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The Carbonylation and Hydroformylation Reactions with Certain Indole Derivatives[1]

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The reaction of carbon monoxide at elevated pressures and temperatures with the N-potassium salts of various 2- and 3-substituted indole derivatives has been investigated. The results indicate that the indole carbonylation reaction, as it is termed, can be used to prepare 3-indolecarboxaldehydes provided the 2-position is not too hindered sterically or substituted with electron-withdrawing groups. A new compound, N-formylindoline was prepared and found to have formylating properties. Indole and substituted indoles presumably because of their aromatic character have been found to react in the hydroformylation reaction either by being reduced to dihydro-derivatives or not at all.

A previous paper[2] has shown that 3-indolecarboxaldehyde can be prepared by reaction between carbon monoxide and potassium indole under pressure. The present paper records the results of the carbonylation reaction as well as the hydroformylation reaction with certain other indole derivatives.

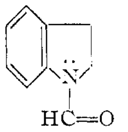
Carbonylation.—When substitution reactions are carried out on indole or substituted indoles, the entering group usually attacks the pyrrole ring. In view of this general unreactivity of the benzene portion of indole, attempts to extend the carbonylation reaction were limited to those indoles having substituent groups in the pyrrole ring. Since the nitrogen must be unsubstituted to allow salt formation, the following 2- or 3-substituted indoles were prepared by known methods: 2-methylindole, 2-phenylindole, 2-*p*-tolylindole, 2-(*p*-methoxyphenyl)-indole and 3-methylindole. Addition of each to the stoichiometric amount of potassium amide in liquid ammonia gave the corresponding potassium salt. The potassium salt in dimethylformamide was treated with carbon monoxide under the conditions (135–150° and *ca.* 490 atm. resp.) which had proved optimum for the case of potassium indole.[2]

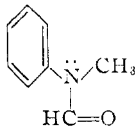
Of the compounds mentioned above, 2-methylindole gave 2-methyl-3-indolecarboxaldehyde in 56% yield. Both 2-*p*-tolylindole and 2-(*p*-methoxyphenyl)-indole showed some evidence of reacting with carbon monoxide, the reaction products giving positive tests with 2,4-dinitrophenylhydrazine reagent. However no products pure enough to be analyzed or characterized were isolated. None of the other compounds gave evidence of aldehyde formation and each was recovered from its respective reaction mixture in amounts representing 85% or higher of the starting material.

These results can be explained partially by a consideration of the electronic and steric effects of the substituent groups. It would be expected that salt formation with its introduction of possible anion centers at positions 1 and 3 in indole would tend to outweigh any contributions of electron-releasing effects from the substituent groups. However, electron-attracting groups, or substituents which allow the spreading of negative charge could lower the electron density of the pyrrole ring sufficiently to prevent an electrophilic attack by carbon monoxide. Apparently the latter effect is operating in the case of the 2-phenyl derivatives of indole; the *p*-substituted members being electron releasing tend to reverse the electron-sink effect, at least enough to allow a small amount of carbonyl-containing compounds to be formed. On the other hand, the inductive and steric effects of the methyl group in 2-methylindole being relatively small the yield obtained is essentially that from indole[2] itself. The negative result with 3-methylindole can be attributed to the blocking of the reactive 3-position and to the unlikelihood of carbanion formation at position-2.

That no N-formylated products were isolated is probably due to the great ease of hydrolysis of *N-formylindoles*, together with their tendency to isomerize to the 3-derivatives at moderate temperatures. This is in contrast to N-formylindoline which was prepared in good yield from potassium indoline and carbon monoxide using indoline as solvent. The structure of this new compound was established by analysis, by alkaline hydrolysis to yield indoline and by an independent synthesis from formic acid and indoline in toluene. Melting points of the compound prepared by either method were the same and showed no depression on mixing.

The similarity of structure of N-formylindoline to N-methylformanilide suggested the use of the former in the N-methylformanilide synthesis of 3-indolecarboxaldehyde.[3] A 24% yield of 3-indolecarboxaldehyde was obtained using N-formylindoline as a formylating agent for indole.





Hydroformylation.[4]—There appear to be no reports of the hydroformylation reaction with nitrogen heterocycles. Since bases[5] are reported to suppress the hydroformylation reaction, only neutral nitrogen heterocycles were considered for trial (indole and substituted indoles). A less compelling, though supporting, reason for the choice is that indole is the only nitrogen heterocycle that has been formylated using *carbon monoxide*. The indoles tried were indole, N-methylindole, N-phenylindole, N-acetylindole, 2-methylindole, 2-phenylindole and 3-allylindole.

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(1) Submitted by J. T. S. to the Temple University Graduate Council in partial fulfillment of the requirements for the Ph.D. degree.

(2) F. T. Tyson and J. T. Shaw, THIS JOURNAL, **74**, 2273 (1952).

(3) A. C. Shabica, E. E. Howe, J. B. Ziegler and M. Tishler, *ibid.*, **68**, 1156 (1946).

(4) For a review of the hydroformylation reaction see "Unit Processes in Organic Synthesis," McGraw-Hill Book Co., Inc., New York, N. Y., 1952, p. 555.

(5) I. Wender, R. Levine and M. Orchin, THIS JOURNAL, **72**, 4375 (1950).

Of these compounds only indole and 3-allylindole gave any drop in pressure under hydroformylating conditions conductive to aldehyde formation: that is, a mild temperature (*ca.* 130°), an initial pressure (at room temperature) of 231 atm. of synthesis gas[6] and the presence of dicobalt octacarbonyl. The drop in pressure for indole and 3-allylindole was 45 and 90% of theory, respectively. However no new characterizable compounds were isolated in either case; 44% of the initial indole was recovered but none of the 3-allylindole. In the case of the 3-allylindole, the use of ethyl orthoformate to convert any aldehyde formed to the acetal was tried without success. This procedure has had considerable success in the isolation and stabilization of labile aldehydes.[7] That almost all of the 3-allylindole reacted, as was evidenced by the drop in pressure, indicated that the dicobalt octacarbonyl catalyst was not inactivated by the nitrogen system. In the low temperature (130°) reactions dicobalt octacarbonyl was used while at the higher temperature (*ca.* 180°) cobalt acetate was used as a catalyst. The latter is converted *in situ* to dicobalt octacarbonyl at elevated temperatures.

Since dicobalt octacarbonyl was not inactivated by the indole nucleus, it was of interest to determine whether reduction would take place under "reducing" conditions (180°) of the hydroformylation reaction. Inasmuch as the true catalyst of the reaction is a strong acid, cobalt hydrocarbonyl, it was necessary to use indoles which have shown some resistance[8] to attack by acids; therefore, 2-methylindole and 2-phenylindole were tried. Both of these compounds were reduced to their corresponding 2,3-dihydro-derivatives in 26 and 9% yield, respectively. These results are in accord with what might be expected from the relationship[9] between aromatic character and the type of reaction that occurs when an unsaturated molecule is treated with carbon monoxide and hydrogen in the presence of a cobalt catalyst.

Experimental[10]

Equipment.—Unless otherwise noted the pressure reactions were carried out in an Aminco autoclave #406-35 BX3, of 120-ml. capacity, fabricated with 18-8 stainless steel with standard heater and shaker assembly.

General Considerations.—The preformed dicobalt octacarbonyl used in the hydroformylation reactions carried out under mild conditions (130°) was prepared from either Raney cobalt[11] or cobalt(II) carbonate.[12] The yields were 15 and 39%, respectively. A benzene solution of the dicobalt octacarbonyl was kept in and dispensed from a Pyrex pressure bottle with a stopcock as described by Adkins.[12] After a particular batch of catalyst had been prepared, its activity was always tested by trying it on cyclohexene or ethyl crotonate. The negative experimental results mentioned previously, which will not be reported below and which involved the use of such preformed dicobalt octacarbonyl, cannot therefore be attributed to a faulty catalyst.

2-Methyl-3-indolecarboxaldehyde.—To a 120-ml. autoclave was added 16.9 g. (0.1 mole) of potassium 2-methylindole dissolved in 50 ml. of dry dimethylformamide. The potassium 2-methylindole was prepared from potassium amide and 2-methylindole[13] in the same general fashion given for the preparation of potassium indole in a previous paper.[2] The autoclave was then purged several times with 40.8 atm. of carbon monoxide and then filled with carbon monoxide to 415 atm. at 20°. After shaking for 5 minutes to allow equilibrium to be attained, the observed pressure was 402 atm. The temperature was increased to 150° while shaking and was held there ±2° for 4 hr. On cooling to room temperature, the observed drop in pressure was 40.8 atm. (1.01 moles). The contents of the autoclave, an orange solution, were diluted with 1 liter of water and steam distilled. The oil present in the steam distillate solidified after the mixture was chilled in ice. Two grams of impure 2-methylindole melting at 52–55° was obtained after filtration of the steam distillate. The residue from the steam distillation was made neutral to litmus with glacial acetic acid, heated to boiling and filtered. The solids left on the filter paper were heated with 1 liter of boiling water and filtered; the process was repeated once more. From the combined filtrates on cooling, was obtained 8.2 g. of a yellow solid melting at 199–201°, which gave a voluminous red precipitate with 2,4-dinitrophenylhydrazine reagent. A recrystallization of this yellow solid from hot water using a little decolorizing carbon gave colorless needles melting at 201.5–202.5°. A picrate was made using a portion of these white needles and was found to melt at 181–182° dec. Boyd and Robson[14] give the melting point of 2-methyl-3-indolecarboxaldehyde and its picrate as 201–202° and 181° dec., respectively. It will be noted as was observed before,[2] that the mole drop in pressure was always greater than the moles of aldehyde obtained.

Under essentially the same general reaction conditions the potassium salts of 2-*p*-tolylindole and 2-(*p*-methoxyphenyl)-indole gave small amounts of reaction products which furnished positive tests with 2,4-dinitrophenylhydrazine reagent. No pure products could be isolated.

N-Formylindoline from the Carbonylation Reaction.—To a 120-ml. autoclave was added 15.7 g. (0.1 mole) of potassium indoline dissolved in 23.8 g. (0.2 mole) of indoline. The potassium indoline was prepared in the general way as indicated previously[2] from potassium amide and indoline.[15] The autoclave was then purged several times with 40.8 atm. of carbon monoxide, the temperature being 21°. After shaking the autoclave for 1 hour at 150°, it was cooled to 21°, the observed drop in pressure being 122 atm. (0.4 mole). The residual gases were vented and a red, tacky substance was found in the autoclave. This was treated alternately with 25-ml. portions of ether and water until completely removed. Three layers formed on standing. The ether and water layer were decanted away from the bottom layer which was a black viscous tarry material. The ether layer was distilled on the steam-cone and the residue, a brown oil was then fractionally distilled under vacuum. A forerun of indoline boiling at 80–85° under 2–3 mm. pressure and weighing 3.3 g. was obtained. The main fraction of material was collected at 123–125° under 2–3 mm. of pressure and solidified to a tan solid on standing at room temperature. Increasing the temperature above 123–125° gave no other products and decomposition of the tarry material in the flask took place. A considerable amount of decomposition products was left in the Claisen flask. The tan solid weighed 18.5 g. and had the odor of indoline. Recrystallization from 60–70° petroleum ether yielded 15.2 g. of long colorless needles melting at 62–63° which on admixture with a sample of N-formylindoline prepared by the formic acid azeotropic method showed no depression. Concentration of the petroleum ether filtrate afforded 1.3 g. more of the same material which melted at 61–62°; over-all yield 112% based on potassium indoline. Some of the indoline solvent must have been converted to potassium indoline during the course of the reaction to account for the yield being over 100%.

Anal. Calcd. for C_9H_7NO: C, 73.45; H, 6.16; N, 9.52; O, 10.87. Found: C, 73.39; H, 6.00; N, 9.54; O, 10.90.

Two grams of N-formylindoline was refluxed with 25 ml. of 5% aqueous potassium hydroxide for 30 minutes and an oil was formed. Isolation of the oil with ether followed by

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(6) CO:H_2, 1:1.

(7) P. Pino, *Gazz. chim. ital.*, **81**, 625 (1951).

(8) H. Fischer and K. Pistor, *Ber.*, **56**, 2313 (1923).

(9) I. Wender, M. H. Storch and M. Orchin, THIS JOURNAL, **72**, 4842 (1950).

(10) All melting points and boiling points are uncorrected.

(11) H. Adkins and G. Krsek, THIS JOURNAL, **70**, 383 (1948).

(12) I. Wender, H. Greenfield and M. Orchin, *ibid.*, **73**, 2656 (1951).

(13) C. F. H. Allen and J. VanAllen, *Org. Syntheses*, **22**, 94 (1942).

(14) W. J. Boyd and W. Robson, *Biochem. J.*, **29**, 555 (1935).

(15) F. E. King, J. A. Barltrop and R. J. Wetley, *J. Chem. Soc.*, **277** (1945).

evaporation of ether gave 1.5 g. of an oily substance possessing the odor of indoline. The picrate of the substance melted at 173–174°; the picrate of indoline[15] melts at 174°.

Preparation of N-Formylindoline by an Azeotropic Method.—A mixture of 60.6 g. (0.51 mole) of indoline, 48 g. of 92–93% formic acid and 1000 ml. of toluene was distilled slowly using a 3-foot indented column, and an azeotrope boiling at 87–88° was observed. The temperature then gradually rose to 108–110° and remained there during the rest of the distillation. Approximately 800 ml. of toluene was collected over a 10-hour period. Upon distillation of the residue, a forerun of 3 g. boiling at 80–114° under 2 mm. pressure was discarded and the main portion of 64.3 g. was collected at 115–117° under 2 mm. pressure. The distillate solidified on standing to a tan-colored solid but had a wet, shiny appearance and a slight odor of indoline. The entire 64.3 g. of crude N-formylindoline was recrystallized from 60–70° petroleum ether using a small amount of decolorizing carbon. Forty grams of N-formylindoline melting at 62–63° was obtained as a first crop. Concentration of the filtrates after filtering off the colorless needles yielded 10 g. more, the product melting at 61–62°; over-all yield 67%. A mixed melting point with N-formylindoline from the carbonylation reaction showed no depression.

Preparation of 3-Indolecarboxaldehyde using N-Formylindoline as a Formylating Agent.—A solution of 6 g. (0.0408 mole) of N-formylindoline and 60 ml. of ethylene dichloride was cooled to 0° and 6.3 g. (0.0408 mole) of phosphorus oxychloride was added with stirring. After stirring for 3 minutes, 4.0 g. (0.0342 mole) of indole was added and the solution was stirred for an additional 25 minutes at 0°. The ice-salt-bath was then removed and 7.08 g. (0.0708 mole) of calcium carbonate was added. The mixture was rapidly heated to reflux and maintained at this temperature for 30 minutes. During this time hydrogen chloride was evolved. The reaction mixture was cooled and a solution of 27 g. of sodium acetate in 27 ml. of water containing 5 g. of ice was added to the flask. The ethylene dichloride was removed by steam distillation. The residual solution was diluted to 400 ml., heated to reflux, treated with decolorizing carbon and filtered. The solids on the filter paper were extracted once more using 400 ml. of boiling water. The combined filtrates were allowed to crystallize. A pale-yellow product, I, was collected and allowed to dry in the air at room temperature. It weighed 2.4 g. and melted over the range 170–190°. One-tenth gram of I was refluxed with 10 ml. of aqueous 3% potassium hydroxide for 5 minutes and the odor of indoline was noted. The solution on cooling was made neutral to litmus with glacial acetic acid and on cooling the solution in ice, tan-colored needles formed. The solution was heated to reflux, treated with a very small amount of decolorizing carbon, filtered and the filtrate was chilled in ice. A very small quantity of white needles formed (enough only to take a few melting points) which after isolation and drying in an oven at 105° were found to melt at 193–195°. A mixed melting point with an authentic sample of 3-indolecarboxaldehyde showed no depression. The 2.3 g. of I remaining was treated in the same fashion and furnished 1.2 g. of 3-indolecarboxaldehyde melting at 193–195°, 24%.

2-Methylindoline.—Cobalt(II) acetate tetrahydrate was used in this reaction since it is more easily handled and at elevated temperatures is converted *in situ* to dicobalt octacarbonyl. Thirteen and one-tenth grams (0.1 mole) of 2-methylindole, 2.5 g. (0.01 mole) of cobalt(II) acetate tetrahydrate and 40 ml. of benzene was added to a 120-ml. autoclave. The autoclave was purged 3 times with 40.8 atm. of carbon monoxide and pressured first with carbon monoxide to 122 atm. and then with hydrogen to 244 atm., the temperature being 20°. After shaking for 5 minutes the equilibrium pressure attained was 231 atm. The autoclave was heated to 180 ± 5° within 40 minutes and held at this temperature for 4 hours, after which time the drop in pressure was insignificant. On cooling to 20° the observed drop in pressure was 45.9 atm. (approximately 57% of the theoretical).

The contents of the autoclave were centrifuged, the dark red liquid decanted from a small amount of solids, and benzene was removed by distillation at atmospheric pressure. The pressure was then lowered to 2.5 mm. and the residue was distilled rapidly. The 9 g. of distillate was redistilled at 2.5 mm. and separated into 3 fractions: A, 1.6 g., b.p. 71–78°; B, 3 g., b.p. 78–90°; C, 4 g., b.p. 117–121°.

Fraction C solidified on cooling and was recrystallized from aqueous methanol, crude melting point, 50–54°. Odor and its boiling point range indicated that it was probably recovered 2-methylindole. The recrystallized material melted at 56–57°, lit.[16] 56°.

Fractions A and B were combined and dissolved in 50 ml. of ether and extracted 5 times with 5-ml. portions of 5% hydrochloric acid. The ether layer, after drying over sodium sulfate and evaporation on the steam-bath, yielded 0.5 g. of the solid obtained in fraction C.

The combined acid extracts were neutralized with a solution of 10% sodium hydroxide and then extracted with three 20-ml. portions of ether. The ether solution was dried over sodium sulfate and distilled at atmospheric pressure. After removal of the ether on the steam-bath, the residue distilled at 225–227°, 3.5 g. The picrate from this liquid melted at 157–158°. Literature[17] values for the boiling point of 2-methylindoline and melting point of the picrate of 2-methylindoline are 227–230° and 158–159°, respectively. It was concluded that this liquid was 2-methylindoline and that 2-methylindole had undergone reduction rather than hydroformylation.

2-Phenylindoline.—Eleven and six-tenths grams (0.06 mole) of 2-phenylindole, 2.5 g. (0.009 mole) of cobalt(II) acetate tetrahydrate and 44 ml. of benzene were added to a 120-ml. autoclave. After carrying out the same operations of purging, pressuring and shaking for 5 minutes as have been indicated previously, the total pressure of 1:1 carbon monoxide and hydrogen was 252 atm. at 20°. The temperature was increased to 185 ± 5° within 30 minutes and was held at this temperature for 3 hours. On cooling the autoclave to 20° the observed drop in pressure was 20.4 atm. (*ca.* 25% of the theoretical). The contents of the autoclave were centrifuged and the clear red liquid was decanted away from a very small amount of dark colored solids.

The benzene in the red solution was removed by distillation on the steam-bath, a cobalt mirror forming on the wall of the flask. The residue was treated with 100 ml. of ether, stirred and heated on the steam-bath for a few minutes and filtered. The filtrate was extracted with three 30-ml. portions of 15% hydrochloric acid. The ether layer was distilled and the solid residue, 7 g., which turned a light-green color on drying in a vacuum desiccator melted at 165–172°.

On recrystallization from 95% ethyl alcohol, the white solid melted at 186–188°, mixed melting point with 2-phenylindole, 186–188°.

The acid layer was neutralized with a 10% solution of sodium hydroxide and the product isolated with ether. After removal of the ether by distillation, there was an oily residue weighing 1 g. The chloroplatinate derivative of the oil melted at 190–191° using a preheated bath. The chloroplatinate derivative[17] of 2-phenylindoline melts at 192° using a preheated bath. Thus, 2-phenylindole when it did react in the hydroformylation reaction also was hydrogenated rather than hydroformylated.

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[16] D. A. Shirley and P. A. Roussel, THIS JOURNAL, **75**, 375 (1953).

[17] H. Adkins and K. Coonradt, *ibid.*, **63**, 1563 (1941).