Table I refer only to metrazol-induced convulsions. The compounds are arranged in the order of increasing molecular weights. The maximum dosage employed was 500 mg./kg. At this level very few derivatives were entirely without activity. An appreciable number of the compounds gave complete protection against convulsive doses of metrazol to laboratory animals at a dosage of 125 mg./kg. of the drug, five rats being used at each dose level. It may be noted that in general the more active compounds are those containing either a hydrogen or a methyl as the nitrogen substituent. The α- or β-substituent may vary at least from methyl through butyl. Alkyls higher than butyl were not included in this study.

Acknowledgment.—Pharmacological studies were made by Dr. Graham Chen, Mr. Charles Ensor and Miss Ruth Portman. Analytical data were determined by Mr. C. E. Childs, Miss Virginia Pawlik and Mrs. Geraldine Koch of this Laboratory.

Experimental

α-Butyl-α-methylsuccinic Acid (VI, R_1 = methyl, R_2 = butyl, R_3 = H).—Several of the substituted succinic acids were prepared by the following method. To 121 g. (0.62 mole) of ethyl α-cyano-β-butyl-α-methylacrylate, prepared by the method of Cope, *et al.*,[8] from butyl methyl ketone and ethyl cyanoacetate, and 200 ml. of 50% ethanol was added 65 g. (1.0 mole) of potassium cyanide. The mixture was heated on a steam-bath until a clear solution was formed. After cooling, the solution was diluted with 500 ml. of water and made acid to congo red with 12 *N* hydrochloric acid. An oil precipitated which was removed before extraction of the aqueous layer with 250 ml. of ether. The organic fractions were combined and washed with 100 ml. of water, two 100-ml. portions of saturated sodium bicarbonate solution and finally 100 ml. of water. After the ether solution was dried over anhydrous magnesium sulfate and concentrated on a steam-bath, the residue was distilled *in vacuo*, b.p. 141–145° (2.3 mm.), yield 80 g. (58%).

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: N, 12.61. Found: N, 12.46.

Eighty grams (0.36 mole) of the ethyl α,β-dicyano-β-methylheptanoate and 400 ml. of 12 *N* hydrochloric acid were refluxed together for 20 hours. After cooling, the oily layer was removed, dissolved in an excess of 10% aqueous sodium hydroxide, charcoaled and filtered. On acidification of the filtrate an oil was obtained which solidified after standing several days. The product was recrystallized from ether; m.p. 91–93°, yield 40 g. (59%).

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.44; H, 8.51. Found: C, 57.40; H, 8.66.

α,α-Diethyl-β-methylsuccinic Acid (VI, R_1 = R_2 = ethyl, R_3 = methyl).—This acid has been prepared[12] previously, but the yield is improved substantially by the procedure described below.

To a solution of 91 g. (0.5 mole) of ethyl α-cyano-β,β-diethylacrylate[8] in 200 ml. of 95% ethanol was added 32.5 g. (0.5 mole) of potassium cyanide. The mixture was heated on a steam-bath until a clear solution was formed and then cooled to 25°. Seventy-one grams (0.5 mole) of methyl iodide was added. After refluxing for 4 hours the mixture was stirred with 400 ml. of water. The oil was separated and the aqueous layer extracted twice with 100-ml. portions of ether. The combined organic fractions were dried over anhydrous magnesium sulfate, concentrated on a steam-bath then distilled *in vacuo;* b.p. 178–179° (22 mm.), yield 75 g. (67%).

Sixty-seven grams (0.3 mole) of the α,β-dicyano-α-methyl-β,β-diethyl propionate was mixed with 150 ml. of concentrated sulfuric acid, 75 ml. of glacial acetic acid and 75 ml. of water and refluxed for 16 hours. The solution was cooled and mixed with 600 g. of chipped ice. The oil which formed was removed and the aqueous layer extracted twice with 200-ml. portions of ether. Concentration of the combined organic fraction gave a residue which was dissolved in an excess of 10% aqueous sodium hydroxide. After extracting with 100 ml. of ether, charcoaling and filtering the aqueous filtrate was acidified to congo red with 12 *N* hydrochloric acid. The oily product solidified on standing and was recrystallized from ethyl acetate by the addition of petroleum ether. The white crystalline product melted at 99–102°, yield 35 g. (62%).

α-Butyl-α-ethylsuccinimide (II, R = R_3 = H, R_1 = butyl, R_2 = ethyl).—The following procedure is typical for the preparation of the succinimides listed in Table I.

Ten grams of α-butyl-α-ethylsuccinic acid was added portionwise to a flask containing 15 ml. of concentrated ammonium hydroxide. The contents of the flask were heated until the internal temperature was 200°. The cooled residue was dissolved in ether, charcoaled and filtered. Dilution of the filtrate with petroleum ether produced the imide in the form of a white, crystalline solid.

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(12) J. Colonge and D. Joly, *Ann. chim.*, **18**, 286 (1943).

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE RICHARDSON CHEMICAL LABORATORY OF TULANE UNIVERSITY]

Metalation of Indole, N-Methylindole and N-Phenylindole with n-Butyllithium[1a]

BY DAVID A. SHIRLEY[1c] AND PHILIP A. ROUSSEL[1b]

RECEIVED AUGUST 25, 1952

Action of excess *n*-butyllithium on indole followed by carbonation with solid carbon dioxide gave only N-indolecarboxylic acid in 61% yield. There was no evidence of C-metalation under a variety of experimental conditions. N-Methylindole was metalated in the 2-position in 78% yield. N-Phenylindole with excess butyllithium showed evidence of dimetalation through the isolation of a dicarboxylic acid, probably 1-(2′-carboxyphenyl)-2-indolecarboxylic acid, and a cyclic ketone probably derived from the same dilithio compound. Both of the products represented a yield of dimetalation of about 55%. Reaction products of some of the lithioindole derivatives with a variety of reagents are reported.

The metalation of indole and certain of its derivatives with *n*-butyllithium was undertaken to provide information concerning the position of attack by this organometallic compound. As has been shown in the past, principally by Gilman and coworkers, introduction of a lithium atom into heterocyclic nuclei usually involves a position not attacked in ordinary electrophilic substitution processes. This has provided a useful technique in heterocyclic chemistry.

The reaction of indole with Grignard reagents gives an >N–MgX type which has been studied extensively by Oddo and co-workers[2a] and Majima and co-workers.[2b] Carbonation of this substance

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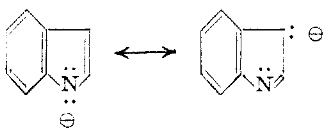
(1) (a) Presented before the Seventh Southwest Regional Meeting of the American Chemical Society, Austin, Texas, Dec. 7, 1951. (b) Eli Lilly and Co. Research Fellow, 1951–1952. Now at E. I. du Pont de Nemours and Co. Jackson Laboratory, Deepwater, N. J. (c) Department of Chemistry, University of Tennessee, Knoxville, Tenn.

(2) For example see (a) B. Oddo and G. Sanna, *Gazz. chim. ital.*, **51**, II, 337–342 (1921) (*C. A.*, **16**, 1423 (1922)); (b) R. Majima and M. Kotake, *Ber.*, **55B**, 3865 (1922).

at room temperature gives the 1-carboxylic acid but reaction with a variety of other substances such as ketones, acid halides and pyridine yield the corresponding 3-substituted types. The formation of 1- or 3-substituted types seems to be somewhat temperature dependent since carbonation at higher temperatures gives the 3-acid.[3]

Treatment of indole with a slight excess of *n*-butyllithium and carbonation by pouring over solid carbon dioxide gave 1-indolecarboxylic acid in 61% yield. We attempted to introduce a second lithium atom by the use of fourfold excesses of organometallic compound, reaction temperatures up to the reflux temperature of *n*-butyl ether and reaction times up to 48 hours. In no case was there any evidence of C-metalation as indicated by carbonation. This is in sharp contrast to the behavior of phenothiazine or carbazole[4] in which there is first replacement of the N–H bond with an N–Li bond and then metalation in good yield in the position ortho to the nitrogen atom. This lack of reactivity of N-lithioindole toward *n*-butyllithium would appear to be due to stabilization of the anion (Ia ⟷ Ib), a situation which would be less likely in the N-lithiocarbazole, for example, since structures corresponding to Ib would involve higher energy quinoid forms in one of the adjacent benzene rings.



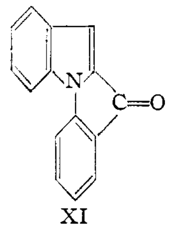
Ia Ib

In view of the failure of indole to undergo C-metalation, we next tried N-methylindole which contains no imino-hydrogen atom. This compound metalated smoothly in 78% yield in the 2-position as determined by the amount of 1-methyl-2-indolecarboxylic acid (III) obtained by carbonation. The structure of this acid was proved by its identity to the product of Fischer indole synthesis from the α-methyl-α-phenylhydrazone of pyruvic acid (IV) as shown in the accompanying diagram.

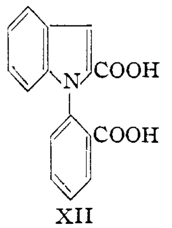
The metalation of N-methylindole in the 2-position provides a new example of the fact that heterocyclics frequently metalate with *n*-butyllithium in positions not reached by other substitution reactions. Indole and its N-alkyl and N-acyl derivatives monosubstitute in the 3-position practically without exception. Furthermore, we see here an additional example of the tendency of metalation to involve a position adjacent to the hetero atom.

N-Methyl-2-lithioindole was allowed to react with a variety of reagents as shown in the accompanying diagram.

The metalation of N-phenylindole provided some unexpected results. Reaction with a 4 to 5 molar excess of *n*-butyllithium followed by carbonation in the usual manner gave two products. The first product was shown by analysis and neutralization equivalent to be an N-phenylindoledicarboxylic acid. It was formed in only 12–15% yield. The second product, formed in about 40% yield, was a neutral ketone. Analyses and molecular weight determination on the ketone and analysis of its oxime showed a composition corresponding to XI. We believe that the ketone XI probably has the structure shown and that the dicarboxylic acid also formed has the structure XII. These products would result from the dimetalation of N-phenylindole in the 2- and 2′-positions. The formation of the larger proportions of ketone XI under normal conditions of carbonation is not unexpected in view of some results by Gilman and Van Ess.[5] They showed that relative yields of benzophenone and benzoic acid formed in the carbonation of phenyllithium could be influenced between wide limits by control of the relative amounts of organometallic and carbon dioxide present at the time of reaction. A large excess of organometallic favored ketone formation while a large excess of carbon dioxide favored acid formation. In the carbonation of 2,2′-dilithio-1-phenylindole, ketone formation would be favored even in the presence of large excesses of carbon dioxide, since after reaction of one lithium atom with a molecule of carbon dioxide, an intramolecular reaction with the remaining lithium atom has a greater probability than an intermolecular process involving another carbon dioxide molecule.



XI



XII

There remains however the proof of the structure of the ketone and dicarboxylic acid. We attempted an independent synthesis of the ketone XI by ring closure of 1-phenylindole-2-carboxylic acid chloride with a variety of Friedel–Crafts catalysts. However, we were unable to obtain any product corresponding to a cyclic ketone. This route was inherently difficult because of the sensitivity of the indole nucleus to strong Lewis acid types. There are only two positions of substitution on the N-phenylindole structure which would allow the ready ring closures to a cyclic ketone. These are the 2,2′-positions and the 6,2′-positions. Metalation in the 6-position is considered highly unlikely in view of the well-established greater activity of the pyrrole ring of indole compared with the benzene ring and the high yield of metalation in the 2-position of N-methylindole.

The dimetalation of aromatic types with *n*-butyllithium under ordinary conditions is rather rare. The highly reactive thiophene nucleus, for example, shows no tendency toward dimetalation under mild conditions.[6] 9-Phenylcarbazole, structurally related to our 1-phenylindole, however, dimetalates[7] readily both lithium atoms entering the 9-phenyl group in the two ortho positions.

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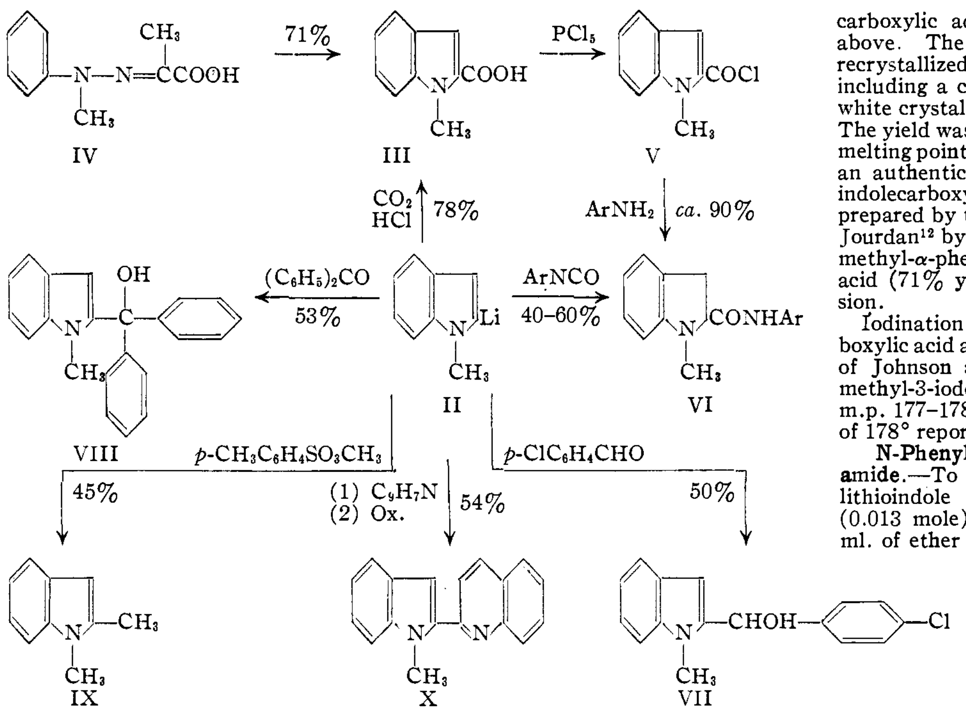
(3) B. Oddo, *Gazz. chim. ital.*, **42**, 1, 361 (1912) (*C. A.*, **6**, 2234 (1912)).

(4) (a) H. Gilman, D. A. Shirley and P. R. Van Ess, THIS JOURNAL, **66**, 625 (1944); (b) H. Gilman and R. H. Kirby, *J. Org. Chem.*, **1**, 146 (1936).

(5) H. Gilman and P. R. Van Ess, THIS JOURNAL, **55**, 1258 (1933).

(6) H. Gilman and D. A. Shirley, *ibid.*, **71**, 1870 (1949).

(7) H. Gilman and C. G. Stuckwisch, *ibid.*, **65**, 1729 (1943).



Acknowledgment.—The authors would like to acknowledge the aid of the Eli Lilly and Company of Indianapolis in the form of a research grant to Tulane University.

Experimental[8]

1-Indolecarboxylic Acid.—To a solution of n-butyllithium[9] (0.1 mole) in 70 ml. of ether was added slowly a solution of 9.4 g. (0.08 mole) of indole in 20 ml. of ether. After a two-hour reflux period the mixture was poured over a slurry of excess crushed solid carbon dioxide in dry ether. After evaporation of carbon dioxide, the mixture was hydrolyzed by addition of excess water. The ether layer was separated and extracted with two 10-ml. portions of water. The combined aqueous layers were acidified with concentrated hydrochloric acid and the precipitated white solid recrystallized twice from ethanol. The acid weighed 7.8 g. (61%) and melted with decomposition at 107–108°. Oddo[10] gives 108° as the melting point of 1-indolecarboxylic acid.

1-Methylindole.—The procedure given below was the best method found after a study of various reaction conditions. A mixture of 25 g. (0.22 mole) of indole, 41.0 g. (0.22 mole) of methyl p-toluenesulfonate, 23.3 g. (0.22 mole) of anhydrous sodium carbonate and 75 ml. of xylene was heated under reflux with stirring for 90 hours. The mixture was cooled, filtered and the filtrate washed with 20 ml. of ether. The combined xylene filtrate and ether wash was dried over calcium chloride and distilled. There was obtained about 20 g. (70%) of 1-methylindole, b.p. 78–79° at 2.0 mm. pressure. This product was contaminated with varying amounts of unreacted indole which was largely eliminated by redistillation with a 10–20% loss in yield.

A picrate derivative prepared by mixing ethereal solutions of 1-methylindole and picric acid melted at 148–150°, reported[11] 150°.

1-Methyl-2-indolecarboxylic Acid (III).—1-Methylindole (6.55 g. or 0.05 mole) dissolved in 25 ml. of anhydrous ether was added to a solution of n-butyllithium prepared from 27.4 g. (0.20 mole) of n-butyl bromide and the resulting mixture stirred and heated to reflux for eight hours. The resulting green solution was carbonated and the crude carboxylic acid isolated as described above. The crude carboxylic acid was recrystallized twice from 90% ethanol including a charcoal treatment to give white crystals melting at 207.5–208.5°. The yield was 6.8 g. or 78%. A mixed melting point between this material and an authentic specimen of 1-methyl-2-indolecarboxylic acid, m.p. 207–208°, prepared by the method of Fischer and Jourdan[12] by the ring closure of the α-methyl-α-phenylhydrazone of pyruvic acid (71% yield), showed no depression.

Iodination of 1-methyl 2-indolecarboxylic acid according to the procedure of Johnson and co-workers[13] gave 1-methyl-3-iodo-2-indolecarboxylic acid, m.p. 177–178°, compared with a value of 178° reported by Johnson.

N-Phenyl-1-methyl-2-indolecarboxamide.—To a solution of 1-methyl-2-lithioindole prepared from 1.77 g. (0.013 mole) of 1-methylindole in 70 ml. of ether was added cautiously 6.4 g. (0.054 mole) of phenyl isocyanate dissolved in 40 ml. of ether. The resulting mixture was stirred and heated under reflux for one hour. Absolute ethanol (25 ml.) was added and the mixture stirred for thirty minutes after which it was poured into 100 ml. of cold water. The ether layer was separated and the residue after evaporation of ether recrystallized three times from 85% ethanol using a charcoal treatment on the last recrystallization. There was obtained 1.4 g. (42%) of amide, m.p. 170–170.5°.

Anal. Calcd. for $C_{16}H_{14}N_2O$: N, 11.19. Found: N, 11.00, 11.01.

The use of ethanol for treatment of the reaction mixture prior to hydrolysis was found to be an effective method of removing the excess phenyl isocyanate. The ethyl N-phenylcarbamate formed with ethanol was removed by recrystallization much more easily than the N,N'-diphenylurea formed from water treatment.

N-α-Naphthyl-1-methyl-2-indolecarboxamide.—This compound, m.p. 191–192°, was formed according to the above procedure using α-naphthyl isocyanate. Recrystallization of the product was from acetone and the yield was 52%.

Anal. Calcd. for $C_{20}H_{16}N_2O$: N, 9.32. Found: N, 9.18, 9.21.

N-(p-Methoxyphenyl)-1-methyl-2-indolecarboxamide.—Prepared as above in 40% yield the product melted at 152–153°.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: N, 10.00. Found: N, 10.15.

N-(o-Tolyl)-1-methyl-2-indolecarboxamide.—Prepared as above in 63% yield the product melted at 172.5–173°.

Anal. Calcd. for $C_{17}H_{16}N_2O$: N, 10.60. Found: N, 10.71, 10.79.

1-Methyl-2-indolyl-(p-chlorophenyl)-carbinol (VII).—To a solution of 1-methyl-2-lithioindole, prepared from 5.0 g. (0.038 mole) of 1-methylindole, in 70 ml. of ether was slowly added a solution of 5.62 g. (0.04 mole) of p-chlorobenzaldehyde in 30 ml. of ether. After a 1-hour reflux period, 50 ml. of water and 30 ml. of 10% hydrochloric acid were added. The ether layer was separated, dried and the solvent evaporated. The residue was recrystallized three times from ethanol including one charcoal treatment to give 5.2 g. (50%) of white crystal, m.p. 135–136°.

Anal. Calcd. for $C_{16}H_{14}ClNO$: N, 5.16. Found: N, 5.26.

1-Methyl-2-indolyldiphenylcarbinol (VIII).—The reaction of benzophenone with 1-methyl-2-lithioindole as de-

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(8) All melting points were determined on a Fisher melting point apparatus and are uncorrected.

(9) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, THIS JOURNAL, **71**, 1499 (1949).

(10) B. Oddo and L. Sessa, *Gazz. chim. ital.*, **41**, I, 234 (1911) (*C. A.*, **5**, 2638 (1911)).

(11) L. Marion and C. W. Oldfield, *Can. J. Research*, **25B**, 1 (1947).

(12) E. Fischer and F. Jourdan, *Ber.*, **16**, 2241 (1883).

(13) J. R. Johnson, R. B. Hasbrouck, J. D. Dutcher and W. F. Bruce, THIS JOURNAL, **67**, 423 (1945).

scribed above gave a viscous oil which resisted crystallization. The oil was precipitated three times by cooling its solution in petroleum ether (b.p. 35-60°). A yield of 2.5 g. (53%) was obtained.

Anal. Calcd. for $C_{22}H_{19}NO$: N, 4.47. Found: N, 4.31.

1-Methyl-2-(2'-quinolyl)-indole (X).—A solution of 1.6 g. (0.012 mole) of quinoline in 20 ml. of ether was added to a solution of 1-methyl-2-lithioindole, prepared from 1.5 g. (0.0114 mole) of 1-methylindole, in 70 ml. of ether. The mixture was refluxed and stirred for one hour, cooled and hydrolyzed with 20 ml. of water. After stirring for 10 minutes, 3 ml. of nitrobenzene was added to oxidize the intermediate dihydro compound, and the mixture was stirred and refluxed for 30 minutes. The ether layer was separated, dried and the ether removed by distillation. The residual semi-solid was extracted five times with 15-ml. portions of warm 10% hydrochloric acid and the combined extracts made alkaline with 10% sodium hydroxide. The precipitated solid was recrystallized twice from 95% ethanol with one charcoal treatment to give 1.5 g. (54%) of light yellow crystals melting at 174.5–175.5°.

Anal. Calcd. for $C_{18}H_{14}N_2$: N, 10.85. Found: N, 10.43, 10.92.

1,2-Dimethylindole (IX).—A solution of 22.7 g. (0.122 mole) of methyl *p*-toluenesulfonate in 40 ml. of ether was added to a solution of 1-methyl-2-lithioindole, prepared from 8.0 g. (0.061 mole) of 1-methylindole, in 200 ml. of ether. A large quantity of solid precipitated during the addition and the mixture was stirred and refluxed for 1.5 hours during which 75 ml. of ether was added in order to keep the mixture sufficiently fluid. Excess water was added cautiously and the ether layer was separated and distilled. A fraction boiling at 85–92° at 1.2 mm. pressure was collected and this solidified into a colorless solid, m.p. 54–55°. Marion and Oldfield[11] report 1,2-dimethylindole to melt at 56°. The yield was 4.0 g. or 45%.

A picrate derivative melted at 123–124.5°. The literature value[12] is 125°.

1-Methyl-2-indolecarboxamide.—1-Methyl-2-indolecarboxylic acid (3.48 g. or 0.019 mole) was converted to the acid chloride[13] and to it was added 75 ml. of cold concentrated ammonia solution. The resulting mixture was held at 80° for 30 minutes. The solid was filtered off and recrystallized from 95% ethanol to give 3.42 g. (98%) of amide, m.p. 170–171°.

Anal. Calcd. for $C_{10}H_{10}N_2O$: N, 16.08. Found: N, 15.95, 16.01.

Treating the acid chloride with aniline gave N-phenyl-1-methyl-2-indolecarboxamide identical in melting point and mixed melting point with that prepared earlier from 1-methyl-2-lithioindole and phenyl isocyanate. The yield was 70%.

Metalation of 1-Phenylindole.—1-Phenylindole was prepared by the method of Fischer and Hess[14] by the ring closure of the diphenylhydrazone of pyruvic acid followed by decarboxylation of the resulting 1-phenyl-2-indolecarboxylic acid. The over-all yield was around 20–25%.

To a solution of 0.06 mole of *n*-butyllithium in 60 ml. of ether was added 2.0 g. (0.0104 mole) of 1-phenylindole in 10 ml. of ether. The mixture was stirred and refluxed for 12 hours during which it turned a characteristic orange color. After carbonation and hydrolysis in the usual manner, the ether layer was separated, washed with two portions of water and treated as described below.

The aqueous layer and the water washes were combined and acidified with hydrochloric acid. Acidification caused separation of a liquid phase which was separated, dried, and allowed to stand at room temperature for 48 hours. The resulting semi-solid was dissolved in dilute base, treated with charcoal and reprecipitated with acid. The resulting white solid was recrystallized from methanol to yield crystalline acid, m.p. 240–241° dec. The product weighed 0.43 g. corresponding to 15% of 1-(*o*-carboxyphenyl)-2-indolecarboxylic acid (XII).

Anal. Calcd. for $C_{16}H_{11}NO_4$: N, 4.98; neut. equiv., 140. Found: N, 5.01; neut. equiv., 144.

The ether layer above was evaporated and the orange solid remaining was recrystallized twice from ethanol using charcoal to give 0.90 g. of yellow-orange needles, m.p. 169–170.5°. This represents a 42% yield of compound corresponding to the ketone XI.

Anal. Calcd. for $C_{15}H_9NO$: C, 82.17; H, 4.14; N, 6.39; mol. wt., 219. Found: C, 82.12, 82.03; H, 4.34, 4.44[15]; N, 6.42, 6.47; mol. wt. (Rast), 217, 220.

An oxime derivative of the ketone was prepared according to the vigorous oximation procedure of Bachmann and Boatner.[16] The product melted at 235.5–237.5° dec.

Anal. Calcd. for $C_{15}H_{10}N_2O$: N, 11.97. Found: N, 12.21.

N-Phenyl-1-phenyl-2-indolecarboxamide.—A solution of 1-phenyl-2-indolecarboxylic acid chloride (prepared from 1.14 g. or 0.005 mole of acid) in 50 ml. of chloroform was mixed with a solution of 10 ml. of aniline in 10 ml. of chloroform. After a 30-minute reflux period, the solvent was distilled off and the residue triturated with 10% hydrochloric acid and then washed thoroughly with water. The residue was recrystallized three times from ethanol using charcoal to yield 1.24 g. (80%) of the anilide, m.p. 168.5–169°.

Anal. Calcd. for $C_{25}H_{16}N_2O$: N, 8.98. Found: N, 9.09.

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(14) E. Fischer and O. Hess, *Ber.*, **17**, 559 (1884).

(15) Carbon and hydrogen analyses by Gallbraith Analytical Laboratories, Knoxville, Tenn.

(16) W. E. Bachmann and C. H. Boatner, THIS JOURNAL, **58**, 2097 (1936).