dehyde showed absorptions at 2040 and 2130 cm^{-1} indicative of the C–D stretching of the –CDO group. Its nmr spectrum showed only a single peak at δ 1.1 ppm and no absorption in the δ 8–12-ppm region, indicating the absence of the aldehydic proton. The deuterium content in the aldehyde was determined to be greater than 99% by mass spectroscopy.

All the liquid aldehydes were checked for purity on an F & M 5750 research chromatograph before being dissolved in water for oxidation studies. Because of the high volatility of some of these aldehydes, the concentration of the aqueous solutions was determined analytically. Solutions of formaldehyde, acetaldehyde, propionaldehyde, and butyraldehyde were determined by the hydroxylamine hydrochloride method.[26] Solutions of chloroacetaldehyde and dichloroacetaldehyde were determined by the dinitrophenylhydrazine method.[27]

Kinetic measurements were made by following the decrease in the chromium(VI) concentration spectrophotometrically at 432 nm using a Cary Model 15 double-beam spectrophotometer. All the kinetic experiments were run at 25°. The pseudo-first-order rate constant of the chromium(VI) oxidation of the aldehydes was obtained from the slope of the plot of log $(A_t - A_\infty)$ *vs.* time, where A_t and A_∞ were the absorbance at 432 nm of the reaction mixture at time t and at infinity, respectively. The second-order rate constants, k_{obsd}, were obtained from the pseudo-first-order rate constants and the analytical concentration of the aldehyde.

Registry No.—Chromium, 7440-47-3.

(26) S. Siggia, "Quantitative Organic Analysis via Functional Groups," 2nd ed, Wiley, New York, N. Y., 1963, p 74.

(27) Reference 26, p 92.

Borane Reduction of 3-Substituted 2-Indolinones

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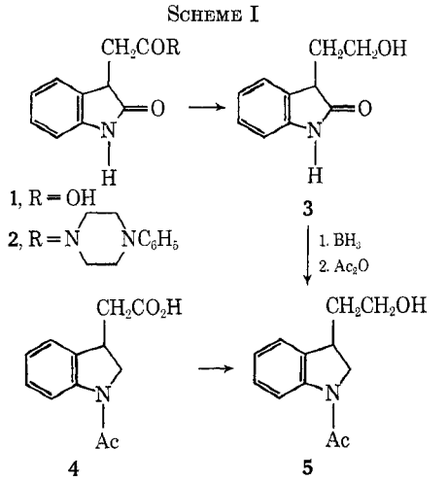
The utility of borane for the preparation of indolineethanols (**9**) by reduction of 3-(2-hydroxyethyl)-2-indolinones (**3**), alkyl 2-oxo-$\Delta^{3,\alpha}$-indolineglycolates (**7**), and alkyl 2-oxo-3-indolineacetates (**8**) is illustrated.

We required certain 3-indolineethanols as intermediates for another investigation, and their preparation from 3-substituted 2-indolinones by reductive procedures seemed a distinct possibility. The reduction of 2-indolinones by hydride reagents has been the subject of numerous reports which lack consistency. An early report[1] indicating that lithium aluminum hydride was useful for this purpose is unfounded.[2] However, several investigators have indicated that borane possesses the capacity for such reductions, although the efficiency of this agent for reduction of 2-indolinone and certain 3-substituted derivatives is subject to variability.[2c,3] In this laboratory application of the commercially available reagent[4] to 2-indolinone gave 46% of indoline. Accordingly, the utility of borane for the reduction of certain 3-substituted 2-indolinones was studied.

Initially the preparation of indolineethanol (**9a**) by reduction of the heretofore elusive "oxytryptophol" (**3**)[5] was undertaken. The required 3-(2-hydroxyethyl)-2-indolinone (**3**) was prepared by conversion of 2-oxo-3-indolineacetic acid (**1**)[6] into a mixed carbonic anhydride with ethyl chlorocarbonate; the formation of the anhydride was established by its conversion into the amide **2** with 1-phenylpiperazine (see Scheme I). Reduction of the anhydride with sodium borohydride[7] gave 52% of the required alcohol **3**. This material was then reduced with borane to give 49% of 3-indolineethanol which was characterized as the *N*-acetyl derivative **5**; the last compound also was prepared by reduction of 1-acetylindolineacetic acid (**4**)[8] with borane. The preparation of **5** by the second procedure further illustrates the sharp difference in rate of reaction with borane observed for carboxylic acids and amides.[9]

Scheme I



The above transformations met our requirements in principle. However, the preparation of **5** and congeners from 2-indolinones requires three successive reductions, for the synthesis of **1** can only be accomplished by catalytic hydrogenation of benzyl 2-oxo-$\Delta^{3,\alpha}$-indolineglycolate.[6] Therefore, we sought to circumvent the numerous operations by investigating the reduction of intermediates prior to **1**.

These studies were conducted with derivatives of 2-indolinone (**6a**), 5,6-dimethoxy-2-indolinone (**6b**),[10]

(1) P. A. S. Smith and T. Yu, *J. Amer. Chem. Soc.*, **74**, 1096 (1952).

(2) (a) P. L. Julian and H. C. Printy, *J. Amer. Chem. Soc.*, **71**, 3206 (1949); (b) C. B. Hudson and A. V. Robertson, *Aust. J. Chem.*, **20**, 1699 (1967); (c) K. N. Kilminster and M. Sainsbury, *J. Chem. Soc., Perkin Trans. 1*, 2264 (1972).

(3) (a) H. Plieninger, H. Bauer, W. Bühler, J. Kurze, and U. Lerch, *Justus Liebigs Ann. Chem.*, **680**, 74 (1964); (b) K. M. Biswas and A. H. Jackson, *Tetrahedron*, **24**, 1145 (1968); (c) S. A. Monti and R. R. Schmidt, *ibid.*, **27**, 3331 (1971); (d) H. Sirowej, S. A. Khan, and H. Plieninger, *Synthesis*, 84 (1972).

(4) Ventron, Alpha Inorganics, Beverly, Mass.

(5) E. Wenkert and E. C. Blossey, *J. Org. Chem.*, **27**, 4656 (1962).

(6) P. L. Julian, H. C. Printy, R. Ketcham, and R. Doone, *J. Amer. Chem. Soc.*, **75**, 5305 (1953).

(7) Y. G. Perron, L. B. Crast, J. M. Essery, R. R. Fraser, J. C. Godfrey, C. T. Holdrege, W. F. Minor, M. E. Neubert, R. A. Partyka, and L. C. Cheney, *J. Med. Chem.*, **7**, 483 (1964).

(8) H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **28**, 2794 (1963).

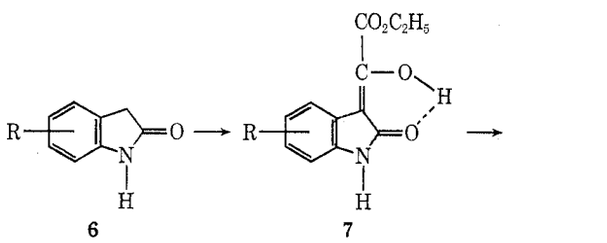
(9) H. C. Brown, P. Heim, and N. M. Yoon, *J. Amer. Chem. Soc.*, **92**, 1637 (1970).

(10) G. N. Walker, *J. Amer. Chem. Soc.*, **77**, 3844 (1955).

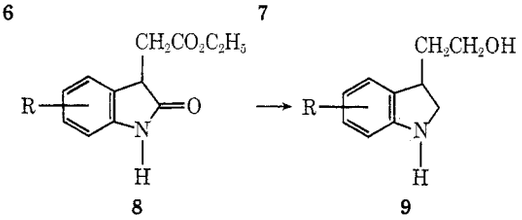
and 5,6-methylenedioxy-2-indolinone (**6c**).[11] Our preparation of the last substance from the known[12] 4,5-methylenedioxy-2-nitrophenylacetic acid involved Fischer esterification, catalytic hydrogenation of the ester, and hydrolysis of the reduction product with acetic acid. This three-stage process gave 73% of **6c**, whereas repetition of the literature procedure for its synthesis, involving reduction of the nitrophenylacetic acid in acetic acid, furnished only 26% of product.

Base-catalyzed condensation of the 2-indolinones **6** with ethyl oxalate gave the ethyl 2-oxo-$\Delta^{3,\alpha}$-indolineglycolates **7** (see Scheme II).[13] These isatylidene

SCHEME II



6 **7**



8 **9**

a, R = H
b, R = 5,6-$(CH_3O)_2$
c, R = 5,6-CH_2O_2

derivatives were converted into the ethyl 2-oxo-3-indolineacetates **8** by reduction with zinc amalgam in acetic acid or catalytic hydrogenation.[6] Reduction of substrates **7** and **8** with borane generally proved superior to that of oxytryptophol (**3**) for the preparation of the indolineethanols (see Table I). The reduction of **7a** proved to be the exception, since unidentified side products precluded effective isolation of indolineethanol (**9a**).

Experimental Section

General.—Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Solutions were dried ($MgSO_4$) and concentrated under reduced pressure on a rotary evaporator. The ultraviolet spectra were determined in methanol with a Cary Model 11 recording spectrophotometer, infrared spectra were determined in pressed KBr disks on a Perkin-Elmer Model 21 instrument, and nmr spectra were obtained with a Varian A-60 spectrometer. The petroleum ether used was that fraction having bp 30–60°.

1-(Oxindole-3-acetyl)-4-phenylpiperazine (2).—A solution of 955 mg (5.0 mmol) of oxindole-3-acetic acid (**1**)[6] and 505 mg (5 mmol, 0.7 ml) of triethylamine in 25 ml of tetrahydrofuran was cooled in an ice bath with stirring, and 540 mg (5.0 mmol) of ethyl chloroformate was added dropwise. The resulting mixture was stirred for 10 min, and a solution of 810 mg (5.0 mmol) of 1-phenylpiperazine in 10 ml of tetrahydrofuran was added. The mixture was stirred at 0° for 1 hr and then distributed between ether and water. The organic layer was washed consecutively with 20% acetic acid, water, sodium carbonate solution, and water. The dried solution was evaporated, and the residue was crystallized from acetone–hexane to give 450 mg (27%) of crystals: mp 160–163°; ir max 3.10, 5.84, 6.12, 6.24 μ.

Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.48; H, 6.14; N, 12.33.

3-(2-Hydroxyethyl)-2-indolinone (3).—A solution of 2.35 g (12.6 mmol) of oxindole-3-acetic acid (**1**) in 18 ml of tetrahydrofuran at −5° under argon was treated with 1.71 ml of triethylamine and then 1.53 ml of ethyl chlorocarbonate. The mixture was stirred at −5° for 30 min and then filtered. The filtrate was added dropwise to a cold solution of 1.16 g of sodium borohydride in 18 ml of water, and the solution was then stirred at ambient temperature for 2 hr. The reaction mixture was rendered strongly acid with hydrochloric acid and extracted with ethyl acetate. The organic extracts were washed successively with saline, sodium hydroxide solution, and saline. The dried organic solution was evaporated to give a gum which crystallized from ether to furnish 1.11 g (52%) of white crystals, mp 107–110°. The analytical sample was obtained from acetone–petroleum ether and had mp 111–112°; ir max 3.00, 3.15, 5.92, 6.16 μ.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.62; H, 6.35; N, 7.88.

4,5-Methylenedioxy-2-nitrophenylacetic Acid.—A suspension of 25 g of 4,5-methylenedioxyphenylacetic acid[14] in 110 ml of acetic acid was stirred at 15° while 40.5 ml of concentrated nitric acid was added in portions maintaining the temperature at 40°. The mixture was stirred for an additional 40 min and then added to 800 ml of ice water. The product was collected as 24.5 g of yellow crystals, mp 185–188°. A sample recrystallized from methanol had mp 186–188°; ir max 6.57, 7.56 μ; $\delta_{TMS}^{CDCl_3}$ 3.92 (s, 2, CH_2CO_2H), 6.14 (s, 2, OCH_2O), 6.82 (s, 1, 6-H), 7.61 (s, 1, 3-H).

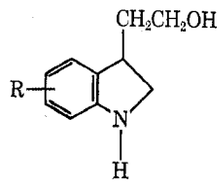
Anal. Calcd for $C_9H_7NO_6$: C, 48.01; H, 3.13; N, 6.22. Found: C, 48.13; H, 3.19; N, 6.24.

Fischer esterification of this material (25 g) with methanol–sulfuric acid gave 23.6 g (88%) of the methyl ester, mp 106–108°.

5,7-Dihydro-6*H*-1,3-dioxolo[4,5-*f*]indol-6-one (6c).—A mixture of 27.7 g (0.1 mol) of methyl 2-nitro-4,5-methylenedioxyphenylacetate and 1.4 g of 10% Pd/C catalyst in 200 ml of ethanol was shaken with hydrogen until the theoretical amount of hydrogen was absorbed. The reaction mixture was filtered and evaporated under reduced pressure to give methyl 2-amino-4,5-methylene-

TABLE I

YIELD OF INDOLINEETHANOLS *via* BORANE REDUCTION OF 2-INDOLINONES



2-Indolinone substrate	—Indolineethanol product— R	Yield, %
3-(2-Hydroxyethyl)-2-indolinone (**3**)	H[a]	49
Ethyl 2-oxo-3-indolineacetate (**8a**)	H[a]	55
1-Acetyl-3-indolineacetic acid (**4**)	H[a]	73
Ethyl 5,6-dimethoxy-2-oxo-3-indolineacetate (**8b**)	5,6-$(CH_3O)_2$[a]	79
Ethyl 5,6-dimethoxy-2-oxo-$\Delta^{3,\alpha}$-indolineglycolate (**7b**)	5,6-$(CH_3O)_2$[a]	47
Ethyl 5,6-dihydro-6-oxo-7*H*-1,3-dioxolo[4,5-*f*]indole-7-acetate (**8c**)	5,6-OCH_2O[b]	57
Ethyl 5,6-dihydro-6-oxo-7*H*-1,3-dioxolo[4,5-*f*]indole-$\Delta^{7,\alpha}$-glycolate (**7c**)	5,6-OCH_2O[b]	43

[a] Characterized as the 1-acetyl derivative. [b] Characterized as the acetate ester of the 1-acetyl derivative.

(11) This name is used to maintain consistency; Chemical Abstracts nomenclature is 5,7-dihydro-6*H*-1,3-dioxolo[4,5-*f*]indol-6-one.

(12) T. Kametani, O. Umezawa, S. Shibuya, K. Ogasawara, M. Ishiguro, and D. Mizuno, *Yakugaku Zasshi*, **83**, 851 (1963); *Chem. Abstr.*, **60**, 449b (1964).

(13) L. Horner, *Justus Liebigs Ann. Chem.*, **548**, 117 (1941).

(14) (a) K. Kindler and T. Gehlhaar, *Arch. Pharm. (Weinheim)*, **274**, 377 (1936); (b) T. R. Shepard, H. D. Porter, J. F. Noth, and C. K. Simmans, *J. Org. Chem.*, **17**, 568 (1952).

dioxyphenylacetate as a white solid. The product from three such reductions was dissolved in 360 ml of acetic acid, purged with argon, and heated at reflux temperature for 1 hr. The hot solution was diluted with water while stirring until crystals appeared. The mixture was cooled to give 44.0 g (83%) of product as crystals, mp 223–226° dec (lit.[12] mp 216–217° dec).

Preparation of 2-Oxo-$\Delta^{3,\alpha}$-indolineglycolates (7).—The following preparation of ethyl 5,6-dimethoxy-2-oxo-$\Delta^{3,\alpha}$-indolineglycolate (**7b**) illustrates the general procedure.

To a solution of 4.82 g (25 mmol) of 5,6-dimethoxyoxindole in 50 ml of dimethylformamide stirred in an ice bath under an argon atmosphere was added 1.25 g of a sodium hydride in oil dispersion (60.2% concentration). The mixture was stirred for 30 min and then a solution of 5.35 g (36.7 mmol) of diethyl oxalate in 25 ml of dimethylformamide was added dropwise. The solution was stirred at ambient temperature for 18 hr and then diluted with 150 ml of water. The aqueous solution was stirred in an ice bath and acidified with hydrochloric acid. The resultant red solid was recrystallized from acetone to give 4.55 g (66%) of red crystals: mp 183–185° dec; ir max 5.75, 6.00, 6.14, 6.57, 6.73 μ; $\delta_{TMS}^{DMSO\text{-}d_6}$ 1.33 (t, 3, J = 8.5 Hz, CH_3CH_2), 3.75, 3.80 (s, 3 each, OCH_3), 4.40 (q, 2, J = 8.5 Hz, CH_3CH_2), 6.64 (s, 1, 7-H), 7.59 (s, 1, 4-H).

Anal. Calcd for $C_{14}H_{15}NO_6$: C, 57.33; H, 5.16; N, 4.78. Found: C, 56.83; H, 5.14; N, 4.26.

Ethyl 5,6-dihydro-6-oxo-7*H*-1,3-dioxolo[4,5-*f*]indole-$\Delta^{7,\alpha}$-glycolate (7c) was similarly obtained in 93% yield. Recrystallized from acetone it had mp 246–248° dec; ir max 5.75, 5.97 μ; $\delta_{TMS}^{DMSO\text{-}d_6}$ 1.33 (t, 3, J = 7.5 Hz, CH_3CH_2), 4.37 (q, 2, J = 7.5 Hz, CH_3CH_2), 6.00 (s, 2, OCH_2O), 6.65 (s, 7-H), 7.43 (s, 4-H).

Anal. Calcd for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05. Found: C, 56.50; H, 3.94; N, 4.97.

Preparation of Ethyl 2-Oxo-3-indolineacetates (8).—The following preparation of the 5,6-dimethoxy derivative **8b** is illustrative. To a suspension of 0.73 g of ethyl 5,6-dimethoxy-2-oxo-$\Delta^{3,\alpha}$-indolineglycolate (**7b**) in 50 ml of acetic acid was added freshly prepared zinc amalgam (from 11 g of zinc and 1.1 g of mercuric chloride). The mixture was stirred under reflux for 16 hr. The mixture was cooled and filtered, and the filtrate was reduced in volume to 10 ml. The residue was diluted with 50 ml of water and extracted with ether. The ether extract was washed with saturated sodium carbonate solution and saturated sodium chloride solution, and evaporated. The resultant solid mass crystallized from acetone–petroleum ether to give 320 mg (46%) of the product: mp 123–124°; ir max 3.14, 5.77, 6.12 μ; $\delta_{TMS}^{CDCl_3}$ 1.23 (t, 3, J = 7.0 Hz, CH_3CH_2), 2.80, 3.04 (m, 2, J_{gem} = 17.0 Hz, $J_{A,B}$ = 8.0 Hz, $J_{A',B}$ = 5.0 Hz, CH_2), 3.78 (m, 3-H), 4.17 (q, 2, J = 7.0 Hz, CH_3CH_2), 6.57, 6.90 (each s, aryl H).

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.34; H, 6.21; N, 5.16.

Ethyl 5,6-dihydro-6-oxo-7*H*-1,3-dioxolo[4,5-*f*]indole-7-acetate (8c) was prepared similarly in 73% yield: ir max 3.12, 5.75, 5.82, 5.98, 6.10 μ; $\delta_{TMS}^{DMSO\text{-}d_6}$ 1.11 (t, 3, J = 7.5 Hz, CH_3CH_2), 2.75–2.92 (m, 2, CH_2CO_2), 3.59 (d t, 1, $CHCH_2CO_2$), 4.04 (q, 2, J = 7.5 Hz, CH_3CH_2), 5.92 (s, 2, OCH_2O), 6.50 (s, 1, 4-H), 6.89 (s, 1, 8-H).

Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.41; H, 4.92; N, 5.31.

Borane Reductions. General Procedure.—A solution of 1.95 g (7.0 mmol) of ethyl 5,6-dimethoxy-2-oxo-3-indolineacetate (**8b**) in 100 ml of tetrahydrofuran stirred in an ice bath under an argon atmosphere was treated with 40 ml of 1 M borane in tetrahydrofuran. The mixture was stirred for 15 hr at ambient temperature and then heated under reflux for 18 hr. The solvent was removed, and the residue was heated at 100° with 100 ml of 1 N hydrochloric acid. The acid solution was cooled, washed with ethyl acetate, chilled in an ice bath, and made alkaline with aqueous sodium hydroxide solution. The alkaline solution was extracted with ethyl acetate. The organic extract was washed with saline, dried, and evaporated to give 1.23 g (79%) of 5,6-dimethoxy-3-indolineethanol (**9b**) as a gum. Schotten–Bauman acetylation gave **1-acetyl-5,6-dimethoxy-3-indolineethanol**, mp 148–150°, after recrystallization from acetone–petroleum ether: uv max 216, 261, 303 mμ (ϵ 19,100, 15,400, 8200); ir max 2.95, 6.10, 6.22 μ.

Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.52; H, 7.30; N, 5.15.

The reduction of other oxindole derivatives is summarized in Table I, and the characterization of the products is given below.

1-Acetyl-3-indolineethanol (**5**) was obtained from ether as white crystals, mp 49–52°.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.97; H, 7.43; N, 6.56.

5-Acetyl-6,7-dihydro-5*H*-1,3-dioxo[4,5-*f*]indole-7-ethyl acetate was prepared by acetylation of the reduction product in pyridine and obtained from acetone–petroleum ether as white crystals: mp 93–94°; ir max 5.75, 6.01 μ.

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.73; H, 5.91; N, 4.97.

Acknowledgment.—We are indebted to Messrs. W. Fulmor and L. Brancone and their associates for supplying spectral data and microanalyses, respectively.

Registry No.—**1,** 2971-31-5; **2,** 40940-09-8; **3,** 3690-95-7; **4,** 40118-10-3; **5,** 40118-11-4; **6c,** 25326-30-1; **7b,** 40119-20-8; **7c,** 40118-21-6; **8a,** 40940-16-7; **8b,** 40118-13-6; **8c,** 40118-22-7; 1-phenylpiperazine, 92-54-6; 4,5-methylenedioxy-2-nitrophenylacetic acid, 40118-17-0; 4,5-methylenedioxy-2-nitrophenylacetic acid methyl ester, 40118-18-1; 4,5-methylenedioxyphenylacetic acid, 2861-28-1; 5,6-dimethoxyoxindole, 6286-64-2; diethyl oxalate, 95-92-1; borane, 13283-31-3; 1-acetyl-5,6-dimethoxy-3-indolineethanol, 40118-15-8; 5-acetyl-6,7-dihydro-5*H*-1,3-dioxolo[4,5-*f*]indole-7-ethyl acetate, 40118-24-9.