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Reaction of Indolylmagnesium Bromide and Chloromethylpyridines. Synthesis of Skatylpyridines and Piperidines (1)

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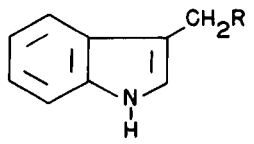
The reaction of indolylmagnesium bromide with the 2-, 3-, and 4-chloromethylpyridines is reported. Methods are described for the preparation of 2-, 3- and 4-skatylpyridine and 2-, 3- and 4-skatylpiperidine.

The synthesis (2-5) of 2-skatylpiperidine (II) has received attention by the drug industry because of the structural relationship to the ergot alkaloids. The over-all yields from simple indole starting compounds have been poor to fair; the best being 43% (3) from 3-indolealdehyde and 2-pyridyllithium followed by hydrogenation of the intermediate 3-indolyl-2-pyridylcarbinol. The simplest procedure (4) involved the one-step reductive alkylation of indole with 2-pyridinecarboxaldehyde, but it proceeded in a 12% yield. 4-Skatylpiperidine (VI) was prepared in a 29% yield (4) by reductive alkylation of indole with 4-pyridinecarboxaldehyde and in a 19% yield (5) from indolylmagnesium bromide and 4-pyridinecarboxaldehyde, followed by hydrogenation of the resulting 3-indolyl-4-pyridylcarbinol. 3-Skatylpiperidine (IVa) has not been previously reported.

It has been our experience that the above methods involving the catalytic reduction of pyridine nuclei in the presence of indoles are very different to reproduce, particularly with regard to obtaining products of suitable purity. In search of a more reproducible method for the preparation of skatylpiperidines we have explored the condensation of indolylmagnesium bromide with the 2-, 3-, and 4-chloromethylpyridines. In the case of the 2- and 3-chloromethylpyridines the 2-skatyl- (I) and 3-skatylpyridines (III) were obtained in 66% and 56% yields respectively. 4-Chloromethylpyridine and the indole Grignard reagent gave 4-skatylpyridine (V) in a 45% crude yield, but this declined to 29% after purification.

Hydrogenation of the skatylpyridines over platinum oxide under a variety of conditions which utilized mild acid catalysis gave poor results in that over reduction took place. Without acid catalysis the reduction was slow and incomplete. It was found that sodium and butanol reduction of these compounds was smoothly effected. Thus 2-skatylpyridine (I) was reduced to 2-skatylpiperidine (II) in a 68% yield, 3-skatylpyridine (III) to 3-skatylpiperidine (IVa) in a 43% yield and 4-skatylpyridine (V) to 4-skatylpiperidine (VI) in a 23% yield. Compound IVa was



I R = 2-pyridyl

II R = 2-piperidyl

III R = 3-pyridyl

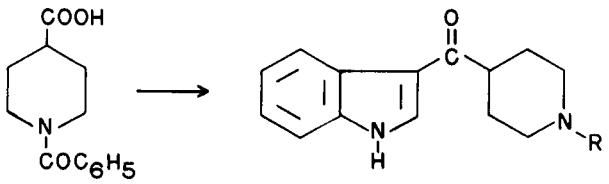
IV (a) R = 3-piperidyl

(b) R = 1-carbomethoxy-3-piperidyl

(c) R = 1-methyl-3-piperidyl

V R = 4-pyridyl

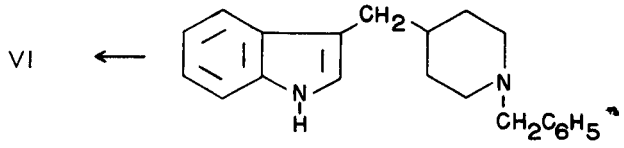
VI R = 4-piperidyl



VII

VIII R = COC_6H_5

X R = H



IX

converted to its crude methyl carbamate (IVb) which was reduced to the *N*-methyl compound (IVc) by lithium aluminum hydride.

A somewhat lengthy, but dependable method for the preparation of 4-skatylpiperidine (VI) was achieved as follows. The acid chloride of *N*-benzoylisonipecotic acid (VII) was condensed with indolylmagnesium bromide to afford the *N*-benzoylketone (VIII) in a 32% yield. Reduction of VIII with lithium aluminum hydride, followed by hydrogenolysis of the benzyl group of the intermediate (IX) gave 4-skatylpiperidine (VI) in a 13.5% over-all yield. Hydrolysis of the benzoyl group in VIII afforded the 4-piperidyl-3-indolylketone (X) in good yield, but subsequent reduction of the ketone with lithium aluminum hydride gave a poor yield of VI.

EXPERIMENTAL

2-Skatylpyridine (I).

To 50 ml. (0.15 mole) of 3 *M* methylmagnesium bromide in ether was added, dropwise with stirring, a solution of 10.0 g. (0.086 mole) of indole in 100 ml. of dry ether. The mixture was stirred at reflux for 1.5 hours, cooled to 0-5°, and 7.0 g. (0.043 mole) of 2-chloromethylpyridine hydrochloride was rapidly added. The ether was removed by distillation as 90 ml. of dry benzene was added dropwise. The resulting mixture was heated at reflux for 3.5 hours, cooled to 0-5°, and 75 ml. of 3 *M* hydrochloric acid and 500 ml. of water was slowly added. The layers were separated and the aqueous layer was washed with another 75 ml. of ether. The acid solution was adjusted to *p*H 8-9 with concentrated ammonia and the mixture was extracted with six 150-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate and evaporated *in vacuo* to leave 8.4 g. of syrup. The syrup was extracted with eight 30-ml. portions of hot cyclohexane and the cyclohexane solution chilled to afford 5.9 g. (66%) of white crystals, m.p. 98-101°. Clemo and Seaton (6) prepared this compound by a more elaborate method and reported a m.p. of 104°. An analytical sample obtained from another run had a m.p. of 95-96°. When a ratio of 3 methylmagnesium bromide:1 indole:1 chloromethylpyridine hydrochloride was used, a 43% yield of I was obtained. For more valuable indoles, this latter procedure would be better as it gives a greater yield for indole expended. With 3 methylmagnesium bromide:3 indole:1 chloromethylpyridine a 60% yield was observed.

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.7; H, 5.81; N, 13.5. Found: C, 80.7; H, 5.78; N, 13.5.

Treatment of I with methyl iodide afforded the methiodide, m.p. 180-183°.

Anal. Calcd. for $C_{15}H_{15}IN_2$: C, 51.4; H, 4.32; I, 36.2. Found: C, 51.3; N, 4.47; I, 36.5.

3-Skatylpyridine (III).

Following the method used above, 50 ml. (0.15 mole) of 3 *M* methylmagnesium bromide was allowed to react with 10.0 g. (0.086 mole) of indole in 100 ml. of ether. The resulting indolylmagnesium bromide was treated with 7.0 g. (0.043 mole) of 3-chloromethylpyridine hydrochloride. The reaction mixture was decomposed with 75 ml. of 3 *M* hydrochloric acid and 300 ml. of water. Upon completion of the work-up the crude syrup (6.6 g.) was extracted with 180 ml. of hot benzene. The benzene extract was diluted with 100 ml. of cyclohexane and chilled for 3 days to afford 2.9 g. (32%) of yellow crystals, m.p. 151-154°. Concentration of the mother liquor yielded another 2.17 g., for a total yield of 56%. An analytical sample, m.p. 154-156°, was similarly prepared from another run. Use of equimolar amounts of indolylmagnesium bromide and 3-chloromethylpyridine hydrochloride gave a 45% yield.

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.7; H, 5.81; N, 13.5. Found: C, 80.5; H, 5.78; N, 13.3.

2-Skatylpiperidine (II).

To a boiling solution of 7.7 g. (0.037 mole) of 2-skatylpyridine (I) in 400 ml. of 1-butanol was rapidly added 15.1 g. (0.66 g. atom) of sodium. After a 0.5 hour reflux period, the sodium had disappeared. The solution was cooled, treated with 350 ml. of ice water and the layers were separated. The aqueous portion was extracted with three 100-ml. portions of ether. The butanol portion was evaporated *in vacuo* and the residue combined with the ether extracts. The ether was twice washed with 100 ml. portions of water, then extracted with three 100 ml. portions of 3 *M* hydrochloric acid. The combined acid extracts were made strongly alkaline with 10% sodium hydroxide and extracted with four 75-ml. portions of ether. The ether was dried over magnesium sulfate and evaporated *in vacuo*. The residue was dissolved in 70 ml. of benzene and allowed to stand several days to afford 5.4 g. (68%) of off-white crystals, m.p. 157-158.5°. The literature observations were: (2) 156-157°; (3) 156-156.5°; (4) 156-157°.

The *N*-acetyl derivative, m.p. 189-190°, was prepared by treatment of II with acetic anhydride and pyridine.

Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 75.0; H, 7.86; N, 10.9. Found: C, 75.0; H, 8.01; N, 11.1.

3-Skatylpiperidine Picrate (IVa).

The reduction of 1.20 g. of 3-skatylpyridine (III) with 2.4 g. of sodium in 60 ml. of 1-butanol as described for the 2-isomer yielded 0.84 g. (68%) of a brown gum. The gum was dissolved in 5 ml. of ethanol and added to 1.02 g. of picric acid in 100 ml. of warm water. Upon standing 24 hours, orange crystals were obtained, 1.21 g. (47% from III), m.p. 96-110°. Recrystallization of a portion from acetone-water yielded an analytical sample, m.p. 95-102°, after drying 30 hours at 56°.

Anal. Calcd. for $C_{20}H_{21}N_5O_7 \cdot \frac{1}{2}H_2O$: C, 53.2; H, 4.88; N, 15.5. Found: C, 53.6; H, 4.94; N, 15.4.

Treatment of IVa as the free base with benzoyl chloride-pyridine afforded the *N*-benzoyl derivative, m.p. 126-128°, after recrystallization from benzene.

Anal. Calcd. for $C_{21}H_{22}N_2O$: C, 79.2; H, 6.96; N, 8.80. Found: C, 79.0; H, 6.95; N, 9.08.

1-Methyl-3-skatylpiperidine (IVc).

To a solution of 1.00 g. (0.0047 mole) of 3-skatylpiperidine (IVa) in 5 ml. of chloroform was added 10 ml. of 3% sodium hydroxide and 0.37 ml. (0.0049 mole) of methyl chloroformate. The mixture was stirred at room temperature for 2 hours and acidified with 6 *M* hydrochloric acid. The chloroform layer was separated and the aqueous layer was extracted with another 10 ml. of chloroform. The combined chloroform extracts were washed with 20 ml. of water, dried over magnesium sulfate and evaporated *in vacuo* to leave 0.83 g. of the crude carbamate (IVb).

aluminum hydride in 25 ml. of tetrahydrofuran by refluxing for 15 hours. The mixture was cooled in ice and the excess hydride was decomposed with ethanol and a little water. The solvent was evaporated *in vacuo* and the residue was suspended in 30 ml. of ether. Water was slowly added until a white, pasty aqueous phase was formed. The ether was decanted and the paste was extracted with another four 30-ml. portions of ether. The ether was dried over magnesium sulfate and evaporated *in vacuo* to leave 0.52 g. of a yellow gum. Trituration with cyclohexane afforded 0.17 g. of crystals, m.p. 112-113.5°.

Anal. Calcd. for $C_{15}H_{20}N_2$: C, 78.9; H, 8.83; N, 12.3. Found: C, 79.1; H, 8.82; N, 11.8.

4-Skatylpyridine (V).

Following the method used above, 14 ml. (42 mmoles) of 3 *M* methylmagnesium bromide in ether was allowed to react with 2.86 g. (24.4 mmoles) of indole in 30 ml. of ether. The resulting indolylmagnesium bromide was treated with 2.0 g. (12.2 mmoles) of 4-chloromethylpyridine hydrochloride. The reaction mixture was decomposed with 19 ml. of 3 *M* hydrochloric acid and 150 ml. of water. Upon completion of the workup, the crude syrup was treated with three 20-ml. portions of hot benzene which upon cooling, gave 1.15 g. (45%) of crystals, m.p. 86-92°. A 200-mg. portion was recrystallized from benzene-cyclohexane to yield 0.128 g., (29%) of pale pink crystals m.p. 108-110°.

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.7; H, 5.81; N, 13.5. Found: C, 80.5; H, 5.88; N, 13.3.

4-Skatylpiperidine (VI).

Method A: A mixture of 1.70 g. (0.005 mole) of VII, 0.41 g. (0.005 mole) of sodium acetate, 0.50 g. of 5% palladium-on-carbon and 25 ml. of ethanol was stirred under an atmosphere of hydrogen. After 1.5 hours the required amount of hydrogen was consumed and the mixture was filtered. The filtrate was evaporated *in vacuo* and the residue dissolved in 20 ml. of water. The solution was made strongly alkaline with 10% sodium hydroxide to precipitate an oil, which crystallized rapidly when seeded to afford 0.87 g. (81%) of

white crystals, m.p. 175-176°. An analytical sample, m.p. 178-180°, was prepared by Gray's procedure (4); Gray reported m.p. 169-173°.

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.5; H, 8.47; N, 13.1. Found: C, 78.2; H, 8.39; N, 12.8.

Method B: The reduction of 0.883 g. (4.25 mmoles) of 4-skatylpyridine with 1.8 g. of sodium in 60 ml. of 1-butanol as described for the 2-isomer yielded 0.582 g. of a syrup which crystallized under cyclohexane to yield 0.353 g., (39%) of tacky crystals, m.p. 135-148°. The product was suspended in 20 ml. of ether, cooled to 0-5°, and hydrogen chloride was bubbled in for 2-3 minutes. The hydrochloride was collected by filtration and dissolved in water. The solution was made basic with 10% sodium hydroxide and extracted with three 20-ml. portions of ether. The combined ether extracts were dried with magnesium sulfate and evaporated *in vacuo* to yield 0.197 g. (23%) of light tan crystals, m.p. 139-142°. The infrared spectrum was identical with material prepared by Method A.

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.5; H, 8.47; N, 13.1. Found: C, 78.4; H, 8.15; N, 13.1.

1-Benzoyl-4-piperidinecarboxylic Acid (VII).

To an ice cold solution of 32.5 g. (0.25 mole) of isonipecotic acid in 750 ml. of 10% potassium carbonate was added 29.3 ml. (0.25 mole) of benzoyl chloride over 10 minutes with stirring. Stirring was continued for 30 minutes at 0-5° and 2 hours at room temperature. The solution was acidified to *p*H 1-2 with 6 *N* hydrochloric acid and extracted with three 150-ml. portions of dichloromethane. The dichloromethane was washed with water, dried over magnesium sulfate, and evaporated *in vacuo* to leave 57 g. of a clear gum. The gum was crystallized from 250 ml. of benzene and 30 ml. of cyclohexane. The crystals were collected, washed with cyclohexane, and dried to leave 47.0 g. (79%); m.p. 129-130°. An analytical sample, similarly prepared from another run, had a m.p. of 133-134°.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 67.0; H, 6.48; N, 6.01. Found: C, 67.1; H, 6.51; N, 5.89.

(1-Benzoyl-4-piperidyl)-3-indolylketone (VIII).

A solution of 12.6 g. (0.058 mole) of *N*-benzoylisonipecotic acid and 6.5 ml. (0.09 mole) of thionyl chloride in 125 ml. of benzene was refluxed 5 hours. The solution was evaporated to dryness *in vacuo*, followed by the addition and evaporation of 20 ml. of benzene. The residue was dissolved in 120 ml. of ether.

To 35 ml. of 3 *M* ethereal methylmagnesium bromide was added 5.5 g. (0.047 mole) of indole in 55 ml. of ether. The mixture was stirred at reflux for 1.5 hours and cooled to 0-5° in an ice bath. The acid chloride solution above was added over 3 minutes and the mixture stirred at room temperature for 4 hours. The mixture was cooled in ice, and 150 ml. of 3 *N* hydrochloric acid was added slowly. The ether layer was separated, washed with 50 ml. of water, and discarded. The combined aqueous portion containing much undissolved material was extracted with 150 and 50 ml. portions of ethyl acetate. The ethyl acetate was washed with 50 ml. of water and 50 ml. of saturated sodium bicarbonate and dried over magnesium sulfate. The solvent was evaporated *in vacuo* to leave 11.0 g. of yellow syrup, which was dissolved in 125 ml. of hot benzene and allowed to stand 2 days. The tan crystals were collected, washed with benzene, and dried to leave 6.3 g. (40%). The crude material was treated with 70 ml. of boiling alcohol, which removed the colored contaminants. The cooled mixture was filtered and the cake dried to leave 4.2 g. Concentration of the filtrate to one-half volume afforded another 0.75 g., total 4.95 g. (32%). A sample, recrystallized for analysis, had m.p. 240-241°; λ max (Nujol) (μ) 3.10 (NH), 6.05 (C=O ketone), and 6.20 (C=O benzamide).

Anal. Calcd. for $C_{21}H_{20}N_2O_2$: C, 75.9; H, 6.07; N, 8.43. Found: C, 76.2; H, 6.19; N, 8.24.

1-Benzyl-4-skatylpiperidine Hydrochloride (IX).

To an ice cold suspension of 8.0 g. of lithium aluminum hydride in 350 ml. of dry tetrahydrofuran was added 19.8 g. of the *N*-benzoyl ketone (VIII) in small portions. The mixture was stirred at reflux for 15 hours and the excess hydride decomposed with ethanol and water. The solvent was evaporated *in vacuo* and the residue was suspended in 75 ml. of ether. Water was added until a white, pasty, aqueous layer formed and the mixture was stirred for a few minutes. The ether was decanted and the residue extracted twice more with 75 ml. portions of ether. The ether was dried over magnesium sulfate and chilled. Hydrogen chloride was bubbled in, to precipitate the hydrochloride salt. The salt was collected and recrystallized from 300 ml. of ethanol to yield 9.3 g.; m.p. 248-250°. A second crop of 1.3 g. was obtained by concentration of the mother liquors. The total was 10.6 g. (52%).

Anal. Calcd. for $C_{21}H_{24}N_2 \cdot HCl$: C, 74.0; H, 7.39; N, 8.21. Found: C, 74.0; H, 7.35; N, 8.10.

3-Indolyl-4-piperidylketone (X).

A mixture of 5.2 g. of (1-benzoyl-4-piperidyl)-3-indolylketone (VIII), 50 ml. of methyl cellosolve, and 50 ml. of 10% sodium hydroxide was refluxed for 15 hours. The solution was evaporated to dryness *in vacuo*, and the residue was treated with 200 ml. of hot water. After chilling for 2 hours, the crystals were collected, washed with water, and dried to leave 2.62 g. (71%). A recrystallization from 40 ml. of ethanol afforded 1.58 g. of white crystals, m.p. 221-224°. A second crop of 0.15 g. was obtained by a concentration of the filtrate to ¼ of its volume.

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.7; H, 7.06; N, 12.3. Found: C, 73.8; H, 7.16; N, 12.3.

An attempt to reduce this ketone with lithium aluminum hydride in hot tetrahydrofuran gave a poor yield of a semi-solid material which refused to crystallize completely. The infrared spectrum of the crude product did not compare well with VI.

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