0.10 g. was obtained by concentration of the mother liquor. The crude product was digested at 50° with 100 ml. of water and then filtered, washed with absolute ethanol and again dried over phosphorus pentoxide to give 4.47 g. (28.2%), m.p. 265° dec. Repeated recrystallization from absolute ethanol with the use of charcoal yielded colorless crystals, m.p. 285° dec.

Anal. Calcd. for $C_5H_6ON_4$: C, 43.47; H, 4.38; N, 40.56. Found: C, 43.32; H, 4.69; N, 40.74.

The compound exhibited an absorption maximum in the ultraviolet (in 0.1 *N* hydrochloric acid) at 265 mμ. After boiling for two hours in 0.1 *N* hydrochloric acid, hydrolysis of the formyl group was complete, and the resulting solution exhibited an absorption maximum at 263.5 mμ, identical with the maximum exhibited by an authentic sample of 4,6-diaminopyrimidine.

Phenylazomalondiamide.—A solution of 18.6 g. of aniline in 120 ml. of 6 *N* hydrochloric acid was diazotized at 5° by the addition of a solution of 13.8 g. of sodium nitrite in 50 ml. of water. After five minutes, the benzenediazonium chloride solution was poured with vigorous stirring into a mixture of 20.42 g. of malondiamide in 200 ml. of water in an ice–salt-bath. With continued stirring, 95 ml. of 5 *N* ammonium hydroxide was added slowly. The reaction mixture, which was then at *p*H 6, was maintained at *p*H 5–6 by the addition of a sodium acetate solution. Stirring was continued for an additional 30 minutes (total stirring time was 45 minutes). The mixture was then removed from the ice-bath and set aside at room temperature for 2.5 hours, and then stored in the refrigerator overnight. The solid product was collected by filtration, washed with a little cold water and dried over phosphorus pentoxide to give 24.7 g. An additional 4.7 g. of product was obtained from the filtrate to give a total yield of 29.4 g. (71.3%), m.p. 220° dec., with preliminary softening. The crude light-brown product was recrystallized from 95% ethanol with the use of charcoal to give soft, yellow-orange needles, m.p. 241° dec. The compound can better be recrystallized from aqueous dimethylformamide or aqueous formamide as bright yellow crystals.

Anal. Calcd. for $C_9H_{10}O_2N_4$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.41; H, 4.83; N, 26.94.

***sym*-N,N′-Bis-(ethoxymethylene)-malondiamidine Monohydrochloride (XIII).**—A mixture of 5.80 g. of malondiamidine dihydrochloride, 30 ml. of ethyl orthoformate and 20 ml. of acetic anhydride was heated under reflux for five hours and the bulk of the solvents was removed by distillation under reduced pressure. The residue was twice digested with 50 ml. of 95% ethanol for a few minutes and the solution was evaporated to dryness. The resulting residue was digested with 50 ml. of boiling 95% ethanol and the mixture stored overnight in an ice-bath to give 4.65 g. (55.8%) of almost colorless crystals, m.p. 215° dec. Three recrystallizations from water with the addition of charcoal gave colorless crystals, m.p. 281° dec., with preliminary darkening above 250°.

Anal. Calcd. for $C_9H_{17}O_2N_4Cl$: C, 43.46; H, 6.89; N, 22.53. Found: C, 43.83; H, 6.73; N, 22.41.

Conversion of XIII to 4-Formylamino-6-aminopyrimidine.—A mixture of 8.65 g. of XIII and 30 ml. of formamide was placed in an oil-bath preheated to 175–180° and the reaction was allowed to proceed at this temperature for 3.5 hours. The mixture was then cooled, diluted with 100 ml. of absolute ethanol and chilled for one hour. The precipitated solid was collected by filtration, washed with absolute ethanol and dried over phosphorus pentoxide, yield 1.3 g. of a brownish-yellow product, m.p. *ca.* 245° dec. The mother liquor yielded an additional 1.18 g. of pale yellow product, m.p. 248° dec., while the second mother liquor yielded 0.41 g. of colorless product, m.p. 266° dec.; total yield 2.89 g. (60.2%). The infrared spectrum of this compound was identical with that given by authentic 4-formylamino-6-aminopyrimidine.

PRINCETON, NEW JERSEY

[CONTRIBUTION FROM THE NUTRITION AND PHYSIOLOGY SECTION, RESEARCH DIVISION, AMERICAN CYANAMID CO., LEDERLE LABORATORIES]

Syntheses of Some Substituted Indole-3-acetic Acids[1]

BY MILON W. BULLOCK AND JOHN J. HAND

RECEIVED JUNE 20, 1956

A series of ethyl 2-methylindole-3-acetates having substituents in the benzene ring have been prepared by a Fischer indole ring closure of the corresponding ethyl levulinate substituted phenylhydrazones. Methods of effecting the ring closure have been compared. The substituted indole-3-acetic acids were prepared by saponification of the esters.

The biological activities of 2-methylindole-3-acetic acid and a few substituted compounds have been compared.[2,3] The activities of the substituted compounds were superior to 2-methylindole-3-acetic acid for certain phytological applications. We have prepared a number of new 2-methylindole-3-acetic acids for testing.

The substituted ethyl levulinate phenylhydrazones which were required as intermediates were prepared by the method of Stevens and Higginbotham.[4] The products were all unstable in air although they could be stored for long periods of time in nitrogen. The yields, melting points and elemental analyses of these intermediates are summarized in Table I.

The ethyl 2-methylindole-3-acetates were prepared by a Fischer indole cyclization of the ethyl levulinate phenylhydrazones. The cyclization could be effected by refluxing the phenylhydrazone with a solution of sulfuric acid in ethanol, fusing with zinc chloride, and by refluxing a mixture of the phenylhydrazone and zinc chloride in xylene. Ethanolic sulfuric acid has been found to be an excellent cyclization catalyst for the preparation of ethyl 2-methylindole-3-acetate from ethyl levulinate phenylhydrazone[5]; however, when this method was employed for the cyclization of the substituted phenylhydrazone, the indole was generally contaminated with unreacted phenylhydrazone. Fusion with anhydrous zinc chloride as described by Stevens and Higginbotham[4] was effective but the procedure was found to be somewhat laborious. Refluxing a mixture of the substituted phenylhydrazone and zinc chloride in xylene has been found to be both effective and convenient. The 2-methylindole-3-acetates prepared are summarized in Table II. The letters refer to the general procedure detailed in the experimental section.

(1) Presented in part at the 129th Meeting of the American Chemical Society, Dallas, Texas, April 9, 1956.

(2) O. L. Hoffman, S. W. Fox and M. W. Bullock, *J. Biol. Chem.*, **196**, 437 (1952).

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

(4) F. J. Stevens and D. H. Higginbotham, *ibid.*, **76**, 2206 (1954).

(5) M. W. Bullock and S. W. Fox, *ibid.*, **73**, 5155 (1951).

TABLE I

SUBSTITUTED PHENYLHYDRAZONES OF ETHYL LEVULINATE

Substituent	Color	Yield, g.	%	M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
3-Chloro-2-methyl	White	47.2	83.5	93.5–95	$C_{14}H_{19}N_2O_2Cl$	9.91	9.82	12.54	12.37
4-Chloro-2-methyl	Yellow	41.3	73	96–100	$C_{14}H_{19}N_2O_2Cl$	9.91	9.73	12.54	12.32
5-Chloro-2-methyl	White	40.1	70.8	94–95	$C_{14}H_{19}N_2O_2Cl$	9.91	10.01	12.54	12.04
2-Methyl	Cream	16.4	33	76–78.5	$C_{14}H_{20}N_2O_2$	11.28	11.26	...	...
4-Methyl	Cream	35.2	70.8	119–120.5	$C_{14}H_{20}N_2O_2$	11.28	11.63	...	...
2,4-Dimethyl	Yellow	31.8	64	98–99	$C_{15}H_{22}N_2O_2$	10.68	10.64	...	...
4-Chloro	Yellow	23.0	93	110–111[a]					

[a] P. P. T. Sah, H. H. Lei and T. Shen, *Sci. Repts. Natl. Tsing Hua Univ.*, [A] **2**, 7 (1933); *C. A.*, **27**, 4222 (1933).

TABLE II

SUBSTITUTED 3-INDOLEACETATES

Substituent	Method	Yield, %	M.p., °C.	Hours of reflux	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
4-Chloro-2,7-dimethyl	A	0	...	4	63.27	63.12	6.07	6.31	5.27	5.29	13.34	13.38
	C	46.0	125.5–126	0.75								
5-Chloro-2,7-dimethyl	A	18.4	166–167	2	63.27	63.25	6.07	6.35	5.27	5.21	13.34	13.21
	B	22.6	166–167	...								
6-Chloro-2,7-dimethyl	A	9.0	153.5–154	4	63.27	63.19	6.07	6.50	5.27	5.24	13.34	13.18
2,5-Dimethyl[a]	A	73.5[b]	...	6								
	C	48.4	45.5–47[c]	0.75	72.70	72.33	7.41	6.96	6.06	6.40	...	...
2,7-Dimethyl	A	0	...	6								
	C	23.6	88.5–89	0.75	72.70	72.80	7.41	7.72	6.06	5.94	...	...
2,5,7-Trimethyl	A	33.7	113.5–114.5	...	73.44	73.05	7.81	8.09	5.71	5.55	...	...

[a] B.p. 160° (0.05 mm.), $n^{20}D$ 1.5660. [b] Yield based on pure acid obtained by saponification of crude ester. [c] This ester was first obtained as an oil, b.p. 160° at 0.05 mm., $n^{20}D$ 1.5660. On standing several weeks it slowly crystallized.

TABLE III

SUBSTITUTED 3-INDOLEACETIC ACIDS

Substituent	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
4-Chloro-2,7-dimethyl	97	226–228	60.64	60.56	5.09	5.57	5.89	5.97	14.92	14.55
5-Chloro-2,7-dimethyl	88	207–211d.	60.64	60.09	5.09	5.22	5.89	5.94	14.92	14.85
6-Chloro-2,7-dimethyl	63.2	133–134d.	60.64	60.21	5.09	5.34	5.89	5.91	14.92	14.78
2,5-Dimethyl	74.5	172–174	70.91	70.46	6.45	6.49	6.89	6.95	...	...
2,7-Dimethyl	80.5	164–165	70.91	70.66	6.45	6.74	6.89	6.79	...	...
2,5,7-Trimethyl	46.8	180–181.5d.	71.86	71.75	6.96	7.27	6.45	6.41	...	...

The acids were prepared by saponification of the purified esters. The yields, melting points and elemental analyses of these are summarized in Table III.

Experimental[6]

The following examples illustrate the methods employed for the preparation of the compounds described in this publication.

Ethyl Levulinate Phenylhydrazones.—A hot solution of the substituted phenylhydrazine hydrochloride (0.2 mole), sodium acetate (18 g., 0.22 mole), 25 ml. of acetic acid in 400 ml. water was added to a hot solution of ethyl levulinate (34.6 g., 0.24 mole) in 100 ml. of water. The product, which separated as an oil, solidified on cooling and was filtered off under nitrogen to prevent decomposition. The crystals were washed once with ethanol and with about 30 ml. of ligroin and dried in an Abderhalden drying apparatus under reduced pressure at 58°. The substituted phenylhydrazones were obtained in nearly pure form. Small samples were recrystallized from ethanol (3A) to obtain analytical samples.

Substituted 3-Indole Acetates. Method A.—The substituted phenylhydrazone (about 0.13 mole), 180 ml. of 2B ethanol and 20 ml. of concentrated sulfuric acid were mixed together and refluxed in an atmosphere of nitrogen for 2 hr. The reaction mixture was poured over a mixture of ice and ether. The organic phase was separated and the aqueous phase extracted once with about 300 ml. of ether. The combined ether extracts were washed with water and with half-saturated sodium bicarbonate solution. The ether solution was dried over sodium sulfate, clarified with Darco G-60 charcoal and filtered. Distillation of the ether left an oily mass which frequently crystallized on cooling. If the crude ester did not crystallize it was distilled *in vacuo*. The esters were recrystallized from 95% ethanol or from a water–ethanol mixture.

Method B.—A 250-ml. 3-neck flask was equipped with a Teflon paddle stirrer and a nitrogen inlet tube. About 0.13 mole of the substituted phenylhydrazone was placed in the flask with 10 g. of anhydrous zinc chloride. The mixture was stirred vigorously and heated in an oil-bath at 125° for 30 minutes and then at 155° for an additional 30 minutes. The reaction mixture was allowed to cool. The melt was distributed between ether and 3 *N* hydrochloric acid. The ether layer was separated and the aqueous phase extracted three times with ether. The ether extracts were combined and dried over sodium sulfate. Distillation of the ether gave the crude ester which was purified by distillation or recrystallization.

Method C.—About 0.13 mole of the substituted phenylhydrazone, 10 g. of anhydrous granular zinc chloride and 70 ml. of xylene was refluxed under nitrogen for 45 minutes. The reaction mixture was diluted with 100 ml. of water followed by 35 ml. of concentrated hydrochloric acid. When the solid material had dissolved, the solution was cooled and ether added. The organic layer was separated and the aqueous layer extracted with ether. The combined extracts were washed with water and with saturated sodium bicarbonate solution. The organic phase was then dried over sodium sulfate and the solvents distilled off leaving an oil or an oily crystalline mass which was purified by distillation or recrystallization.

Substituted 3-Indoleacetic Acids.—The substituted 3-indoleacetates obtained by the above procedures were saponified by refluxing 2 hr. with excess ethanolic potassium hy-

(6) Melting points and boiling points are uncorrected. The elemental analyses were by Mr. L. Brancone and staff.

droxide. The ethanol was distilled off and replaced by water. Acidification with dilute hydrochloric acid gave clean crystalline products which were removed by filtration. The substituted indoleacetic acids were recrystallized readily from an ethanol–water mixture.

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE NUTRITION AND PHYSIOLOGY SECTION, RESEARCH DIVISION, AMERICAN CYANAMID CO., LEDERLE LABORATORIES]

Synthesis of Some Substituted Indole-3-butyric Acids[1]

BY MILON W. BULLOCK AND JOHN J. HAND

RECEIVED JUNE 20, 1956

A series of indole-3-butyric esters and acids having substituents in the benzene ring have been prepared from methyl or ethyl 5-formylvalerate and a substituted phenylhydrazine hydrochloride. The intermediate phenylhydrazones were not isolated but were converted directly to the indole derivative by a Fischer indole ring closure.

Indole-3-acetic acid (heteroauxin) and indole-3-butyric acid have been found useful for certain specialized phytological applications such as propagation of plants by cuttings, prevention of preharvest drop of fruit, etc.[2] Indole-3-acetic acid and other phytologically active compounds have been found to have a synergistic effect when used with streptomycin for the control of certain crop diseases.[3] The biological activity of indole-3-acetic acid for some applications is increased by substitutions in the benzene ring.[4] The activity of the closely related indole-3-butyric acids would be expected to be increased by similar structural modifications. A series of substituted indole-3-butyric acids has been prepared for testing.

The compounds were obtained by essentially a one-step Fischer indole synthesis which consisted of the *in situ* formation of the substituted phenylhydrazone of methyl or ethyl 5-formylvalerate under conditions favorable for ring closure to occur.

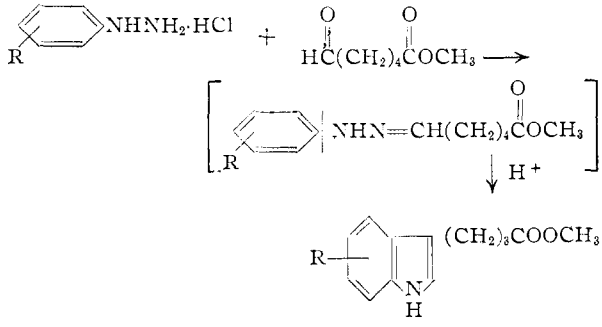

TABLE I

YIELDS AND MELTING POINTS OF PHENYLHYDRAZINE HYDROCHLORIDES

Hydrochloride	Formula	Procedure	Yield, %	M.p., °C.
o-Tolylhydrazine	$C_7H_{11}ClN_2$	A	56.5	195 d.[a]
p-Tolylhydrazine	$C_7H_{11}ClN_2$	A	63	155–160[a]
2,4-Dimethylhydrazine	$C_8H_{13}ClN_2 \cdot 2H_2O$	A	31.5–40	182–184[b]
o-Chlorophenylhydrazine	$C_6H_8Cl_2N_2$	B	50	198–200 d.[c]
m-Chlorophenylhydrazine	$C_6H_8Cl_2N_2$	C	73.5	124–246 d.[d]
p-Chlorophenylhydrazine	$C_6H_8Cl_2N_2$	B	67	221.5–223 d.[e]
2,4-Dichlorophenylhydrazine	$C_6H_8Cl_3N_2$	A	50.3	193–194.5 d.[f]
3-Chloro-2-methylphenylhydrazine	$C_7H_{10}Cl_2N_2$	A	70	239 d.[g]
4-Chloro-2-methylphenylhydrazine	$C_7H_{10}Cl_2N_2$	A	54.2	201–202 d.[h]
5-Chloro-2-methylphenylhydrazine	$C_7H_{10}Cl_2N_2$	A	75.5	215–216 d.[i]
5-Chloro-2-methoxyphenylhydrazine	$C_7H_{10}Cl_2N_2O$	A	58.6	192–193 d.[j]

[a] W. McPherson and G. W. Stratton, THIS JOURNAL, **37**, 908 (1915), prepared the free base but did not report the m.p. of the intermediate hydrochloride. [b] The m.p. of the hydrochloride dihydrate is given as 183° by A. Klauber, *Monatsh. Chem.*, 12, 212 (1891). [c] F. Graziani, *Chem. Zentr.*, **84**, II, 496 (1913), gave m.p. 194° dec. [d] C. Willgerodt and E. G. Muhe, *J. prakt. Chem.*, [2] **44**, 451 (1891), gave m.p. 235–236° dec. [e] F. Graziani, ref. *c* gave m.p. 225–230° dec. [f] F. D. Chattaway and C. F. B. Pearce, *J. Chem. Soc.*, **107**, 32 (1915), gave the decomposition point as about 210°. [g] *Anal.* Calcd. for $C_7H_{10}Cl_2N_2$: C, 43.54; H, 5.22; N, 14.51; Cl, 36.73. Found: C, 43.23; H, 5.34; N, 14.74; Cl, 36.28. [h] *Anal.* Calcd. for $C_7H_{10}Cl_2N_2$: C, 43.54; H, 5.22; N, 14.51; Cl, 36.73. Found: C, 43.28; H, 5.24; N, 14.47; Cl, 36.68. [i] *Anal.* Calcd. for $C_7H_{10}Cl_2N_2$: C, 43.54; H, 5.22; N, 14.51; Cl, 36.73. Found: C, 43.26; H, 5.09; N, 14.76; Cl, 37.02. [j] F. J. Stevens and D. H. Higginbotham, THIS JOURNAL, **76**, 2206 (1954), gave m.p. 195–196° dec.

Attempts to isolate and purify the intermediate phenylhydrazones were unrewarding. The phenylhydrazones were obtained in low yields as gums which could not be satisfactorily purified. The acidic conditions required for the cyclization reaction will convert any trimerized aldehyde to the reactive monomer so that phenylhydrazone formation and cyclization can occur.

The substituted phenylhydrazine hydrochlorides which were required as intermediates were

(1) Presented in part at the 129th Meeting of the American Chemical Society, Dallas, Texas, April 9, 1956.

(2) F. Skogg, "Plant Growth Substances," University of Wisconsin Press, Madison, Wis., 1951.

(3) R. N. Goodman and D. D. Hemphill, *Science*, **119**, 347 (1954); D. D. Hemphill and R. N. Goodman, *ibid.*, **122**, 122 (1955).

(4) O. L. Hoffman, S. W. Fox and M. W. Bullock, *J. Biol. Chem.*, **196**, 437 (1952).