It was filtered off and washed with ethanol and water. After recrystallization from dimethylformamide it melted at 324–326° with softening at 319°, yield 11.5 g. (74%).

$LiAlH_4$ Reduction. 7-Methoxy-10-(2-piperidinoethyl)-thianaphtheno[3,2-b]indole Hydrochloride (Table I, 46).—To a slurry of 1.0 g. of $LiAlH_4$ in 50 ml. of anhydrous ether, 3.8 g. of the above piperidide (Table I, 48) was added over a 15-minute period. The reaction mixture was refluxed with stirring for 16 hours, excess $LiAlH_4$ was then decomposed with ethyl acetate. After slow addition of 4.5 ml. of water and 2.0 ml. of 15% sodium hydroxide, the reaction mixture was filtered. The filter residue was washed thoroughly with ether. The combined filtrates were dried and concentrated *in vacuo*. The residue was converted to the hydrochloride and recrystallized from ethanol. It melted at 263–265° and gave no depression in mixture with material prepared by direct alkylation with 2-piperidinoethyl chloride; yield 3.6 g. (90%).

Anal. Calcd. for $C_{22}H_{24}N_2OS\cdot HCl$: N, 6.99. Found: N, 6.97.

7-Methoxy-10-(α-piperidinoacetyl)-thianaphtheno[3,2-b]indole Hydrochloride (Table I, 47).—A mixture of 2.0 g. of 7-methoxythianaphthenoindole and 10 g. of chloroacetic anhydride was heated to 140–150° for 1.5 hours. After cooling, 60 ml. of water was added. The excess chloroacetic anhydride slowly hydrolyzed and went into solution. The 10-(α-chloroacetyl)-thianaphthenoindole was filtered off and after recrystallization from methyl ethyl ketone, melted at 160–162°, yield 1.1 g. (42%).

Anal. Calcd. for $C_{17}H_{12}ClO_2NS$: C, 61.91; H, 3.67. Found: C, 62.02; H, 3.89.

A solution of 1.1 g. of 10-(α-chloroacetyl)-thianaphthenoindole in 10 ml. of benzene and 0.6 g. of piperidine was refluxed for one hour. The solution was filtered and concentrated *in vacuo*. The residue was recrystallized from ethyl acetate and melted at 152–154°, yield 0.9 g. (71%). The hydrochloride (Table I, 47) melted at 245–250°.

Anal. Calcd. for $C_{22}H_{22}N_2OS$: C, 69.81; H, 5.86. Found: C, 69.86; H, 6.08.

10-(3-Aminopropyl)-thianaphthenoindole (Table I, 3).—To a solution of 3.04 g. of $LiAlH_4$ in 100 ml. of anhydrous ether, 5.6 g. of 10-(2-cyanoethyl)-thianaphthenoindole[5] was added and the reaction refluxed for 20 hours. Excess $LiAlH_4$ was decomposed by addition of 9 ml. of ethyl acetate and after slowly adding 12 ml. of water and 6 ml. of 15% sodium hydroxide the reaction mixture was filtered and the ether solution washed with water and dried. Addition of anhydrous hydrogen chloride precipitated the hydrochloride which was recrystallized from dimethylformamide. It then melted over 300°, yield 5.3 g. (83%).

10-(2-Dimethylaminopropyl)-7-chlorothianaphtheno[3,2-b]indole Methochloride (Table I, 17).—Treatment of a solution of 10 g. of 7-chloro-10-(2-dimethylaminopropyl)-thianaphtheno[3,2-b]indole hydrochloride in 100 ml. of water with 10% aqueous potassium carbonate yielded the free base which after recrystallization from isopropyl alcohol melted at 103–105°. The methochloride was obtained by heating a solution of 3.5 g. of the base in 70 ml. of ethanol with 18 g. of methyl chloride to 90–100° in a sealed steel tube for one hour. After cooling, the pressure was released and the reaction mixture concentrated *in vacuo*. The methochloride was recrystallized from ethanol, m.p. 246–248° dec., yield 3.7 g. (92%).

7-Chloro-10-*n*-propylthianaphtheno[3,2-b]indole. (a) **From Hofmann Degradation of Methochloride.**—To a boiling solution of 2.5 g. of methochloride (Table I, 17) in 25 ml. of water, 6.0 g. of sodium hydroxide flakes was gradually added. Trimethylamine was split off. After five minutes the reaction mixture was cooled and extracted repeatedly with ether. Removal of the ether left a crystalline residue which was recrystallized from hexane. This gave 1.0 g. (53%) m.p. 130–132°, of 7-chloro-10-propenylthianaphthenoindole.

Anal. Calcd. for $C_{17}H_{12}ClNS$: C, 68.56; H, 4.06. Found: C, 68.38; H, 4.06.

Hydrogenation of 0.5 g. of the propenyl derivative in 80 ml. of glacial acetic acid with 0.2 g. of 5% Pd-on-charcoal gave 7-chloro-10-*n*-propylthianaphthenoindole, m.p. 90–92° (from hexane).

Anal. Calcd. for $C_{17}H_{14}ClNS$: C, 68.10; H, 4.71. Found: C, 68.16; H, 4.67.

(b) By Direct Alkylation of 7-Chlorothianaphtheno[3,2-b]indole.—A suspension of 5.2 g. of 7-chlorothianaphthenoindole and 0.8 g. of $NaNH_2$ in 35 ml. of toluene was refluxed for four hours and 2.5 g. of *n*-propyl bromide diluted with 5 ml. of toluene was added. The reaction mixture was kept at 70° for four hours, then cooled and filtered. The filtrate was evaporated to dryness and the residue extracted twice with 30 ml. of hexane. Evaporation of the hexane left a crystalline residue which was recrystallized twice from hexane and melted at 91–94°, yield 0.3 g. (5%).

Anal. Calcd. for $C_{17}H_{14}ClNS$: C, 68.10; H, 4.71. Found: C, 68.18; H, 4.71.

The 7-chloro-10-isopropylthianaphthenoindole was prepared by the same procedure using 2-bromopropane. The product melted at 143–147°.

Anal. Calcd. for $C_{17}H_{14}ClNS$: C, 68.10; H, 4.71. Found: C, 67.74; H, 4.90.

SUMMIT, NEW JERSEY

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

Derivatives of Heteroauxin. II. Some Substituted 2-Methyl-3-indoleacetic Acids[1]

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RECEIVED JULY 30, 1956

The preparation of some 2-methyl-3-indoleacetic acids substituted in the 5- or 4,5-positions and some of their derivatives is described.

A formative type of plant growth activity has been found in some derivatives of 2-methyl-3-indoleacetic acid,[2,3] a structural analog of the naturally occurring plant growth hormone, heteroauxin. Since this type of activity had not previously been noted in derivatives of heteroauxin, several carboxylic functional derivatives of the most active compound, 2-methyl-5-bromo-3-indoleacetic acid, have been prepared to determine the effect of the change in structure upon the biological activity. The methyl, ethyl, isopropyl and butyl esters were prepared by esterification of 2-methyl-5-bromo-3-indoleacetic acid.[2] The ethyl, isopropyl and butyl esters were also prepared directly from levulinic acid, *p*-bromophenylhydrazine hydrochloride, and the anhydrous alcohol by the Fox–Bullock modified Fischer synthesis.[4] The methyl ester was converted into 2-methyl-5-bromo-3-indoleacetamide by

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

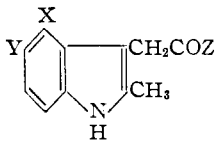
(2) F. J. Stevens and D. H. Higginbotham, THIS JOURNAL, **76**, 2206 (1954).

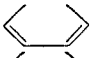
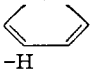
(3) All plant growth tests were performed by the Chemical Corps, Fort Detrick, Md., and will be reported elsewhere.

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

heating with methanolic ammonia under pressure. The procedure of Day,[5] using ammonia in ethylene glycol, failed to give the desired amide under the conditions specified for the preparation of phenylacetamide.

Some additional 2-methyl-3-indoleacetic acid derivatives with substituents involving the 5-position were also prepared for biological testing. Isopropyl and butyl 2-methyl-5-phenyl-3-indoleacetates were prepared from *p*-xenylhydrazine hydrochloride, the levulinic esters and sulfuric acid catalyst.[4] The crude esters obtained were solids and were not distilled under reduced pressure as is customary in this procedure, but were purified by recrystallization. Methyl 2-methyl-5-phenyl-3-indoleacetate was obtained by transesterification of the isopropyl ester and converted into 2-methyl-5-phenyl-3-indoleacetamide. The free acid, 2-methyl-5-phenyl-3-indoleacetic acid, was obtained by saponification of the isopropyl and butyl esters. 2-Methyl-4,5-benzindoleacetic acid,[6] 2,5-dimethyl-3-indoleacetic acid[7] and the corresponding ethyl esters were similarly prepared.[4] Butyl 2,5-dimethyl-3-indoleacetate was prepared by transesterification of the ethyl ester.



	X	Y	Z
I	-H	-Br	$-OCH_3$
II	-H	-Br	$-OC_2H_5$
III	-H	-Br	$-OC_3H_7$ (*iso*)
IV	-H	-Br	$-OC_4H_9$ (*n*)
V	-H	-Br	$-NH_2$
VI	-H	$-C_6H_5$	$-OC_3H_7$ (*iso*)
VII	-H	$-C_6H_5$	$-OC_4H_7$ (*n*)
VIII	-H	$-C_6H_5$	-OH
IX	-H	$-C_6H_5$	$-NH_2$
X			$-OC_2H_5$
XI			-OH
XII	-H	$-CH_3$	$-OC_2H_5$
XIII	-H	$-CH_3$	-OH
XIV	-H	$-CH_3$	$-OC_4H_9$ (*n*)

Experimental

Chemical.—The anhydrous alcohols used were reagent grade and were dried over calcium oxide. Levulinic acid was prepared from a practical grade (Chemo-Puro) by two distillations under reduced pressure. The isopropyl and butyl levulinates were prepared from the purified levulinic acid by esterification. Ethyl levulinate was available commercially (Eastman Kodak Co., research grade). The substituted phenylhydrazine hydrochlorides were prepared by diazotizing the corresponding aniline (Eastman Kodak Co.) and reducing with the appropriate reducing agent as indicated in the literature cited.

Isopropyl 2-Methyl-5-bromo-3-indoleacetate (III). Method A.—A solution of 2-methyl-5-bromo-3-indoleacetic acid[2] (5.4 g., 0.020 mole), isopropyl alcohol (135 ml.), toluene (25 ml.) and sulfuric acid (1 ml.) was refluxed for two hours. The mixture was distilled slowly through a 400-mm. Vigreux column (reflux ratio 1:5) until the boiling point of the alcohol was reached. The solution was poured into ice (200 g.) and extracted with three 50-ml. portions of ether. The ether extract was washed with dil. sodium bicarbonate, then with water, and dried over magnesium sulfate. Evaporation of the solvent gave the crude ester, which was recrystallized from methanol–water, yield 5.1 g. (82%), m.p. 103–103.5°.[8]

Anal. Calcd. for $C_{14}H_{16}O_2NBr$: C, 54.21; H, 5.20; N, 4.52. Found: C, 54.44; H, 4.99; N, 4.42.

Method B.—Essentially the procedure of Fox and Bullock[4] was used to effect a Fischer indole ring closure. One-tenth mole each of levulinic acid, *p*-bromophenylhydrazine hydrochloride,[2] isopropyl alcohol (125 ml.) and sulfuric acid (10 ml.) were refluxed for eight hours. The resulting solution was poured into ice, and extracted with three 200-ml. portions of ether. The extract was washed with dilute sodium bicarbonate, then with water, and dried over magnesium sulfate. Removal of the ether left an oil which solidified upon standing. The solid was washed with petroleum ether, and further purified by dissolving in ethanol, decolorizing, and then adding water to the boiling solution until it was cloudy. The heavy dark oil which precipitated in small quantity was removed by decantation. More water was added and the decantation process repeated until no more oil appeared. Upon cooling, 6.0 g. of colorless crystals of the ester separated, m.p. 101–102.5°. The above purification was repeated and gave 4.6 g. (15%) with m.p. 102.5–103.5°. A mixed m.p. with the product prepared by procedure A showed no depression.

***n*-Butyl 2-Methyl-5-bromo-3-indoleacetate (IV). Method A.**—The yield of IV prepared from 0.020 mole of the acid was 5.5 g. (82%), m.p. 101–102° (from methanol–water).

Anal. Calcd. for $C_{15}H_{18}O_2NBr$: C, 55.57; H, 5.60; N, 4.32. Found: C, 55.58; H, 5.85; N, 4.13.

Method B.—The same procedure was used as for isopropyl ester; yield 6.0 g. (36%) from 0.050 mole of reactants, m.p. 101–102°. The product was identical with that obtained in A.

Ethyl 2-Methyl-5-bromo-3-indoleacetate (II). Method A.—The yield from 1.3 g. (4.85 mmoles) of the acid was 1.1 g. (77%) m.p. 81–83° from chloroform–petroleum ether. A sample recrystallized from ether–petroleum ether had m.p. 83.5–84°.

Anal. Calcd. for $C_{13}H_{14}O_2NBr$: C, 52.72; H, 4.76; N, 4.73. Found: C, 52.44; H, 4.41; N, 4.60.

Method B.—The crude ester obtained from a 0.1-mole run was purified by distillation under reduced pressure. A fraction with b.p. 198–202° (0.8 mm.) was collected, yield 7.3 g. (25%). The distillate solidified and was identical with the compound prepared in A.

Methyl 2-Methyl-5-bromo-3-indoleacetate (I). Method A.—In the esterification of the acid with methanol, benzene was used instead of toluene to aid in the removal of water. The yield from 20 mmoles of acid was 5.5 g. (95%) of product with m.p. 97–99°. Recrystallization from methanol–water gave m.p. 99–100°.

Anal. Calcd. for $C_{12}H_{12}O_2NBr$: C, 51.08; H, 4.29; N, 4.97. Found: C, 50.91; H, 4.43; N, 4.82.

2-Methyl-5-bromo-3-indoleacetamide (V).—A solution of I (3.0 g., 11 mmoles) in methanol (50 ml., saturated with ammonia at 0°) was heated in a stainless steel reaction vessel at 100° for 80 hours. The methanol was evaporated, and the residue recrystallized from methanol–water with decolorization. The yield was 2.1 g. (67%), m.p. 158.5–160°. Another recrystallization from methanol gave 1.3 g. of m.p. 160–161°.

Anal. Calcd. for $C_{11}H_{11}ON_2Br$: N, 10.46. Found: N, 10.3.

Isopropyl 2-Methyl-5-phenyl-3-indoleacetate (VI).—A solution of *p*-xenylhydrazine hydrochloride[9] (20 g., 0.091 mole), isopropyl levulinate (17 g., 0.108 mole), isopropyl alcohol (250 ml.) and concd. sulfuric acid (20 ml.) were refluxed for 20 hours. The cooled solution was poured into ice. The light-cream-colored solid was collected, washed with dil. sodium bicarbonate, water, and was dried. The product was recrystallized from ethanol with decolorization; yield 18 g. (64%), m.p. 149–150°. Approximately the same yield was obtained using levulinic acid instead of the ester.

(5) M. Gordon, J. G. Miller and A. R. Day, THIS JOURNAL, **71**, 1245 (1949).

(6) A. Stecke and E. Fischer, *Ann.*, **242**, 267 (1887).

(7) F. Kogl and D. Kostermans, *Z. physiol. Chem.*, **235**, 201 (1935).

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

(9) Von D. Jerckel and H. Fischer, *Ann.*, **563**, 207 (1949).

Anal. Calcd. for $C_{20}H_{21}O_2N$: C, 78.15; H, 6.89; N, 4.58. Found: C, 78.21; H, 6.85; N, 4.32.

Butyl 2-Methyl-5-phenyl-3-indoleacetate (VII).—*p*-Xenylhydrazine hydrochloride (11.0 g., 0.05 mole), butyl levulinate (8.6 g., 0.050 mole), butyl alcohol (120 ml.) and sulfuric acid (10 ml.) were refluxed for 10 hours. The product was purified by the procedure used for VI. The yield of purified product was 2.7 g. (17%), m.p. 76–76.5°.

Anal. Calcd. for $C_{21}H_{23}O_2N$: C, 78.47; H, 7.21; N, 4.37. Found: C, 78.38; H, 7.04; N, 4.27.

2-Methyl-5-phenyl-3-indoleacetic Acid (VIII).—A solution of isopropyl ester VI (13.5 g., 0.044 mole) and potassium hydroxide (12.0 g., 0.044 mole) in methanol (100 ml.) was refluxed for three hours. The volume was reduced to 50 ml. and diluted with 150 ml. of water. The solution was decolorized, cooled, and acidified by adding 6 *N* hydrochloric acid until the *p*H was 4. The white crystalline precipitate was collected (11.3 g.) and recrystallized from ethanol–water with decolorization, yield 7.5 g. (64%), m.p. 155–156°. A similar yield was obtained from the butyl ester VII.

Anal. Calcd. for $C_{17}H_{15}O_2N$: C, 76.96; H, 5.70; N, 4.97. Found: C, 77.12; H, 5.66; N, 4.93.

2-Methyl-5-phenyl-3-indoleacetamide (IX).—The isopropyl ester VI (3.0 g., 98 mmoles) was transesterified with methanol (60 ml.) and sulfuric acid (0.5 ml.) by refluxing for five hours. The solution was poured into ice, and extracted with ether. The ether solution (150 ml.) was dried, evaporated, and the crude methyl ester, without further purification, was dissolved in methanol (100 ml.) that had been saturated at 0° with ammonia. The solution was heated for 120 hours at 100° in a stainless steel pressure vessel. Decolorization and concentration of the solution yielded 1.85 g. of tan crystals, m.p. 178.5–180°. Recrystallization from ethanol gave 1.35 g. (53%) of product, m.p. 180–181°.

Anal. Calcd. for $C_{17}H_{16}ON_2$: N, 10.6. Found: N, 11.0.

Ethyl 2-Methyl-4,5-benzindole-3-acetate (X).—Levulinic acid (16.0 g., 0.138 mole) and α-naphthylhydrazine hydrochloride[6] (27.0 g., 0.138 mole) were converted under nitrogen to the ester by the Fox–Bullock procedure.[4] The crude ester which was a solid was recrystallized from ethanol–water, yield 5.0 g. (13%), m.p. 135–136°.

Anal. Calcd. for $C_{17}H_{17}O_2N$: N, 5.36. Found: N, 5.09.

2-Methyl-4,5-benzindoleacetic Acid (XI).—A solution of the ethyl ester X (2.5 g., 9.4 mmoles) and potassium hydroxide (1.8 g.) in methanol was refluxed for 3.5 hours. Water (100 ml.) was added and the methanol removed by distillation. The solution was decolorized and acidified with 6 *N* hydrochloric acid to *p*H 4. The precipitated acid (2.0 g.) was recrystallized from acetone–chloroform; yield 1.8 g. (80%), m.p. 189–191° dec. No m.p. for the free acid was reported by Fischer.[6]

Anal. Calcd. for $C_{15}H_{13}O_2N$: N, 5.85. Found: N, 5.61.

Ethyl 2,5-Dimethyl-3-indoleacetate (XII).—Ethyl levulinate (22.2 g., 0.140 mole) and *p*-tolylhydrazine hydrochloride[10] (21.8 g., 0.145 mole) were converted under nitrogen to the ester by the Fox–Bullock procedure.[4] The crude ester, an oil, was distilled, and the fraction with b.p. 201–206° (0.5 mm.) was collected. The distillate solidified upon standing, m.p. 37–38°, yield 21.0 g. (67%).

Anal. Calcd. for $C_{14}H_{17}O_2N$: N, 6.06. Found: N, 5.87.

2,5-Dimethyl-3-indoleacetic Acid (XIII).[7]—Five grams (21.6 mmoles) of the ethyl ester XII was saponified and the free acid obtained in the usual manner; yield 3.6 g. (82%), m.p. 174–177° dec. After several recrystallizations from methanol the m.p. was 177–178° dec. The reported m.p. is 172–173°.[7]

Anal. Calcd. for $C_{12}H_{13}O_2N$: N, 6.89. Found: N, 6.78.

Butyl 2,5-Dimethyl-3-indoleacetate (XIV).—A solution of the ethyl ester XII (10 g., 0.043 mole) in butanol (35 g.) with sulfuric acid (0.5 ml.) as catalyst was refluxed for several hours and then distilled slowly through a Vigreux column until the b.p. of butanol was reached. Saturated sodium bicarbonate was added to the butanol solution to neutrality. The aqueous layer was discarded. The butanol layer was dried and the alcohol removed by distillation under reduced pressure (25 mm.). The residue was distilled at 0.5 mm., b.p. 151–165°, yield 7.5 g. (67%). Redistillation at 0.5 mm. gave b.p. 163–165°.

Anal. Calcd. for $C_{16}H_{21}O_2N$: N, 5.40. Found: N, 5.21.

(10) G. R. Robertson, "Laboratory Practice of Organic Chemistry," The Macmillan Co., New York, N. Y., 1943, pp. 276–277. The procedure given for phenylhydrazine was used.

AUBURN, ALABAMA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

Antiviral Compounds. I. Aliphatic Glyoxals, α-Hydroxyaldehydes and Related Compounds

BY BURRIS D. TIFFANY, JOHN B. WRIGHT, ROBERT BRUCE MOFFETT, RICHARD V. HEINZELMAN, RICHARD E. STRUBE, BROOKE D. ASPERGREN, EDWARD H. LINCOLN AND JOHN L. WHITE

RECEIVED JUNE 12, 1956

Preliminary screening data indicate that six types of aliphatic compounds are highly active against Newcastle disease and influenza viruses in the embryonated egg. These compounds include certain: (1) α-ketoaldehydes, (2) α-hydroxyaldehydes, (3) vicinal triketones, (4) cyclic 1,2-diketones, (5) α-keto primary alcohols and (6) enediols. The preparation of some of these compounds and their derivatives is described.

The discovery in these laboratories[1] that β-isopropoxy-α-ketobutyraldehyde was highly active against Newcastle disease virus in the embryonated egg led to an extensive study to determine what structural features are necessary and sufficient for this antiviral activity. Included in Table I are 95 of the compounds studied, along with activity data derived from a preliminary screen against Newcastle disease virus (NJKD strain) and influenza virus (PR-8 strain) when administered to embryonated eggs. In general, six classes of compounds show moderate or marked activity: (1) α-ketoaldehydes, (2) α-hydroxyaldehydes, (3) vicinal triketones, (4) cyclic 1,2-diketones, (5) α-keto primary alcohols and (6) certain enediols.

In all classes, conversion of the active moieties to relatively stable functional derivatives causes loss of activity, whereas at least part of the activity is retained where the derivatives are of the more labile type. For example, acetals and esters are

(1) G. E. Underwood, Fifth National Medicinal Chemistry Symposium at East Lansing, Michigan, June, 1956.