[CONTRIBUTION FROM THE WILLIAM H. NICHOLS LABORATORY, NEW YORK UNIVERSITY]

SYNTHESIS AND REACTIONS OF INDOLE CARBOXYLIC ACIDS; PYRIDINDOLONES FROM INDOLE-2-CARBOXYACETALYLBENZYLAMIDES

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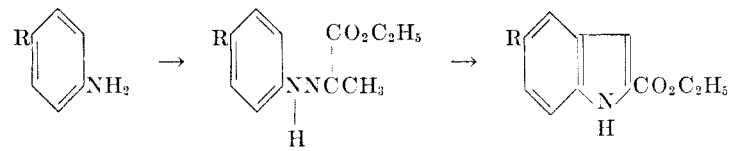
Received February 29, 1952

This study is a continuation of the work in this laboratory on the preparative methods and chemistry of indole derivatives. Of particular interest are those indole carboxylic acids containing the carboxylic acid group in the five position and having an unsubstituted three position. These compounds resemble anesthesine in structure and may be converted to warped amino acids by the Mannich reaction.

An outgrowth of this work is the preparation and ring closure of a few indole-2-carboxybenzylacetalylamides to determine the orienting effects of groups substituted in the five position.



R = COOH
R = $CO_2C_2H_5$
R = CN

I R = COOH
II R = $CO_2C_2H_5$
VI R = CN

III R = COOH

IV R = $CO_2C_2H_5$

In the preparation of 2,5-dicarbethoxyindole (IV) from ethyl pyruvate *p*-carbethoxyphenylhydrazone (I) by the Fischer synthesis (1), zinc chloride is so vigorous a catalyst that a mixture of products results, whereas hydrogen chloride is completely ineffective, as reported by Hughes and Lions (2). When a carboxy group is substituted for the *p*-carbethoxy group of the phenylhydrazone (II), it moderates the reaction and nearly a 50% yield of 2-carbethoxyindole-5-carboxylic acid (III) results. With the cyano group in the same position (IV), and under the same experimental conditions, there is no rearrangement of the phenylhydrazone to an indole, but merely a hydrolysis to pyruvic acid *p*-cyanophenylhydrazone (VII). The latter is very unreactive and after prolonged contact with zinc chloride at 200° only a very small proportion of the starting material is converted to 5-cyanoindole-2-carboxylic acid (X). Table II, Part A, summarizes data on the preparation of three phenylhydrazones by the Japp-Klingemann reaction as modified by Hughes and Lions (2). Part B covers the results obtained with the phenylhydrazones used in the Fischer indole synthesis (1).

The Curtius reaction has been used with varying success on indole-2-carboxylic acids (3). When the carboxylic acid group is in the five instead of the two position a high yield of product is obtained by this method. 2-Carbethoxyindole-5-carboxylic acid (III) is degraded in 90% yield to 2-carbethoxy-5-isocyanatoindole (XVII) and thus provides an excellent route to 5-substituted aminoindoles.

The isocyanate (XVII) can be converted quantitatively to 2-carbethoxy-5-carbethoxyaminoindole (XVIII) with ethanol. Acid hydrolysis of the isocyanate (XVII) followed by esterification gives a 25% yield of 2-carbethoxy-5-aminoindole (XIX). It is presumed that the white crystalline plates which result from the acid hydrolysis of 2-carbethoxy-5-aminoindole (XIX) are 5-aminoindole-2-carboxylic acid (XX). The crystals quickly turned brown on standing in air and the analysis for XX was not within acceptable limits. The urethan ester (XVIII)

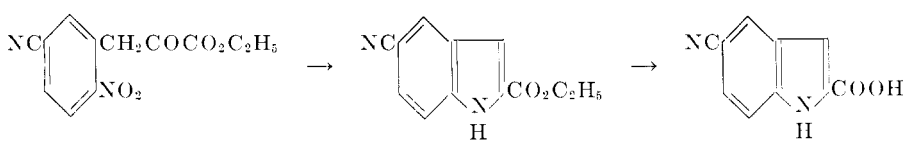
TABLE I

ANALYSES OF COMPOUNDS

COMPOUND NUMBER	FORMULA	CALC'D			FOUND		
		C	H	N	C	H	N
II	$C_{12}H_{14}N_2O_4$	57.59	5.64	11.19	57.61	5.85	11.36
III	$C_{12}H_{11}NO_4$	61.80	4.80	6.01	62.10	5.22	6.33
IV	$C_{14}H_{15}NO_4$	64.35	5.78	5.36	64.35	5.97	5.37
V	$C_{10}H_7NO_4$	—	—	6.82	—	—	7.06
VI	$C_{12}H_{13}N_3O_2$	—	—	18.17	—	—	18.36
VII	$C_{10}H_9N_3O_2$	—	—	20.68	—	—	20.94
VIII	$C_{12}H_{10}N_2O_5$	54.96	3.84	10.68	55.05	4.10	10.88
IX	$C_{12}H_{10}N_2O_2$	67.28	4.70	13.07	67.30	4.82	13.24
X	$C_{10}H_6N_2O_2$	64.52	3.25	15.04	62.95	3.31	14.46
					62.90	3.40	14.61
XI	$C_9H_6N_2$	—	—	19.71	—	—	19.52
XII	$C_{17}H_{22}N_2O_4$	—	—	8.80	—	—	8.60
XIII	$C_{19}H_{26}N_2O_4$	—	—	8.08	—	—	8.21
XIV	$C_{19}H_{24}N_2O_5$	63.30	6.71	7.77	63.57	6.90	7.97
XV	$C_{17}H_{19}N_3O_3$	65.16	6.11	13.41	64.74	6.46	13.10
XVI	$C_{13}H_{15}ClN_2O_4 \cdot 2H_2O$	46.63	5.72	8.37	46.55	6.11	8.32
XVII	$C_{12}H_{10}N_2O_3$	—	—	12.13	—	—	12.44
XVIII	$C_{14}H_{16}N_2O_4$	61.29	5.88	10.22	61.05	5.78	10.09
XIX	$C_{11}H_{12}N_2O_2$	64.69	5.92	13.71	64.75	5.98	13.73
XXI	$C_{12}H_{12}N_2O_4$	58.06	4.87	11.28	58.10	5.18	11.37
XXII	$C_{22}H_{26}N_2O_3$	72.10	7.14	7.63	72.15	7.12	7.62
XXIII	$C_{18}H_{11}N_2O$	78.82	5.14	10.21	78.55	5.43	10.16
XXIV	$C_{25}H_{31}N_3O_5$	66.22	6.89	9.26	66.60	7.11	9.25
XXV	$C_{21}H_{19}N_3O_3$	69.76	5.30	11.63	69.90	5.26	11.95
XXVI	$C_{23}H_{25}N_3O_3$	70.57	6.44	10.73	70.40	6.54	10.39
XXVII	$C_{19}H_{13}N_3O$	76.23	4.38	14.03	75.80	4.38	13.97

is converted to 5-carbethoxyaminoindole-2-carboxylic acid (XXI) with alcoholic potassium hydroxide (77%).

The Reissert indole synthesis (4) proved more fruitful than Fischer's phenylhydrazone method in the preparation of 5-cyanoindole-2-carboxylic acid (X).



VIII IX X

The starting material, 2-nitro-5-cyanotoluene, was synthesized from *m*-nitrotoluene by reduction (90%), acetylation (97%) (5), nitration, and hydrolysis (62%) (6) to 2-nitro-5-aminotoluene; the latter was converted by the Sandmeyer reaction as outlined by Clark and Read (7) to the nitrile, which was isolated by steam distillation. The high purity and 50–65% yield of 2-nitro-5-cyanotoluene represent a considerable improvement over the method of Gabriel and Thieme (8). The base-catalyzed condensation between 2-nitro-5-cyanotoluene and freshly distilled diethyl oxalate gave 5-cyanophenylpyruvate (VIII), which was reduced with zinc and acetic acid to 2-carbethoxy-5-cyanoindole (IX) in an overall yield of 34%. The desired 5-cyanoindole-2-carboxylic acid (X) was obtained

TABLE II

PHENYLHYDRAZONES AND CYCLIZED INDOLE PRODUCTS

A. PHENYLHYDRAZONES PREPARED FROM α-METHYLACETOACETIC ESTER BY THE JAPP-KLINGEMANN REACTION (2)

ETHYL PYRUVATE PHENYLHYDRAZONE	STARTING ANILINE DERIVATIVE	YIELD, %	M.P., °C.	SOLVENT
II	4-CO_2H	59	222	Acetic acid-water
I	4-$CO_2C_2H_5$	58	139.5–140	Benzene-petroleum ether
VI	4-CN	73 (Crude)	157.5–158	Benzene

B. PRODUCTS RESULTING FROM FISCHER INDOLE SYNTHESIS

INDOLE DERIVATIVE	PHENYLHYDRAZONE	YIELD, %	M.P., °C.	SOLVENT
III	II	48	271	Ethanol
IV	I	Low	145–146	Benzene
IX[a]	VI	0	185.5–187	Ethanol
X	VII[b]	Very low	315–330 d	Acetic acid

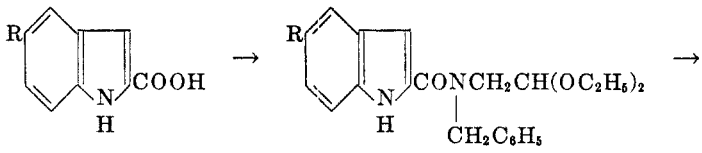
[a] Prepared by Reissert method. [b] Resulted from action of zinc chloride on VI.

by a controlled base hydrolysis of IX, and was identical to the small amount of sample obtained by the Fischer method.

Indole-2-carboxyacetalylbenzylamides in the presence of acids are converted to pyrazinoindolones or isomeric pyridindolones by ring closure on the one or three positions of the indole nucleus respectively.

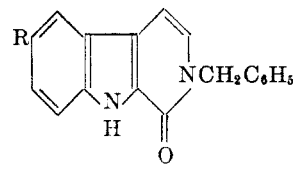
Kermack's work (9) on 6-cyanoindole-2-carboxydimethylacetalylamide led him to conclude that the 6-cyano group inhibits ring formation by decreasing the reactivity of the one and three hydrogen atoms. When there is a 5-cyano group in an N-benzylacetalylamide we have found that ring closure does proceed, with the formation of only one isomer. The pyridindolone structure is assigned to the product (XXVII) on the basis of its infrared spectrum. An unsubstituted five position or a 5-carbethoxyamino group apparently led to the formation of a mixture of products on ring closure, but in each reaction only the

pyridindolone was isolated and identified by its ultraviolet absorption spectrum (10).



R = H
XXI R = $NHCO_2C_2H_5$
X R = CN

XXII R = H
XXIV R = $NHCO_2C_2H_5$
XXVI R = CN



XXIII R = H
XXV R = $NHCO_2C_2H_5$
XXVII R = CN

The acid chlorides of indole-2-carboxylic acid, 5-cyanoindole-2-carboxylic acid (X), and 5-carbethoxyaminoindole-2-carboxylic acid (XXI) are converted to indole-2-carboxyacetalylbenzylamide derivatives by reaction with benzylaminoacetal. The latter is synthesized with slight modification by the method of Rugheimer and Schon (11) from benzylamine and bromoacetal (12). The resulting N-benzylamides, XXII, XXVI, and XXIV, are cyclized with ethereal sulfuric acid and the products purified by fractional recrystallization from dioxane solution. On the basis of comparison with ultraviolet absorption spectra of pyrazino- and pyrid-indolones of known structure (10), the products from XXII and XXIV (Figure 1) are 2-benzylpyrid[*3*,*4*-*b*]indole-1(2*H*)-one (XXIII) and 2-benzyl-6-carbethoxyaminopyrid[*3*,*4*-*b*]indole-1(2*H*)-one (XXV). The ultraviolet absorption spectrum of the product isolated from the cyclization of 5-cyanoindole-2-carboxyacetalylbenzylamide (XXVI) (Fig. 1) does not permit an unequivocal assignment of structure. 2-Benzyl-6-cyanopyrid[*3*,*4*-*b*]indole-1(2*H*)-one (XXVII) is the structure assigned to this product on the basis of its infrared spectrum shown in Fig. 2. The sharp band at 3.1 microns is associated with an N—H stretching vibration (13) and would be found in a pyridindolone but not in a pyrazinoindolone, since it contains no N—H linkage. Marion, Ramsay, and Jones (18) examined the infrared absorption spectra of a number of alkaloids containing the indole nucleus and found the N—H band near 2.9 microns. The shift in XXVII to a longer wave length may result from an interaction between the carbonyl and imino groupings. The sharp band at 4.5 microns is due to the C≡N stretching vibration. Other prominent bands at 6.05, 6.29, 6.29, and 6.41 microns may be due to the N—H bending vibration, phenyl rings, *a*-pyridone ring and/or the carbonyl group. Alkaloids containing the *a*-pyridone ring have two bands appearing near 6.05 and 6.4 microns (18). The band at 6.05

microns may be what has been called the amide I band, found in unsubstituted and N-substituted amides (13).

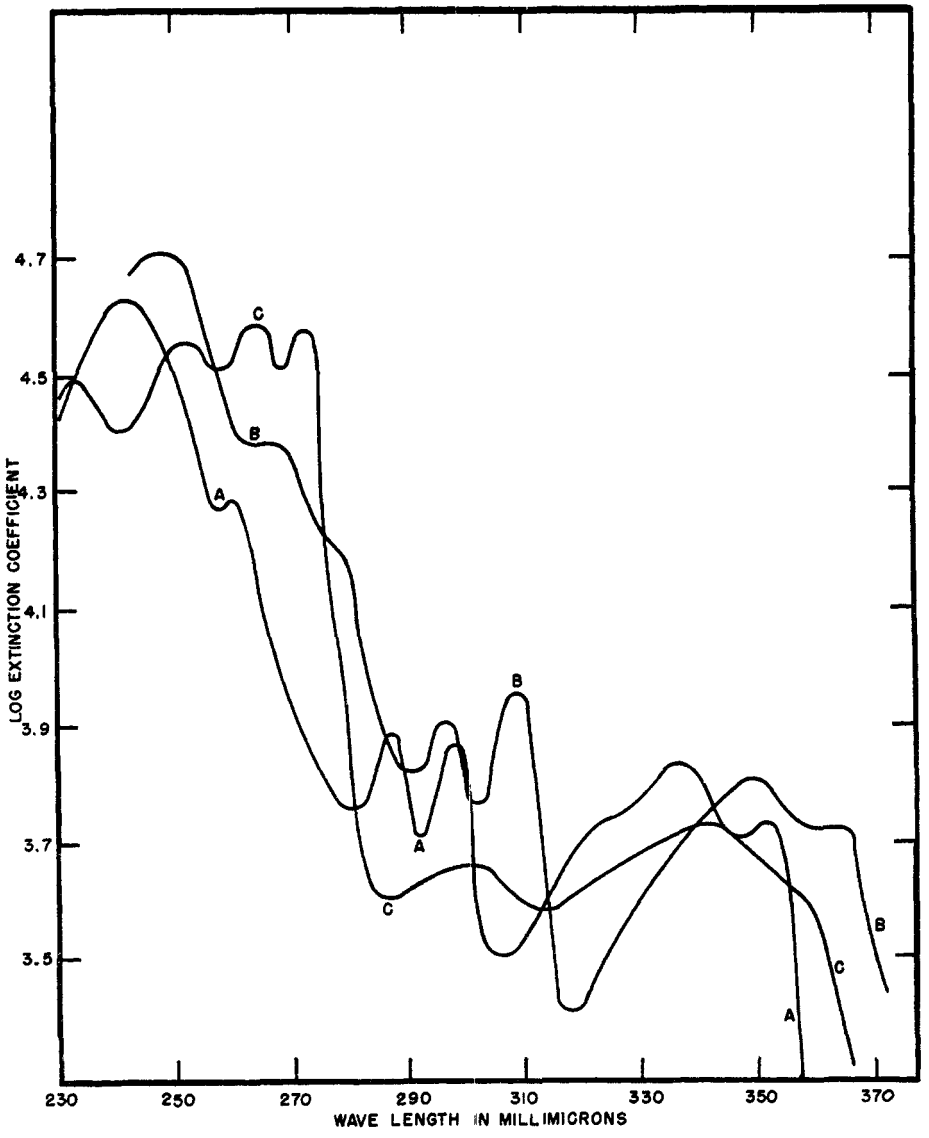


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA OF 2-BENZYLPYRID[3,4-*b*]INDOLE-1(2*H*)-ONE (XXIII) (A); 2-BENZYL-6-CARBETHOXYAMINOPYRID[3,4-*b*]INDOLE-1(2*H*)-ONE (XXV) (B); 2-BENZYL-6-CYANOPYRID[3,4-*b*]INDOLE-1-(2*H*)-ONE (XXVII) (C). (A graph, wave length as abscissa, log extinction coefficient as ordinate.)

Table III summarizes the pertinent data on the preparation and cyclization of the indole-N-benzylacetalylamides, and Table IV the ultraviolet absorption data for the resulting products. The rather striking similarity between the ultra-

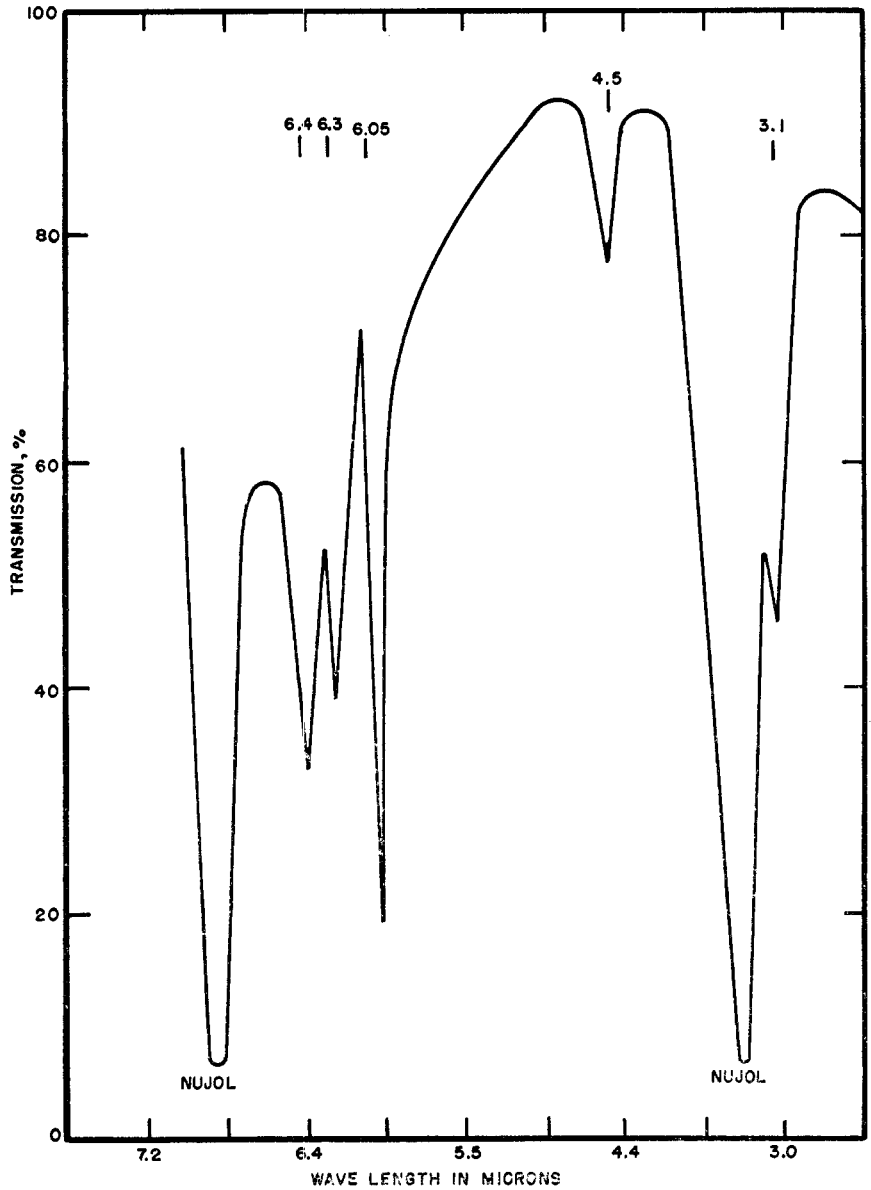


FIG. 2. INFRARED SPECTRUM OF 2-BENZYL-6-CYANOPYRID[3,4-*b*]INDOLE-1(2*H*)-ONE (XXVII) IN NUJOL DISPERSION. (A graph, wave length as abscissa, transmission as ordinate.)

violet absorption spectra of 2-benzylpyrid[3,4-*b*]indole-1(2*H*)-one (XXIII) and 2-methylpyrid[3,4-*b*]indole-1(2*H*)-one (10) points to the insulating nature of the methylene group between the phenyl and the rest of the molecule.

The ultraviolet absorption spectra of the crude cyclized products indicate that only the 5-cyano group directs the ring closure exclusively to position

three. Supporting evidence for the enhanced reactivity of the three position when the cyano group is in position five is found in the high yield obtained with 2-carbethoxy-5-cyanoindole (IX) in the Mannich reaction.

TABLE III

A. INDOLE-2-CARBOXYACETALYLBENZYLAMIDES FROM INDOLE-2-CARBONYL CHLORIDES AND BENZYLAMINOACETAL

AMIDE	INDOLE ACID	ACID CHLORIDE PREPARED WITH (SOLVENT)	YIELD, %	M.P., °C.[b]
XXII	2-CO_2H	$SOCl_2$(Et_2O)	40	108–108.5
XXVI	2-CO_2H, 5-CN	PCl_5(CH_3COCl)	60[a]	129–129.5
XXIV	2-CO_2H, 5-$NHCO_2Et$	$SOCl_2$(Et_2O)	40[a]	125–126

B. PYRIDINDOLONES BY CYCLIZATION OF AMIDES WITH SULFURIC ACID (10)

PYRIDINDOLONE	AMIDE	CRUDE PRODUCT	M.P., °C.	SOLVENT
XXIII	XXII	+ Pyrazinoindolone (?)	293–294	Dioxane
XXVII	XXVI	No Pyrazinoindolone	330–332	Dioxane
XXV	XXIV	+ Pyrazinoindolone (?)	253[c]	Dioxane-water

[a] Based on unrecovered acid. [b] From ethanol. [c] Sample inserted a few degrees below the m.p.

TABLE IV

ULTRAVIOLET ABSORPTION DATA FOR PYRIDINDOLONES

COMPOUND								
XXIII	Max.	mμ	241	259	286	297	334	348
		Log e	4.64	4.30	3.90	3.89	3.85	3.74
H	Min.	mμ	257	281	292	306	344	
		Log e	4.27	3.76	3.70	3.50	3.71	
XXV	Max.	mμ	247	264	295	308	347	
		Log e	4.73	4.41	3.94	3.99	3.82	
$NHCO_2C_2H_5$	Min.	mμ	263	289	301	316		
		Log e	4.40	3.82	3.76	3.40		
XXVII	Max.	mμ	233	250	263	272	301	340
		Log e	4.50	4.57	4.61	4.60	3.65	3.74
CN	Min.	mμ	240	258	267	285	311	
		Log e	4.41	4.61	4.50	3.59	3.57	

Table V summarizes the Mannich reaction on several indole derivatives with formaldehyde and secondary amines. The greater yield obtained using dimethylamine over that with diethylamine appears to agree with Blicke's conclusion that the former is the more reactive in the condensation (14).

Alkaline hydrolysis of one of the Mannich products, 2,5-dicarbethoxy-3-dimethylaminomethylindole (XII), was unsuccessful, no amino acid resulting.

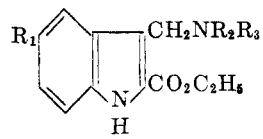
The destructive effect of alkali on compounds of this type has been reported by Bell and Lindwall (15). The acid-catalyzed hydrolysis, however, results in an

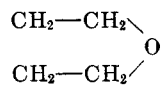
TABLE V

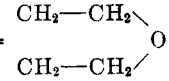
MANNICH BASES RESULTING FROM THE ACTION OF FORMALDEHYDE AND AMINE ON 2,5-DICARBETHOXYINDOLE (IV) AND 2-CARBETHOXY-5-CYANOINDOLE (IX)

MANNICH PRODUCT	INDOLE	AMINE	YIELD, %	M.P., °C.	SOLVENT
XIV	IV	Morpholine	72	150.5–151	Acetone
XV	IX	Morpholine	93	179.5–180	Acetone
XII	IV	Dimethyl	62	134.5–135.5	Methanol
XIII	IV	Diethyl	55 (Crude)	139–140	Methanol

excellent yield (96%) of 3-dimethylaminomethylindole-2,5-dicarboxylic acid (XVI), isolated as the dihydrate hydrochloride.



XIV $R_1 = CO_2C_2H_5$, $R_2R_3 =$ 

XV $R_1 = CN$, $R_2R_3 =$ 

XII $R_1 = CO_2C_2H_5$, $R_2 = R_3 = CH_3$

XIII $R_1 = CO_2C_2H_5$, $R_2 = R_3 = CH_2CH_3$

EXPERIMENTAL

FISCHER METHOD

All melting points are corrected.

p-Aminobenzonitrile. The Sandmeyer reaction with *p*-nitroaniline was carried out as described in Organic Synthesis (7). The product, *p*-nitrobenzonitrile, m.p. 146–147°, was isolated by steam distillation in yields of 50–51%. The reduction of the benzonitrile derivative was effected with stannous chloride and concentrated hydrochloric acid (16) in 57% yield. About 20% of unreacted *p*-nitrobenzonitrile was recovered.

Ethyl pyruvate-p-carbethoxyphenylhydrazone (I), *ethyl pyruvate-p-carboxyphenylhydrazone* (II), and *ethyl pyruvate-p-cyanophenylhydrazone* (VI). These phenylhydrazones were synthesized from α-methylacetoacetic ester and the appropriate aniline derivative (Table II). The m.p. of I was 3° higher than the reported value (2).

2-Carbethoxyindole-5-carboxylic acid (III). An intimate mixture of the recrystallized *p*-carboxyphenylhydrazone of pyruvic ester (II) (13 g., 0.052 mole) and freshly fused, finely powdered zinc chloride (65 g.) in an Erlenmeyer flask was heated in a bath kept at 175°. The solid mixture was stirred with a thermometer which was employed to follow the temperature inside the flask. The temperature rose slowly at first and the mixture underwent a gradual darkening, until at one stage during reaction the fused mass appeared black. When the temperature began to rise more rapidly, and had reached about 165°, the flask

was removed from the bath. The temperature continued to rise to 185°, the color changing to a light brown with an orange cast. A blistering was observed and the odor of indole could be detected. The temperature remained above 180° for a short time and then slowly fell. The zinc chloride was dissolved in water (175 cc., to which 3 cc. of concentrated hydrochloric acid was added) by heating on a steam-bath for an hour and a half. The product was collected and washed several times with cold water. The almost dry crude product was boiled for about one minute in acetic acid (30 cc.) and then allowed to cool. The 2-carbethoxy-5-carboxyindole was filtered off and washed with several portions of cold acetic acid. The yield of bright yellow product was 48% (5.8 g.); m.p. 260–265°. The compound, m.p. 271° from ethanol, gave no color with Ehrlich's reagent (*p*-dimethylaminobenzaldehyde in dilute hydrochloric acid).

2,5-Dicarbethoxyindole (IV). *Method A:* 2-Carbethoxyindole-5-carboxylic acid (III) was esterified with alcoholic hydrogen chloride in 77% yield. The diester separated as long yellow needles from dilute alcohol, m.p. 145–146°. It gave no red color with Ehrlich's reagent. *Method B:* From the action of anhydrous zinc chloride on the *p*-carbethoxyphenylhydrazone of pyruvic ester (I), 2,5-carbethoxyindole could be prepared in small yield. The low yield was due mainly to the vigorous reaction which ensued at the bath temperature of 180°. By controlling the temperature at lower levels it is to be expected that improved yields would result. The diester was obtained by hydrolyzing the alkali-soluble material isolated from the reaction mixture (evidently a considerable amount of hydrolysis had taken place) and esterifying a small recrystallized (glacial acetic acid) sample of this hydrolyzed material with boron trifluoride in absolute alcohol. On recrystallization from dilute alcohol and benzene, the compound melted at 145–146° and gave no depression in melting point with a sample prepared by *Method A*.

p-Cyanophenylhydrazone of pyruvic acid (VII). The Fischer synthesis with phenylhydrazone (VI) and anhydrous $ZnCl_2$ resulted in hydrolysis to an acid compound, m.p. 214°, which did not give a positive test for indole, nor did its decarboxylated product. The compound proved identical to the product isolated from the alkaline hydrolysis (5–10 minutes, 12% potassium hydroxide) of VI. The use of VII in the Fischer synthesis is described under 5-cyanoindole-2-carboxylic acid (X).

Indole-2,5-dicarboxylic acid (V). To crude 2-carbethoxy-5-carboxyindole (1.50 g., 6.45 millimoles), m.p. 260–265°, 9% potassium hydroxide solution (30 cc.) was added and the mixture was refluxed for 3 hours. The hot solution was treated with bone black, filtered, and the cool filtrate acidified with hydrochloric acid (1:1). The yield was nearly quantitative. The yellow solid darkened slightly between 280° and 290° and underwent considerable sintering and decomposition from 290° to 295°.

REISSERT SYNTHESIS

2-Nitro-5-aminotoluene. Starting with *m*-nitrotoluene, the procedure described in Fieser's laboratory manual (5) for the reduction and acetylation of nitrobenzene was carried out to *m*-acetotoluidine in 86% yield. Nitration and hydrolysis of *m*-acetotoluidine was effected without isolation of the intermediate product in 59–62% yields (6), m.p. 134–135.5°.

2-Nitro-5-cyanotoluene. The diazotization of 2-nitro-5-aminotoluene was conducted in glacial acetic acid with concentrated hydrochloric acid and approximately a 30% excess of powdered sodium nitrite. After dilution with water, the solution was added to a cuprous cyanide solution according to the procedure outlined in Organic Synthesis (7). The product was isolated in the pure state by steam distillation, in 50–65% yield. A relatively large amount of material which was not steam distillable crystallized out as long needles from the aqueous residue. This water-soluble white compound melted about 150° and was not investigated further.

Ethyl 2-nitro-5-cyanophenylpyruvate (VIII). The Reissert condensation between diethyl oxalate (28 g.) and 2-nitro-5-cyanotoluene (7.37 g., 45.5 millimoles) was carried out exactly as described by Kermack (9), for the 4-cyano derivative. The ethyl alcohol employed was distilled from sodium ethoxide; the oxalic ester obtained from Eastman Kodak was distilled and the cut from 180–185° was used. Neglecting this latter step gave inferior yields of

product that proved very difficult to purify. This condensation product separated as a sticky mass when the ethanol solution was diluted with water. After drying and trituration with petroleum ether-benzene it weighed 6.9 g., m.p. 81–87.5°, and was used without further purification. Several recrystallizations from benzene and ethanol yielded a bright yellow crystalline compound, m.p. 105–106°.

2-Carbethoxy-5-cyanoindole (IX). The reduction of crude ethyl 2-nitro-5-cyanophenylpyruvate (5.18 g., m.p. 81–87.5°) to the corresponding indole was carried out in 50% acetic acid (41 cc. of glacial acetic in an equal volume of water) with an excess of zinc dust (9.5 g.), as in (9). The yield of slight tan product was 34% from 2-nitro-5-cyano-toluene (2.51 g.), m.p. 175–179°.

A small sample of 2-carbethoxy-5-cyanoindole was converted to indole-2,5-dicarboxylic acid (potassium hydroxide in ethanol-water, 30 hours) which was esterified to 2,5-dicarbethoxyindole (IV) (ethanol, hydrochloric acid), m.p. 141–143.5°. The compound did not depress the melting point of a sample prepared by the Fischer method from phenylhydrazone I.

5-Cyanoindole-2-carboxylic acid (X). Compound IX was hydrolyzed partially to 5-cyanoindole-2-carboxylic acid in 87% yield by Kermack's method (9). This indole acid derivative showed no definite m.p. but underwent considerable decomposition between 315° and 330°. It is insoluble in dioxane, ethyl alcohol, benzene, and acetone, and very slightly soluble in acetic acid. The carbon analysis, although not acceptable, is given in Table I.

A small amount of 5-cyanoindole-2-carboxylic acid resulted from the action of zinc chloride (10 g.) on *p*-cyanophenylhydrazone of pyruvic acid (2.4 g.) (VII) heated in a bath whose temperature was slowly raised from 160° to 200°. After isolating the crude material and removing the alkali-insoluble products, the product was recrystallized from acetic acid (m.p. 214°). Its decomposition product gave a faint red color with Ehrlich's reagent. This was evidently unreacted phenylhydrazone containing small amounts of indole impurity. It was found that a small amount of substance soluble in ammonia was rather insoluble in the glacial acetic acid used for the above recrystallization. This substance darkened about 300° and underwent decomposition over a wide temperature range. Its decomposition product gave a strong indole test with Ehrlich's reagent. The compound was typically insoluble in benzene, acetone, ethyl alcohol, water and only slightly soluble in glacial acetic acid and thus resembled in all respects the sample of 5-cyanoindole-2-carboxylic acid obtained by the Reissert method. The analysis for carbon in this case also proved low.

Anal. Calc'd for $C_{10}H_6N_2O_2$: C, 64.52; H, 3.25.
Found: C, 63.05; H, 3.11.

5-Cyanoindole (XI). 5-Cyanoindole-2-carboxylic acid (0.79 g.) with an equal weight of calcium oxide was heated over an open flame and impure 5-cyanoindole (0.14 g.) was collected as a colorless distillate. After two recrystallizations from dilute ethanol, the compound melted at 104–106°, and gave a red color with Ehrlich's reagent in the cold.

MANNICH REACTIONS

2,5-Dicarbethoxy-3-dimethylaminomethylindole (XII). A cold 36% solution of formaldehyde (208 mg., 2.5 millimoles) was added to a cool solution of 2,5-dicarbethoxyindole (380 mg., 1.46 millimoles) and a 33% aqueous solution of dimethylamine (305 mg., 2.24 millimoles) in glacial acid (2.2 cc.) and the mixture was allowed to stand for one hour. During this time the indole diester separated out. The reaction mixture was heated in hot water (about 70°) for one hour, during which time all the diester had redissolved. After allowing to stand at room temperature overnight, water (7–8 cc.) was added and the sticky solid material which separated was centrifuged to the bottom. Concentrated ammonia was added to the cold solution until most of the acetic acid had been neutralized. After treatment with bone black in the cold, the clear solution was made alkaline with excess ammonia. The yield of almost pure gramine derivative was 62% (288 mg.) melting at 134–135°. After two recrystallizations from methyl alcohol, the white crystals melted at 134.5–135.5°.

By the same procedure there were prepared 2,5-dicarbethoxy-3-diethylaminomethylindole (XIII), 2,5-dicarbethoxy-3-(N-methylenemorpholine)indole (XIV), and 2-carbethoxy-5-cyano-3-(N-methylenemorpholine)indole (XV).

3-Dimethylaminomethylindole-2,5-dicarboxylic acid (XVI). The acid-catalyzed hydrolysis of 2,5-dicarbethoxy-3-dimethylaminomethylindole (58 mg., 0.183 millimole) was accomplished with equal volumes (0.8 cc.) of concentrated hydrochloric acid and water by refluxing for three hours. After allowing the reaction mixture to stand at room temperature for two hours longer, the amino acid hydrochloride which had crystallized out during the period of refluxing was separated from the cold solution and dissolved in the minimum of potassium hydroxide. The insolubles were removed, and the supernatant liquid, after acidification with excess hydrochloric acid, yielded lustrous, silvery white crystals (96.5% yield, 59 mg.) which melted at 229° to a dark liquid, with gas evolution. After one recrystallization from water (bone black), the compound melted at 231° with slight preliminary darkening. When dissolved in water containing a slight excess of nitric acid, the compound gave a white curdy precipitate with silver nitrate solution, which dissolved on addition of excess ammonia. The analysis of the hydrochloride indicated two water molecules of crystallization.

CURTIUS REACTION

2-Carbethoxy-5-isocyanatoindole (XVII). To a suspension of 2-carbethoxy-5-carboxyindole (m.p. 260–265°, 567 mg., 2.43 millimoles) in acetyl chloride (12 g.), phosphorus pentachloride (0.57 g., 2.7 millimoles) was added, and the mixture was stirred for about 2 hours. A calcium chloride tube at the top of a water-cooled condenser excluded moisture. The flask was heated occasionally with water at 60°. The insoluble yellow acid chloride was freed from acetyl chloride and phosphorus oxychloride under reduced pressure. External heating with hot water was used to remove the higher-boiling oxychloride. Acetone (c.p., 10 cc.) was added, followed by aqueous sodium azide (0.22 g., 3.4 millimoles, in 0.66 cc. of water). After 15 minutes of continuous stirring, water (35 cc.) was added, and the mixing was continued for an additional five minutes. The crude flesh-colored azide derivative weighed 594 mg., after drying in a vacuum desiccator.

The rearrangement to the isocyanate was carried out by refluxing for 2 hours in dry toluene (12 cc.). A bright yellow solid was obtained in 90% yield based on 2-carbethoxyindole-5-carboxylic acid (501 mg.) and melted at 171–172°. After recrystallization from dry benzene, the melting point was raised to 172–173°.

2-Carbethoxy-5-carbethoxyaminoindole (XVIII). By refluxing 2-carbethoxy-5-isocyanatoindole (207 mg., 0.90 millimole) in absolute alcohol (10 cc.) for three hours, a 98% yield (243 mg.) of the urethan was obtained. From a benzene-petroleum ether mixture the compound separated as orange-yellow granules, melting at 173.5–174°. The addition of a small amount of the isocyanate derivative depressed the melting point about 20°.

2-Carbethoxy-5-aminoindole (XIX). The hydrolysis of 2-carbethoxy-5-isocyanatoindole (207 mg., 0.90 millimole) was carried out in concentrated hydrochloric acid (7 cc.). After heating the stirred solution for 2½ hours, the water and hydrochloric acid were removed under reduced pressure. The residue, a dark, reddish-brown solid, was heated for three hours with ethanol saturated with hydrogen chloride (6 cc.). The excess hydrogen chloride and solvent were removed under reduced pressure. The hydrochloride was dissolved in hot water and the amino ester brought down with excess ammonia. The weight of the crude product was 92 mg. The amine separated as light orange needles from benzene, m.p. 127–127.5°. The conversion of the isocyanate to the 5-aminoindole derivative was repeated and yields of purified product were about 25%.

5-Aminoindole-2-carboxylic acid (XX). 2-Carbethoxy-5-aminoindole (201 mg., 0.984 millimole) and 20% methyl alcoholic potassium hydroxide (10 g.) containing a few grains of sodium hydrosulfite were heated for a few minutes with hot water. The indole derivative first dissolved in the hot solution but soon after, the potassium salt of the acid precipitated. Heating was continued for about one minute longer with shaking to prevent bumping. After cooling, the solution was centrifuged and the supernatant liquid drawn off. The solid was washed with a few drops of methyl alcohol and the potassium salt dissolved in the

minimum of cold water. The small amount of insoluble matter was removed. Hydrochloric acid (1 volume of acid: 3 volumes of water) was added drop by drop until about the neutral point when a light tan granular solid settled out (124 mg., m.p. 235–237° with darkening at 227°). Further acidification of the mother liquor yielded additional solid (35 mg., m.p. 242–243°). The amino acid crystallized as long white flat plates from water (bone black) but soon turned brown on standing in air (m.p. 271°). The analysis for this compound was not acceptable.

5-Carbethoxyaminoindole-2-carboxylic acid (XXI). 2-Carbethoxy-5-carbethoxyaminoindole (600 mg., 2.17 millimoles) and 5% potassium hydroxide in absolute ethanol (2.1 cc.) were heated over an open flame. The indole ester dissolved almost immediately, and shortly after the yellow-orange potassium salt separated. The reaction mixture was heated in hot water, 80° to 90°, for five minutes. The hot mixture was centrifuged and the supernatant liquid removed. After the potassium salt was washed with hot absolute alcohol (1.8 cc.), it was dissolved in tepid water (2 cc.). Upon acidification, a tan solid (475 mg.) separated melting at 200–205°. After treatment with bone black in alkaline solution, the melting point was raised to 216° (with evolution of gas), and the yield of acid was 77% (412 mg.). The compound separated as white crystals from acetic acid and melted at 222°. By changing the conditions, the melting point could be increased or decreased by several degrees.

Bromoacetal. Bromoacetal was obtained in 76% yield from vinyl acetate, bromine, and absolute alcohol, following the method described by Bedoukian (12).

Benzylaminoacetal. Bromoacetal (35 g., 0.178 mole) was added dropwise over a period of a half hour to benzylamine (39 g., 0.364 mole) with vigorous stirring. The temperature was kept between 130° and 140° with a metal bath. After 45 minutes of continuous stirring, the dark yellow reaction mixture, containing precipitated hydrobromides, was allowed to cool, and excess 10% sodium hydroxide was added. The amino compounds were extracted with ether and after drying over potassium hydroxide for 12 hours, the ether was distilled off under reduced pressure. The mixture was fractionated through a ten-inch column containing glass helices. First fraction: 19 g. of almost pure benzylamine; b.p. 73°, 10–12 mm. Second fraction: 24.5 g. of benzylaminoacetal (62%); b.p. 117°, 1–2 mm.

Indole-2-carboxylic acid. This compound was synthesized from diethyl oxalate and *o*-nitrotoluene in an over-all yield of 31%. The intermediate, 2-nitrophenylpyruvic acid, was reduced with alkaline sodium hydrosulfite solution (17).

PYRIDINDOLONE SYNTHESIS

Indole-2-carboxyacetalylbenzylamide (XXII), *5-carbethoxyaminoindole-2-carboxyacetalylbenzylamide* (XXIV), and *5-cyanoindole-2-carboxyacetalylbenzylamide* (XXVI). The acid chlorides of indole-2-carboxylic acid derivatives were prepared using the reagents in Table III. The thionyl chloride was a commercial grade purified with quinoline and linseed oil (5). The acid chlorides and benzylaminoacetal (two equivalents) were allowed to react in a suitable anhydrous solvent (ether for XXI and XXIV, chloroform for XVI). After an hour the solvent was removed at reduced pressure, ammonia water was added, and the resulting viscous liquid was mixed to induce solidification. Each amide was purified before being used in the cyclizing reaction.

2-Benzylpyrid[3,4-b]indole-1(2H)-one (XXIII), *2-benzyl-6-carbethoxyaminopyrid-[3,4-b]indole-1(2H)-one* (XXV), *and 2-benzyl-6-cyanopyrid[3,4-b]indole-1(2H)-one* (XXVII). The indole amide derivatives (XXII, XXIV, and XXVI) were dissolved in ethereal sulfuric acid (30 cc. of sulfuric acid in 90 cc. of dry ether) (10) and allowed to remain at room temperature for at least a day. During this time little or no solid material separated. Most of the ether was removed at reduced pressure and water and excess ammonia were added. The recovery of crude product in each case was nearly quantitative. The crude products from amides XXII and XXIV melted over a wide range and their ultraviolet absorption spectra suggested the presence of isomeric pyrazinoindolones (by comparison with the curves in Reference 10) in addition to the major pyridindolone component. The ultraviolet absorption spectrum of the crude product from XXVI did not differ from that of the purified specimen (Fig. 1). Color tests on the crude products with Ehrlich's reagent (prepared

for these tests from 1 gram of *p*-dimethylaminobenzaldehyde in 120 cc. of ethanol, to which was added 20 cc. of concentrated hydrochloric acid), indicated that only amide XVI gave a product free of pyrazinoindolone. The products XXIII, XXV, and XXVII gave no color with Ehrlich's reagent, which is supporting evidence that these have the pyridindolone structure.

All *ultraviolet absorption spectra* were obtained in purified ethanol (19) using a Beckman quartz spectrophotometer. The infrared spectrum of XXVII in Nujol dispersion was measured with a single-beam Perkin-Elmer recording infrared spectrophotometer, model 21.

SUMMARY

Several phenylhydrazones of ethyl pyruvate with strong electron-attracting substituents in the *para* position were cyclized with zinc chloride to indole derivatives. Because of the deactivating influence of the cyano substituent, the Reissert method was employed to obtain sufficient quantities of 5-cyanoindole-2-carboxylic acid.

One of the indole-5-carboxylic acids was used in the Curtius reaction to give indoles with an amino group attached directly to the benzenoid part of the molecule.

Three indole-2-carboxyacetalylbenzylamides containing a *meta*-directing (CN), an *ortho-para*-directing ($NHCO_2Et$), and no substituent in the 5-position of the indole were cyclized with acid. Two of the products were identified as pyridindolones by their ultraviolet absorption spectra and the third was also assigned a pyridindolone structure on the basis of its infrared spectrum.

2-Carbethoxy-5-cyanoindole and 2,5-dicarbethoxyindole have been found to undergo the Mannich reaction. Acid hydrolysis of 2,5-dicarbethoxy-3-dimethylaminomethylindole yielded the diacid amine hydrochloride, isolated as a dihydrate.

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