[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Synthesis and Infrared Spectra of Some Indole Compounds[1]

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Examination of the infrared spectra in the solid state of a number of indole compounds substituted in the pyrrole ring shows regularities in the 3200–3400 cm.$^{-1}$ (NH) region and in the 1610–1780 cm.$^{-1}$ (CO and COOH) region. Two effects were observed: (1) in each region the band appeared at a lower frequency for the 3-substituent as compared with the 2-substituent, and (2) electron-withdrawing groups in the 2- or 3-position shifted the NH vibration to lower frequencies and electron releasing groups shifted it to higher frequencies. Four new indole compounds were synthesized: 1,1′-oxalylbis(3-methylindole), bis(1-methyl-3-indolyl)glyoxal, ethyl 1-methylindole-3-carboxylate, and 1-methylindole-3-carboxylic acid. A compound previously assigned both the 2-indolyl diketone and 3-indolyl diketone structures was synthesized independently and shown to be the latter.

The molecular structures of a number of indole compounds have been examined by means of infrared spectral analysis; however, systematic studies reflecting the peculiarities of the indole nucleus are lacking. Of note in this direction is the contribution of Brown, Henbest, and Jones,[3] who listed the principal infrared bands of six indoles and generalized that the strong bands at 1410 and 1550 cm.$^{-1}$ in 2-methylindole and at 1090 cm.$^{-1}$ in 3-methyl- and 3-*n*-propylindole differentiate 2- and 3-alkylindoles. Snyder and Eliel[4] have reported infrared spectra for four indole compounds. Fuson, Josien, Powell, and Utterback[5] studied the NH stretching frequency of indole as a function of concentration in carbon tetrachloride and assigned the band at 3420 cm.$^{-1}$ to associated NH. Recently, Ballantine, *et al.*,[6] have reported that in 3-acylindoles, the NH band and the CO band occur at lower frequencies than for the corresponding 2-substituted compounds. The purpose of the present investigation was to examine more extensively the infrared spectra of indole compounds with the intention of extending the previous studies, particularly that of footnote 6.

Syntheses. Ethyl 1-methylindole-3-carboxylate was synthesized by the action of methyl iodide and ethanolic sodium ethylate on ethyl indole-3-carboxylate. Quantitative saponification gave 1-methylindole-3-carboxylic acid. Non-depression of the mixture melting point and the identity of their infrared spectra showed this sample and the one prepared from bis(1-methyl-3-indolyl)glyoxal by alkali fusion to be identical.

The action of oxalyl chloride upon indole at 37° gave indole-3-glyoxalyl chloride. The structure of this compound was incorrectly assigned by Giua[7] who first reported it in 1924. His proof was based upon fusion with potassium hydroxide which gave indole-2-carboxylic acid. This acid is somewhat unstable at the fusion temperature employed and rearrangement may have taken place during fusion. Thus, Ciamician and Zatti[8] oxidized skatale during fusion with potassium hydroxide, and obtained both indole-2- and indole-3-carboxylic acids, indicating carbon-carbon rupture. In 1954 Speeter and Anthony[9] firmly established the correct structure for indole-3-glyoxalyl chloride when (1) by ammonolysis and reduction with lithium aluminum hydride, tryptamine was obtained, and (2) by alcoholysis the acid chloride was converted to ethyl indole-3-glyoxylate, a compound known for some time.

The assignment of position of carbonyl attachment in bis(3-indolyl)glyoxal also has been a subject of controversy. In 1922 Sanna[10] first isolated this compound from the reaction of oxalyl chloride with indolylmagnesium bromide. This Grignard reagent is active only in the 1- and 3-positions. The assignment of structure as bis(2-indolyl)glyoxal was based upon analysis for the elements, fusion with potassium hydroxide, and oxidation with hydrogen peroxide to indole-2-carboxylic acid. In 1924, however, Majima and Shigematsu[11] repeated the work and criticized the assignment because they found that oxidative fusion with potassium hydroxide had given them indole-3-carboxylic acid. The experience of the latter authors was confirmed in the present study.

Bis(3-indolyl)glyoxal is an unexpectedly stable compound, remaining unreactive to a refluxing solution of potassium hydroxide in propylene glycol, to benzyl ketone under a wide variety of conditions,

(1) Taken from part of the thesis submitted to the Graduate Faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the M.S. degree, 1956.

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(3) J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 3174 (1952).

(4) H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, **70**, 1857 (1948).

(5) N. Fuson, M. L. Josien, R. L. Powell, and E. Utterback, *J. Chem. Phys.*, **20**, 145 (1952).

(6) J. A. Ballantine, C. B. Barrett, R. J. S. Beer, B. G. Boggiano, S. Eardley, B. E. Jennings, and A. Robinson, *J. Chem. Soc.*, 2227 (1957).

(7) M. Giua, *Gazz. chim. ital.*, **54**, 593 (1924).

(8) G. Ciamician and C. Zatti, *Ber.*, **21**, 1930 (1888).

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

(10) G. Sanna, *Gazz. chim. ital.*, **52 II**, 165 (1922).

(11) R. Majima and T. Shigematsu, *Ber.*, **57B**, 1449 (1924).

and to periodic acid. However, a positive carbonyl test is obtained with 2,4-dinitrophenylhydrazine. Absorption in the infrared at 3311 and 3425 cm.$^{-1}$ suggests that the compound may exist as an enolic ketone. Evidence presented here in support of the 3,3'-assignment, aside from inferences drawn from spectral analysis, is derived from a new synthesis based on the action of an equivalent amount of indolylmagnesium bromide upon indole-3-glyoxalyl chloride which gave a 93% yield of bis(3-indolyl)-glyoxal. Identity was proved by mixture melting point with a sample obtained from a repetition of the Sanna procedure and duplication of infrared spectra of the two samples.

EXPERIMENTAL[12]

General. All of the compounds were prepared and crystallized as indicated in Table 1. Many of the compounds were synthesized from indole or skatole, which were generously supplied by Norda Essential Oils and Chemicals Co., New York. Molecular weights were calculated from cryoscopic measurements in benzene using 0.300 g. of the compound in about 5 ml. of benzene. The procedure was checked for accuracy with benzophenone whose molecular weight was obtained within 5% on each of three successive trials.

1,1'-Oxalylbis(3-methylindole). 3-Methylindolylmagnesium bromide was prepared by adding a solution of skatole (36.1 g., 0.275 moles) in anhydrous ether (50 ml.) to ethylmagnesium bromide (0.275 moles) in anhydrous ether (300 ml.) under nitrogen in a 1 l. flask equipped with a stirrer, vertical water-condenser, and mercury valve. Following the evolution of ethane showed that one hour of reflux was required after addition for completion of the reaction. At 0°, oxalyl chloride (17.0 g., 0.134 mole) in anhydrous ether (50 ml.) was added dropwise. The mixture was refluxed for 1 hr. cooled, and decomposed by the slow addition of 5% sodium bicarbonate (200 ml.). After acidifying cautiously with 5% hydrochloric acid (250 ml.) with stirring, the aqueous layer was discarded and the ether solution was washed until neutral with water and dried over anhydrous sodium sulfate. After filtration, the ether was distilled, the residue was dissolved in acetone (Darco G-60), and recrystallized by the addition of water to incipient precipitation while hot. Another recrystallization from acetone (20 ml.) and water (10 ml.) gave the white product (10.1 g., 23.9%), m.p. 183.6–184.2° (λ_{min} 222 mμ, log ϵ 4.21; 281 mμ, log ϵ 3.91; λ_{max} 255 mμ, log ϵ 4.57; 306 mμ, log ϵ 4.10).

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86; mol. wt., 316. Found: C, 76.00; H, 5.02; N, 8.90; mol. wt., 297.

Boiling a small amount of the compound with 5% sodium hydroxide and chilling at 5° for a few hours yielded skatole, which was identified by melting point and mixture melting point with an authentic sample. The compound failed to give a hydrazone when warmed with methanolic 2,4-dinitrophenylhydrazine in the presence of hydrochloric acid. It failed to condense with benzyl ketone in ethanolic potassium hydroxide solution at room temperature or at reflux, conditions under which the compound saponifies. It also failed to condense with *o*-phenylenediamine after one hour's reflux in glacial acetic acid.

Bis(1-methyl-3-indolyl)glyoxal. Oxalyl chloride (6.3 g., 0.05 mole) in anhydrous ether solution (50 ml.) was added dropwise with stirring under nitrogen to a solution of 1-methylindole (13.1 g., 0.10 mole) in anhydrous ether (200 ml.) at room temperature in 2 hr. and allowed to stand overnight. After distilling the mixture to dryness at reduced pressure, the residue was dissolved in acetone (Darco G-60) and recrystallized by the addition of water to incipient precipitation while hot. The solution was cooled, filtered, and dried. Two further recrystallizations from benzene (150 ml.) gave a lustrous white compound (8.1 g., 51.2%), m.p. 268–269°.

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86; mol. wt., 316. Found: C, 76.02; H, 5.08; N, 8.90; mol. wt. 305.

The compound (160 mg.) proved completely unreactive when refluxed with benzyl ketone (100 mg.) and potassium hydroxide (20 mg.) for 4 hr. in propylene glycol (5 ml.), dilution with water returning the original material (150 mg.). The compound was insoluble in 5% hydrochloric acid; it gave an immediate red-brown precipitate with methanolic 2,4-dinitrophenylhydrazine and hydrochloric acid, but failed to react with an equivalent amount of *o*-phenylenediamine when refluxed for 1 hr. in glacial acetic acid.

The compound (1.00 g.) was fused with potassium hydroxide pellets (10.0 g.) in a nickel crucible at 200° for 0.5 hr. with frequent stirring. After cooling, the contents were dissolved in hot water (carbon), filtered, cooled, and brought up to *p*H 3 with 5% hydrochloric acid. Cooling and standing at 5° for 2 hr. gave a slightly red product which was washed with water and dried. Sublimation at 150° (1 mm.) gave a white compound (0.77 g., 69.6%), m.p. 205–206°. A mixture melting point was not depressed, and the infrared spectrum proved identical with that of 1-methylindole-3-carboxylic acid prepared below.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00; neut. equiv., 175. Found: C, 68.34; H, 5.40; N, 7.97; neut. equiv., 174 ± 3.

Ethyl 1-methylindole-3-carboxylate. Metallic sodium (0.100 g., 4.35 milligram atoms) was dissolved in ethanol (5 ml.) previously dried over sodium and distilled. After solution of the sodium was complete, ethyl indole-3-carboxylate (0.700 g., 4.35 mmoles) was added and the solution was refluxed for 15 min. After cooling, methyl iodide (3 ml.) was added. The solution, 15 min. later, was refluxed for 1 hr. and then distilled to dryness at reduced pressure. Ether and water were added for complete solution and the aqueous layer was discarded. The ether solution was washed with water, dilute hydrochloric acid, water again, and then dried over anhydrous sodium sulfate, filtered, evaporated, dissolved in warm ethanol (2 ml.), precipitated with water (2 ml.), and allowed to crystallize overnight at 5°. Filtration, air drying, and then sublimation at 100° (1 mm.) gave a white compound (0.710 g., 80%), m.p. 69.7–70.2°, insoluble in dilute hydrochloric acid.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89; sapon. equiv., 203. Found: C, 71.04; H, 6.33; N, 6.92: sapon. equiv., 204 ± 4.

1-Methylindole-3-carboxylic acid. Ethyl 1-methylindole-3-carboxylate (0.216 g.) was refluxed 4 hr. with 0.0995*N* sodium hydroxide (25.00 ml.), cooled, and titrated to the disappearance of phenolphthalein end point with 0.1030*N* hydrochloric acid (13.90 ml.), indicating the saponification equivalent reported above for the ester. Complete acidification precipitated the acid, which was filtered, air-dried, and sublimed as above to give the white compound (0.181 g., 98.4%), m.p. 205–206°.

Bis(3-indolyl)glyoxal. Indole-3-glyoxalyl chloride was prepared at −20° in 91% yield following the procedure of Giua.[7] It could be stored for short periods in a vacuum desiccator. A solution of indole (5.90 g., 0.05 mmole) in anhydrous ether (10 ml.) was added to ethylmagnesium bromide (0.05 mole) in anhydrous ether (200 ml.). Ethane was evolved for 1 hr. while the solution was refluxed after the addition was completed. The Grignard solution was cooled to −10° and the granular indole-3-glyoxalyl chloride (0.05 mole) was added all at once with efficient stirring and maintained at this temperature for 1 hr. The mixture was allowed to warm to room temperature and stand overnight. After the cautious addition of 200 ml. of cold 5% aqueous sodium

(12) All melting points are corrected.

bicarbonate with stirring, the mixture was filtered. The solids were distilled with steam to remove unreacted indole, filtered hot, air-dried, and then extracted with methanol in a Soxhlet apparatus for 6 hr. After filtering the methanol extract (250 ml.) (Darco G-60), water was added to incipient crystallization and the solution was cooled. Recrystallization of the precipitate from acetone-water (Darco G-60) gave the canary yellow product (13.4 g., 93%), m.p. 279–280°. (λ_{min} 237 mμ, log ε 4.24; 254 mμ, log ε 4.25; 288 mμ, log ε 3.98. λ_{max} 247.5 mμ, log ε 4.28; 266.5 mμ, log ε 4.27; 326 mμ, log ε 4.27.

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72; mol. wt., 288. Found: C, 75.45; H, 4.41; N, 9.13; mol. wt., 281.

A mixture melting point with the compound described by Oddo and Sanna[13] was not depressed, and the two infrared spectra were identical.

The compound proved completely unreactive when refluxed for 16 hr. with benzyl ketone and potassium hydroxide in propylene glycol, dilution with water returning the original material. An immediate precipitate was obtained from a methanolic solution of the diketone when treated with methanolic 2,4-dinitrophenylhydrazine and hydrochloric acid. The diketone is slightly soluble in aqueous 10% potassium hydroxide. It is unreactive in 16 hr. to periodic acid in 80% ethanol containing concentrated sulfuric acid at room temperature.

Ethyl indole-3-glyoxalate. Sample A was prepared by allowing indole-3-glyoxalyl chloride (1.1 g.) to dissolve in anhydrous ethanol (20 ml.) at 5° overnight. The mixture was warmed to 50° under a slow stream of nitrogen for a few minutes to complete solution of the ethyl ester. Water (5 ml.) was added, and the solution was allowed to cool slowly with final chilling to 0°. Filtration gave a lustrous white compound (0.6 g., 55%), m.p. 187°.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.11. Found; C, 66.81; H, 4.93.

Sample B was prepared by the procedure of Elks, Elliott, and Hems.[14]

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.11. Found: C, 66.00; H, 5.19.

Either sample, when heated with concentrated aqueous ammonia, gave indole-3-glyoxamide, m.p. 252°. A mixture melting point of the esters or of the amides gave no depression. An ethanol solution of either sample gave the same ultraviolet spectrum (λ_{min} 230 mμ, log ε 3.62; 262 mμ, log ε 3.98; 283 mμ, log ε 3.46. λ_{max} 256 mμ, log ε 4.00; 267 mμ, log ε 3.99; 322 mμ, log ε 3.99).

The forms of this ester are interconvertible. Recovery of ester after seven days from either solution by concentration at 40° and dilution with an excess of water, followed by filtration and air-drying, gave A.

If, in the preparation of A given above, periods of long heating at reflux or heating in the presence of hydrogen chloride were not avoided, B resulted. At times, samples were obtained that showed absorptions of both the spectra of A and B.

X-ray powder diagrams showed the two samples to be polymorphic. The major peaks and a qualitative estimate of their intensities are listed in Table I. Two different infrared spectra were found for those samples of the ester, and they are given more completely in Table II. Unfortunately no solvent could be found with sufficient transparency in the interesting carbonyl region, which would dissolve a suitable concentration of the keto-ester so as to give solution spectra.

Indole-2-carboxylic acid. Recrystallization of indole-2-carboxylic acid from benzene yields variously either of two polymorphic samples (see Table II). Further, on one occasion crystallization of the acid from a supersaturated solution in ethylene dichloride, the spectrum showed absorption frequencies characteristic of both samples.

TABLE I

X-RAY POWDER DIFFRACTION LINES (Cu Kα-λ = 1.5418)

Preparation A			Preparation B		
2θ	Distance	Intensity	2θ	Distance	Intensity
3i. Ethyl indole-3-glyoxalate					
7.7°	11.5 Å	Medium	7.0°	12.6 Å	Weak
9.0	9.8	Very strong	7.7	11.5	Very strong
14.5	6.10	Weak	9.6	9.2	Very weak
15.4	5.75	Very weak	14.4	6.14	Medium
15.9	5.57	Very weak	14.9	5.94	Medium
17.4	5.09	Weak	15.4	5.75	Strong
18.2	4.87	Medium	16.8	5.27	Weak
			18.4	4.82	Very weak
2c. Indole-2-carboxylic acid					
5.1°	17.3 Å	Strong	5.9°	15.0 Å	Strong
5.9	15.0	Weak	11.8	7.5	Medium
10.3	8.6	Medium	15.0	5.9	Weak
11.8	7.5	Weak	15.5	5.7	Very weak
19.0	4.67	Medium	16.4	5.4	Weak
19.6	4.53	Weak	17.2	5.15	Weak
20.3	4.37	Strong	25.2	3.53	Weak
22.9	3.88	Weak			
24.2	3.67	Medium			
25.0	3.56	Medium			

Indole-3-glyoxalic acid. This compound was prepared according to the procedure of Elks, Elliott, and Hems,[14] dried, and recrystallized from chlorobenzene (λ_{min} 229.5 mμ, log ε 3.68; 282 mμ, log ε 3.61. λ_{max} 256 mμ, log ε 3.99; 312 mμ, log ε 3.92).

Bis(3-indolyl)glyoxal monosodium salt. Metallic sodium (56 mg., 2 m-atoms), weighed under hexane, was added to dry methanol (2 ml.). Bis(3-indolyl)glyoxal (0.576 g., 2 mmoles) was then added and the solution was allowed to stand overnight under methanol vapor. The solution was distilled to dryness at 1-mm. pressure leaving an orange-yellow powder which was used for an infrared spectrum in a potassium bromide disk.

Potassium carboxylate salts—compounds 2a, 2b, 2i, 3e. Samples of these salts for infrared spectra in potassium bromide disks were obtained as in the preceding paragraph. A small weighed amount was mixed with a few milliliters of methanol and an equivalent quantity of alkali was titrated into the mixture. When solution was complete, the solvent was distilled to dryness at 1-mm. pressure at room temperature during 4 hr.

SPECTRA

Polar effects in infrared spectra are currently receiving increased attention.[15,16] The purpose of part of the present investigation is to present the results of examining the spectra of a variety of indole derivatives for regularities. Table III lists the

(13) B. Oddo and G. Sanna, *Gazz. chim. ital.*, **51 II**, 337 (1921).

(14) J. Elks, D. F. Elliott, and B. A. Hems, *J. Chem. Soc.*, 629 (1944).

(15) L. J. Bellamy and R. L. Williams, *J. Chem. Soc.*, 4294 (1957) and preceding papers.

(16) W. R. Vaughan and G. K. Finch, *J. Org. Chem.*, **21**, 1201 (1956).

TABLE II

INFRARED ABSORPTION FREQUENCIES[a]

2a.	Potassium 2-indolylcarboxylate	3425m; 3226w; 3240s; 1529m; 1410s; 1342m; 1330m; 1287w; 1237w cm^{-1}.
2b.	Potassium 3-indolylcarboxylate	3390m; 3257m; 1614vw; 1580w; 1549s; 1515m; 1490w; 1342w; 1331w; 1283w; 1240w cm^{1}
2j.	Potassium N-methyl 3-indolylcarboxylate	3257m; 1614vw; 1538s; 1508m; 1465s; 1429m; 1376m; 1350w; 1313m; 1242m cm^{-1}
3e.	Potassium 3-indolylglyoxalate	3367m; 3165w; 1623m; 1600s; 1511m; 1406m; 1348m; 1308w; 1244w cm^{-1}
2c-A	Indole-2-carboxylic acid	3413m; 1678s; 1577w; 1543m; 1408w; 1453s; 1342w; 1311m; 1263m; 1196w; 1151w; 1119w; 1103w; 937w; 833m; 775m; 749m; 736m
2c-B	Indole-2-carboxylic acid	3356m; 1709s; 1520m; 1441m; 1416m; 1348m; 1305w; 1238m; 1196s; 1163w; 1117w; 846w; 820m; 769s; 741m; 728m
3i-A	Ethyl indole-3-glyoxalate	3185s; 1733s; 1623s; 1587m; 1515m; 1493m; 1437s; 1403w; 1337w; 1316w; 1263s; 1236s; 1154m; 1147m; 1130s; 1094m; 1020m; 940m; 862m; 789m; 763s; 759m; 658m
3i-B	Ethyl indole-3-glyoxalate	3226s; 1724s; 1634s; 1618s; 1590w; 1506s; 1433s; 1401m; 1339w; 1314w; 1267s; 1241s; 1157w; 1130s; 1101w; 1020m; 1008m; 938m; 874m; 819s; 809w; 773m; 743s; 653m
4c.	Bis(3-indolyl)glyoxal	3425m; 3311s; 1623m; 1610s; 1515s; 1495w; 1468w; 1439s; 1416m; 1339w; 1311w; 1242s; 1185w; 1148w; 1136w; 1120s; 1103s; 1087m; 1010w; 874w; 821w; 784m; 779s; 759m; 747m; 735s
4d.	Bis(3-indolyl)glyoxal sodium	3367s; 1623m; 1595s; 1515s; 1460m; 1422s; 1395m; 1333w; 1307m; 1274m; 1241m; 1215m; 1167w; 1143w; 1117m; 1103m; 1087w; 1010w; 965w; 935w; 881m; 853m; 804w; 778s; 748s

[a] Intensity designations: s = strong; m = medium; w = weak.

data obtained for the NH and the CO regions for compounds in the solid state.

The NH region. Three conclusions may be reached from the data of Table III. The first is that the indoles unsubstituted in the 1-position absorb in the range 3425 to 3144 $cm.^{-1}$ This compares with the range reported previously,[5] 3472 to 3378 $cm.^{-1}$ The range reported by Ballantine, *et al.*,[6] for 3-acylindoles begins at slightly lower frequencies, i.e., 3135 $cm.^{-1}$ and that of Tanner[17] at 3020 $cm.^{-1}$. When the 1-position is substituted (1b, 2i, 2j, 2k, 4a, 4b) no band appears in this region. This observation has been made previously[18] for bis(2-pyrryl)glyoxal with absorption at 3340 $cm.^{-1}$ compared to bis(1-methyl-2-pyrryl)glyoxal which shows no band from 4000 $cm.^{-1}$ to 3300 $cm.^{-1}$ and for a number of indoles.[4,6,17] The NH region is also relatively free of CO overtone frequencies—an observation substantiated by the spectra of N-substituted carbonyl indoles (4a, 4b) and indole acids (1d, 2c, 2d, 2j).

The second conclusion is that the frequency at which the NH band appears is affected by the electronegativity of the substituent itself. As has been mentioned earlier, this was first observed by Ballantine on a more limited group of compounds. Thus, with electron-releasing groups the NH band is shifted to frequencies higher than the NH band of indole (1a, c, d, e, f). Electron-attracting groups shift the NH band to lower frequencies, as far as 3144 $cm.^{-1}$ for 3-indolealdehyde (3b).

The third observation is that for a given substituent placed in the 2- or in the 3-position, the one in the 3-position has a larger effect. Thus, the NH band in skatole appears at 3425 $cm.^{-1}$ while that for 2-methylindole is at 3401 $cm.^{-1}$. For an example of an electron-withdrawing group the NH band of indole-2-aldehyde appears at 3185 $cm.^{-1}$ and that for the 3-isomer at 3144 $cm.^{-1}$. Other examples are given in Table I.

Among indole compounds it is well known that polar effects are greater with the 3-substituent than with the 2-substituent. Thus, indole-3-carboxylic acid (K_a = 0.00056) is a weaker acid than indole-2-carboxylic acid (K = 0.0177). Electron release from the vinylogous nitrogen to the carboxylic group has been offered as the reason for the greater effect at 3. For the influence of substituents on the NH band compare 1e and 3e (CH_3); 2a and 2b (—COOK); 2c-A and 2c-B with 2d (—$COOCH_3$); 3a and 3b (—CHO).

The relative order of substituent effect on the NH absorption agrees also with that established by

(17) E. M. Tanner, *Spectrochim. Acta*, 9, 282 (1957).

(18) M. Litt, M. S. Thesis, Polytechnic Institute of Brooklyn, 1953.

TABLE III

PHYSICAL CONSTANTS AND INFRARED ABSORPTION FREQUENCIES (cm.$^{-1}$)

	Compound	M.P., °C. and Recrystallization Solvent	Ref.	N—H	COO	C=O
1 a.	Indole	52.5 Hexane	[a]	3390		
b.	1-Methylindole	[B.p. 115° (12/mm.)]	[b]	——		
c.	2-Hydroxymethylindole	76–77 Hexane and C Cl$_4$	[c]	3378		
d.	3-Indole-3-acetic acid	168 ethylene dichloride	[d]	3378	1706	
e.	2-Methylindole; Methylketole	62 hexane	[e]	3401		
f.	3-Methylindole; Skatole	96 hexane	[a]	3425		
g.	Indole-3-acetaldehyde		[3]			1705
2 a.	Potassium indole-2-carboxylate		[f]	3413	Table	
b.	Potassium indole-3-carboxylate		[f]	3390	Table	
cA.	Indole-2-carboxylic acid	206–207 Benzene	[c,13]	3413	1678	
cB.	Indole-2-carboxylic acid	206–207 Benzene	[g]	3356	1712	
d.	Indole-3-carboxylic acid	222 Aqueous acetone	[h]	3300	1642	
e.	Methyl indole-2-carboxylate	151–152 Aqueous methanol	[h]	3300	1689	
f.	Methyl indole-3-carboxylate	147–148 Aqueous methanol	[i,13]	3257	1669	
g.	Ethyl indole-2-carboxylate	125–126 Aqueous ethanol	[h]	3322	1695	
h.	Ethyl indole-3-carboxylate	124 Aqueous ethanol		3257	1669	
i.	Potassium 1-methylindole-3-carboxylate		[f]	——	Table	
j.	1-Methylindole-3-carboxylic acid	205–206 (Sublimed)	[f]	——	1639	
k.	Ethyl 1-methylindole-3-carboxylate	69–70 Aqueous Ethanol		——	1681	
3 a.	Indole-2-aldehyde	138 Ethyl ether	[j]	3185		1675
b.	Indole-3-aldehyde	198 Dilute ethanol	[k]	3144		1634, 1618
c.	Methyl 3-indolyl ketone	191 Ethanol	[l]	3165		1618
d.	Indole-3-glyoxalyl chloride	138 Ethyl ether	[g]	3236	1792	1629
e.	Potassium indole-3-glyoxalate		[f]	3367	Table	1631
f.	Indole-3-glyoxylic acid	224 Chlorobenzene	[13]	3226	1714	1621
g.	Indole-3-glyoxamide	252 Dilute ethanol	[g]	3425, 3257	1669	1621
h.	Methyl indole-3-glyoxalate	224 Methanol	[g]	3226	1736	1621
iA.	Ethyl indole-3-glyoxalate	187 Ethanol	[g]	3185	1733	1626
iB.	Ethyl indole-3-glyoxalate	187 Ethanol	[13]	3226	1724	1634, 1621
4 a.	Bis(3-methylindol-1-yl) glyoxal	183–184 Aqueous acetone	[f]	——	1689	
b.	Bis(1-methylindol-3-yl) glyoxal	268–269 Aqueous acetone	[f]	——		1623, 1610
c.	Bis(3-indolyl) glyoxal; 3,3-indil	279–280 Aqueous acetone	[f]	3425, 3311		1623, 1610
d.	Bis(3-indolyl) glyoxal monosodium salt		[f]	3367		1623, 1610

[a] Commercially available. [b] R. Stolle, *J. prakt. Chem.*, (2) **128**, 1 (1930); P. Julian, *J. Am. Chem. Soc.*, **71**, 3206 (1949). [c] W. J. Brehm, *J. Am. Chem. Soc.*, **71**, 3514 (1949). [d] C. Heidelberger, *J. Biol. Chem.*, **179**, 139 (1949). [e] L. Marion and C. W. Oldfield, *Can. J. Research*, **25B**, 1 (1947). [f] *Cf.* Experimental. [g] B. Oddo, *Gazz. chim. ital.*, **42I**, 361 (1912). [h] J. R. Johnson, R. B. Hasbrouck, J. D. Dutcher, and W. F. Bruce, *J. Am. Chem. Soc.*, **67**, 427 (1945). [i] A. Michael, *Ber.*, **38**, 2091 (1905). [j] W. I. Taylor, *Helv. Chim. Acta*. **33**, 164 (1950). [k] A. C. Shabica, E. E. Howe, J. B. Ziegler, and M. Tishler, *J. Am. Chem. Soc.*, **68**, 1156 (1946). [l] B. Oddo and L. Sessa, *Gazz. chim. ital.*, **41I**, 240 (1911).

Sutton from an analysis of dipole moment data.[19] Qualitatively, the shifts are in agreement with the Hammett sigma values[20] and the nuclear magnetic resonance shifts given by Gutowsky *et al.*[21] The comparison of the infrared shifts with the Hammett sigma values, which refer to rates of reaction or to equilibria, is strained since the sigma values involve a dependence upon the transition state. A better comparison would be the nuclear magnetic resonance spectra but too few are presently available.

For the two indole-2-carboxylic acids, the NH frequencies at 3413 cm.$^{-1}$ and 3356 cm.$^{-1}$ bracket that of indole, 3390 cm.$^{-1}$. The band at 3356 cm.$^{-1}$ may be a consequence of intermolecular hydrogen bonding, but that at 3413 cm.$^{-1}$ can be rationalized in terms of the *p*-activating effect COO$^-$ group toward nucleophilic substitution.[22] This hypothesis is in agreement with the similar shifts found in the indole carboxylic acid salts (2a, 2b). An alternative explanation may lie in association phenomena,[5] but concentration studies were not made in the present work.

Two different NH bands are evident in 3-indolylglyoxamide, 3427 and 3257 cm.$^{-1}$. The former may be assigned to the unaffected amidic hydrogen, while the latter is consistent with other imidic ring hydrogens.

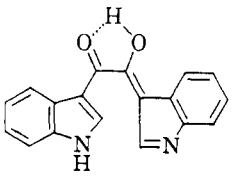
Of interest also are the two absorption frequencies in bis(3-indolyl)glyoxal at 3425 and 3311 cm.$^{-1}$. Models show that with the carbonyl groups cissoid or transoid there can be no intramolecular hydrogen bonding of NH to oxygen. However, tautomerism to a mono-enol would account for the two bands. The sequence of NH frequencies in the series given in Table IV (3-indolyl-CO-R) would tend to

(19) L. E. Sutton, *Proc. Roy. Soc. London*, **133 A**, 668 (1931); C. P. Smyth, *Dielectric Behavior and Structure*, McGraw-Hill Book Co., New York, 1955, p. 314.

(20) H. H. Jaffe, *Chem. Revs.*, **53**, 222 (1953).

(21) H. S. Gutowsky, D. W. McCall, B. R. McGarvey, and L. H. Meyer, *J. Am. Chem. Soc.*, **74**, 4809 (1952).

(22) J. F. Bunnett, R. J. Morath, and T. Okamoto, *J. Am. Chem. Soc.*, **77**, 5055 (1955).



support this conclusion, since normal indole-3-glyoxalic compounds have now been shown to exhibit NH absorption at frequencies about 3200 cm.$^{-1}$ which is considerably out of line with that occurring in (4c).

TABLE IV

R	Compound and Type	NH Frequencies
$-COOC_2H_5$	3i-A keto-ester	3185 cm^{-1}
	3i-B	3226
$-COOCH_3$	3h	3226
$-COOH$	3f keto-acid	3226
$-COCl$	3d keto-acid-chloride	3236
$-CONH_2$	3g keto-amide	3257
$-C(OH)=C-CH=N-Ph$	4c vinylogous keto-imine	3311

Two absorption bands also appear for 2-hydroxymethyl indole. The band at 3378 cm.$^{-1}$ is most likely NH while that at 3247 cm.$^{-1}$ is most likely hydroxyl.

The carbonyl region. The most striking feature of indole spectra in this region is the pronounced shift to lower frequencies which accompanies conjugation with the indole nucleus. Compare, for instance, compounds 2d, 2f, 2h, 2j, and 2k which have carboxyl groups attached directly to the 3-position in indole with compounds 1d, 3f, and 3g where the carboxyl group is separated from the ring by a CH_2 or a CO group (see also footnote 6).

As with the NH region the shift to lower frequencies is greater with 3-substituents than with 2-substituents. For example, see the isomeric aldehydes in Table III.

Carbonyl frequencies have previously been reported as low as 1637 cm.$^{-1}$ for *p*-hydroxyacetophenone and 1634 cm.$^{-1}$ for *p*-aminoacetophenone.[23] The carbonyl absorptions are seen to be restricted to a much narrower range—of the twelve indolealdehydes and ketones, all twelve have absorptions between 1675 and 1618 cm.$^{-1}$.

The absorption of indole-3-glyoxalyl chloride at 1792 cm.$^{-1}$ appears to be in order as do the absorptions of the two amides, compounds 3g and 4a, at 1669 and 1689 cm.$^{-1}$, respectively, while the glyoxalyl chloride also shows medium intensity absorption at 1605 and 1590 cm.$^{-1}$ in addition to carbonyl absorption at 1621 cm.$^{-1}$.

The infrared spectra for the four carboxylate salts are listed in Table IV for the range 3500 to 1250 cm.$^{-1}$. No attempt was made to avoid formation of hydrates and the medium band at 3250 cm.$^{-1}$ indicates their probable presence. One regularity is the medium absorption at 1529 cm.$^{-1}$ for the 2-derivative and 1515–1508 cm.$^{-1}$ for the 3-derivatives.

Bis(3-indolyl)glyoxal shows strong absorption at 1613 cm.$^{-1}$. Because of the unsaturation absorption which occurs in this region for all of the indoles, it is difficult to make a definite assignment. Assignments in this region have been given to $-C(OH)=NH$, the enol form of acetylurethan (w 1608 cm.$^{-1}$);[24a] the $Ph-C(-)=N$ in 2-phenyl-2-thiazoline (s 1605 cm.$^{-1}$),[24b] and the $CH_3-C(-)=N$ in 3,5-dimethylpyrazole (1595 cm.$^{-1}$).[24c] Although it thus appears feasible to assign the band at 1613 cm.$^{-1}$ in bis(3-indolyl)glyoxal to an enolic form, bis[1-methyl-3-indolyl)glyoxal also absorbs at 1610 cm.$^{-1}$ and here tautomerism is not possible.

Throughout this paper it has been noted that there is a greater conjugation with a substituent in the 3-position as compared with one in the 2-position. For pyrrole just the opposite has been observed.[25]

Limitations. Indoles in general may be classified as to solubility as those soluble in organic solvents, typified by indole and alkyl indoles, and those insoluble in organic solvents, typified by indoles with a strongly electron-attracting group in the 2- or 3-position. With the latter category it is not feasible to obtain infrared spectra in solution in solvents which do not themselves absorb in the critical NH and CO regions. Thus, the infrared study of indoles in solution in inert solvents where intermolecular interaction would be minimized compared with the solid state is strongly handicapped. For maximum utility, therefore, comparative infrared analysis has had to be made on indoles in the condensed phase.[26]

Examination of compounds in the condensed phase raises the question of the effect of concentration, and thus association, on the position of the absorption bands. Fuson *et al.*[5] have determined the effect of association for indole. Nevertheless, it was necessary to examine the compounds in the condensed phase. Since spectra in potassium bro-

(23) A. H. Soloway and S. L. Friess, *J. Am. Chem. Soc.*, **73**, 5000 (1951).

(24) H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, *Infrared Determination of Organic Structures*, D. Van Nostrand, New York, 1949, (a) p. 159, (b) p. 211, (c) p. 223.

(25) M. Scrocco and R. Nicolaus, *Atti accad. nazl. Lincei. Rend., Classe sci. fiz., mat. e nat.*, **22**, 500 (1957); *Chem. Abstr.*, **51**, 17455e (1957).

(26) After the work reported here had been completed Tanner[17] pointed up the difference between the spectra of some indoles in the condensed state and in solution. For example, he reports the NH stretching frequency for indole-3-aldehyde as 3140 cm.$^{-1}$ (Nujol) and as 3250 cm.$^{-1}$ (solution in tetrahydrofuran).

mide pellets often afford a degree of resolution comparable to that of solution spectra, in the present study such pellets were employed. It was found, as hoped, that gross effects of intermolecular interaction would be the same or regular and that the comparative study could be made. However, in the solid state different infrared spectra may be observed due to polymorphism, and, indeed, two such cases were found in the present study, namely, ethyl indole 3-glyoxalate and indole-2-carboxylic acid.

In conclusion it is hoped that the correlation of the greater shift for substituents in the 3- as compared to those for the 2-position will prove useful in assigning structure among indole compounds.

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Synthesis of 2-Azetidinones (β-Lactams)

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Eight *N*-substituted α-phenyl-β-amino acids, obtained by the addition of an amine to atropic acid, as well as a number of substituted β-amino acids, prepared by other procedures, were converted into 2-azetidinones. In some cases, esters of the acids were also employed. A useful method for the synthesis of certain 2-azetidinones was found to consist in the interaction of a β-amino acid chloride hydrochloride with dimethylaniline.

Hitherto, only one example of the addition of an amine, hydroxylamine, to atropic acid (α-phenylacrylic acid) has been reported; the reaction product was α-phenyl-β-aminopropionic acid.[3] Atropic acid can be obtained easily from tropic acid by a simple dehydration process.[4] Since tropic acid can now be synthesized readily,[5] it was feasible to prepare atropic acid in relatively large amounts and to study the addition of the following amines to this unsaturated acid: methyl-, allyl-, isopropyl-, cyclohexyl-, hexahydrobenzyl-, benzyl and β-phenylethylamine and aniline.[6] It was of interest to determine the extent to which the β-amino acids obtained (compounds 2, 4, 6, 8, 9, 10, 12, and 14, Table I) and their esters, as well as a number of additional β-amino acids and esters (Tables I and II) prepared by other procedures, could be employed for the synthesis of 2-azetidinones.

The β-amino acids, not obtained by the use of atropic acid, were synthesized in the following manner. Three β-amino acids were obtained by the addition of benzylamine to ethyl acrylate, methyl methacrylate and ethyl crotonate, respectively, and subsequent hydrolysis.

α - Methyl - β - phenyl - β - (benzylamino)-propionic and α,α-dimethyl-β-phenyl-β-(benzylamino)propionic acid were prepared by the alkaline hydrolysis of 1-benzyl-3-methyl-4-phenyl-2-azetidinone[7] and 1-benzyl-3,3-dimethyl-4-phenyl-2-azetidinone,[8] respectively.

β-Phenyl-β-aminopropionic acid was synthesized by interaction of benzaldehyde, malonic acid, and ammonium acetate.[9] This acid was converted into ethyl β-phenyl-β-aminopropionate which was then benzylated and hydrolyzed to yield β-phenyl-β-(benzylamino)propionic acid.[10] When ethyl β-phenyl-β-aminopropionate was hydrogenated and then benzylated, subsequent hydrolysis produced β-cyclohexyl-β-(benzylamino)propionic acid.

Ethyl cyclohexylcyanoacetate[11] was hydrogenated to form ethyl α-cyclohexyl-β-aminopropionate. The latter ester was converted into ethyl α-cyclohexyl - β - (benzylamino)propionate by treatment with benzyl chloride and also by interaction of the ester with benzaldehyde and hydrogenation of the resulting Schiff base. Hydrolysis of ethyl α-cyclohexyl-β-(benzylamino)propionate yielded the corresponding acid.

(1) Abstracted from the Ph.D. dissertation of W. A. Gould, University of Michigan, 1958.

(2) Lilly Endowment Incorporated Fellow.

(3) A. McKenzie and R. C. Strathern, *J. Chem. Soc.*, 82 (1925).

(4) H. S. Raper, *J. Chem. Soc.*, 2557 (1923).

(5) F. F. Blicke, H. Raffelson, and B. Barna, *J. Am. Chem. Soc.*, **74**, 253 (1953).

(6) In addition, α-phenyl-β-dimethylaminopropionic acid was prepared by the addition of dimethylamine to atropic acid.

(7) H. T. Clarke, J. R. Johnson, and R. Robinson, *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949, p. 973.

(8) H. Staudinger, H. W. Klever, and P. Kober, *Ann.*, **374**, 1 (1910).

(9) T. B. Johnson and J. E. Lovak, *J. Am. Chem. Soc.*, **58**, 299 (1936).

(10) R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.*, **71**, 2124 (1949).

(11) E. R. Alexander and A. C. Cope, *J. Am. Chem. Soc.*, **66**, 886 (1944).