Synthesis of Highly Methylated Indole-3-acetic Acids

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Tetramethyl- and pentamethylindole-3-acetic acids and their corresponding esters were prepared by either a modified Fischer indole synthesis or a Verley ring closure. The following compounds were prepared: 2,4,6,7-tetramethylindole, 2,4,5,6,7-pentamethylindole, ethyl 2,4,5,6-tetramethylindole-3-acetate, ethyl 2,4,5,7-tetramethylindole-3-acetate, ethyl 2,4,6,7-tetramethylindole-3-acetate, ethyl 2,5,6,7-tetramethylindole-3-acetate, ethyl 2,4,5,6,7-pentamethylindole-3-acetate, 2,4,5,6-tetramethylindole-3-acetic acid, 2,4,5,7-tetramethylindole-3-acetic acid, 2,4,6,7-tetramethylindole-3-acetic acid, 2,5,6,7-tetramethylindole-3-acetic acid, 2,4,5,6,7-pentamethylindole-3-acetic acid. Also prepared was 2,3,4-trimethylnitrobenzene.

EXPERIMENTAL EVIDENCE indicates that the ring of an auxin molecule must have an unsubstituted position available for attachment to some receptor substance for the molecule to exhibit auxin activity (*5, 8*). That the degree of auxin activity of a substance such as indole-3-acetic acid is affected by the particular position available for attachment on the benzene moiety of the indole nucleus has been fully demonstrated (*8, 11, 12*).

If all the possible isomers of methyl- and polymethylindole-3-acetic acid are tested for auxin activity, the particular position (or positions) available for attachment to a receptor molecule can be determined. Some of these isomers have already been prepared (*4, 7, 9, 13*). This work is part of a general program to prepare and test all the isomers of methyl- and polymethylindole-3-acetic acid for auxin activity.

2,4,5,6-Tetramethyl-, 2,4,5,7-tetramethyl-, and 2,5,6,7-tetramethylindole-3-acetic acids were prepared by a modified Fischer indole synthesis from the appropriately substituted phenylhydrazones of ethyl levulinate. The phenylhydrazones were prepared from substituted phenylhydrazine hydrochlorides, produced by reduction of the diazonium salts obtained from the corresponding trimethylanilines.

2,4,6,7-Tetramethyl- and 2,4,5,6,7-pentamethylindole-3-acetic acids were prepared from the corresponding 3-unsubstituted indoles by reaction with ethyl diazoacetate followed by hydrolysis. The 3-unsubstituted indoles were formed from the appropriate acetanilides by reaction with sodium amide.

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EXPERIMENTAL

Substituted Phenylhydrazine Hydrochlorides. METHOD A. The appropriately substituted anilines (0.04 to 0.08 mole) were diazotized and reduced with stannous chloride by the procedure of Barclay and Campbell (*2*). Results are shown in Table I.

METHOD B. The substituted anilines (0.4 mole) were diazotized, and then reduced with the sulfite ion according to the method of Bullock and Hand (*4*). Results are shown in Table I.

Substituted Indoles. The correspondingly substituted acetanilides were reacted with sodium amide (*1*) to obtain ring closure. Results are shown in Table II.

Substituted Indole-3-acetates. METHOD C. The substituted indoles (0.018 mole) were treated with ethyl diazoacetate according to the procedure of Jackson and Manske (*6*). Results are shown in Table III.

METHOD D. The substituted phenylhydrazones (0.005 to 0.05 mole), prepared from the phenylhydrazines and ethyl levulinate (*12*), were heated under reflux in ethyl alcohol to which a small amount of sulfuric acid had been added. Results are shown in Table III.

Substituted Indole-3-acetic Acids. METHOD E. The substituted indole-3-acetates (10^{-3} mole) were saponified with methanolic potassium hydroxide. The reaction mixture was

Table I. Substituted Phenylhydrazine Hydrochlorides

Substituents	Method	Yield, %	Decomp. Temp., ° C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
2, 3, 4-Trimethyl	A	47	215	$C_9H_{15}ClN_2$	15.01	14.31
2, 4, 5-Trimethyl	A	42	203–205	$C_9H_{15}ClN_2$	15.01	14.97
3, 4, 5-Trimethyl	B	65	194	$C_9H_{15}ClN_2$	15.01	14.97

Table II. Substituted Indoles

Substituents	Yield, %	M.P., ° C.	B.P. at 0.025Mm., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
2,4,6,7-Tetramethyl-	28	42–44	91–93	$C_{12}H_{15}N$	8.09	8.16
2,4,5,6,7-Pentamethyl-	20	116.5–118	62–66	$C_{13}H_{17}N$	7.48	7.40

Table III. Substituted Indole-3-acetates

Substituents	Method	Yield, %	M.P., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
2,4,5,6-Tetramethyl-	D	75	136–138	$C_{16}H_{21}NO_2$	5.40	5.55
2,4,5,7-Tetramethyl-	D	52	151.5–153[a]	$C_{16}H_{21}NO_2$	5.40	5.33
2,4,6,7-Tetramethyl-	C	..	149(d.)	$C_{16}H_{21}NO_2$	5.40	5.36
2,5,6,7-Tetramethyl-	D	35	121.5–122.5	$C_{16}H_{21}NO_2$	5.40	5.30
2,4,5,6,7-Pentamethyl-	C	..	175–176(d.)	$C_{17}H_{23}NO_2$	5.12	5.07

[a] The ester should not be introduced into the m.p. apparatus until the temperature is within 5 to 10° of its m.p. The rate of heating must not exceed 1° per minute.

Table IV. Substituted Indole-3-acetic Acids

Substituents	Method	Reflux Time, Hrs.	Yield, %	M.P., °C.	Recrystallized from	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
2, 4, 5, 6-Tetramethyl	E	2	60	194(d.)	acetone	$C_{14}H_{17}NO_2$	6.06	6.04
2, 4, 5, 7-Tetramethyl	E	6	98	168(d.)	dil. base	$C_{14}H_{17}NO_2$	6.06	6.18
2, 4, 6, 7-Tetramethyl	F	4.5	23[a]	168(d.)	none[b]	$C_{14}H_{17}NO_2$	6.06	6.07
2, 5, 6, 7-Tetramethyl	E	6	63	162–163(d.)[c]	none	$C_{14}H_{17}NO_2$	6.06	6.15
2, 4, 5, 6, 7-Pentamethyl	F	5	5[a]	191(d.)	methanol-water	$C_{13}H_{15}NO_2$	5.71	5.52

[a] Yield based on starting substituted indole. [b] Attempts to recrystallize the acid from organic solvents or to purify it by base-acid treatment resulted in a darkening of the color of the acid and a decrease in its decomposition point. [c] The acid should not be introduced into the melting point apparatus until the temperature is within 5 to 10° of the m.p. of the acid. The rate of heating must not exceed 1° per minute.

poured into water, and the resulting solution was extracted with ether. Addition of 3*N* hydrochloric acid to the cooled hydrolyzate precipitated the indole acids. Results are shown in Table IV.

METHOD F. This method was employed for the hydrolysis of those substituted indole-3-acetates obtained from the corresponding indoles by treatment with ethyl diazoacetate. The distillate from Method C (containing the substituted indole-3-acetate and the unreacted substituted indole) was heated under reflux with aqueous potassium hydroxide. The mixture was filtered (unreacted substituted indole recovered) and the filtrate treated as described in Method E. Results are shown in Table IV.

Preparation of 2,3,4-Trimethylnitrobenzene. The 2,3,4-trimethylnitrobenzene needed to prepare 2,3,4-trimethylphenylhydrazinium chloride is previously unreported. 1,2,3-Trimethylbenzene was nitrated with a mixture of acetic acid, acetic anhydride, and fuming nitric acid (*10*). A 40% yield of the nitro compound was obtained. Reduction, followed by acetylation, gave a compound with m.p., 140° C. The reported m.p. for 2,3,4-trimethylacetanilide is 140° C. (*3*). The boiling point of the 2,3,4-trimethylnitrobenzene at 26 mm. was 156 to 161° C.; $N_d^{28.5}$ 1.5497; d^{29} 1.1226; M.R. calcd. 46.75; M.R. exp. 46.86. Anal. calcd. for $C_9H_{11}NO_2$; N, 8.47. Found: N, 8.45.

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Cis-Trans Isomers of Methyl Substituted Fluorocinnamic and 5-(*o*-, *m*-, and *p*-Fluorophenyl)pentadienoic Acids

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INTEREST in the hypocholesterolemic activity of the geometrical isomers of 3-methyl-5-phenyl-2,4-pentadienoic acid prompted the preparation of a series of fluorophenyl analogs which are described in Table I. The trans isomers were isolated, sometimes from mixtures with other isomers, from the dehydration of the Reformatsky product. The cis isomers were obtained from UV irradiation of the trans isomers or from the β-methylglutaconic acid condensations and decarboxylations. All of the compounds listed in Table I, except those for which the NMR data are aster-