associated counter ions as those within the average radius of the polymer coil.) The associated counter ions do not contribute to anion current[1] and the conductance of a polyelectrolyte is therefore less than that of the corresponding monomeric salt at the same concentration. The polycation naturally has no sharp boundary, on account of intramolecular Brownian motion; we may, however, imagine a zone in which the potential energy of a cation is of the order of kT and define this zone as the periphery of the polycation. Inside this region, a counter ion will be considered as associated with the polycation. A small decrease in potential energy should therefore suffice to remove some of the peripheral counter ions, and thereby increase the population of free ions, and with it the conductance. We would then expect[2] a fairly large Wien effect[3] for polyelectrolytes. The purpose of this note is to present preliminary results which confirm this prediction and which presumably may be taken as additional evidence confirming our model.

A sample of poly-4-vinyl-N-*n*-butylpyridinium bromide[4] was used which has a degree of polymerization of approximately 2000. Strauss[4] found a reduced viscosity of about 12 at a concentration of 0.001 monomolar; the equivalent Einstein sphere would have a radius of the order of 500 Å. Conductances were measured by the Differential Pulse Transformer bridge method[5] over the range 9–18 kv./cm., at 25.00° at a concentration of 0.00105 monomolar in water. Pulse widths of 4, 6 and 11 μsec. were used; balancing was performed visually on single pulses. The experimental results are summarized in Fig. 1, where relative increase in specific conductance, $\Delta\kappa/\kappa_0$, is plotted against field strength in kv./cm. Here, κ_0 is conductance at low voltages and for all practical pur-

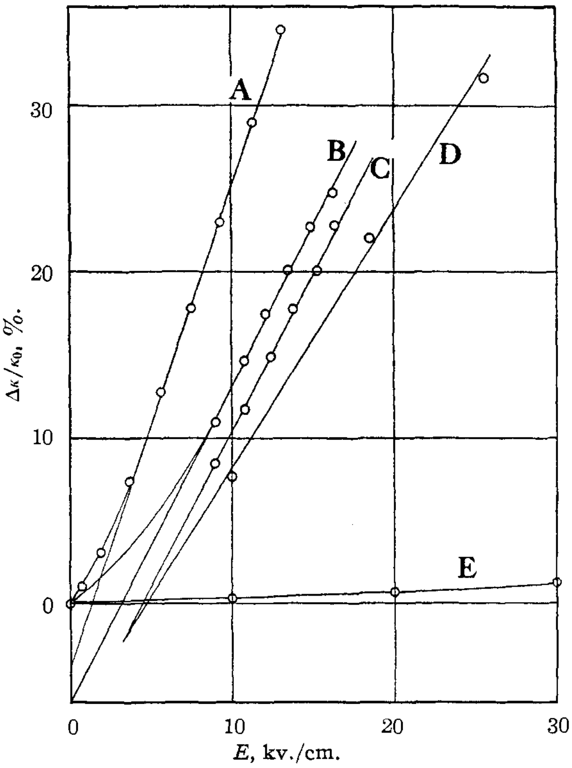

Fig. 1.—Wien effect of poly-4-vinyl-N-*n*-butylpyridinium bromide: A, $(Bz)_3NHPi$; B, 11 μsec.; C, 6 μsec.; D, 4 μsec.; E, $MgSO_4$.

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[1] W. R. Huizenga, P. E. Grieger and F. T. Wall, THIS JOURNAL, **72**, 2636 (1950).

[2] D. Edelson and R. M. Fuoss, *ibid.*, **72**, 306 (1950).

[3] H. C. Ekstrom and C. C. Schmelzer, *Chem. Revs.*, **24**, 367 (1939).

[4] R. M. Fuoss and U. P. Strauss, *Trans. N. Y. Acad. Sci.*, **51**, 836 (1949).

[5] J. A. Gledhill and A. Patterson, Jr., *Rev. Sci. Instruments*, **20**, 960 (1949).