Perhydroindan Derivatives. VI. Derivatives of 1,1a,2,3,4,4a-Hexahydrofluorene-2,9-dione[1]

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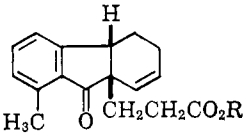
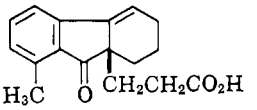
An improved synthetic route to 1a-carboxymethyl-2,9-diketo-8-methyl-*cis*-1,1a,2,3,4,4a-hexahydrofluorene (**7**) is described. The monoethylene ketal **13** of this acid as well as the corresponding methyl and *t*-butyl esters were prepared and the reduction of the two esters was studied. With sodium borohydride, the ester and 9-keto functions were reduced with approximately equal ease.

We have previously described[2] preparative routes to variously substituted 8-methyl-*cis*-hexahydrofluorenones (**1**) which were desired as synthetic precursors for certain degradation products of the gibberellins. This paper reports our further investigation of the diketo ester **10** as well as several improvements in the previously reported[2d] synthesis of this compound. The previously uncharacterized intermediates **7** and **8** in the conversion of the epoxy ester **6** to the diketo ester **10** were isolated and characterized in the course of the work. The mode of formation of the hydroxy ketone **8** from reaction of **6** with aqueous acid combined with the spectroscopic properties (see Experimental) of this lactone suggest that the compound be assigned the stereochemistry indicated.

Samples of the unsaturated acid **11** and the corresponding ester **12** were prepared by application of the Arndt–Eistert reaction to the diazo ketone derived from the unsaturated acid **4**. Although the same acid **11** could be isolated from a Michael reaction of methyl acrylate with the easily accessible mixture of tetrahydrofluorenones **2** and **3** followed by saponification, this route was of little preparative value because of the extreme difficulty of separating the acid **11** from the rather complex reaction mixture containing an acid believed to be **16** as well as other constituents.



11, R = H
12, R = CH_3



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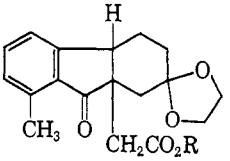
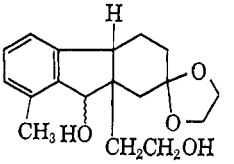
Several attempts to effect an intramolecular acyloin-like ring closure between the ester group and the 2-keto function[3] led to extremely complex product mixtures from which no pure product was isolated. Since it was apparent from the spectra of the crude products that reduction of the 9-keto function was a serious competing reaction, we prepared the various ketal derivatives **13**–**15** in an effort to reduce selectively the 9-keto function. Although reduction of the analogous compound lacking oxygen functions at C-2 had been



13, R = H
14, R = CH_3
15, R = $C(CH_3)_3$



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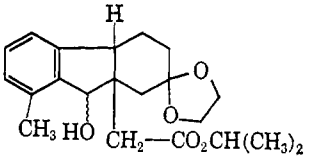

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(1) This research has been supported by research grants from the Directorate of Chemical Sciences, Air Force Office of Scientific Research (Grant No. AF-AFOSR-573), and from the National Science Foundation (Grant No. G-25214).

(2) (a) H. O. House, V. Paragamian, R. S. Ro, and D. J. Wluka, *J. Am. Chem. Soc.*, **82**, 1457 (1960); (b) H. O. House, V. Paragamian, and D. J. Wluka, *ibid.*, **82**, 2561 (1960); (c) H. O. House, R. G. Carlson, H. Müller, A. W. Noltes, and C. D. Slater, *ibid.*, **84**, 2614 (1962); (d) H. O. House and R. G. Carlson, *J. Org. Chem.*, **29**, 74 (1964).

(3) See C. D. Gutsche and I. Y. C. Tao, *ibid.*, **28**, 883 (1963).

accomplished previously[2b] by catalytic hydrogenation over palladium on carbon, this method was not successful with the ester **14**. A variety of reaction procedures for reduction of the keto function of compound **14** with sodium borohydride led either to recovery of the starting material or to the reduction of both the ester and ketone functions to form **17**. The diol **17** was also obtained by reduction of **14** with lithium aluminum hydride. Since in one case, reduction of the keto ester **14** with sodium borohydride in isopropyl alcohol afforded a poor yield of a product, believed to be the isopropyl ester **18**, as well as other products, reduction of the more hindered *t*-butyl ester **15** was examined. However, when sufficiently vigorous conditions were employed with sodium borohydride to effect reduction of the ketone function in **15** (determined by following the loss of ultraviolet absorption), the ester function was also reduced and the diol **17** was the only product isolated. As a consequence of the very hindered nature of the C-9 carbonyl function in ketals **13–15**, the value of further studies with these materials as synthetic intermediates is questionable.

Experimental[4]

Preparation of Starting Materials.—8-Methyl-*cis*-1,1a,2,3,4,4a-hexahydrofluoren-9-one (**1**), m.p. 34–35° (lit.[2b] m.p. 36–37°), was prepared following the previously described[2] reaction sequence except for preparation of 1-cyanocyclohexene by the pyrolysis[5a] of the acetate of cyclohexanone cyanohydrin.[5b] The previously described[2] bromination and dehydrobromination reactions yielded a mixture of the tetrahydrofluorenones containing approximately 50% of the exocyclic isomer **2** and 35% of the endocyclic isomer **3** as well as several minor components.[6] The alkylation of this mixture followed the previous procedure[2c] except that the use of only 1.5 equiv. of potassium *t*-butoxide, permitting the direct saponification of the crude reaction product, was found to be desirable. Thus, from reaction of 28.81 g. (0.146 mole) of the mixture of ketones **2** and **3** with 179 g. (1.17 moles) of methyl bromoacetate in 900 ml. of *t*-butyl alcohol containing 0.218 mole of potassium *t*-butoxide 9.73 g. of the keto acid **4**, m.p. 140–143° (lit.[2c] m.p. 141–143°), and 1.5 g. of the keto acid **5**, m.p. 122–127° (lit.[2c] m.p. 129–130°), were obtained after saponification of the crude neutral product and subsequent fractional crystallization from ether–petroleum ether (b.p. 30–60°) mixtures. The unsaturated keto acid **4** was converted to the epoxy methyl ester **6**, m.p. 103–104° (lit.[2c] m.p. 102.7–103.7°) by known procedures.[2c,d]

Preparation of the Diketo Acid 7 and Its Derivatives.—A solution of 7.28 g. (25.5 mmoles) of the epoxy ester **6** and 1.3 ml. of 70% aqueous perchloric acid in 450 ml. of a 2:1 (by volume) tetrahydrofuran–water mixture was refluxed for 24 hr. and then concentrated under reduced pressure. The white solid which separated was collected and washed with water. A portion of this solid, which contained[7] two components (*cf.* ref. 2c), was recrystallized from acetone–benzene mixtures to separate the pure **hydroxy lactone 8** as white needles, m.p. 197–199°, with infrared absorption[8] at 3480 (associated O–H), at 1770 (γ-lactone C=O), and at 1695 cm.$^{-1}$ (conjugated C=O). The n.m.r. spectrum[9] of the sample has complex absorption in the region δ 7.0–8.0 (3H, aryl C–H) with a doublet (J = 7 c.p.s.) at δ 4.06 (1H, >CH–O–CO–),[10] complex absorption in the region δ 3.3–4.0 (2H, >CH–O– and benzylic C–H), the center two peaks of an AB pattern at δ 2.74 and 2.81 (2H, –CH_2–CO–O–), a singlet at δ 2.56 (3H, aryl CH_3), and complex absorption in the region δ 1.0–2.5 (4H, aliphatic CH_2).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.40; H, 5.97.

Although we were unsuccessful in isolating a pure sample of the second, more soluble product from the reaction, a partially purified sample obtained as a colorless oil, b.p. 170–190° (0.01 mm.), in a short-path still, has spectroscopic properties suggesting that it is also a hydroxy keto γ-lactone ($\bar{\nu}_{max}$[11] 3440, 1780, and 1705 cm.$^{-1}$).

The aforementioned crude hydroxy lactone **8** was oxidized with aqueous chromic acid in acetone to the diketone lactone **9**, m.p. 163–168° (lit.[2c] m.p. 168.5–170°), yield 52% based on the epoxy ester. Reductive cleavage of the lactone **9** with chromium(II) chloride following an earlier procedure[2d] produced the **diketo acid 7**, in 75% yield as white prisms, m.p. 121–122°. An additional recrystallization raised the melting point of the product to 122–123°; the sample had infrared absorption[11] at 3000 (broad, associated carboxyl O–H) and 1705 cm.$^{-1}$ (broad, C=O) with ultraviolet maxima[12] at 251 mμ (ε 13,000) and 298 mμ (ε 2320). The product has an n.m.r. peak[13] at δ 10.61 (1H, COOH) with complex absorption in the regions δ 7.2–8.0 (3H, aryl C–H), 2.6–2.9 (7H, aryl CH_3 and two CH_2–CO groupings), and 1.6–2.5 (4H, CH_2) as well as a broad triplet (J = *ca.* 5 c.p.s.) at δ 3.80 (1H, benzylic C–H).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.54; H, 5.97.

Reaction of the diketo acid **7** with ethereal diazomethane afforded the previously reported **methyl ester 10**, m.p. 93–94° (lit.[2d] m.p. 93–94°). Reaction of 86 mg. (0.30 mmole) of the ester **10** with 65 mg. (0.33 mmole) of 2,4-dinitrophenylhydrazine in refluxing ethanol containing a few drops of hydrochloric acid yielded, after recrystallization from an ethanol–methylene chloride mixture, 130 mg. (93%) of the **mono-2,4-dinitrophenylhydrazone of ester 10** as yellow needles, m.p. 180–182°. The product, which melted at 181–183° after a second recrystallization, has infrared absorption[11] at 3320 (N–H), 1735 (ester C=O), and 1705 cm.$^{-1}$ (C=O) with ultraviolet maxima[12] at 252 mμ (ε 23,800) and 360 mμ (ε 22,200) as well as shoulders at 276 mμ (ε 9500) and 303 mμ (ε 5200). Thus, the product is a nonconjugated 2,4-dinitrophenylhydrazone derived from the less hindered C-2 carbonyl function.

Anal. Calcd. for $C_{23}H_{22}N_4O_7$: C, 59.22; H, 4.75; N, 12.01. Found: C, 58.99; H, 4.87; N, 11.88.

1a-(2-Carboxyethyl)-8-methyl-*cis*-1a,3,4,4a-tetrahydrofluoren-9-one (11). A. From the Keto Acid 4.—To a cold (10°) suspension of the dry sodium salt from 1.70 g. (6.7 mmoles) of the

(4) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated, sodium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer Model 237 infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The n.m.r. spectra were determined at 60 Mc. with a Varian Model A-60 n.m.r. spectrometer. The mass spectra were obtained with a CEC mass spectrometer, either Model 21-130 or Model 21-103. The microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

(5) (a) S. Dev, *J. Indian Chem. Soc.*, **33**, 769 (1956); (b) R. L. Frank, R. E. Berry, and O. L. Shotwell, *J. Am. Chem. Soc.*, **71**, 3889 (1949).

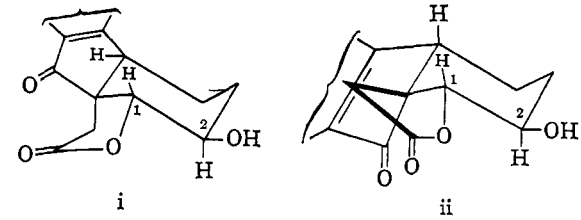
(6) A gas chromatography column packed with silicone gum, no. SE 30, suspended on Chromosorb P was employed for this analysis. The retention times of the various products on this column follow: unknown component A, 14.1 min.; 8-methyl-*cis*-hexahydrofluorenone (**1**), 15.7 min.; unknown component B, 19.0 min.; the endocyclic isomer **3** (and 8-methylfluoren-9-one which is not resolved), 25.8 min.; the exocyclic isomer **2**, 30.3 min.

(7) A thin layer chromatographic plate coated with silica gel and eluted with an ethyl acetate–cyclohexane mixture was employed for this analysis.

(8) Determined as a Nujol mull.

(9) Determined as a solution in dimethylformamide-d_7.

(10) The magnitude of the coupling constant is in agreement with one of the conformations and configurations i or ii for the hydroxy lactone **8** in



i ii

which the protons at C-1 and C-2 bear an approximate diaxial relationship to one another. For a compilation of pertinent coupling constant values, see A. C. Huitric, J. B. Carr, W. F. Trager, and B. J. Nist [*Tetrahedron*, **19**, 2145 (1963)]. The indicated conformations i or ii are also in keeping with the previous observation (ref. 2c) that the diketo lactone **9** derived from **8** has an equatorial acyloxy function. Of the two configurations, structure ii would appear to be the more probable in view of stereochemistry of the precursor, epoxide **6**.

(11) Determined as a solution in chloroform.

(12) Determined as a solution in 95% ethanol.

(13) Determined as a solution in deuteriochloroform.

keto acid **4** in 50 ml. of benzene was added, dropwise and with stirring, 1.4 ml. (16 mmoles) of oxalyl chloride. The resulting mixture was stirred for 1 hr. while being allowed to warm to room temperature and then filtered through glass wool. Concentration of the filtrate under reduced pressure left the crude acid chloride as a solid with infrared absorption[11] at 1805 (acid chloride C=O) and 1710 cm.$^{-1}$ (conjugated C=O in a five-membered ring). A solution of this acid chloride in benzene was treated with excess ethereal diazomethane. After a 30-min. reaction period, the solvents were removed under reduced pressure to leave the crude diazoketone as a yellow oil with infrared absorption[11] at 1705 (C=O), 2120, and 1635 cm.$^{-1}$ (-CO-CH-N_2). To a solution of this diazo ketone in methanol was added, dropwise and with stirring over a 1.5-hr. period, a solution of 500 mg. of silver benzoate in 4.6 g. of triethylamine. The resulting mixture was treated with decolorizing carbon, heated to reflux, and then filtered and concentrated. A solution of the residual liquid in ether was washed with aqueous sodium bicarbonate, dried, and concentrated. The crude product, 1.52 g. of yellow oil, contaminated with a small amount of the methyl ester of the acid **4**,[14] was saponified by reaction with 1.05 g. (16 mmoles) of potassium hydroxide in a refluxing mixture of 40 ml. of methanol and 4 ml. of water for 2.5 hr. The crude acidic product, 1.47 g. of brown oil, was isolated in the usual way and crystallized from an ether–petroleum ether mixture to separate 1.026 g. (57%) of the crude acid **11**, m.p. 108–110°. After decolorization with charcoal, recrystallization afforded 862 mg. (48%) of the pure **keto acid 11** as white needles, m.p. 111–112°, with broad infrared absorption[11] in the 3-μ region (associated carboxyl O-H) and a peak at 1700 cm.$^{-1}$ (C=O). The product has ultraviolet maxima[12] at 251 mμ (ϵ 12,000) and 300 mμ (ϵ 2300) with n.m.r. absorption[13] at δ 11.05 (1H, broad, COOH), 3.33 (1H, broad, benzylic C-H), and 2.61 (3H singlet, aryl CH_3) as well as absorption in the regions δ 6.9–7.7 (3H, aryl C-H), 5.3–6.1 (2H, vinyl C-H), and 1.5–2.6 (8H, aliphatic CH_2).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.45; H, 6.79.

After reaction of 300 mg. (1.1 mmoles) of the acid **11** with excess ethereal diazomethane, the crude neutral product was isolated and distilled in a short-path still to separate 303 mg. (96%) of the **methyl ester 12** as a colorless liquid, b.p. 120–135° (0.13 mm.), n^{30}D 1.5561. The product has infrared absorption[11] at 1725 (ester C=O) and 1695 cm.$^{-1}$ (C=O) with ultraviolet maxima[12] at 250 mμ (ϵ 12,800) and 299 mμ (ϵ 2,600).

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.79; H, 7.02.

B. From the Ketone 2.—A solution of 990 mg. (5.0 mmoles) of the previously described mixture of unsaturated ketones **2** and **3** and 860 mg. (10 mmoles) of methyl acrylate in a mixture of 7 ml. of benzene and 2.4 ml. of methanol containing 5 mmoles of sodium methoxide was allowed to stand for 12 hr. at room temperature and then diluted with water. The organic layer was separated, dried, and concentrated to leave 1.273 g. of yellow liquid containing[14] at least four components. After an involved series of chromatographic separations on silica gel, the components eluted as the second spot[14] from the origin were separated and saponified to give, after recrystallization, 47 mg. of the **unsaturated acid 11**, m.p. 110–111°, which was identified with the previously described sample by a mixture melting point determination and by comparison of infrared spectra. Also isolated was 35 mg. of a partially purified acid as pale yellow crystals from ether–petroleum ether mixtures, m.p. 121–129°. The ultraviolet spectrum[12] of this acid with maxima at 237 mμ (ϵ 28,800), 262 (shoulder, 12,700), and 330 (2340) is very similar to the ultraviolet spectrum of the acid **5**[2a] suggesting that this partially purified component may be the unsaturated acid **16**. Efforts to separate pure samples of the other components in this mixture were unsuccessful.

Preparation of the Ketal Acid 13 and Esters 14 and 15.—A solution of 286 mg. (1.0 mmole) of the diketo ester **10**, 74 mg. (1.2 mmoles) of ethylene glycol, and 19 mg. (0.1 mmole) of *p*-toluenesulfonic acid in 20 ml. of benzene was refluxed for 5 hr. with continuous separation of water. The resulting mixture was washed with aqueous sodium bicarbonate, dried, and concentrated. Crystallization of the residue (333 mg.) from an ether–petroleum ether mixture separated 241 mg. (73%) of the crude ketal, m.p. 111–113°. Recrystallization afforded the pure **ketal ester 14** as white needles, m.p. 111–112°, with infrared absorption[15] at 1728 (ester C=O) and 1702 cm.$^{-1}$ (C=O) and ultraviolet maxima[12] at 250 mμ (ϵ 12,700) and 298 mμ (ϵ 2270). The product has n.m.r. absorption[13] in the regions δ 7.0–7.8 (3H, aromatic C-H) and 1.2–2.5 (6H, aliphatic C-H) with a partially resolved multiplet at δ 3.93 (4H, -CH_2-O) and singlets at δ 3.62 (3H, O-CH_3) and 2.67 (3H, aryl CH_3) as well as two peaks at δ 2.95 and 3.04 which are probably the center lines of an AB pattern for the two protons α to the carbomethoxy function.

Anal. Calcd. for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71; mol. wt., 330. Found: C, 68.99; H, 6.73; mol. wt., 330 (mass spectrum).

To a solution of potassium *t*-butoxide, prepared from 740 mg. (19 mg.-atoms) of potassium and 20 ml. of *t*-butyl alcohol, was added 540 mg. (6.15 mmoles) of ethyl acetate; the resulting mixture was refluxed for 1 hr. to remove any potassium hydroxide present. Then 630 mg. (1.9 mmoles) of the ketal methyl ester **14** was added and the resulting solution was refluxed under a nitrogen atmosphere for 15 hr. The resulting mixture was diluted with ether and then washed with aqueous sodium bicarbonate, dried, and concentrated. Crystallization of the neutral residue, 580 mg. of yellow oil, from an ether–petroleum ether mixture separated 455 mg. (64%) of the **ketal *t*-butyl ester 15** as yellow crystals, m.p. 105–106°. Recrystallization afforded the ketal **15** as white prisms with the same melting point. The sample had infrared absorption[11] at 1720 (shoulder, ester C=O), 1705 (C=O), 1150, and 1175 cm.$^{-1}$ (ketal C-O) with ultraviolet maxima[12] at 248 mμ (ϵ 12,400) and 297 mμ (ϵ 2300); in addition to n.m.r. absorption[13] in the regions δ 7.0–7.7 (3H, aryl C-H) and 1.3–2.5 (6H, aliphatic C-H), the sample has singlets at δ 1.37 [9H, O-C(CH_3)$_3$] and 2.62 (3H, aryl C-H) with a partially resolved multiplet at δ 3.86 (4H, -CH_2-O) and two peaks at δ 2.82 and 2.86 (2H, center peaks of AB pattern for -CH_2-COO-).

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.82; H, 7.66.

The acidic fraction (178 mg.) from this reaction was recrystallized from an ether–petroleum ether mixture to separate 112 mg. (21%) of the ketal acid **13**, m.p. 183–185°. From a comparable reaction, employing 35 mg. of potassium, 100 mg. of the ketal methyl ester **14**, and 3 ml. of *t*-butyl alcohol, where ethyl acetate was not added to destroy any potassium hydroxide present, only 16 mg. of neutral material was separated. The major acidic product, recovered from the aqueous sodium bicarbonate solution in the usual way, separated from an ether–petroleum ether mixture as 35 mg. of yellow crystals, m.p. 179–181°. Recrystallization afforded the pure **ketal acid 13** as white needles, m.p. 183–184°, with broad infrared absorption[11] in the 3-μ region (carboxyl O-H) as well as a band at 1710 with shoulders at 1735 and 1670 cm.$^{-1}$ (C=O). The product has ultraviolet maxima[12] at 249 mμ (ϵ 12,800) and 297 mμ (ϵ 2400) with n.m.r. absorption[16] in the regions δ 7.1–7.8 (3H, aryl C-H) and 1.0–2.5 (6H, aliphatic C-H) as well as a singlet at δ 2.56 (3H, aryl CH_3), a partially resolved multiplet at δ 3.87 (4H, -CH_2-O), and peaks at δ 2.78 and 2.88 (2H, center peaks of AB pattern for -CH_2-COO-).

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.59; H, 6.27.

Reduction of the Ketal Ester 14. A. Preparation of the Diol 17.—A mixture of 34 mg. (0.9 mmole) of lithium aluminum hydride and 100 mg. (0.3 mmole) of the ketal ester **14** in 5 ml. of ether was stirred at 0° for 0.5 hr. and then refluxed for 4 hr. Water was added to the resulting mixture and the ether layer was separated, washed with water, dried, and concentrated. Crystallization of the crude product (96 mg.) from an ether–petroleum ether mixture separated 70 mg. (76%) of the **ketal diol 17** as white needles, m.p. 143–145°. The product has infrared bands[8] at 3600 and 3400 cm.$^{-1}$ (unassociated and associated O-H) but no absorption the 6-μ region attributable to a carbonyl function; the ultraviolet spectrum[12] has only weak absorption (ϵ 750 or less) in the region 240–270 mμ. The product has n.m.r. absorption[16] in the regions δ 6.7–7.3 (3H, aryl C-H), 4.7–5.3 (3H, 2 hydroxyl groups and benzylic >CH-O), 3.5–4.0 (6H, -CH_2O of ketal and primary alcohol), and 1.0–3.0 (12H, aliphatic C-H including a singlet at δ 2.39 for the aryl CH_3 group).

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 70.69; H, 7.93.

B. Formation of the Ester 18.—A solution of 132 mg. (0.4 mmole) of the ketal methyl ester **14** and 15 mg. (0.4 mmole) of sodium borohydride in 6 ml. of isopropyl alcohol was refluxed for

(14) A thin layer chromatography plate coated with silica gel and eluted with benzene was employed for this analysis.

(15) Determined as a solution in carbon tetrachloride.

(16) Determined as a solution in dimethyl sulfoxide-d_6.

3.5 hr. and then concentrated under reduced pressure and diluted with cold, dilute hydrochloric acid. After the resulting mixture had been extracted with ether, the ethereal extract was washed with aqueous sodium bicarbonate, dried, and concentrated. The residual colorless oil (92 mg.) contained[7] at least two components. Chromatography of an 80-mg. portion on 4 g. of Woelm alumina (activity grade II) separated 42 mg. of the more rapidly eluted component (eluted with benzene). Crystallization of this material from an ether–petroleum ether mixture afforded 26 mg. of **hydroxy ketal isopropyl ester 18** as white prisms, m.p. 112–113°. A mixture of this product with the starting methyl ester **14** melted at 88–94°. The product has infrared absorption[11] at 3450 (associated O–H) and 1706 cm.$^{-1}$ (hydrogen-bonded ester C=O) with intense ultraviolet[12] end absorption (ϵ 10,600 at 215 mμ) and weak absorption (ϵ 450 or less) in the region 250–270 mμ.

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83; mol. wt., 360. Found: C, 69.93; H, 7.76; mol. wt., 360 (mass spectrum).

A New Indole Synthesis[1]

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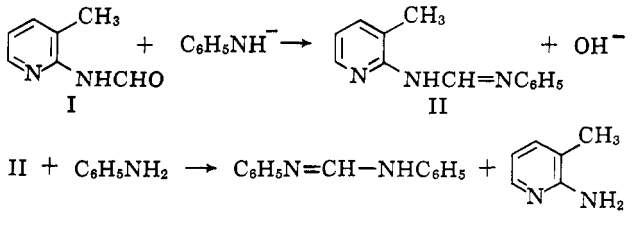
Cyclization of N-(3-methyl-2-pyridyl)-N′-methyl-N′-phenylformamidine and the corresponding isomers, 2-methyl-3-pyridyl- and 3-methyl-4-pyridylformamidines, in the presence of sodium N-methylanilide in boiling N-methylaniline furnished the three isomeric pyrrolopyridines (azaindoles). When this reaction was applied to N-(2-tolyl)-N′-methyl-N′-phenylformamidine in mineral oil at 300°, indole itself was obtained in over 75% yield.

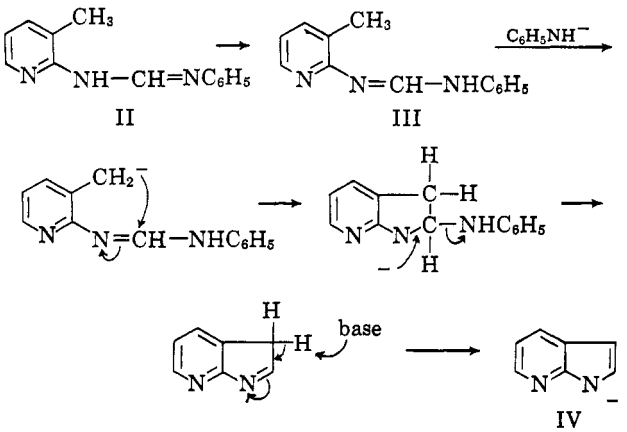
In connection with another problem, the need arose for a preparative synthesis of 1H-pyrrolo[2,3-*b*]pyridine (7-azaindole) that was adaptable for large-scale work. This compound was prepared by Robison[4] who heated a mixture of N-(3-methyl-2-pyridyl)formamide (I) with 6 equiv. of sodium anilide and 2 equiv. of potassium formate without solvent at 300° to obtain the desired product in about 45% yield on a 0.3 *M* scale. This method was patterned after one of Tyson's modifications of the Madelung synthesis[5] for preparing indole. Although Tyson did not establish the course of the reaction, his investigation revealed that the addition of potassium formate to the reaction mixture and the use of either potassium *o*-toluidide or sodium anilide rather than potassium *t*-butoxide helped to increase the yield of indole. The role of the potassium formate is not clear. Tyson suggested that the salt serves as a source of carbon monoxide *in situ* which reacts with the alkali metal toluidide to form the corresponding alkali *o*-formotoluidide which then condenses to form indole.

Repetition of Robison's work revealed that the reaction mixtures were almost intractable and rarely furnished the desired compound in the reported yield. It was found that, by incorporating several modifications including the use of mineral oil as a diluent, fairly consistent yields of 50–63% could be achieved (see Experimental section). In this work it was noted that considerable quantities of N,N′-diphenylformamidine were produced as a by-product, which may have arisen according to the following scheme.



Although the reaction of diarylamidines with aromatic amines has been shown by Roberts[6] to be acid catalyzed, the same authors also found that arylformimidates react slowly at room temperature with aromatic amines to furnish diarylformamidines in the presence of sodium *t*-butoxide.

It is also possible that the 7-azaindole was being formed by a base-catalyzed cyclization of II.



If this hypothesis were correct, then a more suitable precursor for the *in situ* formation of the mixed formamidine, II, should furnish 7-azaindole more readily. When ethyl N-(3-methyl-2-pyridyl)formimidate (V) was heated with 3 moles of sodium anilide in mineral oil at 300°, 7-azaindole was produced in 40% yield, thus obviating the use of potassium formate.

It was felt that the formamidine III was reacting with base in another sense to form the ion VI and that prevention of this reaction would substantially increase the yield of IV. Indeed, the use of sodium N-methylanilide permitted the reaction to be carried out at 200° with a concomitant increase in yield to 52%. The use of N-methylaniline thus has a twofold purpose in that it also prevents the formation of the tautomer II.

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(4) M. M. Robinson and B. L. Robison, *J. Am. Chem. Soc.*, **77**, 6554 (1955); **77**, 457 (1955). Using this method, 6-methyl-7-azaindole and 4-methyl-7-azaindole were prepared in 13 and 24% yield, respectively, by ring closure of the apposite 2-formamidodimethylpyridines: A. Albert and R. E. Willette, *J. Chem. Soc.*, 4063 (1964).

(5) F. T. Tyson, *J. Am. Chem. Soc.*, **72**, 2801 (1950).

(6) R. M. Roberts, R. H. DeWolfe, and J. H. Ross, *ibid.*, **73**, 2277 (1951).