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2-Skatylquinuclidine. A Convenient Synthesis of a 2-Aroylquinuclidine

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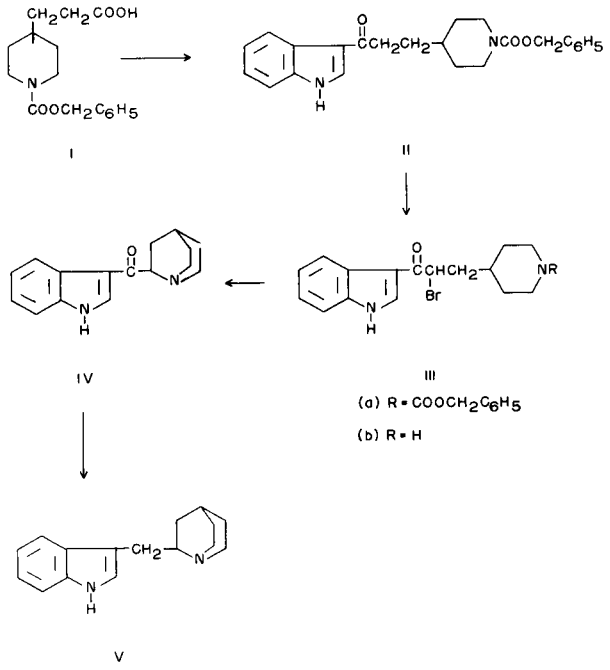
We wish to report a convenient method for construction of the quinuclidine ring, which allowed the preparation of 3-indolyl-2-quinuclidinylketone (IV), the key intermediate for the synthesis of 2-skatylquinuclidine (V).

The acid chloride of β-(1-carbobenzoxy-4-piperidyl)propionic acid (I) was condensed with indolylmagnesium bromide to afford the *N*-carbobenzoxy ketone (II) in a 47% yield. Treatment of II with the novel brominating agent, trimethylphenylammonium tribromide (1), in tetrahydrofuran at room temperature produced the α-bromoketone (IIIa) in a 74% yield. When IIIa was exposed to dry hydrogen bromide in acetic acid at room temperature the carbobenzoxy group was rapidly removed without disturbance of the α-bromoketone moiety. Evaporation of the hydrogen bromide-acetic acid mixture, followed by treatment of the residual piperidyl bromoketone (IIIb) with dilute alkali gave the 3-indolyl-2-quinuclidinyl ketone (IV) in a 22% over-all yield from indole. Reduction of IV with lithium aluminum hydride in hot tetrahydrofuran proceeded smoothly to afford 2-skatylquinuclidine (V).

The infrared spectrum of IV showed only a single shifted NH band (indole N-H), while the ultraviolet spectrum was quite close to that of 3-acetylindole. Brief treatment (30 minutes) of IV with acetic anhydride gave only evidence of indole *N*-acetylation (5.8 μ band in the infrared and dramatic change in ultraviolet). Mild hydrolysis with warm 0.25 *N* sodium hydroxide solution for only 15 minutes regenerated IV. These data do not suggest the presence of a piperidine NH.



EXPERIMENTAL

β-(1-Carbobenzoxy-4-piperidyl)propionic Acid (I).

A mixture of 50.0 g. (0.33 mole) of 4-pyridineacrylic acid, 2.5 g. of platinum oxide and 250 ml. of 2 *N* hydrochloric acid (0.50 mole) was shaken under 3 atmospheres of hydrogen for 18 hours. The theoretical amount of hydrogen (4 equivalents) was consumed and the catalyst was removed by filtration. The filtrate was diluted with 100 ml. of water and an excess of potassium hydroxide pellets was added with cooling to give a strongly alkaline solution. Then at 0-5° was slowly added 65 ml. (0.38 mole) of carbobenzoxy chloride with stirring. The mixture was stirred for 2 hours at room temperature and washed with 150 ml. of chloroform. The aqueous portion was chilled, acidified with 6 *N* hydrochloric acid, and extracted with four 250 ml. portions of ethyl acetate. The extract was dried over magnesium sulfate and evaporated *in vacuo* to leave 77.0 g. of a clear syrup which refused to crystallize; λ max (film) (μ) 5.86-6.0 (C=O of COOH, urethane), 14.3 (benzyl). The syrup was suitable for use in the following step.

β-(1-Carbobenzoxy-4-piperidylethyl)-3-indolylketone (II).

To a solution of 53.5 g. (0.184 mole) of I in 450 ml. of benzene was added 25 ml. (0.345 mole) of thionyl chloride. The solution was refluxed for one hour and was evaporated to a volume of about 50 ml. *in vacuo*. Three 200-ml. portions of dry benzene were added and subsequently evaporated after each addition. The residual acid chloride was dissolved in 350 ml. of benzene.

To 124 ml. (0.372 mole) of a 3*M* ethereal methylmagnesium bromide solution was added a solution of 20.0 g. (0.171 mole) of indole in 140 ml. of ether. The mixture was stirred at reflux for 1.5 hours and cooled to 0-5°. The acid chloride solution above was then added dropwise with vigorous stirring. The resulting mixture was stirred another 3 hours at room temperature, cooled to 0-5° and cautiously acidified with 266 ml. of 3 *N* hydrochloric acid. The solid was collected, washed thoroughly with water and ether, and triturated with benzene to yield 61.5 g. of pink crystals, m.p. 132-140°. The material was extracted with eight 250 ml. portions of hot ethyl acetate. The ethyl acetate was filtered and the filtrate chilled overnight to yield 17.0 g. of white crystals, m.p. 165-167°. Concentration of the mother liquors afforded another 7.3 g., m.p. 165-167°. The residue above from the repeated ethyl acetate extractions was twice extracted with 250 ml. portions of acetone. The acetone was chilled several days to give another 7.0 g., m.p. 163-167°. The total was 31.3 g. (47%). An analytical sample from a different run had m.p. 162-165°.

Anal. Calcd. for $C_{24}H_{28}N_2O_3$: C, 73.8; H, 6.71; N, 7.18. Found: C, 74.1; H, 6.90; N, 7.00.

β-(1-Carbobenzoxy-4-piperidyl-α-bromoethyl)-3-indolylketone (IIIa).

To a solution of 2.39 g. (6.1 mmoles) of 3-indolyl-(1-carbobenzoxy-4-piperidylethyl)ketone in 50 ml. of tetrahydrofuran was added 2.30 g. (6.1 mmoles) of trimethylphenylammonium tribromide. The solution was stirred at room temperature for 15 hours and evaporated to dryness *in vacuo*. The residue was washed with 30 ml. of water, the water was decanted, and another 30 ml. portion of water was added. The mixture was extracted with four 20 ml. portions of chloroform, and the chloroform extracts were washed with three 20 ml. portions of water. The chloroform extract was dried with magnesium sulfate and chromatographed on a column of 80 g. of silica gel, eluting with ethyl acetate, to yield 2.65 g. of brown foam. The product was

crystallized from benzene-cyclohexane to yield 2.13 g. (74%) of gray crystals, m.p. 93-98°. A 300 mg. portion was recrystallized from benzene to yield 0.186 g. of light gray crystals, m.p. 80-82°.

Anal. Calcd. for $C_{24}H_{25}BrN_2O_3$: C, 61.4; H, 5.37; Br, 17.0; N, 5.97. Found: C, 61.4; H, 5.32; Br, 17.3; N, 5.95.

In later runs a higher melting form of III, m.p. 136-138°, was consistently obtained.

3-Indolyl-2-quinuclidinylketone (IV).

To 70 ml. of 32% hydrogen bromide in acetic acid was added 15.0 g. of IIIa and the solution was kept at room temperature for one hour. The solvent was removed *in vacuo* and the residue was dissolved in 100 ml. of water and washed with three 50-ml. portions of ether. The aqueous solution was made strongly alkaline with 10% sodium hydroxide, 150 ml. of chloroform was added and the mixture stirred overnight. The solid was collected, washed with water and dried to leave 8.8 g. of white crystals, m.p. 237-245° (dec.). Recrystallization from 2-methoxyethanol afforded 5.1 g. (63%), m.p. 265-267° (dec.). An analytical sample, similarly prepared, had m.p. 267-269° (dec.); λ max (Nujol) (μ) 3.25 (NH), 6.10 (C=O), 13.3 (Ar); λ max (EtOH) (mμ) 244 (ε, 12,350), 260 sh. (ε, 9,730), 302 (ε, 11,300). 3-Acetylindole; λ max (EtOH) (mμ) 241 (ε, 11,800), 260 sh (ε, 8,100), 297 (ε, 10,900).

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.6; H, 7.13; N, 11.0. Found: C, 75.2; H, 7.16; N, 11.0.

A small sample of IV was allowed to react with acetic anhydride at room temperature for 30 minutes to afford white crystals. The infrared spectrum showed a strong band at 5.8 μ, while the ultraviolet spectrum showed peaks at 220 and 303 mμ. Mild hydrolysis (hot 0.25 *N* sodium hydroxide for 15 minutes) afforded the ketone IV.

2-Skatylquinuclidine (V).

A mixture of 159 mg. (0.0042 mole) of lithium aluminum hydride, 471 mg. (0.0019 mole) of IV and 25 ml. of tetrahydrofuran was stirred at reflux for 15 hours. The mixture was cooled and excess hydride decomposed with ethanol and a little water. The tetrahydrofuran was evaporated *in vacuo* and the residue suspended in 15 ml. of ether. Water was slowly added with stirring until a white, pasty aqueous phase formed. The ether was decanted and the residue was extracted with five 15-ml. portions of ether. The ether was dried over magnesium sulfate and evaporated to leave 399 mg. (90%) of white crystals. Two recrystallizations from benzene yielded 149 mg., m.p. 183-184°.

Anal. Calcd. for $C_{16}H_{20}N_2$: C, 79.9; H, 8.39; N, 11.7. Found: C, 79.9; H, 8.25; N, 11.9.

REFERENCES

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