Research Laboratories, Aldrich Chemical Company

2-Methylene-3-quinuclidinone and Its Derivatives

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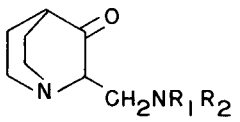
Work carried out recently in these laboratories in the quinuclidine field made available novel synthetic intermediates which have not yet been described in the literature.

The Mannich reaction of 3-quinuclidinone with higher boiling amines such as morpholine or piperidine afforded the expected Mannich bases (I) which distilled without decomposition. On the other hand dimethylamine yielded a Mannich product which deaminated spontaneously on distillation to produce 2-methylene-3-quinuclidinone (II) in almost quantitative yield. This compound exhibited infrared bands at 5.85 μ (carbonyl) and at 6.1 μ (C=CH_2 out of plane in phase deformation).

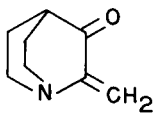
Thus, formation of II by elimination of dimethylamine during the distillation of the Mannich base represents one of the most facile preparations of a heterocyclic α,β-unsaturated ketone (1). The structure of II was further confirmed through 1,2 and 1,4 additions of various nucleophiles which will be the subject of a forthcoming publication.

Although a hydrochloride of II could be prepared under anhydrous conditions which showed the correct infrared absorption of an α,β-unsaturated ketone, a hydrochloride dihydrate (2) (prepared in aqueous alcohol) showed no carbonyl or C=C absorption. The compound has also very poor solubility in water and in alcohol. This suggests a structure of a water-addition product III, which probably exists as a polymer formed through an intermolecular hydrogen bonding. The free base II can be regenerated from the basified solutions of III by distillation.

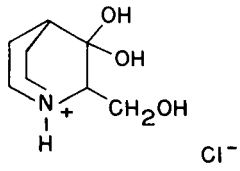
2-Methylene-3-quinuclidinone base also reacted with water to produce solids containing one to three molecules of water. They showed no carbonyl absorption in the infrared, but exhibited a wide band at 6.23 μ. The n.m.r. data are consistent with the structure of hydrated enol IV. The hydrates could be converted into II by distillation; they also underwent normal reactions of II, such as additions of secondary amines.



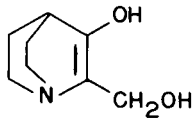
I



II



III



IV

EXPERIMENTAL (3)

2-Methylene-3-quinuclidinone (II).

A solution of 200 g. (1.6 moles) of 3-quinuclidinone, 270 g. (2.4 moles) of 40% aqueous dimethylamine, 194.8 g. (2.4 moles) of 37% aqueous formaldehyde, 250 ml. of ethanol and 100 ml. of water was stirred at reflux for one hour, then at 70° for 17 hours and allowed to cool to room temperature. The solvents and excess reagents were evaporated *in vacuo* and the oily residue fractionally distilled to provide 203 g. (92.5%) of 2-methylene-3-quinuclidinone as a slightly yellow oil, b.p. 91-92°/7 mm., $n_D^{20°}$ 1.5110.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.72; H, 8.09; N, 10.22.

The hydrochloride prepared in ether melted at 243-244° (dec.) and showed infrared absorption at 5.8 μ (C=O) and 6.07 μ (C=C).

Anal. Calcd. for $C_8H_{12}ClNO$: Cl, 20.42. Found: Cl, 20.80.

2-Hydroxymethyl-3,3-dihydroxyquinuclidine hydrochloride (2) (III).

This compound was prepared from II and one equivalent of concentrated hydrochloric acid in 50% aqueous ethanol and recrystallized from water in microprisms, m.p. 284-288° (dec.). Infrared: 3.15 μ (wide band), 6.13 μ (very weak peak).

Anal. Calcd. for $C_8H_{16}ClNO_3$: C, 45.82; H, 7.69; N, 6.69; Cl, 16.91. Found: C, 46.12; H, 7.44; N, 6.78; Cl, 16.48.

2-Hydroxymethyl-3-hydroxyquinuclid-2-enine hydrate (IV).

2-Methylene-3-quinuclidinone was dissolved in water and acetone was added to cloudiness. On standing, a colorless solid precipitated, m.p. 65-66°, which was dried over phosphorus pentoxide. The n.m.r. spectrum in deuterium oxide showed DOH, 5.25 τ (4H); CH at C_4 (triplet, centered around 7.35 τ, 1H); CH_2 in 2-CH_2OH: 5.73 τ (singlet, 2H).

Anal. Calcd. for $C_8H_{13}NO_2 \cdot {}^3/_4H_2O$: C, 56.96; H, 8.67; N, 8.30. Found: C, 56.77; H, 8.16; N, 7.96.

REFERENCES

(1) *Cf.* H. Hellmann and G. Opitz, "α-Aminoalkylierung", Verlag Chemie, CMBH, Weinheim, Bergstr., 1960, pp. 246-248.

(2) Sold by the Aldrich Chemical Company under the name of "2-methylene-3-quinuclidinone hydrochloride dihydrate."

(3) Melting points were corrected and determined in capillary tubes. Infrared spectra were measured as film or nujol mull with a Beckman IR-5A spectrophotometer.

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