Preparation of 3,4,4a,5,11,11a-Hexahydro-1,4-ethano-1*H*-benzo[5,6]cyclohepta-[1,2-*b*]pyridin-6-(2*H*)one

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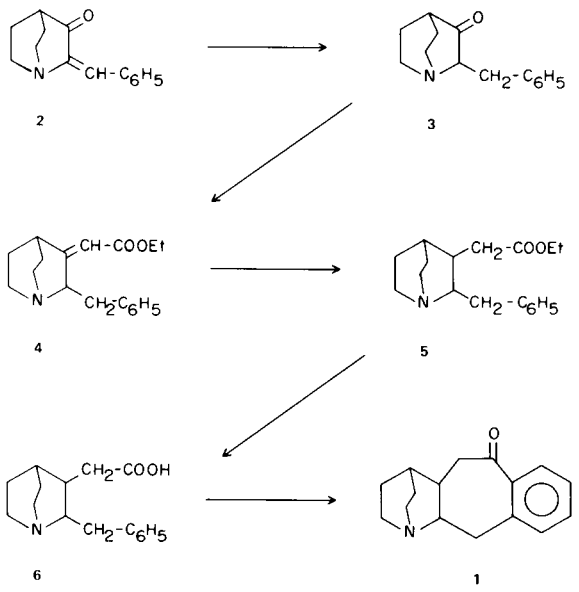
For a study of some structure-biological activity relationships in another project, it was necessary to prepare relatively large amounts of the title compound **1**. The synthetic scheme shown proceeded smoothly and was adaptable to large scale runs.

The readily available 3-quinuclidinone hydrochloride was converted into the 2-benzylidene derivative, **2**, by a slight modification of the method previously described (1). Catalytic hydrogenation using 5% palladium on carbon gave 2-benzyl-3-quinuclidinone, **3**. The reaction



of **3** with triethyl phosphonoacetate in the presence of sodium hydride in dimethylformamide yielded the unsaturated ester **4** which was hydrogenated to the saturated ester **5**. Saponification to acid **6** and subsequent intramolecular ring closure gave the title compound **1**. Cyclization was effected by two methods, excess aluminum chloride on the acid chloride in carbon disulfide (Method 1) or the polyphosphoric acid cyclization directly on acid **6** (Method 2). The former, although a little more tedious, gave a cleaner product in better yield.

EXPERIMENTAL (2)

2-Benzylidene-3-quinuclidinone (**2**).

A solution of 39.6 g. of potassium hydroxide in 240 ml. of methanol was added dropwise with stirring at 0 to 5° to a suspension of 3-quinuclidinone hydrochloride (96.9 g., 0.6 mole) and benzaldehyde (96 g., 0.9 mole) in 120 ml. of methanol. The mixture was permitted to warm to room temperature and heated on the steam bath overnight. The solution was poured into water and steam distilled. The residue was cooled and the precipitated yellow product was filtered, air dried, and recrystallized from benzene-hexane to give 111 g. (87%) of **2** having a m.p. of 129-130° (reported m.p. 133° (1)); ir: 5.85 μ (C=O) and 6.1 μ (C=C).

2-Benzyl-3-quinuclidinone (**3**).

A solution of 2-benzylidene-3-quinuclidinone, **2** (59.1 g., 0.27 mole) in 900 ml. of absolute ethanol was reduced in a Parr hydrogenator in the presence of 15 g. of 5% palladium on carbon and 60 psi hydrogen pressure at room temperature. The theoretical quantity of hydrogen was taken up in 15 minutes but the reduction was continued for an additional 60 minutes. The catalyst was removed, and the filtrate was concentrated *in vacuo* on the steam bath. The residue was recrystallized from petroleum-ether (b.p. 30-60°) to give 50.5 g. (86%) of a white solid, m.p. 79-81°; ir: 5.78 μ (C=O).

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.57. Found: C, 78.17; H, 8.27; N, 6.43.

2-Benzyl-3-carbethoxymethylidenequinuclidine (**4**).

To a cooled (0-5°) suspension of sodium hydride (52%, 21 g., 0.5 mole) in 1 l. of dry DMF was added with stirring, triethylphosphonoacetate (112.1 g., 0.5 mole) and the mixture was stirred for 30 minutes. At 0° a solution of **3** (107 g., 0.5 mole) in 100 ml. DMF was added dropwise and the solution was then stirred for 20 hours at room temperature. The reaction mixture was poured into ice water and the precipitate was filtered, air dried, and recrystallized from petroleum ether to give 109 g. (76%) of a white solid having m.p. of 87-88°; ir: 5.87 μ (C=O ester) and 6.10 μ (C=C).

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.96; H, 8.41; N, 4.89.

2-Benzyl-3-carbethoxymethylquinuclidine (**5**).

The unsaturated ester, **4**, (118 g., 0.41 mole) in 1 l. of ethanol was hydrogenated at 60 psi hydrogen pressure at room temperature and 15 g. of 5% palladium on carbon. The reduction was permitted to run an additional hour after the theoretical amount of hydrogen was absorbed. The catalyst was removed and the residue was distilled to give 97.7 g. (84.3%) of a light yellow liquid having a b.p. of 172-174° (0.025 mm.); ir: 5.75 μ.

Anal. Calcd. for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.36. H, 8.96; N, 4.75.

2-Benzyl-3-carboxymethylquinuclidine (**6**).

A solution of ester **5** (86.1 g., 0.3 mole), 80 g. of potassium hydroxide, 90 ml. of water and 600 ml. of ethanol was heated under reflux for 6 hours and the solvents removed *in vacuo*. The residue was dissolved in water (about 200 ml.) and after a preliminary extract with ether, was acidified with acetic acid to give 77 g. (95%) of acid **6** having a m.p. of 240-245° after recrystallization from 2-propanol.

Anal. Calcd. for $C_{16}H_{21}NO_2 \cdot \frac{1}{2} H_2O$: C, 71.61; H, 8.26; N, 5.22. Found: C, 72.18; H, 8.07; N, 5.13.

3,4,4a,5,11,11a-Hexahydro-1,4-ethano-1*H*-benzo[5,6]cyclohepta-[1,2-*b*]pyridin-6-(2*H*)-one, (**1**).

Method 1.

To a solution of acid **6** (50.0 g., 0.193 mole) in 1 l. of anhydrous benzene was added 50 g. of thionyl chloride, and the mixture was heated on the steam bath under reflux for 2 hours. The excess solvents were reomved *in vacuo* and to the residue was added 2 l. of dry carbon disulfide. At room temperature aluminum chloride (77 g., 0.58 mole) was added portionwise and the mixture stirred at room temperature overnight. The excess solvent was removed by distillation and dilute (10%) hydrochloric acid was added to dissolve the residue. After a preliminary ether extract, the aqueous solution was made strongly basic with 50% sodium hydroxide, and the product was extracted with ether. The ether solution was washed with water, dried over sodium sulfate, the ether was removed and the residue was distilled to give 26.9 g. (58%) of product having a b.p. of 214-220° (1 mm.). The product crystallized on cooling and was recrystallized from petroleum ether; m.p. 85.87°; ir: 6.0 μ.

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.88; H, 8.15; N, 5.70.

Method 2.

A mixture of acid **6** (10 g.) and 300 g. of commercial polyphosphoric acid was heated with stirring at 140-145° for 2 hours and poured while still warm onto ice. The solution was basified with sodium hydroxide (50%) and extracted with ether. The ether solution was processed as in Method 1 to give 3 g. of ketone **1** having melting point of 80-83°. The ir and behavior of this material on thin layer chromatography were identical to **1** prepared by method 1.

The nmr spectrum of **1** taken on a Varian A-60A in deuteriochloroform using TMS as internal reference shows multiplets at δ 1.4-2.1 (6H); δ 2.4-3.4 (9H) and δ 7.1-7.6 (4H), (3).

REFERENCES

(1) G. R. Clemo and E. Hoggarth, *J. Chem. Soc.*, 1243 (1939).

(2) Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected.

(3) We are indebted to Mr. James Morton of the Physical Analytical Department of the Schering Corporation for his interpretation of the nmr spectrum.

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