

scribed, into 1-methylheptamethylenimine (hydrochloride, m.p. 162–164°) and 1,1-diphenyl-1-cyano-2-methyl-2-propene (m.p. 65–66°). The latter substance was reduced to 1-amino-2,2-diphenyl-3-methyl-3-butene and this product was hydrogenated to 1-amino-2,2-diphenyl-3-methylbutane (4.8 g.). The thiourea derivative melted at 157–158°.

4,4-Diphenyl-5-methyl-6-(1-heptamethylenimino)-3-hexanone (XVI).—The nitrile XIII (17.3 g.), dissolved in 40 cc. of toluene, was added to ethylmagnesium bromide which had been prepared from 9.0 g. of ethyl bromide, 2.0 g. of magnesium and 50 cc. of ether. After the ether had been removed, the mixture was refluxed for 6 hours, treated with ammonium chloride solution, the organic layer was separated and the aqueous portion extracted with benzene. The solvents were removed from the combined organic layer and extract and the residue distilled; b.p. 158–163° (0.05 mm.), yield 13.0 g. An ethereal solution of the distillate was treated with hydrogen chloride. The precipitated mixture of hydrochlorides was dissolved in hot isopropyl alcohol. 1,1-Diphenyl-2-methyl-3-(1-heptamethylenimino)-propane (XVII) hydrochloride precipitated from the cold solution; yield 3.0 g., m.p. 195.5–196.5° after recrystallization from methanol-ethyl acetate. This compound was also synthesized in a separate experiment which is described below.

Anal. Calcd. for $C_{23}H_{32}NCl$: C, 77.14; H, 9.01; N,

3.92; Cl, 9.93. Found: C, 77.13; H, 9.05; N, 3.96; Cl, 9.99.

Upon the addition of ether to the mother liquor, the dihydrochloride of 3-imino-4,4-diphenyl-5-methyl-6-(1-heptamethylenimino)-hexane precipitated in an impure form; m.p. 146–148° dec.

Anal. Calcd. for $C_{23}H_{38}N_2Cl_2$: Cl, 15.80. Found: Cl, 14.84.

When this product was refluxed with 30 cc. of constant boiling hydrochloric acid for 40 hours, 4,4-diphenyl-5-methyl-6-(1-heptamethylenimino)-3-hexanone hydrochloride (9.5 g., 46%) was obtained; m.p. 199–200° after recrystallization from methanol-ethyl acetate.

Anal. Calcd. for $C_{26}H_{38}ONCl$: C, 75.44; H, 8.77; N, 3.38; Cl, 8.57. Found: C, 75.54; H, 8.74; N, 3.28; Cl, 8.52.

1,1-Diphenyl-2-methyl-3-(1-heptamethylenimino)-propane (XVII).—A mixture of 4.2 g. of 2,2-diphenyl-3-methyl-4-(1-heptamethylenimino)-butyronitrile, 1.9 g. of sodamide and 40 cc. of xylene was refluxed for 12 hours. After the addition of water the organic layer was separated, the solvent removed and the residue distilled; b.p. 158–161° (1 mm.), yield 3.8 g. (98%). The hydrochloride melted at 195–196°; mixed m.p. 195–196°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ALABAMA POLYTECHNIC INSTITUTE]

Preparation of Some Substituted 2-Methyl-3-indoleacetic Acids^{1,2}

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2-Methyl-5-bromo-, 2-methyl-7-bromo-, 2-methyl-5,7-dibromo-, 2,7-dimethyl-5-bromo-, 2-methyl-4-chloro-7-methoxy- and 2-methyl- (4 or 6)-chloro-3-indoleacetic acids have been prepared from the properly substituted phenylhydrazones of ethyl levulinate by the Fischer indole synthesis. 2-Methoxy-5-chlorophenylhydrazine, the hydrochloride and acetyl derivatives have been prepared.

The preparation of some substituted 2-methyl-3-indoleacetic acids has been reported.³ The activity of these compounds as plant growth regulators varies with the nature of the substituting groups and their positions in the indole nucleus.^{3,4} The work presented here is part of a general program to increase the number of such derivatives available for phytological investigations correlating structure with activity. The new acids were prepared from the appropriately substituted ethyl levulinate phenylhydrazones using a modified Fischer synthesis.⁵ The phenylhydrazones were prepared from ethyl levulinate and the substituted phenylhydrazine which was liberated from its hydrochloride in aqueous solution by sodium acetate. In the preparation of the substituted phenylhydrazine hydrochlorides it was found that an excellent method of purification consisted of liberating the free base from the crude phenylhydrazine hydrochlorides, extracting with ether and reprecipitating the hydrochloride from the dried ether solution with hydrogen chloride. The free substituted phenylhydrazines are not very stable in air, while

the hydrochlorides can be stored for long periods without decomposition. All of the phenylhydrazines with the exception of 2-methoxy-5-chlorophenylhydrazine have been characterized previously as free bases but not in all cases as hydrochlorides. The melting point of 2-methyl-4-bromophenylhydrazine hydrochloride was found to be considerably higher than that reported in the literature.⁶ Anhydrous zinc chloride was used as catalyst in the ring closure and an atmosphere of carbon dioxide was maintained, since the phenylhydrazones decompose in air. Only one product was isolated from the cyclization of ethyl levulinate, *m*-chlorophenylhydrazine, although both 2-methyl-4-chloro- and 2-methyl-6-chloro-3-indoleacetic acids are possible. Fox and Bullock obtained two products from the cyclization of the *m*-chlorophenylhydrazone of β -formylpropionic acid with ethanolic sulfuric acid.⁷ The position of the halogen in the single compound obtained is under investigation.

Experimental

All m.p.'s (capillary) are uncorrected.

Substituted Phenylhydrazine Hydrochlorides.—All of the phenylhydrazine hydrochlorides were prepared by Hewitt's procedure,⁸ except the product was allowed to precipitate overnight. The precipitate was filtered, and washed once with concd. hydrochloric acid. The product was purified

(1) From the thesis by Don H. Higginbotham presented to the Graduate School in partial fulfillment of the requirements for the M.S. Degree.

(2) This research was supported in part by the Grant-in-Aid Program of the Alabama Polytechnic Institute.

(3) F. J. Stevens and S. W. Fox, *THIS JOURNAL*, **70**, 2263 (1948).

(4) F. J. Stevens, Ph.D. thesis, Iowa State College, 1947.

(5) E. Fischer, *Ber.*, **19**, 1563 (1886).

(6) I. Michaelis, *ibid.*, **26**, 2190 (1893).

(7) S. W. Fox and I. M. W. Bullock, *THIS JOURNAL*, **73**, 2756 (1951).

(8) J. T. Hewitt, *J. Chem. Soc.*, **59**, 209 (1891).

by the method described above, and dried over sulfuric acid and sodium hydroxide pellets under reduced pressure. The yields of substituted phenylhydrazine hydrochlorides are reported in Table I.

TABLE I
SUBSTITUTED PHENYLHYDRAZINE HYDROCHLORIDES

Substituent	M.p., °C. dec.	Yield, %	Formula	Nitrogen, % ^a	
				Calcd.	Found
4-Bromo	219-221	85	C ₆ H ₅ N ₂ ClBr	12.57	12.4
2-Bromo	196-198	75	C ₆ H ₅ N ₂ ClBr	12.57	12.5
2,4-Dibromo	203-204	79	C ₆ H ₃ N ₂ ClBr ₂	9.27	9.0
3-Chloro	234-235 ^b	76	C ₆ H ₅ N ₂ Cl ₂
2-Methyl-4-bromo	203-204 ^c	64	C ₇ H ₁₀ N ₂ ClBr	11.80	11.6
2-Methoxy-5-chloro	195-196	80	C ₇ H ₁₀ N ₂ Cl ₂	13.46	13.4

^a Nitrogen by micro Dumas. ^b Willgerodt and Mühle give 235-236°. ^c Michaelis gives 183-183.5° for a compound prepared by bromination of *o*-tolylhydrazine.⁶

Substituted Phenylhydrazines.—To 2-methoxy-5-chlorophenylhydrazine hydrochloride (2.1 g., 0.01 mole) in water (100 ml.) was added a solution of sodium acetate (1.0 g. in 25 ml. of water). The precipitate which formed was filtered off and recrystallized from ethanol-water; yield 0.6 g. (35%) of needles, m.p. 69-70°.

Anal. Calcd. for C₇H₉O₂N₂Cl: N, 16.23. Found: N, 16.0.

Small quantities of all the phenylhydrazine hydrochlorides were converted similarly to the free hydrazines, and in all cases the physical properties corresponded with the values reported in the literature.^{6,9-11}

Anal. Calcd. for C₉H₁₁O₂N₂Cl: N, 13.07. Found: N, 12.9.

In like manner 2-methyl-4-bromophenylhydrazine was converted into acetyl 2-methyl-4-bromophenylhydrazine; yield 0.3 g. (50%), m.p. 171-172° (Michaelis gives 172°).

Substituted Ethyl Levulinate Phenylhydrazones.—A hot aqueous solution (100 ml.) of substituted phenylhydrazine hydrochloride (0.045 mole), sodium acetate (0.045 mole) and acetic acid (9 ml.) was added to a hot solution of ethyl levulinate (7.7 g., 0.055 mole) in water (100 ml.). The oily phenylhydrazones which precipitated at once and solidified upon cooling, were removed by filtration in an atmosphere of carbon dioxide, since they slowly decompose in air. The crystals were washed once with 95% ethanol and dried over sulfuric acid under reduced pressure. The substituted phenylhydrazones of ethyl levulinate obtained by the above general procedures are shown in Table II.

Substituted 2-Methyl-3-indoleacetic Acids.—The phenylhydrazones obtained above (approximately 0.04 mole) were transferred to a tall 200-ml. beaker provided with a carbon dioxide inlet and a mechanical stirrer. After adding anhydrous zinc chloride (10 g.), the mixture was heated in an oil-bath at 125° and vigorously stirred. When evolution of gases ceased (approximately 10 min.) the melt was cooled and distributed between ether and dilute hydrochloric acid (1:4). The acid solution was extracted several times with ether. The combined ether solutions were dried over magnesium sulfate and the ether evaporated under reduced pressure. The residue was refluxed with potassium hydroxide (5 g.) in methanol (50 ml.) for three hours. Water (50 ml.) was added and most of the methanol was removed by evaporation under reduced pressure. More water was added to dissolve the potassium salt, and the solution was extracted twice with ether, which was discarded. The aqueous solution was boiled to remove dissolved ether, cooled and acidified with hydrochloric acid. The substituted indoleacetic acids precipitated as light tan to brown

TABLE II
SUBSTITUTED PHENYLHYDRAZONES OF ETHYL LEVULINATE

Substituent	Yield, g. (%)	M.p., °C.	Formula	Carbon, %		Hydrogen, %	
				Calcd.	Found	Calcd.	Found
4-Bromo	12 (85)	112-114	C ₁₃ H ₁₇ O ₂ N ₂ Br	49.85	49.6	5.47	5.38
2,4-Dibromo	14.3 (81)	70-70.5	C ₁₃ H ₁₅ O ₂ N ₂ Br ₂	39.82	39.4	4.11	4.40
2-Methyl-4-bromo	14.0 (96)	114.5-115	C ₁₄ H ₁₉ O ₂ N ₂ Br	51.38	51.2	5.58	6.14
2-Methoxy-5-chloro	12.3 (93)	59.5-60	C ₁₄ H ₁₉ O ₃ N ₂ Cl	56.49	56.5	6.43	6.24
3-Chloro	11.8 (98)	119-120	C ₁₃ H ₁₇ O ₂ N ₂ Cl	58.11	58.5	6.34	6.49
2-Bromo	12.5	Oil					

TABLE III
SUBSTITUTED 3-INDOLEACETIC ACIDS

Substituent	Yield, %	M.p., °C., dec.	Recryst. solvent	Formula	Analyses, ^a %			
					N	Calcd. X	N	Found X
2-Methyl-5-bromo	58	188-189	Methanol-water	C ₁₁ H ₁₀ O ₂ NBr	5.23	29.80	5.26	29.59
2-Methyl-7-bromo	28	160-161	Methanol-water	C ₁₁ H ₁₀ O ₂ NBr	5.23	29.80	5.37	29.66
2-Methyl-5,7-dibromo	34	231-232	Acetone-chloroform	C ₁₁ H ₈ O ₂ NBr ₂	4.03	46.06	4.00	46.03
2,7-Dimethyl-5-bromo	34	191-192	Acetone-chloroform	C ₁₂ H ₁₂ NO ₂ Br	4.96	28.33	5.03	28.15
2-Methyl-4-chloro-7-methoxy	23	237-238	Acetone-chloroform	C ₁₂ H ₁₂ O ₃ NCl	5.52	13.98	5.55	14.13
2-Methyl-(4 or 6)-chloro	39	195-196	Acetone-chloroform	C ₁₁ H ₁₀ O ₂ NCl	6.26	15.85	6.41	16.16

^a Halogen by modified method of Rausher in E. Clark, "Semi-Micro Quantitative Analysis," Academic Press, Inc., New York, N. Y., 1943, p. 53. Nitrogen by micro-Kjeldahl.

Substituted Acetylphenylhydrazines.—To 2-methoxy-5-chlorophenylhydrazine (0.5 g.) was added acetic anhydride (3 ml.). After a few minutes water (50 ml.) was added and the precipitate collected; 0.4 g. (65%) of needles was obtained, m.p. 158-159°. Recrystallization from ethanol-water did not change the melting point.

(9) C. Willgerodt and E. G. Mühle, *J. prakt. Chem.*, [2] **44**, 451 (1891).

(10) M. Busch and E. Muessdorfer, *ibid.*, [2] **75**, 137 (1907).

(11) M. Meyer, *Ann.*, **272**, 219 (1893).

solids, which were removed by filtration. The crude acids were dissolved in acetone, in which they were very soluble, and decolorized with Norite. Most of the acetone was evaporated off and chloroform was added to the hot solution until crystallization began. After cooling, the crystals were removed by filtration. An alternate procedure for purification consisted of decolorizing in methanol and then adding the methanol solution dropwise to a large quantity of water. The results are shown in Table III.

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