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THE SYNTHESIS OF SEVERAL METHYL α-METHOXYINDOLEACETATES RELATED TO THE NATURAL AUXIN, INDOLEACETIC ACID

W. REEVE, R. SUTER HUDSON and C. W. WOODS[1]
Chemistry Department, University of Maryland

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Abstract—A series of compounds closely related to methyl 3-indoleacetate have been prepared starting with an indole and oxalyl chloride, and proceeding through an acylated keto ester and hydroxy ester to the final α-methoxy ester. All of the α-methoxy esters had a high degree of activity when tested as plant-growth regulators, and the results obtained provide additional evidence that the presence of a side chain α-methoxy group in the arylacetate series increases translocation in plants in a very striking manner. The I.R. adsorption spectra of the compounds contain several unusual features, and these are discussed.

A SERIES of α-methoxyphenylacetic acids has been prepared[2] and many have a high degree of physiological activity as plant growth regulators.[3] Since it appeared that the substitution of the methoxy group into the side chain of arylacetic acids increases the physiological effectiveness and the translocatability of the latter compounds in plants, it was decided to prepare compounds related to the plant regulator, 3-indoleacetic acid, but with a methoxy group in the side chain.

Indole was treated with oxalyl chloride and then with methanol to form the known methyl 3-indoleglyoxylate (Ia) in 88 per cent yield. These reactions were found to occur in a satisfactory manner only if the ether solvent and the methanol were completely free of water. Traces of hydronium ion caused extensive indole polymerization whereas the methyl oxonium ion or the diethyl oxonium ion did not, even though present in high concentrations.

The keto ester (Ia) was acetylated with acetic anhydride and sodium acetate at steam bath temperature to form the N-acetyl derivative (IIa). The conditions are milder than those required to acetylate indole itself; the carbonyl group adjacent to the ring apparently facilitates the reaction. The carbonyl group could be reduced to the carbinol (IIIa) by either hydrogen in the presence of a palladium catalyst, or in somewhat better yield by means of freshly prepared aluminum amalgam suspended in moist ether. The methylation of the hydroxyl group was accomplished by Purdie's method with methyl iodide and silver oxide in yields which varied from 0–85 per cent depending upon the experimental conditions. To obtain the optimum yield, the silver oxide was prepared by adding a solution of sodium hydroxide in methyl alcohol to a slight excess of a concentrated silver nitrate aqueous solution. In this way, a more active silver oxide free of sodium hydroxide was obtained. A two or three hour reaction time at 20–25° for the methylation yielded the crystalline acetate in optimum yield; longer periods of time or higher temperatures caused the yield to decrease

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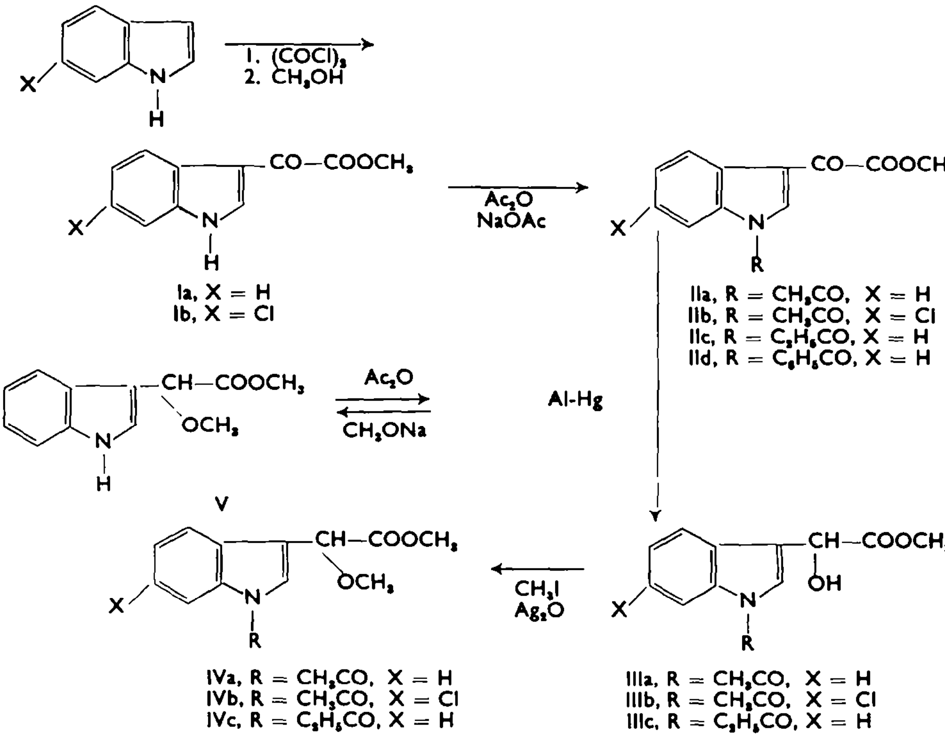
[1] Eastman Kodak Fellow, 1956–1957.

[2] W. Reeve and E. L. Compere, Jr., *J. Amer. Chem. Soc.* **83**, 2755 (1961) and earlier papers.

[3] J. W. Mitchell, B. C. Smale and H. W. Preston, *J. Agr. Food Chem.* **7**, 841 (1959).

drastically. The crystalline methyl N-acetyl-α-methoxy-3-indoleacetate (IVa) on treatment with an equivalent amount of sodium methoxide in methanol yielded the methyl α-methoxy-3-indoleacetate (V) in 68 per cent yield. In one experiment, this material was successfully reacetylated to yield crystalline IVa by refluxing with acetic anhydride and sodium acetate, but subsequent attempts to obtain the crystalline acetate (IVa) by this method were unsuccessful. The free acid was unstable. It could be obtained by hydrolyzing the ester (V) with sodium hydroxide in methanol at room temperature for 24 hours, and then acidifying with dilute hydrochloric acid. It was a colorless oil at first but changed to a dark red solid in about an hour and later completely resinified.



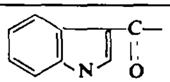
Prior to the development of the above synthesis, numerous alternative syntheses were tried with no success. Of particular interest is the fact that indole-3-aldehyde will not react with bromoform and methanolic potassium hydroxide, a method which has worked quite well with a number of aromatic aldehydes.[2]

In view of the potent plant growth regulating properties of the methyl N-acetyl-α-methoxy-3-indoleacetate (IVa), two related compounds were prepared. In one, the acetyl group on the indole nitrogen was replaced by a propionyl group; in the other, a chlorine atom was introduced into the benzenoid ring. The synthesis of the N-propionyl derivative started with the propionylation of the methyl 3-indoleglyoxylate and followed the same sequence of reactions as shown in the equations for the synthesis of the acetyl derivative. The propionyl group was introduced in 70 per cent yield by the use of propionyl chloride in pyridine. The ketone group was reduced in 83 per cent yield with aluminum amalagam, and the hydroxyl group was methylated in 92 per cent yield to give the methyl α-methoxy-1-propionyl-3-indoleacetate (IVc). Likewise, the benzoyl derivative IId was prepared, but subsequent reactions were unsuccessful.

The starting material for the chloro derivative was 6-chloroindole which was prepared from 4-chloro-2-nitrotoluene by the method of Rydon and Tweddle.[4] The subsequent synthesis followed the same sequence of reactions shown by the equations. The reaction with the oxalyl chloride occurred with even less difficulty from the formation of indole polymers, presumably because the chlorine atom stabilized the indole ring system. The acetylation, reduction, and methylation steps occurred in 59, 71, and 80 per cent yields, respectively.

Infrared Spectra. I.R. spectra were obtained on all of the compounds prepared; the data are summarized in Table 1.

TABLE 1. I.R. FREQUENCY ASSIGNMENTS FOR INDOLE COMPOUNDS, WAVENUMBERS, cm^{-1}[a]

Compound	Me Group of Ester	Ester Carbonyl	Keto Group	Amide Carbonyl	>N—H—O—H		 C=O	*o*-Disubst. Benzene
Ia	1425	1740	1630		3220			758
IIa	1450	1738	1675	1738			1540	765
IIIa	1458	1735		1720		3550		765
IVa	1460	1755		1720				753
V	1465	1750			3320			755
Ib	1415, 1445	1735	1630		3220			
IIb	1430, 1465	1735	1670	1735			1540	
IIIb	1435, 1470	1748		1720		3480		
IVb	1445, 1475	1765		1725				
IIc	1450	1730	1670	1730			1540	765
IIIc	1462	1740		1726		3420		752
IVc	1458	1760		1723				758
IId	1450	1738	1675	1715			1540	760

[a] Compounds were run both as Nujol mulls and as melts on a Beckman Infrared Spectrophotometer Model IR-5.

There are several unusual features in these spectra. Although three carbonyl groups are present in compounds IIa, IIb, IIc and IId, only two absorption bands in the carbonyl region were observed in the spectrum of compounds IIa, IIb and IIc. The lower of the observed frequencies was assigned to the ketonic carbonyl group, both because the band at 1630–1675 cm^{-1} consistently disappeared when the ketonic carbonyl group was reduced, and because there is an analogy with a series of similar compounds studied by Tanner.[5]

The designated ketonic carbonyl absorption frequencies of the unacylated indoles are below the range assigned to α,β-unsaturated ketones or α-keto esters and are above that assigned to α,β-unsaturated-β-amino ketones.[6] α,β-Unsaturated-β-amino ketones

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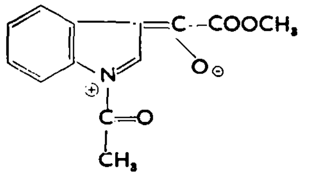
[4] H. N. Rydon and J. C. Tweddle, *J. Chem. Soc.* 3499 (1955).

[5] E. M. Tanner, *Spectrochim. Acta* **9**, 282 (1957).

[6] L. J. Bellamy, *The Infrared Spectra of Complex Molecules* pp. 132 and 184. John Wiley, New York (1958).

have a strong absorption band near 1540 cm^{-1},[7] as do all the keto amides examined here, and for a while it was thought that this might be the characteristic ketonic carbonyl absorption band. However, unlike α,β-unsaturated-β-amino ketones, compounds Ia and Ib were found to have near normal N-H stretching frequency. Finally, the assignment of the 1540 cm^{-1} band to a much lowered ketonic carbonyl frequency was precluded by the appearance of three other absorption bands in the carbonyl region of compound IId. Strong absorption near 1540 cm^{-1} in similar indole compounds has been observed[5] and attributed to a resonance mode of the fused ring system of indole, and the evidence obtained in this work seems to substantiate this finding.

The assigned amide carbonyl frequencies of the keto amides are higher (1735 cm^{-1} vs normal 1680 cm^{-1}) than that assigned to normal tertiary amides and are coincident with the ester carbonyl absorption in the case of compounds IIa, IIb and IIc. This high amide carbonyl frequency may be due to an increased positive charge on the indole nitrogen resulting from a contribution to the ground state of the molecule formulated as follows for compound IIa.



This would account for the rather low ketonic carbonyl frequency observed and the raised amide carbonyl frequency. The relatively low N-H stretching frequency of compound Ia and Ib seems to indicate a mesomeric shift in this direction since in compound V, where this shift is not possible, the N-H stretching frequency is normal.

All of the chloro substituted indoles have absorption bands at 642 cm^{-1}.

Physiological activity in plants. All of the compounds prepared were examined by Mitchell and Linder[8] of the U.S. Department of Agriculture. The methyl α-methoxy-3-indoleacetate (V) and all of the methyl N-acyl-α-methoxy-3-indoleacetates (IVa, b, c) were far more active than methyl 3-indoleacetate or 3-indoleacetic acid when application was made to the leaf of an intact bean plant and the angle of bending of the stem was measured. Under these conditions, translocation becomes of importance and all of the compounds with an α-methoxy group were very strikingly more readily absorbed and translocated than were methyl 3-indoleacetate or 3-indoleacetic acid. The most active compound was IVa with an α-methoxy group and an N-acetyl group. Replacing the N-acetyl group with a propionyl group gave compound IVc with somewhat reduced activity. Introduction of chlorine into the indole ring also resulted in reduced activity (IVb). Under test conditions where the measured response is not influenced appreciably by translocation, the activity of these materials appeared to be much closer to that of methyl 3-indoleacetate or 3-indoleacetic acid.

The above results made it of interest to examine methyl N-acetyl-3-indoleacetate to determine the physiological effect of an acetyl group in the absence of a side chain

[7] N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank and D. J. Wallace, *J. Amer. Chem. Soc.* **71**, 3337 (1949).

[8] J. W. Mitchell and P. J. Linder, *J. Agr. Food Chem.* **10**, 82 (1962).

methoxy group. It was found to have reduced activity relative to the unacetylated methyl 3-indoleacetate, and was much less active against bean plants than compound IVa with the methoxy group in the side chain.

In all cases, the α-hydroxy compounds (IIIa, b, c) had no activity, presumably because they were metabolized by the plant.

EXPERIMENTAL

All m.ps are corrected. Analyses are by Dr. F. J. Kasler.

Methyl 3-indoleglyoxylate (Ia). This preparation followed the procedure of Shaw *et al.*,[9] except the acid chloride was not isolated but was converted directly to the methyl ester by the dropwise addition of a three-fold excess of methanol (distilled from magnesium methoxide) to the reaction mixture. Precautions were taken to prevent the presence of traces of moisture in the apparatus and the solvents. The ether was freshly dried over phosphorus pentoxide and the methanol over magnesium methoxide. From 82 g indole and 100 g oxalyl chloride, there was obtained 124 g (85% yield crude material, m.p. 221–222°, suitable for the next step. After two recrystallizations from methanol, m.p. 230°, the highest reported value being 230–231°.[9]

Methyl 1-acetyl-3-indoleglyoxylate (IIa). The above glyoxylate (214 g), 300 ml acetic anhydride and 120 g sodium acetate were heated with stirring on a steam bath for 3 hr. After pouring onto crushed ice and air drying the precipitated product, 129 g (87% of theory) was obtained, m.p. 130–132° (Lit. value, 130°.[10]).

Methyl 1-acetyl-3-indoleglycollate (IIIa). This new compound was prepared by a modification of the procedure previously used with similar compounds[10] using aluminum amalgam.[11] Thirty grams of heavy duty aluminum foil ("Kaiser Foil") in 6" by 1" strips, loosely folded, was treated for 1 min with 10% sodium hydroxide solution and then washed by decantation with several portions of water and twice with absolute ethanol. It was then covered with a 2% aqueous mercuric chloride solution for 2 min, and the amalgamated aluminum washed with water, ethanol and finally anhydrous ether. It was stored under anhydrous ether and used within an hr. To use, it was placed in a 5-1, three-necked flask and stirred for 3 hr with 129 g methyl 1-acetyl-3-indoleglyoxylate dissolved in 2 l. anhydrous ether to which was added 20 ml water and 20 ml methanol. The mixture was filtered and the residue repeatedly extracted with warm acetone. The combined ether and acetone filtrates were evaporated, and the crystalline residue washed once with 100 ml cold ether and then recrystallized from 200 ml hot acetone. The yield of methyl 1-acetyl-3-indoleglycollate was 73 g, m.p. 121–123°, equivalent to 56% of theory. The analytical sample was recrystallized from benzene. (Found: C, 63·43; H, 5·56; N, 5·83; Calc. for $C_{13}H_{13}O_4N$: C, 63·15; H, 5·29; N, 5·67%).

Methyl 1-acetyl-α-methoxy-3-indoleacetate (IVa). This preparation followed the classical Purdie methylation procedure,[12] but the preparation of the silver oxide described below, was a critical factor. Ten grams of the methyl 1-acetyl-3-indoleglycollate, 20 g silver oxide, and 45 ml methyl iodide were stirred together for 4 hr at room temp in a flask equipped with a condenser fitted with a calcium chloride tube. The mixture was diluted with anhydrous ether, filtered, and the volatile material in the filtrate removed on a steam bath. On diluting the residual oil with 10 ml anhydrous ether and cooling and scratching in a salt-ice bath, white methyl 1-acetyl-α-methoxy-3-indoleacetate crystallized. After 30 min, it was filtered and washed with 5 ml cold ether. There was obtained 8·5 g, m.p. 58–59° (81% yield). Recrystallization once from absolute ethanol and once from ethyl acetate raised the m.p. to 60·5–61·5°, but the nitrogen and methoxyl analyses were slightly off. To purify the material, 2 g was reacetylated with 10 ml acetic anhydride and 2 g sodium acetate at the reflux temp for 3 hr. The material was isolated by pouring the mixture into ice and water. The oil was extracted into 20 ml ether, and the ether solution washed repeatedly with 5% sodium bicarbonate solution to remove the acetic acid. On concentrating the solution and cooling for 2 days at −15°, crystals formed, m.p. 59–60·5° after recrystallization from anhydrous ether. (Found:

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[9] K. N. F. Shaw, A. McMillan, A. G. Gundmundson and M. D. Armstrong, *J. Org. Chem.* **23**, 1177 (1958).

[10] J. W. Baker, *J. Chem. Soc.* **157**, 458 (1940).

[11] I. Vogel, *J. Chem. Soc.* 597 (1927).

[12] T. Purdie and W. Pitkeathly, *J. Chem. Soc.* **75**, 153 (1899); A. McKenzie, *Ibid.* **75**, 753 (1899).

C, 64·44; H, 5·88; N, 5·54; OCH_3, 23·54; Calc. for $C_{14}H_{15}O_4N$: C, 64·36; H, 5·79: N, 5·36; OCH_3, 23·76%).

The silver oxide used in this reaction was prepared by dissolving 8 g sodium hydroxide in 200 ml methanol, and adding this solution slowly and with stirring to a solution of 36 g silver nitrate in 50 ml water. It was filtered, washed with 50 ml methanol and several portions of ether, and then air dried. It was pulverized to pass through a 100 mesh screen and stored in a dark bottle until used.

Methyl α-methoxy-3-indoleacetate (V). Three grams of the acetyl derivative IVa was added to a sodium methoxide solution prepared from 0·262 g sodium and 20 ml dry methanol. After standing overnight, the reaction mixture was poured into 50 ml ice cold 1:1 hydrochloric acid, and the oil extracted with ether. The ether extract was washed with a sodium bicarbonate solution and water, then dried over magnesium sulfate, and the ether evaporated. There was obtained 1·7 g (68% yield) white crystalline material, m.p. 127–128·5°. Recrystallization from benzene and from ethyl acetate raised the m.p. to 129–130°. (Found: C, 65·82; H, 5·85; N, 6·78; OCH_3, 28·23; Calc. for $C_{12}H_{13}O_3N$: C, 65·74; H, 5·98; N, 6·39; OCH_3, 28·32%).

Methyl 6-chloro-3-indoleglyoxylate (Ib). This was prepared in the same way as compound Ia. From 10 g 6-chloroindole,[4] there was obtained 14 g glyoxylate (89% yield), m.p. 273–275° after 2 recrystallizations from acetone. (Found: C, 55·72; H, 3·47; N, 6·10; Calc. for $C_{11}H_8NO_3Cl$: C, 55·59; H, 3·39; N, 5·89%).

Methyl 1-acetyl-6-chloro-3-indoleglyoxylate (IIb). This was prepared in the same way as compound IIa except a sixty fold excess of acetic anhydride was used, and the mixture was refluxed for 45 min. The crude product was dissolved in boiling absolute ethanol and the solution decolorized with carbon On cooling, yellow needles (0·6 g; 51%), m.p. 133–134°, were obtained from 1·0 g Ib. (Found: C, 55·99; H, 3·66; N, 5·24; Calc. for $C_{13}H_{10}NO_4Cl$: C, 55·82; H, 3·60; N, 5·01%).

Methyl 1-acetyl-6-chloro-3-indoleglycollate (IIIb). This was prepared by the same procedure as compound IIIa except the reaction was complete in 20 min since a larger excess of amalgamated aluminum foil was used. For 1·0 g IIb, 1 g amalgamated aluminum was used, and 0·7 g (71% yield) white, crystalline glycollate was obtained, m.p. 132·5–133·5° after 2 recrystallizations from benzene. (Found: C, 55·50; H, 4·28; N, 5·27; Cl, 12·30; Calc. for $C_{13}H_{12}NO_4Cl$: C, 55·43; H, 4·29; N, 4·97; Cl, 12·59%).

Methyl 1-acetyl-6-chloro-α-methoxy-3-indoleacetate (IVb). Starting with 0·80 g glycollate IIIb, 15 ml methyl iodide, 2 g silver oxide and following the same procedure as described for IVa except for the reaction period being 2 hr, there was obtained 0·66 g (80% theory) white crystalline compound, m.p. 90–93°. This was purified by stirring with a small amount of ether so as to dissolve only a portion of the solid, and the mixture filtered. The filtrate, when cooled, deposited white crystals m.p. 93–94°. (Found: C, 57·10; H, 5·06; N, 4·69; OCH_3, 20·83; Calc. for $C_{14}H_{14}O_4NCl$: C, 56·86; H, 4·77; N, 4·74; OCH_3, 20·99%).

Methyl 1-propionyl-3-indoleglyoxylate (IIc). Twenty grams methyl 3-indoleglyoxylate (Ia) was reacted at 80° for 1 hr with 20 ml propionyl chloride dissolved in 200 ml pure pyridine. The hot solution was poured into 400 ml ice cold 1:1 hydrochloric acid, and the solid which separated was washed by thoroughly mixing with more hydrochloric acid solution, then with 5% sodium bicarbonate solution, and finally water. The moist product was recrystallized twice from acetone; 18 g (70% of theory) was obtained, m.p. 131·5–132·5°. An analytical sample was obtained by washing a benzene solution with 6 N hydrochloric acid to remove traces of pyridine, then with sodium bicarbonate solution and water. After drying the benzene solution and removing the solvent, the crystalline residue was crystallized 4 times from benzene using decolorizing carbon. The material then melted at 133·5–134°. (Found: C, 64·64; H, 4·88; N, 5·20; Calc. for $C_{14}H_{13}O_4N$: C, 64·86; H, 5·06; N, 5·40%).

Methyl 1-propionyl-3-indolegylcollate (IIIc). Starting with 16 g IIc m.p. 132°, 5 g aluminum amalgam, 500 ml anhydrous ether to which was added 10 ml methanol and 5 ml water, and following the previously described procedure with a 2 hr reaction time, there was obtained 13 g (83% yield), m.p. 120–122°. The analytical sample was recrystallized twice from benzene, but the m.p. was unchanged. (Found: C, 64·56; H, 6·05; N, 5·47; Calc. for $C_{14}H_{15}O_4N$; C, 64·36; H, 5·79; N, 5·36%).

Methyl α-methoxy-1-propionyl-3-indoleacetate (IVc). Starting with 2·0 g glycollate IIIc, 25 ml methyl iodide, 4 g silver oxide, and following the previously described procedure but with a reaction time of 2 hr, 1·95 g (92% yield) IVc, m.p. 97–100° was obtained. It was isolated by cooling the oil obtained, dissolved in 10 ml ether, to −70° and scratching the container. A small sample recrystallized twice from benzene melted at 99·5–100·5°. (Found: C, 65·68; H, 6·40; N, 5·00; OCH_3 21·92; Calc. for $C_{15}H_{17}O_4N$: C, 65·44; H, 6·22; N, 5·09; OCH_3, 22·50%).

Methyl 1-*benzoyl*-3-*indoleglyoxylate* (IId). Sixty grams methyl 3-indoleglyoxylate (Ia) was reacted at 80° for 1 hr with 58 ml benzoyl chloride dissolved in 500 ml pure pyridine. Methanol (15 ml) was added to destroy excess benzoyl chloride, and the reaction mixture was heated another ½ hr. The hot solution was poured into 400 ml ice cold 1:1 hydrochloric acid, and the solid filtered off. The filter cake, in a beaker, was washed repeatedly with cold 1:1 hydrochloric acid, sodium bicarbonate solution and water. The air dried material was recrystallized from 1200 ml acetone using decolorizing carbon and yielded 73 g (79% yield), m.p. 171·5–173·5°. The analytical sample was recrystallized twice from benzene, m.p. 172–173°. (Found: C, 70·08; H, 4·21; N, 4·75; saponification equiv., 158; Calc. for $C_{18}H_{13}NO_4$: C, 70·35; H, 4·26; N, 4·56%, saponification equiv., 154).

Methyl 1-*acetyl*-3-*indoleacetate*. Methyl 3-indoleacetate was prepared by the method of Jackson[13] by refluxing 0·75 g indoleacetic acid for 3 hr with 30 ml methanol containing a little hydrogen chloride. There was obtained 0·7 g yellow oil, b.p. 160° (bath temp) at 0·5 mm Hg. The oil could not be made to crystallize. The oil was acetylated by refluxing 0·6 g with 25 ml acetic anhydride and 2 g anhydrous sodium acetate for 4 hr. The reaction mixture was poured into ice water, the product extracted with ether, and the ether extract washed with sodium bicarbonate solution and then with water. The product was isolated by distillation yielding 100 mg, b.p. approx 150 at 0·5° mm Hg. (Found: OCH_3, 12·60; sapon. equiv., 122; Calc. for $C_{13}H_{13}O_2N$: OCH_3, 13·42%; sapon. equiv., 116).

After standing several weeks, the oil slowly began to crystallize. I.R. analysis of the solid product showed strong absorption at the following frequencies in cm^{-1}: 3000, 1750, 1710; 1460, and 750, A weak absorption peak appeared at 3420 cm^{-1}.

Acknowledgement—The authors wish to acknowledge the assistance of Dr. Ellis R. Lippincott, Dr. F. X. Powell and Mr. T. E. Kenny in obtaining and interpreting the I.R. spectra.

(13) R. W. Jackson, *J. Biol. Chem.* **88**, 659 (1930).