[Contribution from the Research Laboratories of the Upjohn Company]

The Reaction of Ethyl 3-Indoleglyoxylate with Methylmagnesium Iodide

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Received August 18, 1961

Condensation of ethyl 3-indoleglyoxylate (I) with methylmagnesium iodide gave the acyloin 1-(3-indolyl)-2-hydroxy-2-methyl-1-propanone (II), while with an excess of the reagent 2-(3-indolyl)-3-methyl-2,3-butanediol (III) resulted. Reduction of II with lithium aluminum hydride produced 1-(3-indolyl)-2-methyl-2-propanol (VI) and 1-(3-indolyl)-2-methyl-1,2-propanediol (VII), while reduction of II with sodium borohydride afforded the diol VII and an alcohol of uncertain structure. Alkylation of II gave 1-[3-(1-methyl)-indolyl]-2-hydroxy-2-methyl-1-propanone (IV) which gave rise to 2-[3-(1-methyl)-indolyl]-3-methyl-1,4-butanediol (V) on reaction with methylmagnesium iodide or methyllithium.

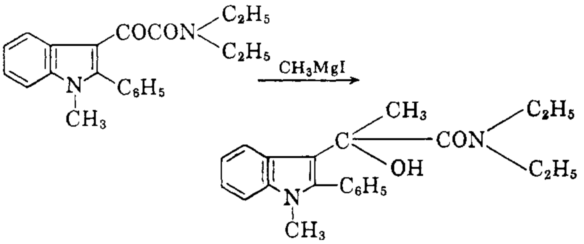
In connection with our interest in indole systems which would incorporate the hydroxyl, diol, or acyloin groupings, we have investigated the condensation of ethyl 3-indoleglyoxylate (I) with methylmagnesium iodide.

We found that the reaction of I with four equivalents of methylmagnesium iodide gave rise, after two hours of refluxing, to a 57% yield of 1-(3 indolyl)-2-hydroxy-2-methyl-1-propanone (II). Compound II gave an oxime; it also showed the expected ultraviolet spectrum of the 3-acyl-*N*-unsubstituted indole system characterized by maxima at 243, 255.5, and 300 mμ and the appearance of a new maximum at 336 mμ in alkaline solution.[1] The infrared spectrum showed a strong band at 1607 cm.$^{-1}$ typical of the vinylogous amide system.[2,3]

When the solution of I in tetrahydrofuran was refluxed for four hours with eight equivalents of methylmagnesium iodide a 53% yield of 2-(3-indolyl)-3-methyl-2,3-butanediol (III) was obtained.

Clearly, I shows considerable specificity when condensed with methylmagnesium iodide. The carbethoxy group is more reactive, and therefore undergoes the reaction before the carbonyl function of the *N*-unsubstituted vinylogous amide system becomes involved.

A recent paper[4] has appeared which reports that *N*,*N*-dimethyl(or diethyl)-1-methyl-2-phenyl-(or *p*-chlorophenyl)-3-indolylglyoxylamides react with Grignard reagents to give hydroxyamides; *e.g.*,



This system illustrates how much the ketonic character of the first carbonyl group in the side chain varies as a function of substituents on nitrogen and C-2 of the indole nucleus. The methyl group on nitrogen prevents anion formation which otherwise would destroy some of the ketonic character. The phenyl group sterically inhibits conjugation of the carbonyl group with the indole nucleus, and thus forces the carbonyl group to behave like a normal ketone. As a result, the ketonic function reacts much faster than the amidic group, although tertiary amides can react readily with Grignard reagents.[5]

Several simple transformations of the acyloin II were carried out. Alkylation with dimethyl sulfate gave 1-[3-(1-methyl)indolyl]-2-hydroxy-2-methyl-1-propanone (IV) which, in turn, afforded 2-[3-(1-methyl)indolyl]-3-methyl-1,4-butanediol (V) on reaction with either methylmagnesium iodide or, preferably, with methyllithium.

The ratio of products obtained on reduction of II with lithium aluminum hydride differs with the solvent employed. When ether was used as solvent, a 42% yield of the C—O cleavage product, 1-(3-indolyl)-2-methyl-2-propanol (VI), and a 25% yield of the normal addition product, 1-(3-indolyl)-2-methyl-1,2-propanediol (VII) was obtained. With tetrahydrofuran 48% of VI and 14% of VII resulted. The more polar solvent seems to enhance the vinylogous amide character of the side chain. Compound VI proved identical with an authentic sample of the substance prepared by condensation of ethyl 3-indoleacetate and methylmagnesium iodide.

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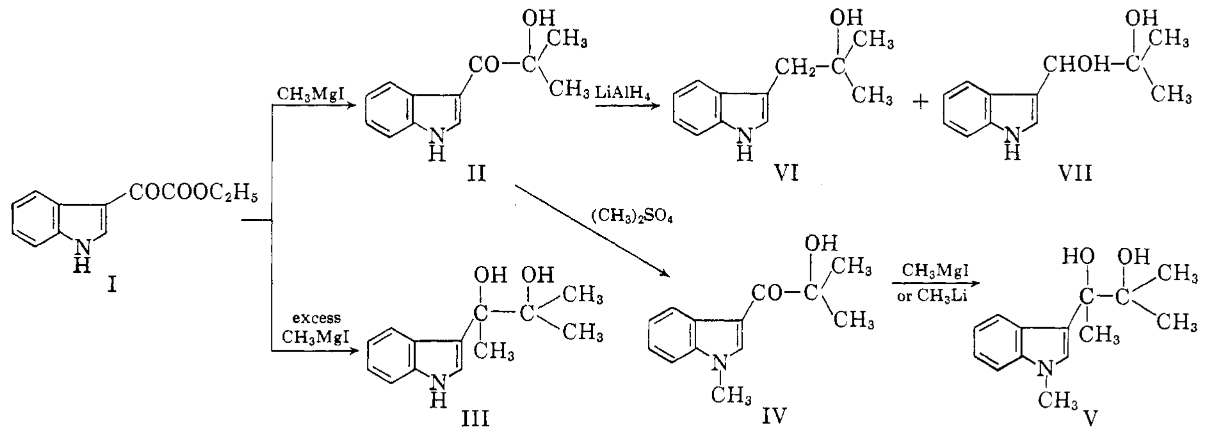
(1) This shift is frequently seen with simple 3-acyl-*N*-unsubstituted indole systems, but is not a general phenomenon, *e.g.*, it does not obtain when the 5-benzyloxy substituent is present as in the case of 5-benzyloxy-3-acetylindole and 3-(β-dimethylaminopropionyl)-5-benzyloxyindole[2] and in the case of the γ-[3-(5-benzyloxy)-indolyl]-γ-ketopropylphosphonic acid series.[3] This shift is also absent in cases where the 3-acyl substituent is sterically hindered [W. C. Anthony, *J. Org. Chem.*, **25**, 2049 (1960)].

(2) J. Szmuszkovicz, *J. Am. Chem. Soc.*, **81**, 1180 (1960).

(3) J. Szmuszkovicz, *J. Am. Chem. Soc.*, **80**, 3782 (1958).

(4) A. F. Ames, D. E. Ames, C. R. Coyne, T. F. Grey, I. M. Lockhart, and R. S. Ralph, *J. Chem. Soc.*, 3388 (1959).

(5) M. S. Kharash and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice Hall, Inc., New York, 1954, p. 870.



Reduction of II with sodium borohydride gave a 59% yield of diol VII and a small yield of a compound isomeric with VI. Possibly this compound ($C_{12}H_{15}NO$) is a rearrangement product, perhaps of the Tiffenau type.[6] A reasonable structure for this product is represented by 3-indoleisopropylcarbinol. Attempts to prepare this substance by reduction of 3-indolylisopropylketone with lithium aluminum hydride or sodium borohydride were not successful. An excess of lithium aluminum hydride produced 3-isobutylindole, whereas a stoichiometric amount afforded some polymer and unchanged ketone.

EXPERIMENTAL[7,8]

Ethyl 3-indoleglyoxylate (I). 3-Indoleglyoxylyl chloride was prepared according to the literature.[9] The corresponding ethyl ester (I) was prepared according to ref. 10a and melted at 186–187°.[10b] Ultraviolet spectrum showed λ_{max} 255 (9875); 268 (9700); 274 (8250); 323 (9850). Infrared spectrum showed NH: 3140; C=O: 1724, 1620; C=C: 1582, 1515, 1495.

1-(3-Indolyl)-2-hydroxy-2-methyl-1-propanone (II). A solution of ethyl indole 3-glyoxylate (86.88 g., 0.4 mole) in 2 l. tetrahydrofuran was added during 1 hr. to a solution of methylmagnesium iodide prepared from methyl iodide (277 g.; 1.6 moles) and magnesium (40.8 g., 1.68 g.-atoms) in 1 l. of ether. The mixture was refluxed for 2 hr., and the resulting suspension was allowed to stand for 2 days. It was then decomposed with a solution containing 214 g. of ammonium chloride in 1 l. of water. The aqueous layer was extracted with ether (4 × 250 ml.) and the combined organic solution washed with water, dilute sodium thiosulfate solution, and saturated salt solution. It was then dried through sodium sulfate and evaporated[11] to give a brown oil. The oil was dissolved in benzene whereupon crystallization occurred to give 40 g. of the acyloin; m.p. 164.5–165.5°. The second crop amounted to 6.51 g.; m.p. 161–163.5°. Total yield, 57%. The analytical sample was obtained by recrystallization from benzene-methanol followed by acetone–petroleum ether (30–60°) and melted at 164.5–165.5°. Ultraviolet spectrum showed λ_{max} 243 (8250); 255.5 (9300); 300 (12,775); in 0.01N alcoholic potassium hydroxide: 243 (11,000); 262 (9925); 301 (11,450); 336 (3200). Infrared spectrum showed OH/NH: 3325, 3200; C=O: 1607; C=C: 1582, 1562, 1510, 1497.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.13; H, 6.27; N, 6.81.

2-(3-Indolyl)-3-methyl-2,3-butanediol (III). A solution of ethyl indole-3-glyoxylate (32.6 g., 0.15 mole) in 750 ml. of tetrahydrofuran was added during 1 hr. and 45 min. to a solution of methylmagnesium iodide prepared from methyl iodide (170 g.; 1.2 moles) and magnesium (30.6 g., 1.251 g.-atoms) in 750 ml. of ether. The resulting thick suspension was stirred and refluxed for 4 hr. The mixture was worked up as before[11] to give a brown oil. It was dissolved in 50 ml. of benzene, seeded, and allowed to crystallize overnight to give 17.35 g. (53% yield) of the diol melting at 133–136°. Further recrystallization from benzene-methanol gave material melting at 138.5–139.5°, unchanged on recrystallization from benzene. Ultraviolet spectrum showed λ_{max} 221 (35,150); 274 (5500); 281 (5900); 289 (5125). Infrared spectrum showed OH/NH: 3500, 3400, 3220; C=C: 1617, 1570, 1530, 1497; C—O/C—N: 1112, 1067.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.59; H, 7.67; N, 6.23.

1-[3-(1-Methyl)]indolyl]-2-hydroxy-2-methyl-1-propanone (IV). A solution of the acyloin II (2.03 g.; 0.01 mole) in 100 ml. of acetone was added to a solution of potassium hydroxide (11.2 g.; 0.2 mole) in 50 ml. of water.[12] Dimethyl sulfate (9.5 ml.; 0.1 mole) was added during 15 min., and the solution was stirred an additional 35 min. Acetone was evaporated at 50° *in vacuo* until the initially formed oil solidified completely. Water (150 ml.) was added, and the solid was filtered; 2.0 g., m.p. 135–143°. Crystallization from benzene afforded 1.8 g. (83%) of prisms melting at

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(6) Tiffenau and Dorlencourt, *Compt. rend.*, **143**, 126 (1906).

(7) Melting points were taken in a capillary tube and are uncorrected. Ultraviolet spectra (recorded in mμ) were determined in 95% ethanol using a Cary spectrophotometer Model 19. Infrared spectra (recorded in cm.$^{-1}$) were determined in Nujol using a Perkin-Elmer recording infrared spectrophotometer Model 21. Skellysolve B is commercial hexane, b.p. 60–70°, made by Skelly Oil Co., Kansas City, Mo. Florisil is a magnesia–silica gel adsorbent manufactured by Floridin Co., Tallahassee, Fla.

(8) The author is indebted to Prof. D. J. Cram for stimulating discussions, to Mr. W. A. Struck and his associates for microanalyses, to Mr. M. F. Grostic and Mr. J. E. Stafford for infrared and ultraviolet data, and to Mr. L. G. Laurian for laboratory assistance.

(9) M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6208 (1954).

(10)(a) Brit. Patent **778,823**; m.p. 183.5–184.5°. (b) B. Oddo and A. Albanese, [*Chem. Abstr.*, **22**, 1176 (1928)] condensed indolylmagnesium bromide with ethyloxalyl chloride; m.p. 186°. Elks, Elliot, and Hems, [*J. Chem. Soc.*, 629 (1944)] condensed indole with diethyl oxalate in the presence of sodium ethoxide and pyridine; m.p. 176–178°.

(11) This type of work-up was used throughout the Experimental.

(12) This general procedure has been described by C. B. Barrett, R. J. S. Beer, G. M. Dodd, and A. Robertson, *J. Chem. Soc.*, 4810 (1957).

142–143°. The analytical sample melted at 142.5–143.5° (from benzene). Ultraviolet spectrum showed λ_{max} 211 (26,675); 246 (13,525); 305 (14,375); no change in alkali. Infrared spectrum showed OH: 3420; C═O: 1615, 1610.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.96; H, 7.13; N, 6.60.

The oxime of 1-(3-indolyl)-2-hydroxy-2-methyl-1-propanone (II). A mixture of the acyloin (2.03 g., 0.01 mole), hydroxylamine hydrochloride (6.95 g., 0.01 mole), and 15 ml. of pyridine was heated on the steam bath for 4.5 hr. The resulting dark brown solution was cooled in ice. Water (160 ml.) was added, and the cloudy solution was extracted four times with ether (about 800 ml.). The ethereal solution was washed twice with saturated salt solution, dried through sodium sulfate, and evaporated *in vacuo* on the steam bath. The resulting yellow oil was dissolved in benzene containing a small amount of methanol and afforded 1.6 g. (73.5% yield) of the oxime melting at 164–165°. The analytical sample was obtained by recrystallization from benzene–methanol (Nuchar 190-N) in the form of colorless needles, m.p. 168.5–169.5°. Ultraviolet spectrum showed λ_{max} 217 (33,240); f 258 (6100); 272 (7450); 279 (7775); 287 (6725); no change in alkali. Infrared spectrum showed OH/NH: 3300, 3140; C═N: 1667, 1655; C═C: 1620, 1590, 1575, 1530, 1490.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.96; H, 6.54; N, 13.01.

2-[3-(1-Methyl)indolyl]-3-methyl-1,4-butanediol (V). A. *With methylmagnesium iodide.* A solution of IV (10.0 g., 0.0461 mole) in 280 ml. of warm benzene was added during 20 min. to a solution of methylmagnesium iodide prepared from methyl iodide (65.4 g., 0.461 mole) and magnesium (11.8 g., 0.484 g.-atom) in 600 ml. of ether. Within 3 hr. of refluxing the initially formed precipitate dissolved, and the solution was refluxed for an additional 16 hr. The mixture was worked up as before[11] to give an oil. It was dissolved in about 10 ml. of ether and allowed to crystallize in the refrigerator overnight to give 3.4 g. of material melting at 87–88°. The filtrate was evaporated to dryness and the resulting product (5.73 g.) was dissolved in benzene (20 ml.) and chromatographed on Florisil (180 g.). Elution with 3% acetone–Skellysolve B (7 l.) gave 4.5 g. of oily solid which was crystallized from ether (*ca.* 15 ml.) and Skellysolve B (*ca.* 10 ml.) to give colorless prisms; 1.58 g., m.p. 89–90.5°; total yield 46.6%. The analytical sample melted at 90.5–91° [from ether–petroleum ether (b.p. 30–60°)]. Ultraviolet spectrum showed λ_{max} 223 (37,225); f 280 (5450); 287 (5825); f 296 (5000). Infrared spectrum showed OH: 3380; C═C: 1610, 1565, 1540, 1480.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.20; H, 7.97; N, 6.23.

B. *With methyllithium.* A solution of methyllithium was prepared from lithium (16.5 g., 2.38 moles) and methyl iodide (153 g., 1.08 moles) in 800 ml. of ether. It was added during 15 min. to a solution of IV (23.5 g., 0.108 mole) in benzene (1080 ml.). The mixture was refluxed for 1.5 hr. and worked up as before,[11] but using benzene for extraction. The resulting pale green oil (30.3 g.) was crystallized with seeding from *ca.* 40 ml. of ether to give 13.9 g. of the diol melting at 87.5–89.5°. The second crop was obtained by addition of petroleum ether (b.p. 30–60°) to the filtrate and cooling and amounted to 6.87 g., m.p. 88–90°. The third crop was 2.25 g.; total yield 97.3%. This compound was identical (infrared) with the sample obtained above by reaction with methylmagnesium iodide.

Reduction of II *with lithium aluminum hydride.* A. *In ether.* A solution of the acyloin II (2.03 g., 0.01 mole) in 250 ml. of ether was added during 15 min. to a solution of lithium aluminum hydride (2.0 g., 0.0256 mole) in 100 ml. of ether. The resulting suspension was refluxed for 3 hr. It was then cooled in ice and decomposed, in succession, with 2 ml. of water, 2 ml. of 15% sodium hydroxide, and 6 ml. of water. The mixture was stirred for 15 min., filtered, and the solid washed well with ether. The ethereal filtrate was dried over sodium sulfate and evaporated at room temperature *in vacuo* to give a pale yellow oil (2.16 g.) which tended to color on exposure to air. The oil was dissolved in 10 ml. of benzene and chromatographed on 60 g. of Florisil. Elution with 1% acetone–Skellysolve B (6700 ml.), followed by 2% acetone–Skellysolve B (1 l.) and 3% acetone–Skellysolve B (1 l.) gave 0.80 g. (42% yield) of colorless rods (m.p. 92–93°) after crystallization from benzene–Skellysolve B. It was identical (infrared, mixed m.p.) with an authentic sample of 1-(3-indolyl)-2-methyl-2-propanol (VI, see below). Further elution with 5% acetone–Skellysolve B (1650 ml.) gave a small amount of noncrystallizable oil. Elution with 7.5% acetone–Skellysolve B (2250 ml.), followed by 10% acetone–Skellysolve B (1950 ml.) afforded 0.51 g. (25% yield) of 1-(3-indolyl)-2-methyl-1,2-propanediol (VII) as small prisms melting at 109–111°. The analytical sample melted at 110–110.5° (from benzene). Ultraviolet spectrum showed 219 (35,750); 274 (5740); 280.5 (6160); 289 (5360); no change in alkali. Infrared spectrum showed OH: 3480, 3430, NH: 3180; C═C: 1657 (W), 1612, 1588, 1513, 1495; C═N: 1230, 1170, 1165, 1150, 1105; C—O: 1068, 1017, 995; ring: 827, 820, 772, 760, 735, 717.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.30; H, 7.47; N, 6.34.

B. *In tetrahydrofuran.* When the lithium aluminum hydride reduction was run in boiling tetrahydrofuran for 3.25 hr. using 3.06 g. of acyloin in 30 ml. of tetrahydrofuran and 3 g. of lithium aluminum hydride in 150 ml. of tetrahydrofuran and the reaction mixture worked up as above, chromatography afforded 48% yield of VI (eluted with 1–4% acetone–Skellysolve B) and 13.6% of a compound eluted with 10% acetone–Skellysolve B which melted at 80–80.5° (prisms from benzene) and proved to be a polymorph of VII obtained previously by the ether procedure (m.p. 110–110.5°). The two polymorphs showed identical infrared spectra in chloroform, and the mixed m.p. was 93–104°.

Synthesis of α,α-dimethylindole-3-ethanol (VI). *From indole-3-acetic acid.* Ethyl indole-3-acetate[13] was prepared from indole-3-acetic acid, methanol, and concd. sulfuric acid in 77.5% yield; it was distilled from an oil-jacketed flask, b.p. (outside T) 175–185°; n_D^{25} 1.5695. A solution of ethyl indole-3-acetate (45 g., 0.222 mole) in 200 ml. of ether was added during 25 min. to a solution of methylmagnesium iodide prepared from methyl iodide (126 g., 0.888 mole) and magnesium (22.6 g., 0.932 g.-atom) in 600 ml. of ether. The mixture was refluxed for 3.5 hr., then allowed to stand overnight and worked up as before[11] to give a brown oil. It was crystallized from 100 ml. of ether and 180 ml. of petroleum ether (b.p. 30–60°) to give a slightly oily solid. It was recrystallized from 50 ml. of benzene and 20 ml. of petroleum ether to give prisms melting at 92–93.5° (27.98 g.). The original filtrate was evaporated to dryness and the residue crystallized from benzene–petroleum ether to give 8.52 g., melting at 92–93°. Total yield of VI was 87%. The analytical sample melted at 92–93° (from benzene). Ultraviolet spectrum showed λ_{max} 276 (5475); 282 (6000); 290 (5225). Infrared spectrum showed OH/NH: 3490, 3270; C═C: 1662 (W), 1613, 1590, 1575, 1533; C—N/C—O: 1260, 1238, 1215, 1113; ring: 777, 738.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.51; H, 8.19; N, 7.56.

Reduction of II *with sodium borohydride.* A. *In the cold.* A solution of the acyloin II (17.75 g., 0.0875 mole) in 100 ml. of methanol was added to a solution of sodium borohydride (17.75 g.) in 100 ml. of methanol with ice-cooling at such a rate that the temperature did not rise above 8°. The resulting solution was stirred for 2.5 hr. while cooling in ice. Ether (200 ml.), ethyl acetate (100 ml.), water (100 ml.), and 100 ml. of saturated salt solution were added; the layers were separated and the aqueous layer was ex-

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(13) T. Hoshino and K. Shimodaira, *Ann.*, **520**, 19 (1935); R. W. Jackson, *J. Biol. Chem.*, **88**, 659 (1930); R. C. Elderfield, B. Fischer, and J. M. Lagowski, *J. Org. Chem.*, **22**, 1376 (1957).

tracted with ethyl acetate (6 × 100 ml.). The combined organic solution was washed with saturated salt solution (5 × 50 ml.), dried through sodium sulfate, and evaporated *in vacuo* at 30° to give 16.8 g. of yellow gum. It was dissolved in benzene (100 ml.), filtered from a small amount of solid, evaporated to get rid of water, treated with Magnesol, filtered, and allowed to crystallize overnight. A mixture of colorless crystals and a yellow oil resulted. Ether (10 ml.) was added to dissolve the oil. The crystals were filtered and washed with ether–petroleum ether (b.p. 30–60°) (1:1) to give 6.84 g. of VII melting at 109–110.5°. It was identical with the sample prepared by lithium aluminum hydride reduction (infrared, mixed m.p.). The second crop amounted to 2.2 g., melting at 104–109°. The mother liquor was evaporated to dryness, and the residue was dissolved in 40 ml. of benzene and 5 ml. of acetone, filtered from a small amount of a colorless precipitate (0.1 g., m.p. 220–225°, not investigated further) and chromatographed on 230 g. of Florisil. The 5% acetone–Skellysolve B (1 l., 73.7 mg.) and 7.5% fractions (1 l., 29.4 mg.) were discarded. Elution with 10% acetone–Skellysolve B (5 l.) gave 1.18 g. of the starting material melting at 164–165° after recrystallization from benzene (identified by infrared and mixed m.p.). Elution with 15% acetone–Skellysolve B (5 l.) gave 1.45 g. of VII melting at 109–110° (identified by mixed m.p.). Total yield of this product was 59%. Further elution with 20% acetone–Skellysolve B (1 l.) gave 131 mg. (discarded). Elution with 25% acetone–Skellysolve B (2 l.) gave 954.4 mg. of a product which was crystallized from benzene (10 ml.) as small prisms melting at 134° efferv. Two additional recrystallizations from benzene did not alter the melting point. This compound was identical with the product (m.p. 124–125° efferv.; clear 135°) obtained by sodium borohydride reduction carried out at room temperature (see below) as determined by comparison of the ultraviolet and infrared (in chloroform) spectra and mixed m.p. (s 115; efferv. 130–133°; clear at 136°).

B. *At room temperature.* A solution of the acyloin II (1.02 g., 5 mmoles) in 10 ml. of methanol was added to a solution of sodium borohydride (1.0 g., 0.0264 mole) in 15 ml. of methanol while cooling in ice. The solution was then allowed to stand at room temperature for 21 hr. It was evaporated at 30° *in vacuo* to about half the volume and cooled in ice. Water (50 ml.) was added, followed by 2 ml. of acetic acid. The solution was extracted thrice with chloroform, washed with water, then sodium bicarbonate solution, saturated salt solution, dried through sodium sulfate, and evaporated at 30° *in vacuo* to give 0.67 g. of a yellow oil. It was dissolved in benzene, and petroleum ether (b.p. 30–60°) was added to give 0.58 g. of a powder; this was dissolved in 5 ml. of benzene and chromatographed on 18 g. of Florisil. Elution with 5% (850 ml.; 32.2 mg.), 7.5% (1 l., 56.6 mg.), and 10% acetone–Skellysolve B (750 ml., 56.2 mg.) gave fractions which resisted crystallization. Further elution with 10% acetone–Skellysolve B (2750 ml.) gave 379 mg. of solid fractions, m.p. range 123–135° efferv. Crystallization from benzene afforded 0.33 g. of small prisms melting at 123–124° efferv. and clear at 135°. The product was recrystallized by dissolving in 25 ml. of benzene and 1 ml. of methanol and evaporating down to about 5 ml.; m.p. 124–125° efferv. and clear at 135°. Ultraviolet spectrum showed λ_{max} 219 (28,200); 275 (4800); 280 (5200); 289 (4650). Infrared spectrum showed OH/NH: 3500, 3390, 3235; C=C: 1515, 1585, 1542, 1492; C—O/C—N: 1157, 1107, 1073, 1020, 967; ring: 800, 742, 735, 685, 680. The NMR spectrum[14] was consistent with 3-indoleisopropylcarbinol.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40; active H, 2. Found: C, 76.68; H, 8.32; N, 6.72; active H, 1.96.

Reduction of 3-indolyl isopropyl ketone with lithium aluminum hydride. 3-Indolyl isopropyl ketone[15] was prepared in 65% yield from indole, dimethylisobutyramide, and phosphorus oxychloride essentially as described for 3-indolecarboxaldehyde.[16] The analytical sample melted at 126–127.5° (from methanol); ultraviolet spectrum showed λ_{max} 241 (13,175); f 256 (9400); 295 (12,750); in base: 241 (12,150); 258 (9500); 296 (12,100); f 328 (2250). Infrared spectrum showed NH: 3,140; C=O: 1620, 1610; C=C: 1578, 1550, 1520, 1495; ring: 745.

A. *With excess of lithium aluminum hydride.* A solution of 3-indolyl isopropyl ketone (3.74 g., 0.02 mole) in 200 ml. of ether was added during 15 min. to a solution of lithium aluminum hydride (0.76 g., 0.02 mole) in 100 ml. of ether under nitrogen. The mixture was stirred for 45 min. and was then decomposed by adding 5 ml. of water over a 15-min. period, while cooling in ice. The resulting suspension was filtered and the pale blue ethereal solution evaporated to dryness *in vacuo* to give 4 g. of a light blue oil which showed no residual carbonyl absorption in the infrared. The crude oil was dissolved in 100 ml. of benzene and 10 ml. of acetone and chromatographed on 200 g. of Florisil. Elution with Skellysolve B (1.6 l.) gave 1.791 g. of crystalline 3-isobutylindole; m.p. 31–32°, unchanged after sublimation. Ultraviolet spectrum showed λ_{max} 223 (35,400); sh 276 (5450); 282 (5950); 290 (5200). Infrared spectrum showed NH: 3400; =CH: 3040; C=C: 1620, 1595, 1580, 1493; ring: 800, 768, 743.

Anal. Calcd. for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09. Found: C, 83.28; H, 8.80; N, 8.28.

Further elution with varying proportions of acetone in Skellysolve B gave fractions which could not be characterized.

B. *With stoichiometric amount of lithium aluminum hydride.* A solution of lithium aluminum hydride (0.380 g., 0.01 mole) in 100 ml. of ether was added dropwise during 20 min. to a solution of 3-indolyl isopropyl ketone (3.74 g., 0.02 mole) in 200 ml. of ether with stirring and in a nitrogen atmosphere. The mixture was stirred for 0.5 hr. It was then decomposed with 5 ml. of water, filtered, and the resulting blue filtrate was evaporated to dryness *in vacuo* at 35° to give 3.2 g. of a blue oil. Infrared spectrum showed a band at 1625 (s), indicative of the starting material. The oil was dissolved in minimum of benzene and chromatographed on 160 g. of Florisil. Elution with 6% acetone–Skellysolve B (1280 ml.) gave 0.261 g. (discarded). Elution with 9% acetone–Skellysolve B gave 1.611 g. of the starting material (m.p. 125–126°; mixed m.p. showed no depression). Further elution with 12% acetone–Skellysolve B (1280 ml.) gave 0.409 g. of a brown powder; A, m.p. 155° efferv. Fractions obtained with the same volume of 15% acetone–Skellysolve B (B, 0.253 g.) and 20% acetone–Skellysolve B (C, 0.236 g.) had a similar melting point. Elution with 50% acetone–Skellysolve B (1280 ml.) afforded 0.323 g. of material which was dissolved in 10 ml. of ether and precipitated by addition of methanol to give 0.150 g. of an almost colorless solid; D, m.p. 195–200° efferv. Fractions A, B, C, and D had similar ultraviolet and infrared spectra. The following are the data for fraction D: ultraviolet spectrum (in dimethylformamide-ethanol) showed sh 280 (a = 37.00); 291 (40.32); sh 300 (37.80). Infrared spectrum showed OH/NH: 3400, 3320, 3220; =CH: 3040; 1698 (W); C=C: 1616, 1555 sh; ring: 760, 737.

Anal. Found C, 83.51; H, 7.59; N, 8.24; mol. wt. (by the isothermal distillation method), 1,533.

Attempted reduction of 3-indolyl isopropyl ketone with sodium borohydride did not lead to any well defined product.

KALAMAZOO, MICH.

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(14) Run by Dr. G. Slomp.

(15) C. Alberti, *Gazz. Chim. Ital.*, **87**, 720 (1957); *Chem. Abstr.*, **52**, 15,533^4 (1958), prepared this compound from indole, ethylmagnesium bromide, and isopropionyl chloride; m.p. 131–132° (from dilute alcohol).

(16) P. N. James and H. R. Snyder, *Org. Syntheses*, **39**, 30 (1959).