Synthesis of Indoles from 4-Oxo-4,5,6,7-tetrahydroindoles. III.[1a] Introduction of Substituents by Electrophilic Substitution

WILLIAM A. REMERS*[1b] AND MARTIN J. WEISS

Process and Preparations Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York 10965

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The general method of indole synthesis by way of 4-oxo-4,5,6,7-tetrahydroindoles has been extended by a variety of electrophilic substitution reactions, including bromination, nitration, acylation, and formylation. An order of selective substitution was established as follows: $C_2 > C_3 > C_5$, except in certain Vilsmeier–Haack formylations of 2-substituted compounds. When the pyrrole ring of a 4-oxo-4,5,6,7-tetrahydroindole was substituted with a strong electron-withdrawing group, electrophilic substitution was diverted to C_3. Most of the 6,7-dihydroindoles prepared in this investigation could be dehydrogenated to the fully aromatic indoles, but many of the new 4-oxo-4,5,6,7-tetrahydroindoles were resistant to dehydrogenation. Vilsmeier–Haack formylation of certain 4-oxo-4,5,6,7-tetrahydroindoles led directly to fully aromatic indoles which had a 4-chloro-5-(dimethylaminomethyl) pattern of substitution.

Discussion

A general approach to the synthesis of indoles from 4-oxo-4,5,6,7-tetrahydroindoles was outlined in the preceding article in this series.[1] The present article is concerned with extending this approach by a variety of electrophilic substitution reactions of 4-oxo-4,5,6,7-tetrahydroindoles and conversion of the resulting products into novel indoles.

There are three possible sites for electrophilic substitution of **3a**, the parent 4-oxo-4,5,6,7-tetrahydroindole. Two of these sites, C_2 and C_3 are in the pyrrole ring, and the third, C_5, is provided by enolization of the carbonyl group. The relative rates of substitution in the pyrrole ring and at C_5 will obviously be influenced by the rate and extent of this enolization. Important conjugation between the carbonyl group and pyrrole nitrogen[1] affects this factor, and others, in the electrophilic substitutions.

In a preliminary experiment, the acid-catalyzed deuterium exchange of **3a** in CD_3OD was determined. This experiment (Table I) revealed no appreciable difference in the rates of exchange of the C_2 and C_3 protons, but their exchange rates were approximately double those of C_5 protons. Although this experiment afforded no basis for the prediction of selective reactivity between C_2 and C_3, LCAO–MO calculations for the relative π energies of hypothetical pyrrolenine cation intermediates for electrophilic substitution at these positions indicated a preference for substitution at C_2 (the α-pyrrole position).[2]

TABLE I

ACID-CATALYZED DEUTERIUM EXCHANGE IN 4-OXO-4,5,6,7-TETRAHYDROINDOLE (**3a**)[a]

Proton	% exchange at times, hr				
	0[b]	1	2	7	26[c]
2	33	75	86	86	87
3	33	75	86	86	87
5,5	17	50	71	83	83

[a] A 12% solution of **3a** in CD_3OD in an nmr tube was treated with one small drop of DCl and the solution was kept at 25° between measurements. [b] The short time between preparation of the sample and completion of the nmr spectrum caused the indicated exchanges. [c] The figures in this column represent the maximum possible exchange, since four exchangeable protons were present in starting **3a**.

The group of experiments described in the sequel have established that, as anticipated above, C_2 is the preferred site of electrophilic substitution in **3a**. Thus, Vilsmeier–Haack formylation[3] of **3a** afforded, as the only isolable product, a 2-formyl derivative **4a** in which the 4-oxo substituent had been replaced by a vinyl chloride function. The location of the formyl group at C_2 was established by dehydrogenation (DDQ) of **4a** to 4-chloroindole-2-carboxaldehyde which differed from the known 4-chloroindole-3-carboxaldehyde[4] in infrared and ultraviolet spectra, melting point, and mixture melting point (Experimental Section). Treatment of **3a** with 1 equiv of 70% perchloric acid in acetic anhydride gave the crystalline perchlorate salt of the 2-acetyl derivative **7**.[5] The free base formed when this salt was dissolved in water. Assignment of the acetyl substituent to C_2 follows from the ultraviolet spectrum of **7**, which is significantly different from that of the 3-

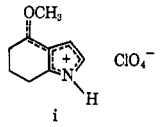
(1) (a) For part II, see W. A. Remers, R. H. Roth, G. J. Gibs, and M. J. Weiss, *J. Org. Chem.*, **36**, 1232 (1971). A portion of this work has been previously communicated: W. A. Remers and M. J. Weiss, *J. Amer. Chem. Soc.*, **87**, 5262 (1965); also M. J. Weiss, G. R. Allen, Jr., G. J. Gibs, J. F. Poletto, and W. A. Remers, "Topics in Heterocyclic Chemistry," R. C. Castle, Ed., Wiley–Interscience, New York, N. Y., 1963. (b) To whom inquiries should be addressed at the Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, Ind. 47907.

(2) These calculations were based upon the parameters $\alpha_N{}^+ = \alpha_C + 2.0\beta$, $\alpha_O = \alpha_C + 1.5\beta$. The total π-electron energies for the pyrrolenine cations corresponding to electrophilic substitution at C_2 and C_3 were 11.93 and 11.82β, respectively. Thus C_2 substitution is favored by *ca.* 2 kcal/mol if it is assumed that β = 18 kcal/mol.

(3) Recent reviews of the Vilsmeier–Haack reaction include the following: G. Hazebroucq, *Ann. Pharm. Fr.*, **24**, 793 (1966); M. R. deMaheas, *Bull. Soc. Chim. Fr.*, 1989 (1962).

(4) B. A. Whittle and E. H. Young, *J. Med. Chem.*, **6**, 378 (1963).

(5) Treatment of **3a** with 70% perchloric acid in excess methyl orthoformate afforded *O*-methyl perchlorate i (see Experimental Section). This



i

type of O-alkylation is related to the O-alkylations of enamino ketones reported by A. I. Meyers, A. H. Reine, and R. Gault, *Tetrahedron Lett.*, 4049 (1967); however, in contrast to enamino ketones, **3a** does not react with a weak electrophile like methyl iodide.

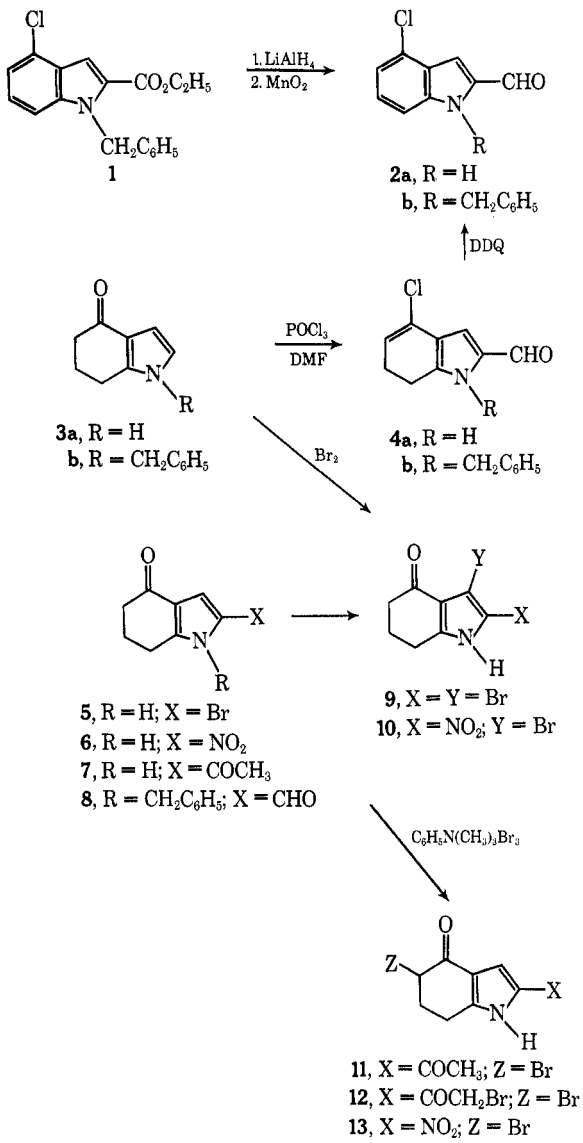
acetyl-4-oxo derivative **17**.[6] A similar line of reasoning supports the conclusion that the product **6** obtained from nitration of **3a** is substituted at C_2, since its ultraviolet spectrum is unlike that of **16**, which must bear the nitro group at C_3.

The products isolated from bromination of **3a** depended upon the nature of the brominating agent. Thus bromine in acetic acid afforded mainly the 2,3-dibromo derivative **9**, whereas the more selective phenyltrimethylammonium tribromide furnished a single monobromo derivative **5** in good yield. The location of the bromine atom at C_2 (rather than C_3) of **5** has not been confirmed; however, this is the most probable position by analogy to the other electrophilic substitutions.

The presence of a benzyl substituent on the nitrogen of a 4-oxo-4,5,6,7-tetrahydroindole (*e.g.*, **3b**) apparently did not change the preferred site of formylation from C_2, since the product **4b** of the Vilsmeier–Haack reaction with **3b** in three of four experiments was of the same type as that obtained from **3a**. In one of these four experiments, conducted as nearly as possible under conditions identical with those of the other three, the product isolated (**8**) had undergone formylation (probably at C_2), but it retained the 4-oxo group. It is possible that **8** is an intermediate the formation of **4b**, but this point was not investigated further. Location of the formyl group of **4b** at C_2 was established by dehydrogenation to indole derivative **2b**, which was identical in infrared spectrum, melting point, and mixture melting point with a sample of **2b** prepared by an unequivocal route from methyl 1-benzyl-4-chloroindole-2-carboxylate (**1** → **2b**). The ultraviolet absorption spectrum of **2b** was nearly identical with that of 4-chloroindole-2-carboxaldehyde (**2a**) (Scheme I).

When substituents were present at the 2 position of a 4-oxo-4,5,6,7-tetrahydroindole, electrophilic substitution generally occurred at the 3 position. Thus bromination and nitration of the 1-ethyl-2-methyl derivative **14c** afforded the corresponding 3-bromo and 3-nitro derivatives **15** and **16**, respectively.[7] Furthermore, treatment of 2,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindole **14b** with acetic anhydride and perchloric acid gave the 3-acetyl derivative **17**. Vilsmeier–Haack formylation of **14c** and **14a** appeared to afford exceptions to this generalization, since only the corresponding 4-chloro-

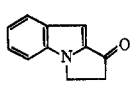
SCHEME I



5-carboxaldehydes **19b** and **19a** were isolated when the former compounds were warmed with 1 equiv of phosphorus oxychloride in excess dimethylformamide. However, the yields of isolated products were very low in both examples (6 and 2.5%, respectively), with much tar formation. Even if these products represent the main course of electrophilic substitution of **14c** and **14a**, it is not certain that this means a preference for C_5 over C_3. In the presence of phosphorus oxychloride these compounds might have been converted first into the corresponding 4-chloro-6,7-dihydroindoles and then formylation of the resulting vinyl pyrrole system might have been preferred at C_5.[8]

When either **14c** or its 6-methyl homolog **14d** were warmed with 2 equiv of phosphorus oxychloride in dimethylformamide, an unexpected result was obtained. In each case there were two products, one neutral and the other basic. The neutral products were shown (Experimental Section) to be the 4-chloro-3,5-dicarboxaldehydes **20a** and **20b**, resulting from the anticipated formylations at both C_3 and C_5. However, the basic products **21b** and **21c** had fully aromatic indole

(6) In making this assignment it is necessary to rule out the possibility that in the 2,3-disubstituted compound **17** steric inhibition forces the acetyl group out of the plane of the pyrrole ring and thus distorts the chromophore. There are several pertinent model compounds which demonstrate that this is not an important factor at the 2 and 3 positions of indole derivatives. Thus 2-acetyl-3-methylindole [W. E. Noland and R. J. Sunderberg, *J. Org. Chem.*, **28**, 884 (1963)] has an uv chromophore nearly identical with that of

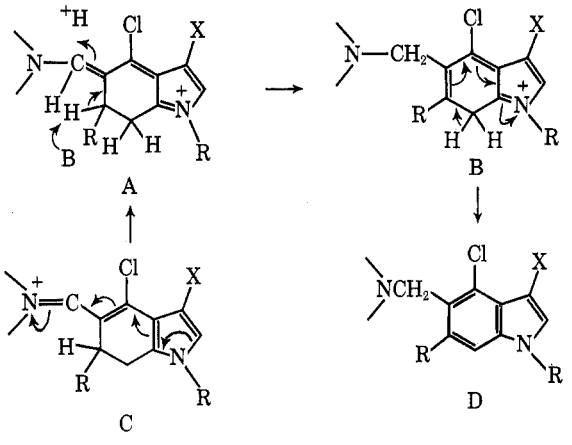


in which the carbonyl group is held in the plane of the pyrrole ring: W. A. Remers and M. J. Weiss, *J. Med. Chem.*, **8**, 700 (1965). In contrast, the uv chromophore of 3-acetylindole differs widely from that of these compounds. Furthermore, the uv spectra of all compounds in the group including indole-2-carboxylic acid and its 1-methyl, 3-methyl, and 5-methyl derivatives are nearly identical: R. Andrisano and T. Vitali, *Gazz. Chim. Ital.*, **87**, 949 (1957). Steric inhibition does distort uv chromophores at certain other indole positions, for example, in 1-acylindolines: A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, New York, N. Y., 1964.

(7) Preparation of 2-bromo-3-methyl-4-oxo-4,5,6,7-tetrahydroindole from bromine and the corresponding 2-unsubstituted compound has been reported: Belgian Patent 670,797 (1965); *Chem. Abstr.*, **65**, 12174*b* (1966).

(8) Formylation of vinyl-substituted aromatic compounds readily occurs (ref 3).

systems and instead of a 5-formyl group they had a 5-dimethylaminomethyl group. The genesis of these basic products is uncertain, but one hypothetical pathway involves the interaction of the dihydroindole and immonium[9] systems as shown in C → D. In these



structures X represents either hydrogen or a group which is precursor to the 3-carboxaldehyde function.

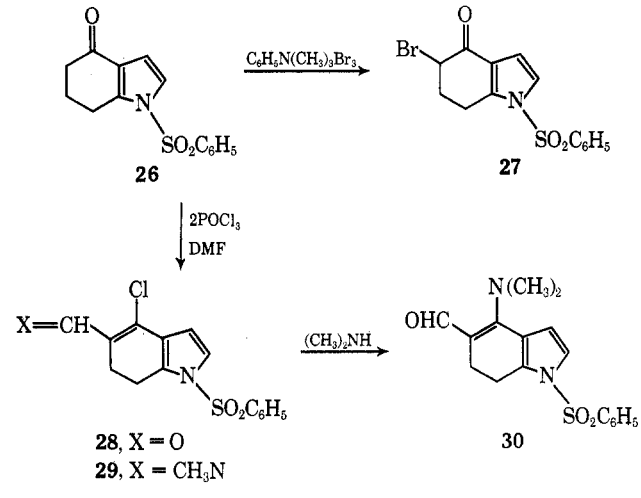
Treatment of **14a** with 2 equiv of phosphorus oxychloride in dimethylformamide also gave a 5-dimethylaminomethyl-substituted indole **21a**, but in extremely low yield.

When Vilsmeier–Haack formylation of 1-ethyl-2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindole (**14e**) was conducted under the same conditions as described above (2 equiv of phosphorus oxychloride), the product **18** differed from **14e** only by a 3-formyl substituent. No reaction of the 5-methylene-4-oxo system was apparent, which suggests important hindrance of the 5 position by the *gem*-dimethyl groups at C_6 (Scheme II).

The presence of an electron-withdrawing substituent in the pyrrole ring of a 4-oxo-4,5,6,7-tetrahydroindole has a pronounced effect upon the relative ease of electrophilic substitution in the remaining positions. If this substituent is only weakly electron withdrawing (*e.g.*, bromine), the electrophilic substitution can take place in the pyrrole ring. However, a strong electron-withdrawing group such as acetyl or benzenesulfonyl so deactivates the pyrrole ring that electrophilic substitution is favored at C_5. Thus treatment of 2-bromo-4-oxo-4,5,6,7-tetrahydroindole (**5**) with phenyltrimethylammonium tribromide afforded the 2,3-dibromo derivative **9**, whereas this same reagent converted the corresponding 2-acetyl analog **7** into a mixture which contained the 5-bromo derivatives **11** and **12**. No 3-bromo derivatives were found in this mixture. Similar bromination of 1-benzenesulfonyl-4-oxo-4,5,6,7-tetrahydroindole (**26**) gave the 5-bromo derivative **27**.[10] Only 4-chloro-5-carboxaldehyde **28** was obtained upon Vilsmeier–Haack formylation of **26**, even when 2 equiv of phosphorus oxychloride was present.

An interesting variation in the selectivity of bromination was encountered with 2-nitro-4-oxo-4,5,6,7-tetrahydroindole (**6**). When this compound was treated with phenyltrimethylammonium tribromide in tetrahydrofuran, the product was the 5-bromo derivative **13**. In contrast, bromination with this same reagent in dimethylformamide afforded only the 3-bromo isomer **10**. We do not know whether this difference in site of substitution is due to specific solvent effects or merely to dimethylformamide scavenging the HBr needed to promote enolization of the 4-carbonyl group.

Thus far, the electrophilic substitution reactions of a variety of 4-oxo-4,5,6,7-tetrahydroindoles have been described. In order to utilize the products of these reactions for indole synthesis, it was necessary to do certain further chemical transformations and to dehydrogenate to the fully aromatic indoles. The 4-chloro-6,7-dihydro-5-carboxaldehyde system of compounds such as **20a** and **28** provided a convenient entry for new substituents into the 4 position by way of addition–elimination type sequences. Thus the chlorine of **20a** was replaced by a methoxyl group (affording **22**) when it was treated with sodium methoxide. In similar fashion, dimethylamine replaced the chlorine of **28** to give **30**. Unfortunately, this type of transformation was not applicable in all cases. An amine such as methylamine which could react irreversibly with an aldehyde carbonyl tended to do so in preference to displacing the chlorine. For example, methylamine converted **28** into imine **29**.



Dehydrogenation of most of the 6,7-dihydroindoles described above was readily produced by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[11] in dioxane. The conversions of **4a** and **2a** to **4b** and **2b**, respectively have already been mentioned. Additional examples are the dehydrogenations of **20a** and **22** to **23** and **24**, respectively. Recrystallization of the 3,5-dicarboxaldehyde **23** from methanol afforded an acetal derivative **25** in which the 5-formyl group, but not the 3-formyl group, had reacted with the methanol. The structure of this derivative was inferred from comparisons of its ultraviolet absorption spectrum with those of related indole-3- and -5-carboxaldehydes (Experimental Section).

In contrast to 4-oxo-4,5,6,7-tetrahydroindoles substituted with alkyl groups,[1,12] most of the 4-oxo-4,5,6,7-tetrahydroindoles substituted with electron-withdrawing groups could not be dehydrogenated by heating with

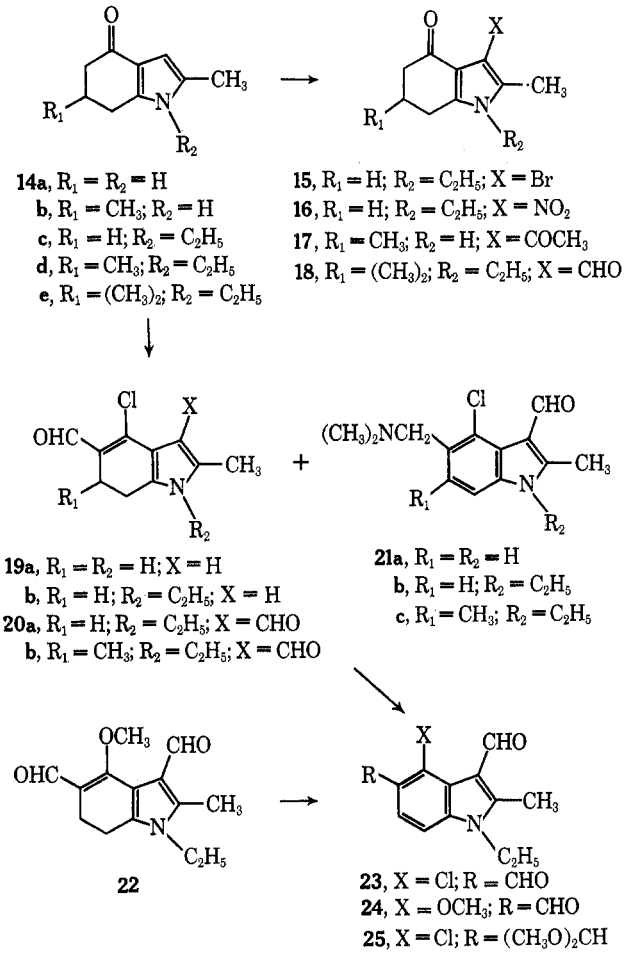
(9) The identification of indole bearing this type of immonium group at C_3 from a Vilsemeier–Haack formylation was reported by G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

(10) These 5-bromo-4-oxotetrahedroindoles are important to the preparation of indole derivatives containing heterocycles such as aminothiazole fused to the 4,5 positions (ref 1).

(11) E. A. Braude, A. G. Brooke, and R. P. Linstead, *J. Chem. Soc.*, 3569 (1954).

(12) S. Hauptmann, H. Blume, G. Hartmann, D. Haendel, and P. Francke, *Z. Chem.*, **6**, 183 (1966).

SCHEME II



palladium on charcoal.[13] They were also resistant to dehydrogenation by DDQ. Thus important limitations are imposed upon the generality of this approach to the synthesis of novel indoles. Although the dehydrobromination of 5-bromo-4-oxo-4,5,6,7-tetrahydroindoles was generally an unsatisfactory procedure, we were able to obtain a small amount of the corresponding 4-hydroxyindole from **27**.[1] Finally, we note that, whereas dehydrogenation of 1-benzyl-4-chloro-6,7-indole-2-carboxaldehyde (**4b**) by DDQ furnished the corresponding 4-chloroindole **2b**, treatment of **4b** with palladium on charcoal in refluxing cumene afforded the related dechlorinated compound, 1-benzylindole-2-carboxaldehyde.

Experimental Section[14a]

4-Chloro-6,7-dihydroindole-2-carboxaldehyde (4a).[14b]—A solution of formylating complex was prepared by dropwise addition of 6.13 g (40 mmol) of phosphorus oxychloride to 30 ml of stirred, ice-cooled *N*,*N*-dimethylformamide (drying tube on apparatus). This complex was then treated with a solution of 5.40 g (40 mmol) of **3a**[15] in 30 ml of *N*,*N*-dimethylformamide. The resulting orange solution was heated on a steam bath for 1 hr,[16] cooled, and poured onto crushed ice. It was then made distinctly basic with 10 *N* NaOH and extracted with methylene chloride (150 ml). This extract was washed with water, dried, and concentrated. The residue was purified by adsorption chromatography on magnesia–silica gel with methylene chloride as solvent. Concentration of the yellow eluate gave, after washing with ether, 1.82 g (25%) of **4a** as pale yellow needles which decomposed above 130°. The decomposition point was unchanged after recrystallization from methylene chloride–hexane: ir 3.05 (NH), 3.53 and 6.05 μ (CHO); uv max 224 mμ (ϵ 11,000), 257 (8800), 332 (3100); nmr ($CDCl_3$) δ 9.37 (s, CHO), 6.90 (s, pyrrole ring), 5.83 (t, J = 4.5 Hz, $CH_2CH{=}C$), 3.0–2.0 ppm (m, 4, CH_2CH_2).

Anal. Calcd for C_9H_8ClNO: C, 59.51; H, 4.44; N, 7.71. Found: C, 59.78; H, 4.33; N, 7.41.

4-Chloroindole-2-carboxaldehyde (2a).—A solution of 908 mg (5 mmol) of **4a** in 20 ml of dioxane was treated portionwise with a solution of 1.35 g (5 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 10 ml of dioxane. After 3 hr the resulting mixture was filtered, the filtrate was concentrated, and the residue was treated with ether. The crude crystalline product was purified by liquid–liquid partition chromatography on diatomaceous earth with a heptane–methanol solvent system.[17] Concentration of eluate corresponding to the major peak detected at 310 mμ afforded 192 mg (21%) of **2a** as pale yellow solid, which had mp 189–192° after recrystallization from CH_2Cl_2–petroleum ether: ir 3.05 (NH), 3.50, 5.95 μ (CHO); uv max 238 mμ (ϵ 17,400), 307 (22,600); nmr ($CDCl_3$) δ 11.2 (NH), 9.90 (s, CHO), 7.6–7.1 ppm (m, 4, aromatic).

Anal. Calcd for C_9H_6ClNO: C, 60.17; H, 3.37; Cl, 19.73; N, 7.80. Found: C, 60.04; H, 3.46; Cl, 20.24; N, 7.50.

The mixture melting point with authentic 4-chloroindole-3-carboxaldehyde[4] (mp 175–178°) was at 135–143° (droplets 120°). The ir and uv spectra of the two compounds differed; for the 3-carboxaldehyde isomer the uv max were 215 mμ (ϵ 34,000), 245 (12,100), 267 (7700), 308 (9900).

2-Bromo-4-oxo-4,5,6,7-tetrahydroindole (5).—A solution of 270 mg (2 mmol) of **3a** in 5 ml of tetrahydrofuran was treated dropwise with a solution of 752 mg (2 mmol) of phenyltrimethylammonium tribromide[6] in 3 ml of tetrahydrofuran. After 2 hr the mixture was filtered and the filtrate was concentrated. The residue was treated with CH_2Cl_2 and 5% sodium bicarbonate solution. The organic layer was washed with saline solution, dried, and concentrated, and the residual solid was crystallized from methanol–water. This procedure gave 210 mg (49%) of a white solid: mp 175° dec; ir 3.15 (NH), 6.12 μ (C=O); uv max 213 mμ (ϵ 32,000), 235 (14,400), 281 (12,300); nmr (DMSO-d_6) δ 11.9 (NH), 6.30 (s, pyrrole), 2.9–1.7 ppm (m, 6, aliphatic).

Anal. Calcd for C_8H_8BrNO: C, 44.89; H, 3.77; Br, 37.34; N, 6.55. Found: C, 44.41; H, 3.66; Br, 37.79; N, 6.52.

2-Acetyl-4-oxo-4,5,6,7-tetrahydroindole (7).—To a stirred, ice-cooled suspension of 405 mg (3 mmol) of **3a** in 10 ml of acetic anhydride was added 0.43 ml (3 mmol) of 70% perchloric acid. An orange solution formed initially, but crystallization then occurred. The crystals of **7** perchlorate (yield 650 mg) were washed with acetic anhydride and ether and dried under vacuum.

Anal. Calcd for $C_{10}H_{12}NO_2 \cdot HClO_4$: C, 43.25; H, 4.36; Cl, 12.77; N, 5.05. Found: C, 43.55; H, 4.73; Cl, 12.61; N, 4.79.

When this crystalline perchlorate was dissolved in water the free base rapidly crystallized. Recrystallization from boiling water gave **7** as pale yellow plates: mp 185–188°; ir 3.25 (NH), 6.02–6.20 μ (broad, two C=O); uv max 224 mμ (ϵ 15,100), 262 (6300), 297 (14,800); nmr ($CDCl_3$) δ 10.8 (NH), 7.33 (d, J = 4.5 Hz, pyrrole), 2.99 (t, 2, CH_2CO), 2.17 ppm (s, 3, CH_3).

When this preparation was repeated on a 4.05-g scale, a 2.05-g (39%) yield of **7**, mp 187–189°, was obtained. The uv spectrum of **7** differs widely from that of the 3-acetyl analog **17**.

6,7-Dihydro-4-methoxy-5*H*-indole Perchlorate (i).[5]—An ice-cooled suspension of 405 mg (3 mmol) of **3a** in 3 ml of methyl orthoformate was treated with 0.43 ml (3 mmol) of 70% perchloric acid. A solution formed immediately and then crystallization occurred. The colorless crystals of i were washed well with ether and dried under vacuum. They then had mp 121–125°: ir 3.1–3.25 (NH), 6.25 (w, C=C?), 8.8, 9.0, and 9.25 μ (all s, ClO_4); nmr (CD_3CN) δ 7.05 (m, pyrrole), 6.74 (m, pyrrole), 4.42 (s, 3, OCH_3), 3.1–2.0 ppm (m, 6, aliphatic).

(13) Hauptmann also noted that 4-oxo-4,5,6,7-tetrahydroindoles substituted with an electron-withdrawing group (carbethoxy) could not be dehydrogenated by palladium on charcoal (ref 12).

(14) (a) General procedures are given in ref 1a; (b) this experiment was first performed by R. H. Roth.

(15) H. Stetter and R. Lauterbach, *Justus Liebigs Ann. Chem.*, **655**, 20 (1962).

(16) Indoles and pyrroles substituted with electron-withdrawing groups require higher temperatures for formylation than do the corresponding unsubstituted compounds; see W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Amer. Chem. Soc.*, **86**, 402 (1964).

(17) For a detailed description of this chromatography procedure (developed by C. Pidacks), see M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

Anal. Calcd for $C_9H_{12}NO \cdot ClO_4$: C, 43.30; H, 4.84; Cl, 14.20; N, 5.61. Found: C, 43.43; H, 4.83; Cl, 14.02; N, 5.52.

2,3-Dibromo-4-oxo-4,5,6,7-tetrahydroindole (9). A. From 3a.—A solution of 270 mg (2 mmol) of **3a** in 3 ml of warm acetic acid was treated dropwise with 320 mg (2 mmol) of bromine. Decolorization was instantaneous. Dilution of the resulting mixture with 7 ml of water caused white crystals to separate. Recrystallization from ethanol–water gave 182 mg (31%) of **9** as white prisms, mp 162–163° dec. Successive recrystallization from CH_2Cl_2–hexane (two times) and methanol gave mp 175° dec: ir 3.1–3.3 (NH), 6.10 μ (C=O); uv max 213 mμ (ϵ 32,000), 243 (16,000), 282 (8900); nmr (DMSO-d_6) no pyrrole protons, 2.9–1.9 ppm (m, 6, aliphatic).

Anal. Calcd for $C_8H_7Br_2NO$: C, 32.79; H, 2.41; Br, 54.66; N, 4.78. Found: C, 32.74; H, 2.26; Br, 54.72; N, 4.64.

B. From 5.—This preparation was done according to the method described for **5**. From 214 mg of **5** and 376 mg of phenyltrimethylammonium tribromide was obtained 146 mg of a white solid, mp 173° dec, undepressed upon admixture of **9** prepared as described above. The ir spectra of these samples were superimposable.

2-Acetyl-5-bromo-4-oxo-4,5,6,7-tetrahydroindole (11) and 5-Bromo-2-bromoacetyl-4-oxo-4,5,6,7-tetrahydroindole (12).—This preparation was conducted as described for **5**. From 354 mg of **5** and 752 mg of phenyltrimethylammonium tribromide was obtained a viscous oil which was resolved into its components by liquid–liquid partition chromatography on diatomaceous earth with a heptane–ethyl acetate–methanol–water system (70:30:17:4) and recording spectrophotometer set at 300 mμ.[17] Two major and two minor peaks were observed in that order. Concentration of the eluate from the first peak gave 43 mg of **12** as pale yellow solid: mp 183–184° dec after recrystallization from CH_2Cl_2–hexane; ir 3.05 (NH), 5.85 and 6.05 μ (C=O); uv max 235 mμ (ϵ 8400), 312 (12,300); nmr (DMSO-d_6) δ 12.5 (NH), 7.51 (d, J = 4.5 Hz, pyrrole), 4.80 (t, J = 12 Hz, $COCHBrCH_2$), 4.65 (s, 2, $COCH_2Br$), 3.1–2.7 ppm (m, 4, CH_2CH_2).

Anal. Calcd for $C_{10}H_9Br_2NO_2$: C, 35.85; H, 2.68; N, 4.18. Found: C, 36.32; H, 2.66; N, 4.30.

Concentration of the eluate from the second peak gave, after recrystallization from CH_2Cl_2–hexane, 41 mg of **11** as yellow solid with mp 157–159°: ir 3.05 (NH), 5.85, 6.05 μ (C=O); uv max 230 mμ (ϵ 13,500), 265 sh (8700), 303 (16,400); nmr (DMSO-d_6) δ 12.0 (NH), 7.29 (d, J = 4.5 Hz, pyrrole), 4.75 (t, J = 12.0 Hz, $COCHBrCH_2$), 3.0–2.4 (m, 4, CH_2CH_2), 2.38 ppm (s, 3, CH_3).

Anal. Calcd for $C_{10}H_{10}BrNO_2$: C, 46.89; H, 3.93; Br, 31.20; N, 5.47. Found: C, 47.13; H, 3.94; Br, 31.09; N, 5.21.

From the third peak was obtained 10 mg of yellow solid, mp 176–177° after recrystallization from CH_2Cl_2–hexane. This solid appeared to be 2-bromoacetyl-4-oxo-4,5,6,7-tetrahydroindole by nmr [(DMSO-d_6) δ 7.39 (d, J = 4.5 Hz, pyrrole), 4.59 (s, 2, $COCH_2Br$), 3.0–2.0 ppm (m, 6, aliphatic)], but it could not be fully characterized. The fourth peak afforded 14 mg of starting material.

2-Nitro-4-oxo-4,5,6,7-tetrahydroindole (6).—A mixture of 540 mg (4 mmol) of **3a** and 3 ml of concentrated sulfuric acid was cooled in an ice–salt mixture and treated portionwise with 340 mg (4 mmol) of sodium nitrate in 3 ml of concentrated sulfuric acid. After this addition was completed, the mixture was stirred for 10 min and then poured onto ice. The product separated as pale tan crystals which were dried in air and recrystallized from methanol–water. This procedure gave 170 mg (24%) of **6** as pale yellow needles: mp 217–272° dec; ir 3.2–3.5 (NH), 6.05 (C=O), 6.65 and 7.40 μ (CNO_2); uv max 221 mμ (ϵ 12,500), 334 (12,100); nmr (DMSO-d_6) 13.3 (NH), 7.20 (s, pyrrole), 2.81 (t, 2, J = 14 Hz, $COCH_2CH_2$), 2.3–1.9 ppm (m, 4, $COCH_2CH_2CH_2$).

The uv spectra of this **6** differed considerably from that of the 3-nitro analog **16**. In larger scale preparation of **6** yields up to 32% were obtained.

3-Bromo-2-nitro-4-oxo-4,5,6,7-tetrahydroindole (10).—To a solution of 180 mg (1 mmol) of **6** in 2 ml of *N,N*-dimethylformamide was added dropwise a solution of 376 mg (1 mmol) of phenyltrimethylammonium tribromide in 0.5 ml of *N,N*-dimethylformamide. After 2 hr the resulting solution was diluted with water which caused crystallization of **10** as a white product (180 mg, 69% after it was washed with water and dried under vacuum) that did not melt below 360°. The analytical sample was recrystallized from *N,N*-dimethylformamide–water: ir 3.2–3.6 (NH), 6.05 (C=O), 6.65 and 7.40 μ (NO_2); uv max 233 mμ (ϵ 16,000), 338 (13,000); nmr (DMSO-d_6) δ 13.7 (NH), no pyrrole protons, 2.87 (t, 2, J = 14 Hz, $COCH_2$), 2.6–2.0 ppm (m, 4, $COCH_2CH_2CH_2$).

Anal. Calcd for $C_8H_7BrN_2O_3$: C, 37.10; H, 2.72; N, 10.81. Found: C, 37.44; H, 2.78; N, 10.82.

5-Bromo-2-nitro-4-oxo-4,5,6,7-tetrahydroindole (13).—A solution of 420 mg (2.33 mmol) of **6** in 35 ml of tetrahydrofuran was treated dropwise with a solution of 876 mg (2.33 mmol) of phenyltrimethylammonium tribromide in 3 ml of tetrahydrofuran. After 2 hr the mixture was filtered and the filtrate was concentrated under reduced pressure. The residual solid was washed well with water and ether and dried in air. This procedure gave 550 mg (91%) of **13** as a white solid, which had mp 215° dec after recrystallization from acetone–hexane: ir 3.10 (NH), 5.96 (C=O), 6.65 and 7.40 μ (NO_2); uv max 228 mμ (ϵ 12,000), 335 ϵ13,000); nmr (DMSO-d_6) δ 13.7 (NH), 7.35 (s, pyrrole), 4.83 (t, 2, J = 10 Hz, $COCHBrCH_2$), 3.1–2.4 ppm (m, 4, aliphatic).

Anal. Calcd $C_8H_7BrN_2O_3$: C, 37.10; H, 2.72; N, 10.81. Found: C, 36.90; H, 2.36; N, 10.28.

1-Benzyl-4-chloro-6,7-dihydroindole-2-carboxaldehyde (4b).—This compound was prepared by the procedure described for **4a**, except that 2 equiv of phosphorus oxychloride was used. From 4.5 g of **3b**[1] and 3.06 g of phosphorus oxychloride in 21 ml (total) of *N,N*-dimethylformamide was obtained 4.76 (88%) of **4b** as a tan solid which had mp 116–119° after recrystallization from ether: ir 3.50 and 6.10 μ (CHO); uv max 251 mμ (ϵ 10,500), 275 sh (8700), 330 (3000); nmr ($CDCl_3$) ϵ 9.35 (s, CHO), 7.4–7.0 (m, 5, phenyl), 6.85 (s, pyrrole), 5.60 (t, J = 4.5 Hz, CH_2-CH=CCl), 5.5 (s, 2, benzylic), 2.8–2.5 ppm (m, 4, CH_2CH_2).

Anal. Calcd for $C_{16}H_{14}ClNO$: C, 70.71; H, 5.19; Cl, 13.05; N, 5.15. Found: C, 70.76; H, 5.71; Cl, 13.06; N, 5.40.

1-Benzyl-4-oxo-4,5,6,7-tetrahydroindole-2-carboxaldehyde (8).—In one of four attempts to prepare **4b** from **3b**, a different product **8** was obtained upon work-up of the reaction mixtures. From 9.0 g of **3b** and 12.2 g of phosphorus oxychloride was obtained 6.71 g (66%) of **8** as a pale yellow crystals, mp 110–114°. Recrystallization from CH_2Cl_2–hexane gave mp 114–116°: ir 6.05 μ (C=O); uv max 234 mμ (ϵ 15,000), 260 inflection (7100), 298 (12,000); nmr (DMSO-d_6) δ 9.59 (s, CHO), 7.40 (s, pyrrole), 7.3–6.9 (m, 5, phenyl), 5.61 (s, 2, benzylic), 2.75 (t, 2, J = 14 Hz, $COCH_2$), 2.5–1.9 ppm (m, 4, aliphatic).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; N, 5.97. Found: C, 75.66; H, 6.14.

1-Benzyl-4-chlorindole-2-carboxaldehyde (2b). A. From 4b.—Solutions of 554 mg (2 mmol) of **4b** in 8 ml of dioxane and 455 mg (2 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 4 ml of dioxane were combined. After 30 min the mixture was filtered and the filtrate was concentrated. The residual solid was extracted with ether–hexane. Upon concentration, this extract gave pale yellow crystals, mp 85–92°, which were nearly identical in ir spectra with **2b** prepared below. Purification by liquid–liquid partition chromatography on diatomaceous earth with a heptane–methanol solvent system and recording spectrophotometer set at 300 mμ gave, after concentration of the eluate from the main peak, pale yellow crystals, mp 94–96°, undepressed upon admixture of **2b** prepared as described below. The ir spectra of these two samples were superimposable.

B. From 1.—To a suspension of 860 mg (7.5 mmol) of potassium *tert*-butoxide in 30 ml of dry benzene was added a slurry of 1.57 g (7.5 mmol) of methyl 4-chloroindole-2-carboxylate. The mixture was stirred at reflux temperature for 1 hr, cooled, and treated with 950 mg (7.5 mmol) of benzyl chloride. This mixture was heated 16 hr at reflux temperature, cooled, and poured into water. The benzene layer was washed with water, dried, and concentrated to a viscous oil which gave white crystals of starting material upon trituration with ether. The ether phase was decanted and concentrated to a colorless oil. This oil, after purification by adsorption chromatography on magenesia–silica gel, weighed 1.2 g and showed no NH stretch in the ir.

Without further purification, this sample of **1** was dissolved in 5 ml of ether and treated with 150 mg of lithium aluminum hydride, added in small portions. After 1 hr the mixture was treated with water and the ether layer was washed with water, dried, and concentrated. Recrystallization of the residual solid from ether–hexane gave 398 mg (37% from **1**) of the corresponding alcohol as white prisms: mp 95–97°; ir 2.9 μ (OH), no carbonyl; nmr (DMSO-d_6) ϵ 7.5–6.8 (m, 8, phenyl and indole benzene ring), 6.50 (s, pyrrole), 5.50 (s, 2, benzylic), 5.41 (t, J = 6 Hz, CH_2OH), 4.63 ppm (d, 2, J = 6 Hz, CH_2OH).

Anal. Calcd for $C_{16}H_{14}ClNO$: C, 70.71; H, 5.19; Cl, 13.05; N, 5.15. Found: C, 70.77; H, 5.10; Cl, 13.32; N, 5.44.

A solution of 50 mg of this alcohol in 10 ml of ether was stirred with 300 mg of manganese dioxide for 16 hr. The mixture was filtered and the filtrate was concentrated, affording a viscous oil that crystallized upon scratching. Two recrystallizations from ether–hexane gave **2b** as pale yellow prisms: mp 93–96°; ir 3.50, 6.0 μ (CHO); uv max 239 mμ (ϵ 17,000), 307 (21,000), 340 (5700) inflection; nmr (DMSO-d_6) δ 10.0 (s, CHO), 7.59 (s, pyrrole), 7.4–7.0 (m, 8, phenyl and indole benzene ring), 5.87 ppm (s, 3, benzylic), no aliphatic protons.

Anal. Calcd for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.49; Cl, 13.14; N, 5.19. Found: C, 70.65; H, 4.49; Cl, 13.36; N, 5.51.

3-Bromo-1-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydroindole (15).—This compound was prepared by the procedure described for **5**. From 885 mg of **14c**[18] was obtained 810 mg (64%) of **15** as white needles: mp 96–98° after recrystallization from hexane; ir 6.0 μ (C=O); uv max 254 mμ (ϵ 11,000), 284 (4600); nmr ($CDCl_3$) showed no pyrrole hydrogen.

Anal. Calcd for $C_{11}H_{14}BrNO$: C, 51.58; H, 5.51; N, 5.47. Found: C, 51.83; H, 5.49; N, 5.45.

1-Ethyl-2-methyl-3-nitro-4-oxo-4,5,6,7-tetrahydroindole (16).—This compound was prepared by the procedure described for **6**. From 1.06 g of **14c**[18a] was obtained 1.01 g (76%) of **16** as a tan solid, mp 125–127°. Recrystallization from methanol gave yellow needles: mp 140–142°; ir 5.95 (C=O), 6.65 and 7.40 μ (NO_2); uv max 215 mμ (ϵ 18,700), 245 (6700), 279 (5800), 320 (4700); nmr (DMSO-d_6) showed no pyrrole proton.

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.44; H, 6.50; N, 12.52.

4-Chloro-1-ethyl-6,7-dihydro-2-methylindole-5-carboxaldehyde (19b).—This compound was prepared by the procedure described for **4a**. From 1.77 g of **14c** was obtained a dark semisolid which was purified by adsorption chromatography on magnesia–silica gel with CH_2Cl_2 as solvent. Concentration of the yellow eluate gave **19b** as a yellow solid which was recrystallized from ether–hexane. It then weighed 124 mg (6%) and had mp 105–107°: ir 3.50, 6.15 μ (OCHC=C); uv max 237 mμ (ϵ 8100), 250 (6300), 310 (6000), 390 (15,000); nmr ($CDCl_3$) δ 10.2 (s, CHO), 6.25 (s, pyrrole), 3.90 (q, 2, J = 16 Hz, NCH_2CH_3), 2.82 (broad s, 4, CH_2CH_2), 2.25 (s, 3, C=CCH_3), 1.27 ppm (t, 3, J = 16 Hz, NCH_2CH_3).

Anal. Calcd for $C_{12}H_{14}ClNO$: C, 64.42; N, 6.31; Cl, 15.85; N, 6.25. Found: C, 64.70; H, 6.35; Cl, 15.73; N, 6.06.

4-Chloro-5-(dimethylaminomethyl)-1-ethyl-2-methylindole-3-carboxaldehyde (21b) and 4-Chloro-1-ethyl-6,7-dihydro-2-methylindole-3,5-dicarboxaldehyde (20a).—These compounds were prepared by the procedure described for **4b**. From 10.62 g of **14c** and 12 ml of phosphorus oxychloride was obtained, following the sodium hydroxide treatment, a mixture which was extracted with 300 ml of CH_2Cl_2. This extract was shaken with 150 ml of water containing 15 ml of 3 N HCl. The layers were separated and the acidic layer was basified with NaOH and extracted with CH_2Cl_2. This extract was washed with saline, dried, and concentrated. Recrystallization of the residue from methanol afforded 4.69 g (28%) of **21b** as white prisms: mp 95–96°; ir 3.50, 6.08 μ (CHO); uv max 222 mμ (ϵ 34,000), 248 (10,500), 274 (7400), 315 (1100); nmr ($CDCl_3$) 11.2 (s, CHO), 7.23 (d, J = 8 Hz, ortho aromatic), 7.10 (d, J = 8 Hz, ortho aromatic), 4.73 (q, 2, J = 16 Hz, NCH_2CH_3), 3.65 (s, 2, HCH_2C=C), 2.86 (s, 3, C=CCH_3), 2.23 (s, 6, $N(CH_3)_2$), 1.39 ppm (t, 3, J = 16 Hz, NCH_2CH_3).

Anal. Calcd for $C_{15}H_{19}ClN_2O$: C, 63.31; H, 6.85; Cl, 12.72; N, 10.05. Found: C, 63.94; H, 6.89; Cl, 12.81; N, 9.81

The organic layer from the HCl treatment was washed with dilute sodum bicarbonate solution, dried, and concentrated, and the residue was purified by absorption chromatography on magnesia–silica gel with CH_2Cl_2 as solvent. The yellow eluate was concentrated and the residual solid was recrystallized from methanol. This procedure gave 2.10 g (14%) of **20a** as yellow prisms: mp 128–135°; ir 3.50, 6.10 μ (CHO); uv max 228 mμ (ϵ 28,000), 306 (9000), 375 (15,000); nmr ($CDCl_3$ δ 10.7 (s, CHO), 10.4 (s, CHO), 4.03 (q, 2, J = 16 Hz, NCH_2CH_3), 2.80 (broad s, 4, CH_2CH_2), 2.65 (s, 3, C=CCH), 1.35 ppm (t, 3, J = 16 Hz, NCH_2CH_3).

Anal. Calcd for $C_{13}H_{14}ClNO_2$: C, 62.04; H, 5.21; Cl, 14.09; N, 5.57. Found: C, 61.61; H, 5.51; Cl, 14.50; N, 5.72.

4-Chloro-5-(dimethylaminomethyl)-1-ethyl-2,6-dimethylindole-3-carboxaldehyde (21c) and 4-Chloro-1-ethyl-6,7-dihydro-2,6-dimethylindole-3,5-dicarboxaldehyde (20b).—These compounds were prepared by the procedure described for **21b** and **20a**. From 11.46 g of **14c** and 12 ml of phosphorus oxychloride was obtained from the acidic extract, after recrystallization from methanol, 5.37 g (31%) of **21c** as white prisms: mp 108–110°; ir and uv spectra closely related to **21b**; nmr differed from **21b** only by replacement by CH_3 (s, ϵ 2.45 ppm) of the hydrogen at C_6. The proton at C_7 was now s, δ 7.7 ppm.

Anal. Calcd for $C_{16}H_{21}ClNO_2$: C, 65.63; H, 7.23; Cl, 12.11; N, 9.57. Found: C, 65.47; H, 7.43; Cl, 12.51; N, 9.35.

From the neutral extract was obtained 1.78 g (11%) of **20b** as yellow plates, mp 110–113°. Recrystallization from CH_2Cl_2–ether–hexane gave mp 120–122°: ir and uv spectra closely related to **20a**; nmr differed from **20a** only by replacement by CH_3 (d, J = 8 Hz at δ 1.00 ppm) of one hydrogen at C_6. The remaining hydrogen at C_6 was now a multiplet at δ 3.30 ppm.

Anal. Calcd for $C_{14}H_{16}ClNO_2$: C, 63.27; H, 6.07; Cl, 13.35; N, 5.27. Found: C, 63.59; H, 6.36; Cl, 13.60; N, 5.27.

4-Chloro-1-ethyl-2-methylindole-3,5-dicarboxaldehyde (23).—This compound was prepared by the procedure described for **2b** from **4b**. From 103 mg of **20a** was obtained 318 mg (70%) of **23** as white crystals, mp 157–159°. Recrystallization from hexane gave mp 160°: ir 3.35, 3.50, 5.9, 6.05 μ (CHO); uv max 253 mμ (ϵ 32,000), 307 (11,000), 331 (6600); nmr ($CDCl_3$) δ 10.9 (s, CHO), 10.5 (s, CHO), 7.79 (d, J = 8 Hz, ortho aromatic) 7.37 (d, J = 8 Hz, ortho aromatic), 4.25 (q, 2, J = 16 Hz, NCH_2CH_3), 2.87 (s, 3, C=CCH_3), 1.41 ppm (t, 3, J = 16 Hz, NCH_2CH_3).

Anal. Calcd for $C_{13}H_{12}ClNO_2$: C, 62.52; H, 4.84; N, 5.61. Found: C, 62.19; H, 4.41; N, 5.39.

1-Ethyl-6,7-dihydro-4-methoxy-2-methylindole-3,5-dicarboxaldehyde (22).—A mixture of 300 mg (1.2 mmol) of **20a**, 84 mg (1.5 mmol) of sodium methoxide, and 15 ml of methanol was kept at room temperature for 3 days and concentrated, and the residue was treated with CH_2Cl_2 and water. The organic layer was washed with water, dried, and concentrated, whereupon the residue crystallized. Recrystallization from methanol–water gave 137 mg (45%) of **22** as white plates: mp 110–120°; ir 3.4, 3.5, 6.1 μ (CHO); uv max 235 mμ (ϵ 24,000), 300 (10,500), 368 (21,000).

Anal. Calcd for $C_{14}H_{17}NO_3 \cdot H_2O$: C, 63.38; H,7.22; N, 5.28. Found: C, 63.86; H, 7.60; N, 5.73.

1-Ethyl-4-methoxy-2-methylindole-3,5-dicarboxaldehyde (24).—This compound was prepared by the procedure described for **2a**. From 103 mg of **22** was obtained 62 mg of a white solid, mp 168–176°. This solid was purified by liquid–liquid partition chromatography on diatomaceous earth with a heptane–methanol system and recording spectrophotometer set at 305 mμ.[17] Concentration of the eluate from the major (second) peak gave 25 mg (25%) of **24** as white prisms: mp 186–190°; ir 3.3, 3.5, 5.95, 6.00 μ (CHO); uv max 251 mμ (ϵ 33,000), 305 (6900), 337 (4900); nmr ($CDCl_3$) δ 10.5 (s, CHO), 10.4 (s, CHO), 7.71 (d, J = 8 Hz, ortho aromatic), 7.20 (d, J = 8 Hz, ortho aromatic), 4.25 (q, 2, J = 16 Hz, NCH_2CH_3), 4.03 (s, 3, OCH_3), 2.87 (s, 3, C=CCH_3), 1.41 ppm (t, 3, J = 16 Hz, NCH_2CH_3).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.52; H, 5.89; N, 5.80.

2-Acetonyl-5,5-dimethylcyclohexane-1,3-dione.—A suspension of 70 g (0.5 mol) of dimedone in 175 ml of methanol was treated with a solution of 28 g (0.5 mol) of potassium hydroxide in 50 ml of water. The resulting solution was cooled in an ice bath and treated with 46.3 g (0.5 mol) of chloroacetone. After 3 days the mixture was filtered and the filtrate was concentrated. The residual solid was dissolved in sodium hydroxide solution (pH 10), washed two times with CH_2Cl_2, and acidified (pH 2). The precipitated solid was dissolved in 300 ml of CH_2Cl_2 and this solution was dried and concentrated on a steam bath as hexane was added. Cooling when the first crystals appeared afforded 62 g (63%) of white crystals, mp 134°.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.08; H, 8.17.

1-Ethyl-2,6,6-trimethyl-4-oxo-4,5,6-tetrahydroindole (14e).—A mixture of 39.2 g of 2-acetonyl-5,5-dimethylcyclohexane-1,3-dione, 36.0 g of ethylamine, and 150 ml of methanol was heated in a steel pressure vessel at 150° for 2 hr, cooled, and concentrated under reduced pressure, whereupon partial crystallization ensued. The crystals were filtered free of adhering dark viscous liquid and recrystallized two times from cyclohexane. Re-

(18) (a) W. A. Remers and M. J. Weiss, *J. Amer. Chem. Soc.*, **88**, 804 (1966); (b) R. H. Roth, W. A. Remers, and M. J. Weiss, *J. Org. Chem.*, **31**, 1012 (1966).

crystallization of the resulting material (low yield, mp 94–100°) from methanol–water gave **14e** as white crystals: mp 97–103°; ir 6.07 μ (C=O); uv max 254 mμ (ϵ 9200), 290 (6300).

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.11; H, 9.11; N, 6.81.

1-Ethyl-2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindole-3-carboxaldehyde (18).—This compound was prepared by the procedure for **4b**. From 6.15 g of **14e** and 6 ml of phosphorus oxychloride was obtained, after adsorption chromatography on magnesia–silica gel with CH_2Cl_2 as solvent and recrystallization from CH_2Cl_2–ether–hexane, 1.57 g (27%) of **18** as yellow crystals, mp 138–141°. Another such recrystallization gave mp 147–149.5°: ir 3.5, 6.0, 6.05 μ (CHO and C=O); uv max 218 mμ (ϵ 21,500), 244 (6800), 279 (8000), 303 (8300).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.75; H, 8.17; N, 6.09.

3-Acetyl-2,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindole (17).—An ice-cooled suspension of 401 mg (2.5 mmol) of **14b**[15] in 4 ml of acetic anhydride was treated with 0.36 ml (2.5 mmol) of 70% perchloric acid. A clear solution formed, but the perchlorate salt not be induced to crystallize from it. The mixture was poured into ice water, where crystallization resulted following hydrolysis of the acetic anhydride. The white crystals were dried in air and recrystallized from 10 ml of methanol to give 270 mg (525) of **17** with mp 201–207°. Another recrystallization gave mp 203–206°: ir 3.1–3.4 (NH), 6.0, 6.1 μ (C=O); uv max 239 mμ (ϵ 6000), 268 (7500), 293 (8700); nmr (DMSO-d_6) δ no pyrrole proton, 2.41 (s, 3, CH_3), 2.25 (s, 3, CH_3), 2.8–2.0 (m, 5, $CH_2CH_2CH_2$), 1.17 ppm (d, 3, J = 12 Hz, $CHCH_3$).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.65; H, 7.42; N, 6.67.

4-Chloro-6,7-dihydro-2-methylindole-5-carboxaldehyde (19a).—This compound was prepared by the procedure described for **4a**. From 5.96 g of **14a**[15] and 6.12 g of phosphorus oxychloride was obtained 1.07 g of an amber oil. Purification of this oil by liquid–liquid partiton chromatography on diatomaceous earth with a heptane–ethyl acetate–methanol–water system (70:30:17:4) and recroding spectrophotometer set at 296 mμ gave upon concentration of the eluate from the second major peak (holdback volume 1.0–2.0) 205 mg of **19a** as a yellow solid. This product had mp 122–124° dec after two recrystallizations from methanol–water: ir 3.05 (NH), 3.4, 3.5, 6.15 μ (OHCC=C); uv max 233 mμ (ϵ 12,000), 302 (6500), 387 (13,500).

Anal. Calcd for $C_{10}H_{10}ClNO$: C, 61.38; H, 5.15; Cl, 18.12; N, 7.16. Found: C, 61.85; H, 5.47; Cl, 18.05; N, 6.96.

4-Chloro-5-(dimethylaminomethyl)-2-methylindole-3-carboxaldehyde (21a).—This compound was prepared by the procedure described for **23a** and **24a**. From 745 mg of **14a**[15] was obtained, following work-up of the acid extract and two recrystallizations from methanol, 30 mg (2.4%) of **21a** as white plates: mp 164–164.5°; ir 3.15 (NH), 3.55, 3.60, 6.07 μ (CHO); uv max 222 mμ (ϵ 22,000), 247 (12,500), 272 (9400), 310 (11,000).

Anal. Calcd for $C_{13}H_{15}ClN_2O$: C, 62.27; H, 6.03; Cl, 14.15. Found: C, 61.82; H, 6.39; Cl, 14.33.

From the neutral fraction was obtained 2 mg of yellow solid that decomposed above 180° and had an uv spectrum [235 mμ (ϵ 13,200), 302 (8000), 375 (8800)] which closely resembled that of **20a**; however, complete characterization was not possible.

1-Benzenesulfonyl-4-chloro-6,7-dihydroindole-5-carboxaldehyde (28).—This compound was prepared by the procedure described for **4b**. From 11.0 g of **26**[15] and 12.3 g of phosphorus oxychloride was obtained 5.8 g (45%) of **28** as a nearly white solid, mp 150–154°. Recrystallization from acetone–hexane gave colorless prisms: mp 150–154°; ir 3.5 6.02 μ (CHO); uv max 228 mμ (ϵ 18,000), 265 sh (7200), 346 (9800); nmr ($CDCl_3$) δ 10.0 (s, CHO), 7.25 (d, J = 4 Hz, pyrrole), 6.50 (d, J = 4 Hz, pyrrole), 3.2–2.2 ppm (m, 4, CH_2CH_2).

Anal. Calcd for $C_{15}H_{12}ClNO_3S$: C, 56.01; H, 3.76; Cl, 11.02; N, 4.35; S, 9.96. Found: C, 56.31; H, 3.66; Cl, 11.18; N, 4.31; S, 10.01.

1-Benzenesulfonyl-4-(dimethylamino)-6,7-dihydroindole-5-carboxaldehyde (30).—A solution of 324 mg of **28** in 20 ml of tetrahydrofuran was saturated with dimethylamine. After 20 hr the mixture was filtered and the filtrate was diluted with CH_2Cl_2 and shaken with water. The organic layer was dried and concentrated to an oil which crystallized upon trituration with ether. These crystals weighed 166 mg (50%) and had mp 113–117°. Two recrystallizations from CH_2Cl_2–hexane gave **30** as yellow prisms: mp 138–139°; ir 3.5, 6.25 μ (OHCC=CN); uv max 252 mμ (ϵ 8200), 318 (6400), 405 (14,000); nmr ($CDCl_3$); nmr ($CDCl_3$) δ 9.69 (s, CHO), 8.0–7.5 (m, 5, phenyl), 7.29 (d, J = 4 Hz, pyrrole), 6.45 (d, J = 4 Hz, pyrroie), 3.21 (s, 6, $N(CH_3)_2$), 2.70 ppm (broad s, 4, CH_2CH_2).

Anal. Calcd for $C_{17}H_{18}N_2O_3S$: C, 61.79; H, 5.49; N, 8.48; S, 9.71. Found: C, 61.89; H, 5.69; N, 8.10; S, 9.70.

1-Benzenesulfonyl-4-chloro-6,7-dihydro-5-(*N*-methylformididoyl)indole (29).—A solution of 324 mg of **28** in 15 ml of methanol was treated with excess methylamine. After 2 days the mixture was filtered and the tan crystalline product, 225 mg (69%), mp 158–159°, was recrystallized from CH_2Cl_2–hexane. This procedure gave **29** as yellow prisms: mp 158–159°; ir 3.5, 6.2 μ (N=CHC=C); uv max 227 mμ (ϵ 14,000), 265 sh (5300), 330 (8400).

Anal. Calcd for $C_{16}H_{15}ClN_2O_2S$: C, 57.40; H, 4.52; N, 8.37; S, 9.58. Found: C, 57.48; H, 4.89; N, 8.54; S, 9.45.

4-Chloro-1-ethyl-2-methylindole-3,5-dicarboxaldehyde-5-(dimethylacetal) (25).—In one experiment **23** was prepared from **20a** as described above; however, the crude product was recrystallized from hot methanol. This procedure gave the corresponding 5-dimethylacetal **25** as white needles: mp 141–143°; ir 3.5, 6.12 μ (CHO); uv max 224 mμ (ϵ 34,000), 247 (16,500), 275 (10,000), 315 (12,000); nmr ($CDCl_3$) δ 11.1 (CHO), 7.67 (d, J = 8 Hz, ortho aromatic), 7.37 (d, J = 8 Hz, ortho aromatic), 5.91 (s, $CH(OCH_3)_2$), 4.19 (q, 2, J = 16 Hz, NCH_2CH_3), 3.50 (s, 6, $(OCH_3)_2$), 2.87 (s, 3, CH_3), 1.40 ppm (t, 3, J = 16 Hz, NCH_2CH_3).

Anal. Calcd for $C_{15}H_{18}ClNO_3$: C, 60.92; H, 6.13; Cl, 11.99. Found: C, 61.27; H, 6.61; Cl, 12.59.

The uv spectrum of **25** closely resembled that of **21b** but differed considerably from that of 1-ethyl-4-hydroxy-2-methylindole-5-carboxaldehyde[15a] [uv max 245 mμ sh (ϵ 24,500), 261 (36,500), 290 (11,000), 305 (15,000)] which suggests that the acetal was formed selectively by the 5-carboxaldehyde.

1-Benzylindole-2-carboxaldehyde 2,4-Dinitrophenylhydrazone.—A mixture of 544 mg of **4b**, 125 mg of 10% palladium on charcoal, and 8 ml of cumene was stirred 2 hr at reflux temperature, cooled, filtered, and concentrated under reduce pressure. The oily residue (370 mg) gave a negative Beilstein test. A 312-mg portion of it was dissolved in 30 ml of hot ethanol and treated with 264 mg of 2,4-dinitrophenylhydrazine in 0.3 ml of concentrated HCl. The mixture was boiled for 5 min and cooled, and the brick-red solid product was washed with cold ethanol. Recrystallization from methanol–pyridine gave dark red prisms: mp 237–249°; uv max 315 mμ (ϵ 12,000), 405 (31,000); nmr (DMF-d_7) 10.2 (s, NH), 9.03 (s, C=CCHN), 8.91 (s, J = 3 Hz), 8.25 (dd, J = 3, J = 8 Hz), 7.67 (d, J = 8 Hz, protons on dinitrophenylhydrazinyl benzene ring), 7.29 (m, 10, protons on indolyl and phenyl rings), 6.11 ppm (s, 2, benzylic).

Anal. Calcd for $C_{22}H_{17}N_5O_4$: C, 63.61; H, 4.13; N, 16.86. Found: C, 63.06; H, 4.27; N, 16.90.

Registry No.—**2a**, 27932-08-7; **2b**, 18603-30-0; **4a**, 18518-43-9; **4b**, 4657-77-6; **5**, 27784-79-8; **6**, 27784-80-1; **7**, 27784-81-2; **7** perchlorate, 27784-82-3; **8**, 27784-83-4; **9**, 24836-93-9; **10**, 27784-85-6; **11**, 27784-86-7; **12**, 27784-87-8; **13**, 27784-88-9; **14e**, 27784-89-0; **15**, 27784-90-3; **16**, 27784-91-4; **17**, 27784-92-5; **18**, 27784-93-6; **19a**, 18518-54-2; **19b**, 4657-74-3; **20a**, 4657-75-4; **20b**, 18518-60-0; **21a**, 27784-98-1; **21b**, 4657-76-5; **21c**, 27932-10-1; **22**, 4657-78-7; **23**, 4583-54-4; **24**, 4660-03-1; **25**, 27787-33-3; **28**, 4583-62-4; **29**, 18518-56-4; **30**, 4657-79-8; i, 27787-37-7; alcohol melting at 95–97°, 27787-38-8; 2-acetonyl-5,5-dimethylcyclohexane-1,3-dione, 13148-87-3; 1-benzylindole-2-carboxaldehyde 2,4-DNP, 27787-40-2.

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