removed and fitted for distillation. The bath temperature was raised gradually as distillation proceeded, and the internal temperature rose to 160°. After 3 hr. the melt was poured into a mixture of 200 ml. of 95% ethanol and 20 ml. of concentrated hydrochloric acid. The solution was diluted slowly with acetone until the final volume approximated 700–800 ml. The yellow solid was separated by filtration and then hydrolyzed by stirring for 4 hr. under reflux with 150 ml. of concentrated hydrochloric acid and 300 ml. of water. The colorless tetrahydrochloride was filtered and washed with 95% ethanol. Small portions could be recrystallized from 4:1 water–concentrated hydrochloric acid mixture, but few samples could be obtained in analytical purity. Recrystallization from water yielded the yellow dihydrochloride.

NORTH CHICAGO, ILLINOIS

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

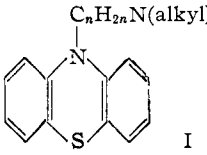
Thianaphtheno[3,2-b]indoles

BY L. H. WERNER, D. C. SCHROEDER AND S. RICCA, JR.

RECEIVED SEPTEMBER 17, 1956

A series of 10H-thianaphtheno[3,2-b]indoles was prepared by the Fischer indole reaction of phenylhydrazines with 3-hydroxythianaphthenes. These were alkylated in the 10-position with dialkylaminoalkyl chlorides. A number of these compounds showed antihistaminic activity.

Interest in the diverse and remarkable pharmacological activity of 10-dialkylaminoalkylphenothiazines (I),[1] *e.g.*, chloropromazine, promethazine and

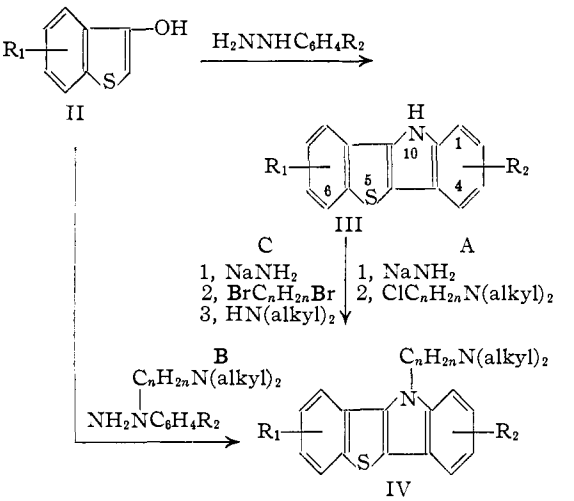


I

profenamine, induced us to synthesize 10-substituted thianaphtheno[3,2-b]indoles (IV) (Table I). The preparation of this type of compound had been studied previously by McClelland and D'Silva[2] and Dalgliesh and Mann.[3] However, their studies did not include compounds with basic sidechains at the 10-position.

The thianaphthenoindoles prepared in this series were obtained by a Fischer indole reaction of appropriately substituted 3-hydroxythianaphthenes (II)[4] with phenylhydrazines in glacial acetic acid. These 10H-thianaphtheno[3,2-b]indoles are easily obtained as they crystallize readily from the reaction mixture. In most cases, the basic sidechain was then attached by conversion to the sodio-derivative with sodium amide and treatment with a dialkylaminoalkyl chloride (procedure A). Three additional approaches also were studied. In general, the procedure we have designated as A gave the best yields. 3-Hydroxythianaphthenes (II) can react directly with N^2-substituted phenylhydrazines to give 10-substituted thianaphtheno[3,2-b]indoles (procedure B). This method was, for example, used to prepare 10-(2-diethylaminoethyl)-thianaphthenoindole (Table I, 4) and 10-(5-diethylamino-2-pentyl)-7-methoxythianaphthenoindole (Table I, 50).

The reaction of the sodio-derivative of III with an alkylene dibromide and treatment of the 10-(ω-bromoalkyl)-thianaphthenoindole with a secondary amine (procedure C) also gave the desired compounds (IV), but in a poorer yield than procedure A. The fourth approach studied is illustrated by the following example: 7-methoxy-10-(2-piperi-



R_1 = H, halogen, CH_3, OCH_3, OC_2H_5
R_2 = H, Cl, OCH_3, NO_2

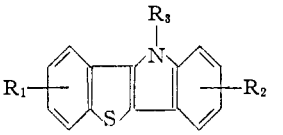
dinoethyl)-thianaphthenoindole (Table I, 46) can be prepared by $LiAlH_4$ reduction of the piperidide of 7-methoxythianaphthenoindoleacetic acid (Table I, 48). In addition, 10-(3-aminopropyl)-thianaphthenoindole (Table I, 3) was prepared by the $LiAlH_4$ reduction of 10-(2-cyanoethyl)-thianaphthenoindole.[3]

Dalgliesh and Mann[3] had found that a substituent in the 4-position of the 3-hydroxythianaphthene or in the 2-position of the phenylhydrazine blocked the formation of the thianaphthenoindole ring system. We have reinvestigated the reaction between 6-chloro-3-hydroxy-4-methylthianaphthene and phenylhydrazine in acetic acid and found that 7-chloro-9-methyl-thianaphthenoindole is formed (Table I, 64). Likewise, we were able to prepare the 9-chloro- (Table I, 23) and the 8,9-dichlorothianaphthenoindole (Table I, 58) from 4-chloro- and 4,5-dichloro-3-hydroxythianaphthene, respectively. On the other hand, we can

(1) P. Viaud, *J. Pharm. and Pharmacol.*, **6**, 361 (1954).
(2) E. W. McClelland and J. L. D'Silva, *J. Chem. Soc.*, 227 (1932).
(3) C. E. Dalgliesh and E. G. Mann, *ibid.*, 653 (1947).
(4) A large number of substituted 3-hydroxythianaphthenes have been prepared as intermediates in the synthesis of thioindigos. They have been reviewed by H. D. Hartough and S. L. Meisel in "The Chemistry of Heterocyclic Compounds. Compounds with Condensed Thiophene Rings," A. Weissberger, Consulting Editor, Interscience Publishers, Inc., New York, N. Y., 1954, pp. 63–79.

TABLE I

DERIVATIVES OF THIANAPHTHENO[3,2-*b*]INDOLE



No.	R_1	R_2	R_3	Formula	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	H	H[a,2]	$C_{14}H_9NS$	252–253						
2	H	H	$(CH_2)CH_2CH_2N(CH_3)_2\cdot HCl$	$C_{19}H_{20}N_2S\cdot HCl$	189–191	66.16	65.77	6.14	6.24		
3	H	H	$CH_2CH_2CH_2NH_2\cdot HCl$	$C_{17}H_{16}N_2S\cdot HCl$	>300	64.44	65.02	5.41	5.34	8 84	8.82
4	H	H	$CH_2CH_2N(C_2H_5)_2\cdot HCl$	$C_{20}H_{22}N_2S\cdot HCl$	191–193	66.93	66.80	6.46	6.70	7.81	7 48
5	H	H	$CH_2CH(CH_3)N(CH_3)_2\cdot HCl$	$C_{19}H_{20}N_2S\cdot HCl\cdot H_2O$	227–231	62.88	63.16	6.39	5.99		
6	H	H	$CH_2CH_2CH_2N$(N-methylpiperazine)$\cdot HCl$	$C_{23}H_{26}N_2S\cdot HCl$	200–204	69.23	68.78	6.82	7.22		
7	7-Cl	H	H[b]	$C_{14}H_8ClNS$	275	65 25	65.29	3.13	3.26		
8	7-Cl	H	$CH_2CH_2N(Et)_2\cdot HCl$	$C_{20}H_{21}ClN_2S\cdot HCl$	213–215	61.07	61.30	5.64	5.77		
9	7-Cl	H	$CH_2CH(CH_3)N(CH_3)_2\cdot HCl$	$C_{19}H_{19}ClN_2S\cdot HCl$	262–264	60.16	60.06	5.31	5.13		
10	7-Cl	H	$CH_2CH_2CH_2N(Et)_2\cdot HCl$	$C_{21}H_{23}ClN_2S\cdot HCl$	185–187	61.91	62.04	5.94	5.94		
11	7-Cl	H	$CH_2CH_2CH_2N(CH_3)_2\cdot HCl$	$C_{19}H_{1}ClN_2S\cdot HCl$	273–275	60.16	60.14	5.31	5.34		
12	7-Cl	H	CH_2CH_2N(pyrrolidine)$\cdot HCl$	$C_{20}H_{19}ClN_2S\cdot HCl$	>300	61.38	61.37	5.15	5.22		
13	7-Cl	H	CH_2CH_2N(piperidine)$\cdot HCl$	$C_{21}H_{21}ClN_2S\cdot HCl$	275–278	62.21	62.24	5.47	5.71		
14	7-Cl	H	CH_2CH_2N(morpholine)$\cdot HCl$	$C_{20}H_{19}ClN_2OS\cdot HCl$	288–292	58.96	58.69	4.95	5.08		
15	7-Cl	H	$CH_2CH_2NHC_2H_5\cdot HCl$	$C_{18}H_{17}ClN_2S\cdot HCl$	322–324	59.18	59.59	4.97	5.12		
16	7-Cl	H	$CH_2CH_2N(CH_3)_2\cdot HCl$	$C_{18}H_{17}ClN_2S\cdot HCl$	295–300	59.18	59.21	4.97	5.29		
17	7-Cl		$CH_2CH(CH_3)N^+(CH_3)_3Cl^-$	$C_{20}H_{22}Cl_2N_2S\cdot C_2H_5OH$	247–250	60.19	60.26	6.42	6.29		
18	8-Cl	H	H[c]	$C_{14}H_8ClNS$	222–225						
19	8-Cl	H	$CH_2CH(CH_3)N(CH_3)_2\cdot HCl$	$C_{19}H_{19}ClN_2S\cdot HCl\cdot{}^1/_2C_2H_5OH$	255–256	59.69	59.64	5.76	5.62		
20	6-Cl	H	H[3]	$C_{14}H_8ClNS$	229–232	65.24	65.17	3.13	3.17		
21	6-Cl	H	$CH_3C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{19}H_{19}ClN_2S\cdot HCl$	256–259	60.16	59.73	5.31	5.61		
22	6-Cl	H	$CH_2CH_2CH_2N(CH_3)_2\cdot HCl$	$C_{19}H_{19}ClN_2S\cdot HCl\cdot{}^1/_2H_2O$	172–176	58.76	58.78	5.53	5.45	7.21	6.99
23	9-Cl	H	H[b]	$C_{14}H_8ClNS$	124–128	65.24	64.92	3.13	3.41	5.43	5.09
24	9-Cl	H	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{19}H_{19}ClN_2S\cdot HCl$	252–255	60.16	59.86	5.31	5.40		
25	H	2 Cl	H[b]	$C_{14}H_8ClNS$	258–260	65.24	65.14	3.13	3.35	5.43	5.46
26	H	2-Cl	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{19}H_{19}ClN_2S\cdot HCl$	182–184	60.16	60.18	5.31	5.66	7.38	7.32
27	H	2-Cl	$CH_2CH_2CH_2N(CH_3)_2\cdot HCl$	$C_{19}H_{19}ClN_2S\cdot HCl$	261–263	60.16	59.76	5.31	5.38	7.38	7.32
28	H	2-Cl	CH_2CH_2N(pyrrolidine)$\cdot HCl$	$C_{21}H_{21}ClN_2S\cdot HCl$	264–266	62.21	62.27	5.47	5.74	6.91	6.69
29	H	4-Cl	H[b]	$C_{14}H_8ClNS$	164–166	65.24	65.17	3.13	3.43	5.43	5.58
30	H	4-Cl	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{19}H_{19}ClN_2S\cdot HCl$	225–227	60.16	59.69	5.31	5.52	7.38	7.13
31	H	4-Cl	CH_2CH_2N(pyrrolidine)$\cdot HCl$	$C_{21}H_{21}ClN_2S\cdot HCl$	284–286	62.21	61.99	5.47	5.41	6.91	6.98
32	H	3-Cl	H[d]	$C_{14}H_8ClNS$	281–283	65.24	65.18	3.13	3.19		
33	H	3-Cl	$CH_2C(CH_1)HN(CH_3)_2\cdot HCl$	$C_{19}H_{19}ClNS\cdot HCl$	245–247	60.16	59.96	5.31	5.57		
34	8-Br	H	H[e]	$C_{14}H_8BrNS$	223–225	55.64	55.31	2.67	2.79	4.63	4.45
35	8-Br	H	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{19}H_{19}BrN_2S\cdot HCl$	260–262	53.84	53.73	4.75	4.99		
36	7-Br	H	H[f]	$C_{14}H_8BrNS$	280–283	55.64	55.58	2.67	2.71		
37	7-Br	H	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{19}H_{19}BrN_2S\cdot HCl$	257–258	53.84	53.56	4.76	4.98		
38	8-F	H	H[g]	$C_{14}H_8FNS$	241–243	69.69	70.07	3.34	3.56		
39	8-F	H	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{19}H_{18}FN_2S\cdot HCl$	258–260	62.88	62.42	5.55	5.78		
40	7-F	H	H[h]	$C_{14}H_8FNS$	261–264					5.80	5.77
41	7-F	H	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{19}H_{19}FN_2S\cdot HCl$	267–271					7.72	7.67
42	8-CH_3	H	H[i]	$C_{15}H_{11}NS$	222–224	75.91	75.93	4.67	4.42		
43	8-CH_3	H	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{20}H_{22}N_2S\cdot HCl$	204–205	66.92	66.86	6 46	6.26		
44	7-CH_3O	H	H[i]	$C_{15}H_{11}NOS$	275–277	71.12	71.17	4.38	4.44		
45	7-CH_3O	H	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{20}H_{22}N_2OS\cdot HCl$	272–274	64.07	63.88	6.18	6.19		
46	7-CH_3O	H	CH_2CH_2N(pyrrolidine)$\cdot HCl$	$C_{22}H_{24}N_2OS\cdot HCl$	263–265	65.90	65.58	6.29	6.39	6.99	6.97
47	7-CH_3O	H	$COCH_2N$(pyrrolidine)$\cdot HCl$	$C_{22}H_{22}N_2O_2S\cdot HCl$	245–250					6.75	6.56
48	7-CH_3O	H	CH_2CON(pyrrolidine)	$C_{22}H_{22}N_2O_2S$	324–326					7.40	7.37
49	7-CH_3O	H	$(CH_3)_2N$(pyrrolidine)$\cdot$d-tartrate	$C_{25}H_{32}N_2OS\cdot C_4H_6O_6\cdot 2H_2O$	81–85	59.38	59.42	6.98	6.72		
50	7-CH_3O	H	$CH(CH_3)_2N(Et)_2\cdot$d-tartrate	$C_{24}H_{36}N_2OS\cdot C_4H_6O_6\cdot 2H_2O$	105–108	57.91	57.86	6.94	7.27	4.83	4.98
51	7-CH_3O	H	CH_2CH_2Br	$C_{17}H_{14}BrNOS$	159–162	56.67	56.45	3.92	3.85		
52	7-C_2H_5O	H	H[i]	$C_{16}H_{13}NOS$	255–259	71.89	71.69	4.90	4.82		
53	7-C_2H_5O	H	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{21}H_{24}N_2OS\cdot HCl$	295–297	64.84	64.70	6.48	6.67		
54	H	3-NO_2	H[i]	$C_{14}H_8N_2O_2S$	350 dec.						
55	H	3-NO_2	$CH_2CH_2N(Et)_2\cdot HCl$	$C_{20}H_{21}N_3O_4S\cdot HCl$	248–252	59.47	59.86	5.48	5.65	10.40	10.26
56	7,8-diCl	H	H[b]	$C_{14}H_7Cl_2NS$	247–249	57.55	57.13	2.42	2.49		
57	7,8-diCl	H	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{19}H_{18}Cl_2N_2S\cdot HCl$	267–269	55.14	54.97	4.62	4.63	6.77	6.79
58	8,9-diCl	H	H[b]	$C_{14}H_7Cl_2NS$	188–190	57.55	57.01	2.42	2.41	4.79	4.78
59	8,9-diCl	H	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{19}H_{18}Cl_2N_2S\cdot HCl$	272–274	55.14	55.33	4.62	4.82		
60	7 Cl	3 Cl	H[j]	$C_{14}H_7Cl_2NS$	260–262	57.55	57.28	2.42	2.46		

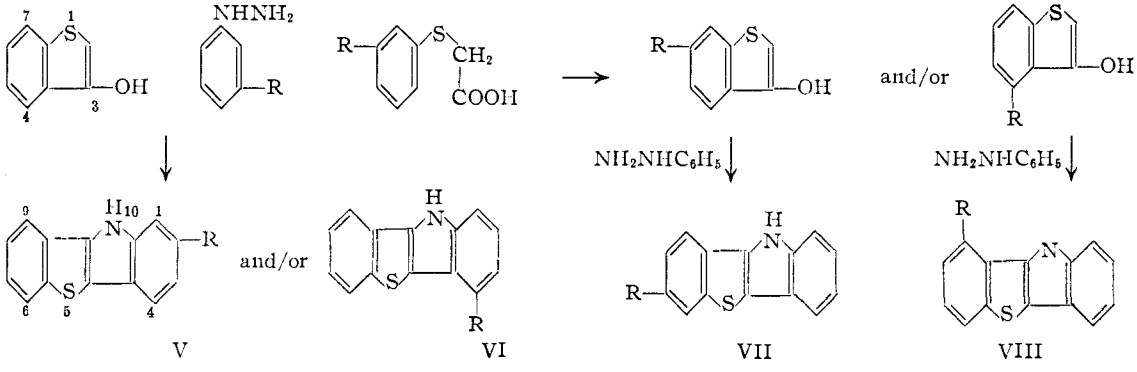
TABLE I (*Continued*)

No.	R_1	R_2	R_3	Formula	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
61	7-Cl	3-Cl	$CH_2CH_2CH_2N(CH_3)_2\cdot HCl$	$C_{19}H_{18}Cl_2N_2S\cdot HCl$	275	55.14	55.25	4.63	4.78		
62	7-Cl	2-Cl	H[k]	$C_{14}H_7Cl_2NS$	237–239	57.55	57.30	2.42	2.55		
63	7-Cl	2-Cl	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{19}H_{18}Cl_2N_2S\cdot HCl$	267–270	55.14	54.77	4.63	4.81		
64	7-Cl, 9-CH_3	H	H[b]	$C_{15}H_{10}ClNS$	168–172	66.28	66.26	3.71	3.83	5.15	5.14
65	7-Cl, 9-CH_3	H	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{20}H_{21}ClN_2S\cdot HCl$	252–255	61.07	60.78	5.64	5.64		
66	7-Cl	3-OCH_3	H[l]	$C_{15}H_{10}ClNOS$	232–234	62.59	62.92	3.50	3.53		
67	7-Cl	3-OCH_3	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{20}H_{21}ClN_2OS\cdot HCl$	225–229	58.67	58.80	5.42	5.62		
68	7-CH_3O	3-Cl	H[m]	$C_{15}H_{10}ClNOS$	300	62.59	62.49	3.50	3.53		
69	7-CH_3O	3-Cl	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{20}H_{21}ClN_2OS\cdot HCl$	270–272	58.67	58.50	5.42	5.45		
70	7-CH_3O	3-CH_3O	H[n]	$C_{16}H_{13}NO_2S$	253–255	67.83	68.00	4.62	4.72		
71	7-CH_3O	3-CH_3O	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{21}H_{24}N_2O_2S\cdot HCl$	244–246	62.29	62.33	6.22	6.40		
72	7-C_2H_5O	3-Cl	H[o]	$C_{16}H_{12}ClNOS$	295–300	63.67	63.57	4.01	4.08		
73	7-C_2H_5O	3-Cl	$CH_2CH_2CH_2N(CH_3)_2\cdot HCl$	$C_{21}H_{23}ClN_2OS\cdot HCl$	292–294	59.57	59.16	5.71	6.14		
74	7-C_2H_5O	3-Cl	$CH_2C(CH_3)HN(CH_3)_2\cdot HCl$	$C_{21}H_{23}ClN_2OS\cdot HCl$	282–285	59.57	59.81	5.71	5.82		

[a] E. W. McClelland, *J. Chem. Soc.*, 1588 (1929). [b] See Experimental part for preparation. [c] F. S. Fowkes and E. W. McClelland, *J. Chem. Soc.*, 187 (1941). [d] Prepared according to general procedure from 3-hydroxythianaphthene and 4-chlorophenylhydrazine.[8] [e] Prepared according to general procedure from 5-bromo-3-hydroxythianaphthene (R. Pummerer, *Ber.*, **42**, 2275 (1909)) and phenylhydrazine. [f] Prepared according to general procedures from 6-bromo-3-hydroxythianaphthene and phenylhydrazine. [g] Prepared according to general procedures from 5-fluoro-3-hydroxythianaphthene (J. E. Cole, U. S. Patent 2,061,186 (Nov. 17, 1936) and H. A. Lubs and A. L. Fox, U. S. Patent 2,061,200 (Nov. 17, 1936)) and phenylhydrazine. [h] Prepared according to general procedures from 6-fluoro-3-hydroxythianaphthene (see preceding reference) and phenylhydrazine. [i] Prepared from 6-methoxy-3-hydroxythianaphthene (P. Friedlander, *Ber.*, 49, 955 (1916)) and phenylhydrazine according to general procedure. [j] Prepared from 6-chloro-3-hydroxythianaphthene[7] and 4-chlorophenylhydrazine[8] according to general procedure. [k] Prepared from 6-chloro-3-hydroxythianaphthene[7] and 3-chlorophenylhydrazine[8] according to general procedure. [l] Prepared from 6-chloro-3-hydroxythianaphthene[7] and 4-methoxyphenylhydrazine (J. Altschul, *Ber.*, **25**, 1842 (1892)) according to general procedure. [m] Prepared from 6-methoxy-3-hydroxythianaphthene (P. Friedlander, ref. *i*) and 4-chlorophenylhydrazine according to general procedure. [n] Prepared from 6-methoxy-3-hydroxythianaphthene (P. Friedlander, ref. *i*) and 4-methoxyphenylhydrazine (J. Altschul, ref. *l*) according to general procedure. [o] Prepared from 6-ethoxy-3-hydroxythianaphthene (P. Friedlander, ref. *i*) and 4-chlorophenylhydrazine according to the general procedure.

confirm that 1-hydroxynaphtho[2,1-b]thiophene does not yield an indole derivative with phenylhydrazine in acetic acid. The 10H-9-substituted thianaphthenoindoles differ from those unsubstituted in the 9-position in that they melt lower and are considerably more soluble in benzene and acetic acid.

When either the phenylhydrazine or the S-phenylthioacetic acid, used in preparing the 3-hydroxythianaphthene, has *meta*-substituents, formation of two or more thianaphthenoindole positional isomers is possible (V–VIII). Assignment of the positions of the substituents in these cases was made on the basis of the infrared spectra.



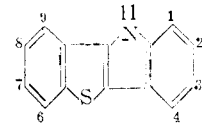
The region of the infrared spectra most applicable for interpretation is the out-of-plane carbon and hydrogen deformation vibrations. Absorption bands are given in Table II. The 2- and 7-chloro compounds indicated the presence of 1,2,4-trisubstituted benzene, thus ruling out possible substitution at C-4 and C-9, respectively. The 4- and 9-chloro compounds had bands characteristic of 1,2,3-trisubstituted benzene which eliminated positions 2 and 7, respectively. For the 2,7- and 3,7-dichloro compounds, the spectra contained bands which could only be attributed to 1,2,4-trisubstituted benzene. This eliminated 4,7- and 3,9-substituents, respectively; the 7,8-dichloro compounds had the band associated with 1,2,4,5-tetrasubstituted benzene, and the 8,9-dichloro compound had a band attributed to a 1,2,3,4-tetrasubstituted benzene.

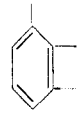
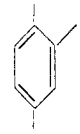
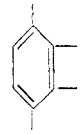
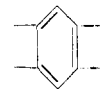
Dimethylaminopropyl-2-chloride was treated with all thianaphthenoindoles of this series. It has been reported that alkylation with dimethylaminopropyl-2-chloride gives two isomers due to the formation of an intermediate cyclic iminium derivative. This has been studied especially in the case of Amidone.[5] For this reason we investigated the structure of 7-chloro-10-(2-dimethylaminopropyl)-thianaphthenoindole (Table I, 9). The reaction product obtained by alkylation of 7-chlorothianaphthenoindole with dimethylaminopropyl-2-chloride was isolated as the hydrochloride in approximately 60% yield after repeated recrystallization. Further recrystallization did not

(5) E. M. Schultz, C. M. Robb and J. M. Sprague, THIS JOURNAL, **69**, 188 (1947).

TABLE II

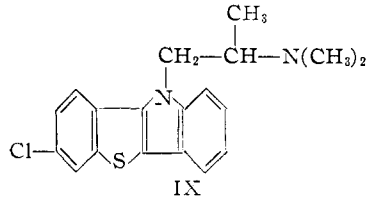
INFRARED BANDS OF THE BENZENE MOIETY OF CHLORINATED THIANAPHTHENOINDOLES



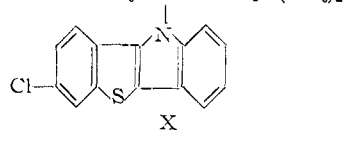
Substituents	NH					
None	3398	728(m), 739(s)				
2-Cl	3391	728(m), 755(s)		802(s), 869(m)		
3-Cl	3395	728(m), 753(s)		808(s), 859(m), 867(m)		
4-Cl	3404	728(s), 750(s)	728(s), 766(s)			
6-Cl	3388	742(s)	712(m), 778(m)			
7-Cl	3400	730(m), 745(s), 749(s)		819(s), 871(m)		
8-Cl	3411	730(w), 742(s)		812(s), 870(m)		
9-Cl	3422	722(s)	722(s), 761(m)			
2,7-diCl	3419			791(s), 799(s), 852(m)		
3,7-diCl	3418			810(s), 820(s), 870(m)		
7,8-diCl	3414	747(s), 750(s)				870(s), 877(s)
8,9-diCl	3426	732(m), 752(s)			820(m)	

s = strong, m = medium, w = weak; a Perkin–Elmer, model 21, infrared spectrophotometer was used. The prism was rock salt and the solvent was Nujol.

affect the melting point of 262–264°. Quaternization of the base with methyl chloride gave the methochloride (Table I, 17) which was subjected to a Hoffmann degradation. The resulting unsaturated compound was hydrogenated and then found to be identical by analysis and mixed melting point with 7-chloro-10-*n*-propylthianaphthenoindole prepared from *n*-propyl bromide and 7-chlorothianaphthenoindole. A pronounced depression in a mixed melting point was found with the 10-isopropyl derivative. These results indicate that the product melting at 262–264° is 7-chloro-10-(2 - dimethylaminopropyl) - thianaphthenoindole (IX) and not 7-chloro-10-(2-dimethylamino-1-methylethyl)-thianaphthenoindole (X).



IX



X

Pharmacology.—The compounds were tested by our Macrobiology and Microbiology Divisions. They showed interesting antihistaminic activity. In particular, the 2-dimethylaminopropyl sidechain and substitutions at the 7-, 8- and 9-positions seemed to enhance the activity. Substitutions in the 2-, 3- and 4-positions weakened the effect.

Acknowledgments.—We wish to thank Mr. L. Dorfman and his associates for the infrared absorption spectra, their interpretation and for the analytical data. We also thank Dr. G. C. Finger of the State Geological Survey Division, University of Illinois, for a sample of 3-fluoroaniline.

Experimental[6]

Preparation of 10H-Thianaphtheno[3,2-b]indoles. General Procedure: 7-Chlorothianaphthenoindole (Table I, 7).—A solution of 118 g. (0.64 mole) of 6-chloro-3-hydroxythianaphthene[7] in 1200 ml. of glacial acetic acid was warmed to 80°; 76 g. (0.7 mole) of phenylhydrazine was added over three minutes with stirring. The reaction mixture was heated for one hour during which the product separated in the form of shiny platelets. After cooling, the 7-chlorothianaphtheno[3,2-b]indole was filtered off washed with acetic acid and dried; yield 126 g. (76%), after recrystallization from toluene m.p. 275°. Exactly the same procedure was used for the preparation of the other 10H-thianaphthenoindoles.

Preparation of 3-Hydroxythianaphthenes from S-Phenylthioacetic Acids. General Procedure: 4-Chloro- and 6-Chloro-3-hydroxythianaphthene.—A mixture of 61.5 g. (0.3 mole) of 3-chlorophenylthioacetic acid, 180 g. of tetrachloroethane and 43.5 g. (0.32 mole) of phosphorus trichloride was heated slowly to 90° and kept at 90–93° for 3.5 hours. After standing for 16 hours at room temperature the solution was decanted from some sediment and added dropwise to a suspension of 45 g. (0.34 mole) of powdered anhydrous aluminum chloride in 360 g. of tetrachloroethane. The reaction mixture was kept at 60–65° for 25 minutes and then poured over ice and water. After decomposing all the aluminum chloride complex, the tetrachloroethane layer was separated, washed with water, dried, and concentrated to a small volume *in vacuo*. On cooling, red crystals of 6-chloro-3-hydroxythianaphthene (19.1 g. (34%), m.p. 140–145°) separated and were filtered off. The mother liquors, after concentrating, yielded 8.6 g. (15%) of crude 4-chloro-3-hydroxythianaphthene, m.p. 90–92°.

This same procedure was followed for the preparation of 5-chloro-, 7-chloro, 5-bromo-, 6-bromo-, 5-fluoro-, 6-fluoro-, 5-methyl-, 4,5-dichloro- and 5,6-dichloro-3-hydroxythianaphthene.

9-Chlorothianaphtheno[3,2-b]indole (Table I, 23).—A mixture of 18.5 g. of crude 4-chloro-3-hydroxythianaphthene, 180 ml. of glacial acetic acid and 11 g. of phenylhydrazine were heated for one hour on the steam-bath. After

(6) (a) All melting points are uncorrected and were taken by the capillary tube method in an aluminum block. (b) We wish to thank Mr. F. A. Moller, Miss M. A. Connolly and Miss P. M. Oke for technical assistance.

(7) P. Friedlander and L. Sander, *Ber.*, **57**, 648 (1924); C. Hansch and B. Schmidhalter, *J. Org. Chem.*, **20**, 1058 (1955).

standing at room temperature for 16 hours the reaction mixture was filtered and concentrated *in vacuo*. The crystalline residue was recrystallized from ethyl acetate and twice from alcohol and then melted at 124–128°. The yield of purified material was only 1 g. (4%).

2-Chloro- and 4-Chlorothianaphtheno[3,2-b]indole (Table I, 25, 29).—A mixture of 33.3 g. of 3-hydroxythianaphthene, 310 ml. of glacial acetic acid and 26.3 g. of *m*-chlorophenylhydrazine[8] was heated for one hour on the steam-bath. At this point the product crystallized and, after cooling, was filtered off and recrystallized from benzene; yield 17.4 g. (30%) of 2-chlorothianaphtheno[3,2-b]-indole, m.p. 262–264°. The acetic acid mother liquors were concentrated *in vacuo* and yielded 14.1 g. (25%) of 4-chlorothianaphtheno[3,2-b]indole, which after recrystallization from benzene melted at 164–166°.

S-(3-Bromophenyl)-thioacetic Acid. General Procedure.—To a solution of 37.2 g. of *m*-bromothiophenol[9] in 100 ml. of ethanol was added 18 g. of sodium hydroxide dissolved in 18 ml. of water. On addition of 20.4 g. of chloroacetic acid, dissolved in 50 ml. of ethanol, heat was evolved and crystalline material separated. The reaction mixture was refluxed with stirring for two hours and then concentrated *in vacuo*. The residue was dissolved in water and washed with ether. On acidifying the aqueous solution, the 3-bromophenylthioacetic acid precipitated. It was filtered off, dried and recrystallized from benzene; yield 31.3 g. (65%), m.p. 87–89°. The same procedure was used for the preparation of the S-phenylthioacetic acids required for the preparation of the 4-chloro-, 6-chloro- and 7-chloro-3-hydroxythianaphthene, 5-bromo- and 6-bromo-3-hydroxythianaphthene, for 5-fluoro- and 6-fluoro-3-hydroxythianaphthene and for 5-methyl-3-hydroxythianaphthene.

7,8-Dichloro- and 8,9-Dichlorothianaphthene[3,2-b]indole (Table I, 56, 58).—To a solution of 37 g. of crude mixture of 4,5- and 5,6-dichloro-3-hydroxythianaphthene[10] in 312 ml. of glacial acetic acid was added 20 g. of phenylhydrazine. The reaction mixture was heated for one hour and then cooled to room temperature overnight. Crystalline material had separated; it was filtered off and recrystallized from benzene. This yielded 15.7 g. (33%) of 7,8-dichlorothianaphtheno[3,2-b]indole, m.p. 247–249°. The acetic acid mother liquors were concentrated *in vacuo* and gave a second crop 7.3 g. (15%) of material that after recrystallization from benzene melted at 188–190° and corresponded to the 8,9-dichlorothianaphthenoindole.

7-Chloro-9-methylthianaphtheno[3,2-b]indole (Table I, 64).—A mixture of 8 g. of 6-chloro-3-hydroxy-4-methylthianaphthene,[11] 40 ml. of glacial acetic acid and 6 ml. of phenylhydrazine were heated on the steam-bath for one hour. Upon cooling, the product, 3.5 g. (32%) of 7-chloro-9-methylthianaphtheno[3,2-b]indole, crystallized. After recrystallization from benzene it melted at 168–172°.

N-Alkylation of Thianaphtheno[3,2-b]indoles. General Procedure.—A suspension of 20 mmoles of the thianaphthenoindole in 40 ml. of toluene was refluxed for four hours with 0.8 g. (20 mmoles) of sodium amide. After cooling to 50–60°, 22 mmoles of the substituted aminoalkyl chloride in toluene solution was added and the reaction mixture refluxed with stirring for three to four hours. After cooling to room temperature, the mixture was filtered, concentrated *in vacuo* and the residue dissolved in ethyl acetate. On addition of anhydrous hydrogen chloride, the hydrochloride precipitated; it was filtered off and recrystallized from alcohol, isopropyl alcohol or dimethylformamide. Normally, a yield in the range of 60–70% of the alkylated product is obtained.

10-(5-Diethylamino-2-pentyl)-7-methoxythianaphtheno-[3,2-b]indole *d*-Tartrate (Table I, No. 50).—Nitrosation of 9.36 g. of N-(5-diethylamino-2-pentyl)-aniline[12] followed by reduction by the method of Eisleb[13] gave 1-phenyl-1-(5-diethylamino-2-pentyl)-hydrazine. Distillation of the crude product gave two fractions: (1) b.p. 128–129° at 1 mm. consisting mainly of the substituted aniline and (2) b.p. 135–142° at 1 mm. calculated on the basis of the N-content to contain 79.6% of the desired hydrazine; yield 3.6 g. (29%).

Anal. Calcd. for $C_{15}H_{27}N_3$: N, 16.85. Found: N, 15.85 (fract. 2).

The above hydrazine (2.49 g.) was refluxed with 1.98 g. of 3-hydroxy-6-methoxythianaphthene in 20 ml. of glacial acetic acid for two hours, then filtered and acidified to *p*H 2 with anhydrous hydrogen chloride and concentrated *in vacuo* to an oil. After addition of 25 ml. of water, insoluble material was filtered off and the filtrate taken to dryness. Unreacted (5-diethylamino-2-pentyl)-aniline and -hydrazine were removed by extraction with concentrated hydrochloric acid. The remaining hydrochloride of (Table I, 50) was converted to the free base by treatment with potassium carbonate solution and extracted into ether; yield 0.5 g. (13%). A picrate was prepared from a sample and melted at 73–78°.

Anal. Calcd. for $C_{24}H_{30}N_2OS \cdot C_6H_3N_3O_7$: N, 11.23. Found: N, 11.51.

The remainder was converted to the *d*-tartrate, m.p. 105–108° (Table I, 50).

10-(2-Diethylaminoethyl)-thianaphtheno[3,2-b]indole Hydrochloride (Table I, 4).—To a solution of 20 g. of 3-hydroxythianaphthene in 250 ml. of glacial acetic acid was added 27.5 g. of 1-phenyl-1-(2-diethylaminoethyl)-hydrazine[13] (prepared from N-(2-diethylaminoethylaniline[14]) then it was heated for two hours to 100–110°). The reaction mixture was cooled, filtered, and acidified by adding an alcoholic solution of hydrogen chloride and concentrated *in vacuo*. The residue was dissolved in 200 ml. of water and extracted once with ether to remove insoluble material. Addition of concentrated hydrochloric acid precipitated the hydrochloride of compound 4 (Table I) which crystallized from isopropyl alcohol and melted at 191–193°, yield 20.1 g. (42%).

10-(2-Bromoethyl)-7-methoxythianaphtheno[3,2-b]indole (Table I, 51) **and 10-(6-Bromohexyl)-7-methoxy-thianaphtheno[3,2-b]indole.**—A suspension of 12.7 g. of 7-methoxythianaphthenoindole and 1.95 g. of sodium amide in 90 ml. of toluene was refluxed for four hours. After addition of 18.8 g. of ethylene dibromide, the reaction mixture was refluxed for an additional 16 hours, cooled and filtered. The filter residue yielded 10.6 g. of unreacted 7-methoxythianaphthenoindole. The filtrate was evaporated to dryness and the 10-(2-bromoethyl)-7-methoxythianaphthenoindole recrystallized from ethyl acetate, m.p. 159–162°, yield 0.8 g. (27% on the basis of reacted material).

An exactly analogous reaction with 1,6-dibromohexane gave the 10-(6-bromohexyl)-7-methoxythianaphthenoindole as a viscous oil which was used without further purification.

7-Methoxy-10-(2-piperidinoethyl)-thianaphtheno[3.2-b]-indole (Table I, 46) **and 7-Methoxy-10-(6-piperidinohexyl)-thianaphtheno[3,2-b]indole *d*-Tartrate** (Table I, 49).—A solution of 0.7 g. of 10-(2-bromoethyl)-thianaphthenoindole and 1 g. of piperidine in 10 ml. of benzene was refluxed for two hours, filtered and concentrated *in vacuo*. The residue was dissolved in ethyl acetate and converted to the hydrochloride of 46 (Table I) by addition of anhydrous hydrogen chloride. After recrystallization from alcohol it melted at 263–265°, yield 0.4 g. (57%).

By the same procedure 10-(6-bromohexyl)-7-methoxythianaphthenoindole was treated with piperidine to give 49 (Table I). The hydrochloride could not be obtained crystalline; therefore the *d*-tartrate was prepared.

Piperidide of 7-Methoxythianaphtheno[3,2-b]indole-10-acetic Acid (Table I, 48).—A suspension of 10.4 g. of 7-methoxythianaphthenoindole and 1.6 g. of sodium amide in 80 ml. of toluene was refluxed for four hours. After adding 7.27 g. of α-chloroacetylpiperidine[15] refluxing was continued for four hours. At the end of the reaction time considerable solid material was present in the reaction mixture.

(8) F. O. Chattaway and W. G. Humphrey, *J. Chem. Soc.*, 1323 (1927).

(9) F. G. Bordwell and H. M. Andersen, THIS JOURNAL, **75**, 6019 (1953).

(10) Obtained by cyclization of S-(3,4-dichlorophenyl)-thioacetic acid (Kalle and Co. German Patent 245,633; "Beilstein," Vol. 6, 1st supplement, p. 150) according to general procedure.

(11) K. Schirmacher and E. Fischer, German Patent 505,159 (Oct. 18, 1927); *C. A.*, **24**, 5769 (1930).

(12) Chiaki Tani, *J. Pharm. Soc. Japan*, **69**, 555 (1949); *C. A.*, **44**, 4435 (1950)

(13) O. Eisleb, German Patent 503,135 (July 25, 1930); *Centr.* **101**, II, 2051 (1930).

(14) W. Schulemann, F. Schonhofer and A. Wingler, German Patent 518,207, Jan. 26, 1927; *C. A.*, **25**, 2437 (1931).

(15) W. A. Jacobs, M. Heidelberger and I. P. Rolf, THIS JOURNAL, **41**, 458 (1919).

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[3] 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]

BY FRANK J. STEVENS, EUGENE C. ASHBY AND WILLIAM E. DOWNEY

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).