[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, AUBURN UNIVERSITY]

# Some Methyl Substituted 3-Indoleacetic Acids[1]

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The preparation of some methyl substituted 3-indoleacetic acids by the Fischer synthesis from substituted phenylhydrazones of ethyl β-formylpropionate and ethyl levulinate is described. The compounds prepared had methyl groups substituted in the following positions: 5-; 7-; 2,7-; 4,7-; 5,7-; 6,7-; 2,4,6-; 2,4,7-; 2,5,7-; and 2,6,7-.

Since the discovery of 3-indoleacetic acid as a naturally occurring plant growth hormone,[3] numerous substituted derivatives of this auxin have been synthesized in the hope of finding biological antagonists, and to study the effect of substitution on biological activity. The finding by Hitchcock[4] that a homolog of indoleacetic acid could simulate the activity of auxins led to the investigation of thousands of organic compounds and many were found that acted as plant growth regulators. Furthermore, many substances which themselves were not active, gave active compounds when proper substitutions were made in the parent molecule. Many hypotheses about the structural requirements for hormonal activity, and mode of action have been proposed.[5] The effect of substitution of halogen on the activity of 3-indoleacetic acid has been investigated,[6,7] but the tests were confined to monohalogen derivatives, a few dihalogen compounds, and a few trisubstituted derivatives of mixed function. In certain phytological tests[8] the activity of methyl substituted indoleacetic acids paralleled those of the corresponding halogen derivatives. A program was therefore initiated to synthesize a complete series of methyl substituted indoleacetic acids, in which all possible positions had been substituted with methyl groups. Such a series of compounds when subjected to phytological studies should give additional information on the mode of action of indoleacetic acid, the effect of polysubstitution on phytological activity, and the positions in the ring that cannot be substituted in order to retain auxin-like activity in the derivatives. In addition, these compounds or some of the intermediates used in preparing them should prove useful in the preparation of antagonists for other indole compounds of biological interest, such as tryptophan or serotonin.

Only seven of the possible sixty-two methyl substituted indoleacetic acids have been reported in the literature. These are the 1-methyl-,[9] 2-methyl-,[10] 5-methyl-,[11] 1,2-dimethyl-,[10] 2,5-dimethyl-,[12] 2,7-dimethyl-,[13] and 2,5,7-trimethyl-3-indoleacetic acids.[13] This paper deals with the preparation of some of the methyl substituted mono-, di-, and trimethyl substituted 3-indoleacetic acids that are unsubstituted in the one position. The ethyl esters of these acids can be made unambiguously by the Fischer synthesis[10] from the properly substituted phenylhydrazones of ethyl levulinate or ethyl β-formylpropionate. The new acids prepared were 7-methyl-, 4,7-dimethyl-, 5,7-dimethyl-, 6,7-dimethyl-, 2,4,6-trimethyl-, 2,4,7-trimethyl-, and 2,6,7-trimethyl-3-indoleacetic acids. The preparation of the 5-methyl derivative,[11] for which adequate laboratory directions are not found in the literature, is also described. Ethyl 2,7-dimethyl-3-indoleacetate was prepared from levulinic acid, absolute ethanol, *o*-tolylhydrazine hydrochloride, and sulfuric acid as catalyst (Fox-Bullock procedure).[14] Bullock and Hand[13] reported that they were unable to prepare this ester from ethyl levulinate *o*-tolylhydrazone by heating with alcoholic sulfuric acid; they used a much shorter reflux time than was presently employed. 2,5,7-Trimethyl-3-indoleacetic acid[13] was also prepared by way of the Fox-Bullock procedure.

Several different acid catalysts and procedures for ring closure of the hydrazones were used in the preparation of the new acids, and as our own and other workers' experiences in this field have shown, no general procedure could be found that gave good results for all of the compounds studied. Even when the same procedure was used for the preparation of closely related compounds, some

(1) This research was supported by a contract with the Chemical Corps, Fort Detrick, Md.

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(13) M. W. Bullock and J. J. Hand, *J. Am. Chem. Soc.*, **78**, 5852 (1956).

(14) S. W. Fox and M. W. Bullock, *J. Am. Chem. Soc.*, **73**, 5155 (1951).

modifications were necessary to insure a pure product. For the derivatives unsubstituted in the two position, fusion of the substituted phenylhydrazones of ethyl β-formylpropionate with anhydrous zinc chloride[15] generally gave the best results, while the Fox-Bullock procedure could not be used. The latter technique, however, proved quite adequate for the preparation of the trimethyl substituted compounds if position two is methyl substituted. In the preparation of ethyl 2,6,7-trimethyl-3-indoleacetate by the Fox-Bullock procedure, sodium 2,3-dimethylphenylhydrazinesulfonate was used instead of the hydrazine hydrochloride. The yield was approximately the same as when the hydrazine hydrochloride was used.

## EXPERIMENTAL

All melting points were taken on a Fisher-Johns apparatus and are uncorrected. The samples were introduced about ten degrees under the reported values.

*Substituted phenylhydrazine hydrochlorides.* These compounds were prepared by diazotizing the corresponding substituted aniline, and reducing the diazonium salt with stannous chloride using essentially the method of Meyer and Lecco.[16] The method of Stevens and Higginbotham[17] was used to purify the hydrochlorides. Sodium 2,3-dimethylphenylhydrazinesulfonate was prepared by the method of Altschul,[18] and portions were converted to the hydrochloride and free base for characterization.[19]

*Ethyl 5-methyl-3-indoleacetate* (I). *Method A.*[20] A hot solution of *p*-tolylhydrazine hydrochloride[21] (11.7 g., 74 mmoles), sodium acetate trihydrate (10.1 g., 74 mmoles), glacial acetic acid (16 ml.), and water (150 ml.) was added to a hot solution of ethyl β-formylpropionate (11.7 g., 90 mmoles) in water (100 ml.). A yellow oil gradually separated and solidified upon cooling. The solid was collected, washed with water, and dried in a nitrogen atmosphere under reduced pressure (water pump) over sulfuric acid. The dried ethyl β-formylpropionate *p*-tolylhydrazone[22] (14.3 g., 61 mmoles) was rapidly mixed with anhydrous zinc chloride (15 g.) and heated with stirring under reduced pressure (41 mm.) at 80° for fifteen minutes and then at 100° until the mixture solidified (two hours). The solid was distributed between ether (150 ml.) and 3N hydrochloric acid (150 ml.) by prolonged shaking. The acid layer was extracted three more times with ether (50 ml. portions), and the combined ether solution was washed thoroughly with sodium carbonate solution (10%) and with water. The ether solution was dried over magnesium sulfate and the ether was removed by distillation. The residue was distilled under reduced pressure with the major portion distilling at 125–160° (1 mm.). The oil solidified upon standing and gave 7.6 g. of crude product, which was washed with petroleum ether and recrystallized from methanol-water solution adjusted to the point of incipient cloudiness. The white solid obtained (5.3 g., 40%) melted at 58.5–60.0°.

*Anal.* Calcd. for $C_{13}H_{15}NO_2$: N, 6.44. Found: N, 6.75.

*Method B.* A solution of ethyl β-formylpropionate *p*-tolylhydrazone (5.2 g., 22.2 mmoles), absolute ethanol (170 ml.), and conc. sulfuric acid (20 ml.) was refluxed for 5 hr. The solution was cooled and poured into ice water (300 ml.) with stirring. The solution was extracted with four portions of ether (75 ml.). The combined ether solution was dried over magnesium sulfate and the ether was removed, the last under reduced pressure (water pump). The dark brown oil residue was distilled under reduced pressure to yield 1.9 g. (39%) of ester, b.p. 130–135° (1 mm.). The ester solidified upon standing. A small sample was recrystallized and melted at 58.5–60°; when mixed with the compound prepared by Method A, no depression of the melting point was observed.

*5-Methyl-3-indoleacetic acid* (II). *Method C.* Ethyl 5-methyl-3-indoleacetate (5.2 g., 23.9 mmoles) was refluxed with methanolic potassium hydroxide (10%, 70 ml.) for 5 hr. After cooling, water (50 ml.) was added and most of the methanol was distilled off under reduced pressure (water pump). Another 50 ml. of water was added and the solution was extracted with ether (three 25-ml. portions). The ether was discarded. The aqueous solution was boiled to remove dissolved ether and after cooling was acidified to *p*H 3 with hydrochloric acid (3*N*). A light brown solid (4.2 g.) separated, and was recrystallized, first from boiling water, and then from methanol-water to give light pink flakes, 2.53 g. (56%), m.p. 151–152.5° dec.. The reported m.p. is 151–152°.[11]

*Ethyl 7-methyl-3-indoleacetate* (III). *o*-Tolylhydrazine hydrochloride (15.0 g., 94.6 mmoles) was converted to 21.2 g. of crude ethyl β-formylpropionate *o*-tolylhydrazone and the indole ester by Method A. The major fraction of distillate (7.9 g.) was collected at 140–146° (0.5 mm.). The oil did not crystallize and was redistilled; 7.0 g. (35%) of the ester was obtained, b.p. 140–142° (0.15 mm.), $n_D^{20}$ 1.5663.

*Anal.* Calcd. for $C_{13}H_{15}NO_2$: N, 6.44. Found: N, 6.32.

*7-Methyl-3-indoleacetic acid* (IV). The above ester, (III), (7.0 g., 32 mmoles) was refluxed with methanolic potassium hydroxide for 2.5 hr., and the acid (IV) was isolated as in Method C except the solution was acidified to pH 2. A light pink solid (4.5 g.) was obtained and purified by dissolving in dilute sodium hydroxide, adjusting to *p*H 4, filtering, and then acidifying to *p*H 2. A light pink solid with m.p. 176–177° dec. was obtained. Recrystallization from methanol-water gave light pink flakes, 3.2 g. (52%), m.p. 181.5–183° dec.

*Anal.* Calcd. for $C_{11}H_{11}NO_2$: N, 7.40. Found: N, 7.86.

*Ethyl 4,7-dimethyl-3-indoleacetate* (V). 2,5-Dimethylphenylhydrazine[19] (20.0 g., 127 mmoles) was converted into ethyl β-formylpropionate 2,5-dimethylphenylhydrazone (26.5 g.) and cyclized to the ester (V) by Method A using a one-hour heating period. The major fraction of ester (V) distillate (b.p. 135–185° at 1 mm.) solidified upon standing and was recrystallized from methanol-water. The crystals were washed with petroleum ether; yield 12.5 g. (50%), m.p. 111–112°. A portion recrystallized from methanol gave a m.p. of 111.5–112.5°.

*Anal.* Calcd. for $C_{14}H_{17}NO_2$: N, 6.05. Found: N, 6.19. The cyclization of ethyl β-formylpropionate 2,5-dimethylphenylhydrazone by alcoholic hydrogen chloride gave a 19% yield of crude ester (V), while alcoholic sulfuric acid gave a very low yield.

*4,7-Dimethyl-3-indoleacetic acid* (VI). The ester (V) (12.5 g., 54 mmoles) was converted to the acid (VI) by Method C except a 2.5 hr. reflux period was used; the yield was 1.9 g. (17%) of short pink needles, m.p. 157–158.5° (dec.).

*Anal.* Calcd. for $C_{12}H_{13}NO_2$: N, 6.89. Found: N, 6.83.

*Ethyl 6,7-Dimethyl-3-indoleacetate* (VII). 2,3-Dimethylphenylhydrazine hydrochloride[19] (13.0 g., 75 mmoles) gave 18.6 g. of crude ethyl β-formylpropionate 2,3-dimethylphenylhydrazone, which was converted by Method A to the

(15) E. Fischer, *Ber.*, 19, 1563 (1866).

(16) V. Meyer and M. T. Lecco, *Ber.*, 16, 2976 (1883).

(17) F. J. Stevens and D. H. Higginbotham, *J. Am. Chem. Soc.*, 76, 2206 (1954).

(18) J. Altschul, *Ber.*, 25, 1842 (1892).

(19) H. Franzen, A. Onsager, and G. Faerden, *J. prakt. Chem.*, 97, 336 (1918).

(20) The general methods A, B, C, and D were used for the preparation of a number of compounds, using the same ratio of reactants.

(21) W. McPherson and G. Stratton, *J. Am. Chem. Soc.*, 37, 906 (1915).

(22) Since the hydrazones are unstable in air, they were not purified further or characterized.

ester (VII) using a one hour heating period. The major fraction of distillate (7.9 g., b.p. 140–146° at 0.08 mm.) was redistilled (b.p. 144–146° at 0.12 mm.); the product solidified on standing and was recrystallized from methanol-water to give 6.3 g. (39%) of white crystals, m.p. 50.5–51.5°.

*Anal.* Calcd. for $C_{14}H_{17}NO_2$: N, 6.05. Found: N, 6.26.

*6,7-Dimethyl-3-indoleacetic acid* (VIII). The ester (VII) was converted to 5.3 g. of crude acid by Method C. The yield of purified acid was 2.7 g. (50%) of white shiny flakes, m.p. 168–169° dec.

*Anal.* Calcd. for $C_{12}H_{13}NO_2$: N, 6.89. Found: N, 7.21.

*5,7-Dimethyl-3-indoleacetic acid* (IX). 2,4-Dimethylphenylhydrazine hydrochloride[18] (13.8 g., 80 mmoles) was converted into ethyl β-formylpropionate 2,4-dimethylphenylhydrazone (17.5 g.), which was cyclized by Method A. The crude ester obtained (8.6 g., b.p. 140–190° at 1 mm.) was converted to the free acid by Method C. Recrystallization from water gave a pale yellow solid, 3.2 g., m.p. 144–146° (dec.), and recrystallization from methanol-water gave 2.7 g. (18%), m.p. 145–146.5° dec.

*Anal.* Calcd. for $C_{12}H_{13}NO_2$: N, 6.89. Found: N, 6.60.

*4,6-Dimethyl-3-indoleacetic acid* (X). 3,5-Dimethylphenylhydrazine hydrochloride (7.0 g., 40.6 mmoles) was converted into ethyl β-formylpropionate 3,5-dimethylphenylhydrazone (8.4 g.) which was cyclized by Method A, except the mixture of hydrazone and zinc chloride was heated for 15 min. at 90° and then for 1.5 hr. at 100°. The major ester distillate (4.1 g., b.p. 155–180° at 1 mm.) was converted to the free acid (3.3 g., m.p. 172.5–174° dec.) by Method C. Two recrystallizations from methanol–water gave 2.2 g. (26%) of white flakes, m.p. 175.5–176.5° dec.

*Anal.* Calcd. for $C_{12}H_{13}NO_2$: N, 6.89. Found: N, 7.12.

*Ethyl 2,7-dimethyl-3-indoleacetate* (XI). *Method D.* A solution of *o*-tolylhydrazine hydrochloride[21] (16 g., 100 mmoles), levulinic acid (12.8 g., 110 mmoles), sulfuric acid (15 ml.), and absolute ethanol (160 ml.) was refluxed for 20 hr. After cooling, the solution was poured into ice water (500 ml.), and extracted with ether (six 75-ml. portions). The combined ether extract was washed with sodium carbonate solution (5%) and then with water. After drying the ether solution over magnesium sulfate and removing the ether, the residue was distilled under reduced pressure. A fraction (5.0 g., 22%, b.p. 159–165° at 0.2 mm.) was collected; after standing several hours the product solidified and was recrystallized from methanol–water. A light tan solid (2.2 g., m.p. 88.5–89.0°) was obtained. Lit.[13] m.p. 88.5–89°.

*Anal.* Calcd. for $C_{14}H_{17}NO_2$: C, 72.7; H, 7.41; N, 6.06. Found: C, 72.5; H, 7.58; N, 5.97.

*2,7-Dimethyl-3-indoleacetic acid* (XII). The ester (XI) (2.2 g., 9.5 mmoles) was converted to the acid (XII) by Method C; 0.9 g. (47%) of light pink solid, m.p. 162.5–163.5° (dec.), was obtained. The same m.p. was obtained by Bullock and Hand.[13]

*Anal.* Calcd. for $C_{12}H_{13}NO_2$: N, 6.89. Found: N, 6.83.

*Ethyl 2,4,6-trimethyl-3-indoleacetate* (XIII). 3,5-Dimethylphenylhydrazine hydrochloride[23] (8.0 g., 46 mmoles) was converted to the ester (XIII) by Method D using an 18 hr. reflux period. The major fraction of distillate (7.6 g., 67%, b.p. 150–165° at 2 mm.) solidified after standing, m.p. 100.5–102°. Recrystallization from methanol–water gave 7.2 g. of white crystals, m.p. 101–102.5°.

*Anal.* Calcd. for $C_{15}H_{19}NO_2$: N, 5.71. Found: N, 5.96.

*2,4,6-Trimethyl-3-indoleacetic acid* (XIV). The ester (XIII) was converted to the acid (XIV) by Method C. A white solid (4.5 g., m.p. 198–201° dec.) was obtained, dissolved in dilute sodium hydroxide, decolorized with Norite, and reprecipitated with dilute hydrochloric acid. Recrystallization from methanol–water gave very light tan crystals, 3.6 g. (75%), m.p. 203.5–204.5° dec.

*Anal.* Calcd. for $C_{13}H_{15}NO_2$: N, 6.44. Found: N, 6.84.

*Ethyl 2,4,7-trimethyl-3-indoleacetate* (XV). 2,5-Dimethylphenylhydrazine hydrochloride[17] (17.0 g., 100 mmoles) was converted to the ester (XV) by Method D except a 20 hr. heating period was used, and the crude product was purified by codistillation with paraffin oil (0.5 mm.). The product, a pale yellow oil, solidified upon cooling and was washed free of paraffin oil with petroleum ether (30–60°); the yield of product was 9.6 g. (39%), m.p. 128–130°. Recrystallization from methanol–water gave 2.7 g. of a white solid, m.p. 128–130°.

*Anal.* Calcd. for $C_{15}H_{19}NO_2$: N, 5.71. Found: N, 5.79.

*2,4,7-Trimethyl-3-indoleacetic acid.* (XVI). The ester (XV) (6.0 g., 24.5 mmoles) was converted to the acid (XVI) by Method C. The yield of purified product was 4.0 g. (75%) of pink scales, m.p. 201–202.5° dec.

*Anal.* Calcd. for $C_{13}H_{15}NO_2$: N, 6.44. Found: N, 6.25.

*Ethyl 2,5,7 - trimethyl - 3 - indoleacetate* (XVII). 2,4-Dimethyl-phenylhydrazine hydrochloride[18] (14.2 g., 82 mmoles) was converted to the ester by Method D. The major distillate (6.2 g., 31%; b.p. 156–166° at 0.2–0.5 mm.) solidified upon cooling, m.p. 107–109.5°. Recrystallization from methanol–water gave 5.4 g. of white fluffy crystals, m.p. 110.5–111.2°.

*Anal.* Calcd. for $C_{15}H_{19}NO_2$: N, 5.71. Found: N, 5.57.

*2,5,7-Trimethyl-3-indoleacetic acid* (XVIII). Method C applied to the ester (XVII) (4.0 g., 16.3 mmoles) gave 2.2 g. of crude acid, which was recrystallized from methanol–water, and then dissolved in dilute sodium hydroxide. After adjusting the pH to 8, the solution was decolorized with Norite, and then acidified with hydrochloric acid to *p*H 2. The product (1.75 g., 50%) had a m.p. of 180–181.5° (Lit. m.p. 181.5°).[13]

*Anal.* Calcd. for $C_{13}H_{15}NO_2$: N, 6.44. Found: N, 6.80.

*Ethyl 2,6,7-trimethyl-3-indoleacetate* (XIX). Sodium 2,3-dimethylphenylhydrazinesulfonate[18] (21.0 g., 88 mmoles) was converted to the ester (XIX) by Method D. The major distillate (5.1 g., 24%; b.p. 167–175° at 0.5 mm.) solidified, and was recrystallized from methanol–water to give 4.6 g. (21%) of white flakes, m.p. 114.5–116°.

*Anal.* Calcd. for $C_{15}H_{19}NO_2$: N, 5.71. Found: N, 5.51.

*2,6,7-Trimethyl-3-indoleacetic acid* (XX). Method C applied to the ester (XIX) (3.1 g., 12.6 mmoles) gave 2.2 g. of acid, m.p. 150–154° (dec.). The acid was dissolved in dilute sodium hydroxide, treated with Norite, and reprecipitated, m.p. 153.5–155° (dec.). Recrystallization from methanol-water gave 1.45 g. (42%) of light pink crystals, m.p. 155–156.5° (dec.).

*Anal.* Calcd. for $C_{13}H_{15}NO_2$: N, 6.44. Found: N, 6.76.

(23) W. Borsche and H. Grott, *Ann.*, **549**, 238 (1941).

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