(VIII) was obtained from 3-benzyl-5-methyldiaziridine in 75% yield and had b.p. 110° (0.125 mm.), $n^{27}D$ 1.5033.

Anal. Calcd. for $C_{15}H_{26}N_2$: C, 68.66; H, 9.99; N, 21.35. Found: C, 68.65; H, 9.82; N, 21.39.

1-Methyl-3-phenyldiaziridine (X).—Benzal-N-methyl Schiff base[17] (47.6 g., 0.4 mole) was added to 200 ml. of 1:1 methanol–water. The mixture was cooled to 0° and 62 g. (2 moles) of monomethylamine was slowly bubbled into the solution. The reaction temperature was lowered to −10° and 52 g. (0.44 mole) of 95% hydroxylamine-O-sulfonic acid was added over a 5-min. period with stirring. The reaction temperature rose to 10° in spite of the Dry Ice–acetone bath and then returned to −10° at which it stirred for 30 min. and then was allowed to slowly rise to room temperature. 1,1-Dimethylhydrazine (60 g., 1 mole) was added slowly and the temperature rose from 35 to 45°. The mixture was cooled to 0° and extracted with six 600-ml. portions of ether and the ether extracts were dried (Na_2SO_4). The ether was removed with a rotary evaporator and the residual oil was distilled to yield 2 g. of benzonitrile, b.p. 45° (0.65 mm.) (identified by infrared) and 41.5 g. (77.5%) of product, b.p. 72–75° (0.4 mm.), $n^{26}D$ 1.6115; infrared: a strong band at 3370 cm.$^{-1}$ (NH).

Anal. Calcd. for $C_9H_{10}N_2$: C, 71.60; H, 7.50. Found: C, 71.56; H, 7.66.

(17) K. N. Campbell, A. H. Somers, and B. K. Campbell, *J. Am. Chem. Soc.*, **66**, 82 (1944).

Antidepressants.[1] II. Derivatives of Polynuclear Indoles

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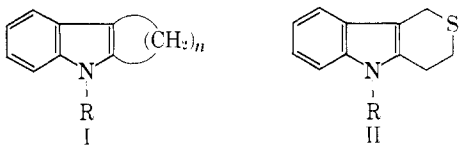
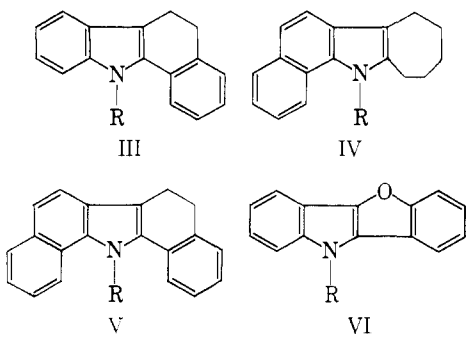
A series of N-substituted derivatives of polycyclic indole systems was prepared and examined for central nervous system activity. Examples of 1,3,4,5-tetrahydrothiopyrano[4,3-*b*]indoles, 5,6-dihydro-11H-benzo[*a*]-carbazole-2,3-pentamethylene-1H-benz[*g*]indole, 5,6-dihydro-13H-dibenzo[*a,i*]carbazole, and 10H-benzofuro-[3,2-*b*]indoles were included. The indole systems required were obtained *via* modifications of the Fischer indole synthesis and converted to N-substituted derivatives by varied methods. Some of the pharmacologic activities of the compounds are discussed.

The first paper[2] in this series described the synthesis and pharmacological behavior of a series of substituted 2,3-polymethyleneindoles (I). Because of the interesting pharmacological properties of certain members of this series, the investigation was extended to include a number of related types. The 1,3,4,5-tetrahydrothiopyrano[4,3-*b*]indoles (II, R = H) were selected



I II

because of an isosteric relationship with the 2,3-pentamethyleneindoles (I, n = 5) previously reported.[2] In an effort to investigate the effect on pharmacological activity of varying the size and shape of the aromatic moiety, analogous N-substituted derivatives of 5,6-dihydro-11H-benzo[*a*]carbazole[3] (III, R = H), 2,3-pentamethylene-1H-benz[*g*]indole (IV, R = H), 5,6-dihydro-13H-dibenzo[*a,i*]carbazole[4] (V, R = H), and 10H-benzofuro[3,2-*b*]indole[5] (VI, R = H), were prepared.



III IV

V VI

Penthian-4-one[6] was obtained from diethyl thiodipropionate by Dieckmann cyclization, followed by saponification and decarboxylation, and was converted directly to 1,3,4,5-tetrahydrothiopyrano[4,3-*b*]-indole[7] (II, R = H) by treatment with phenylhydrazine in glacial acetic acid.[3] In like manner, III, IV, and V were obtained, respectively, from phenylhydrazine and α-tetralone, α-naphthylhydrazine and cycloheptanone, and α-naphthylhydrazine and α-tetralone. 10H-Benzofuro[3,2-*b*]indole (VI, R = H) was prepared from phenylhydrazine and coumaranone as described by Cawley and Plant.[5]

The required dialkylaminoalkyl derivatives were obtained by treatment of an N-sodioindole (from the polycyclic indole and sodium hydride dispersion) with dialkylaminoalkyl chloride in dimethylformamide. After isolation, the products could be purified by distillation or converted directly to a suitable salt for testing. These compounds are shown in Tables I–III.[8]

The results of preliminary pharmacological screening were more promising in the tetrahydrothiopyrano[4,3-*b*]indole (II, R = H) and in the 5,6-dihydro-11H-benzo[*a*]carbazole (III, R = H) series than in the remainder (IV, V, and VI, R = H). Accordingly, II and III were investigated in considerable depth. In addition to a wide variety of dialkylaminoalkyl moieties, the N-(3-aminopropyl) and N-(3-methylaminopropyl)

(1) Paper II in this series.

(2) L. M. Rice, E. Hertz, and M. E. Freed, *J. Med. Chem.*, **7**, 313 (1964).

(3) C. U. Rogers and B. B. Corson, *J. Am. Chem. Soc.*, **69**, 2910 (1947).

(4) N. P. Buu-Hoï, N. Hoán, and N. H. Khôi, *J. Org. Chem.*, **14**, 492 (1949).

(5) S. R. Cawley and S. G. P. Plant, *J. Chem. Soc.*, 1214 (1938).

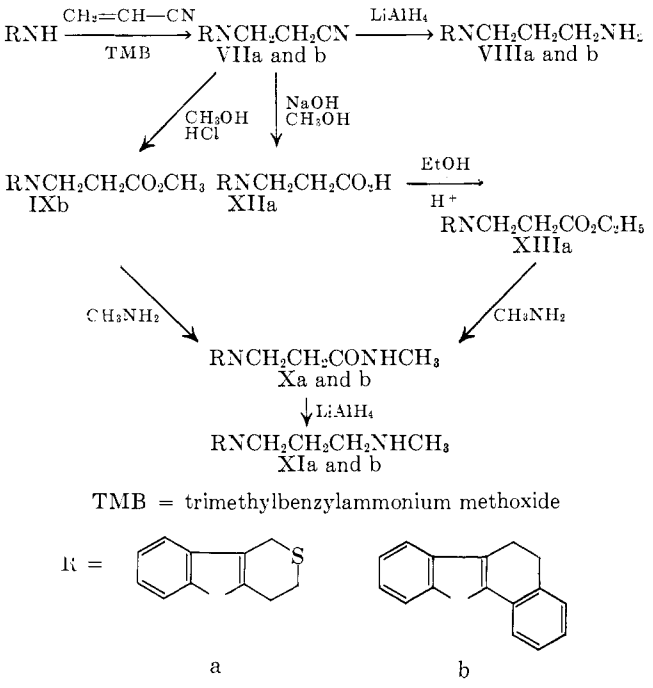
(6) G. M. Bennett and L. V. D. Searah, *ibid.*, 194 (1927).

(7) G. M. Bennett and W. B. Waddington, *ibid.*, 2820 (1929).

(8) In the course of this work, two lower homologs of 10-dimethylaminopropylbenzofuro[3,2-*b*]indole were reported by D. C. Schroeder, P. O. Corcoran, C. A. Holden, and M. C. Milligan, *J. Org. Chem.*, **27**, 586 (1962).

derivatives of II and III were prepared by the route previously described.[2] The unsubstituted compound (II or III, R = H) was cyanoethylated by the addition of acrylonitrile to a benzene solution of II or III containing a catalytic amount of trimethylbenzylammonium methoxide. The cyanoethyl derivatives VIIa and VIIb were reduced with lithium aluminum hydride, yielding VIIIa and VIIIb. To obtain the required monomethyl derivative, VIIb was esterified with anhydrous hydrogen chloride in methanol. When the methyl ester IXb was allowed to stand with methylamine in methanol for several days, a good yield of N-methylamide (Xb) resulted. Treatment of this substance with lithium aluminum hydride produced the N-(3-methylaminopropyl) compound XIb. When this sequence was attempted in the tetrahydrothiopyrano-[4,3-*b*]indole series, treatment of VIIa with hydrogen chloride in methanol apparently caused cleavage of the sulfur-containing ring, as indicated by a strong odor of hydrogen sulfide. The material then underwent extensive resinification, and no definite product could be isolated. As an alternative method, VIIa was hydrolyzed with alcoholic sodium hydroxide and the carboxyethyl compound XIIa was then esterified with ethanol, using sulfuric acid catalyst. The remaining steps were as anticipated: XIIIa with alcoholic methylamine gave N-methyl-1,3,4,5-tetrahydrothiopyrano[4,3-*b*]indole-5-propionamide (Xa), from which N-3-methylaminopropyl-1,3,4,5-tetrahydrothiopyrano-[4,3-*b*]indole (XIa) was obtained by reduction with lithium aluminum hydride. These reactions are sum-

SCHEME I



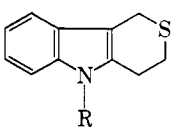
TMB = trimethylbenzylammonium methoxide

R =

a b

TABLE I

5-DIALKYLAMINOALKYL-1,3,4,5-TETRAHYDROTHIOPYRANO[4,3-*b*]INDOLES

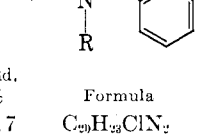


No.	R	M.p.,[a] °C.	Yield, %	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	% S Calcd.	% S Found
1	$(CH_3)_2NCH_2CH_2$	200–201	65.5	$C_{19}H_{24}N_2O_4S$	60.61	60.55	6.43	6.40	7.44	7.61	8.52	8.00
2	$(C_2H_5)_2NCH_2CH_2$	174–177	64.8	$C_{21}H_{28}N_2O_4S$	62.35	62.48	6.98	7.10	6.93	6.91	7.93	7.67
3	$(CH_3)_2NCH(CH_3)CH_2$	169–172	44.4	$C_{20}H_{26}N_2O_4S$	61.51	61.27	6.71	6.55	7.18	6.99	8.21	7.6
4	$C_4H_8NCH_2CH_2$	222–224	64.1	$C_{21}H_{26}N_2O_4S$	62.66	62.38	6.51	6.36	6.90	7.12	7.97	7.83
5	$C_5H_{10}NCH_2CH_2$	217–220	91.0	$C_{22}H_{28}N_2O_4S$	63.43	63.36	6.78	6.87	6.73	6.43	7.69	7.49
6	$C_4H_8ONCH_2CH_2$	189–191	69.2	$C_{21}H_{26}N_2O_5S$	60.26	60.00	6.26	6.54	6.70	6.54	7.66	7.45
7	$(CH_3)_2N(CH_2)_3$	199–200[b]	41.8	$C_{16}H_{23}ClN_2S$	61.80	61.61	7.45	7.30	9.03	9.24	10.30	9.91
8	$(C_3H_7)_2N(CH_2)_3$	150–153	78.8	$C_{24}H_{34}N_2O_4S$	64.54	64.64	7.67	7.59	6.27	6.46	7.18	6.92
9	$(CH_3)_2N(CH_2)_6$	103–107	32.6	$C_{23}H_{32}N_2O_4S$	63.86	63.63	7.46	7.66	6.48	6.57	7.41	7.15

[a] Fumaric acid salt. [b] Hydrochloride: Cl, calcd., 11.42; found, 11.33.

TABLE II

11-DIALKYLAMINOALKYL-5,6-DIHYDRO-11H-BENZO[*a*]CARBAZOLES



No.	R	M.p.,[a] °C.	Yield, %	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
1	$(CH_3)_2NCH_2CH_2$	228-231[b]	80.7	$C_{29}H_{33}ClN_2$	73.49	73.42	7.09	7.18	8.57	8.59
2	$(C_2H_5)_2NCH_2CH_2$	147–150	82.0	$C_{26}H_{30}N_2O_4$	71.86	71.79	6.96	7.05	6.45	6.51
3	$(CH_3)_2NCH(CH_3)CH_2$	159–162	67.1	$C_{25}H_{28}N_2O_4$	71.40	71.61	6.71	6.74	6.66	6.59
4	$(C_5H_{10})NCH_2CH_2$	204.5–206	99.3	$C_{27}H_{30}N_2O_4$	72.62	72.63	6.77	6.88	6.28	6.31
5	$(C_4H_8)NCH_2CH_2$	192.5–194	73.2	$C_{26}H_{28}N_2O_4$	72.20	72.35	6.52	6.70	6.48	6.32
6	$(CH_3)_2N(CH_2)_3$	217–222[c]	93.5	$C_{21}H_{25}ClN_2$	73.65	73.41	7.39	7.28	8.22	8.26
7	$(C_3H_7)_2N(CH_2)_3$	142–144	81.4	$C_{29}H_{36}N_2O_4$	73.08	72.88	7.61	7.74	5.88	5.83
8	$(CH_3)_2N(CH_2)_6$	104–107	85.6	$C_{28}H_{34}N_2O_4$	72.70	72.70	7.41	7.70	6.06	6.07

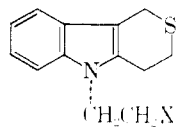
[a] Fumaric acid salt. [b] Hydrochloride: Cl, calcd., 10.85; found, 10.95. [c] Hydrochloride: Cl, calcd., 1028; found, 10.25.

TABLE III
DERIVATIVES OF POLYCYCLIC INDOLES

Structure	R	M.p.,[a] °C.	Yield,[b] %	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
IV	$(CH_3)_2N(CH_2)_3$	184.5–186	100	$C_{26}H_{32}N_2O_4$	70.53	71.46	7.39	7.27	6.42	6.37
	$(C_5H_{10})NCH_2CH_2$	215–216.5	76	$C_{28}H_{34}N_2O_4$	72.70	72.49	7.41	7.23	6.06	6.08
V	$(CH_3)_2N(CH_2)_3$	172–175	100	$C_{29}H_{26}N_2O_4$	74.02	73.73	6.43	6.29	5.95	5.92
VI	$(CH_3)_2N(CH_2)_3$	164.5–166	100	$C_{23}H_{24}N_2O_3$	67.63	67.34	5.92	5.84	6.86	6.81

[a] Fumaric acid salt. [b] Of crude base.

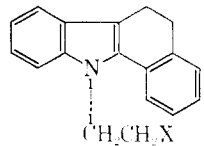
TABLE IV
DERIVATIVES OF 1,3,4,5-TETRAHYDROTHIOPYRANO[4,3-*b*]INDOLE



No.	X	M.p., °C.	Yield, %	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	% S Calcd.	% S Found
1	CN	152–154	68.5	$C_{11}H_{12}N_2S$	69.38	69.42	5.82	5.84	11.56	11.40	13.23	12.92
2	CH_2NH_2[a]	189–190	75.0	$C_{18}H_{22}N_2O_6S$	59.64	59.81	6.12	6.58	7.73	7.69	8.85	8.30
3	COOH	157–158.5	78.0	$C_{14}H_{15}NO_2S$	64.34	64.27	5.79	5.56	5.36	5.21	12.27	12.28
4	$CO_2C_2H_5$	80–82	100.0	$C_{16}H_{19}NO_2S$	66.40	66.19	6.62	6.60	4.84	4.76	11.08	10.85
5	$CONHCH_3$	142.5–143	68.7	$C_{12}H_{14}N_2OS$	65.66	65.55	6.61	6.53	10.21	10.02	11.68	11.08
6	CH_2NHCH_3[b]	190–192	31.1	$C_{13}H_{21}ClN_2S$	60.68	60.47	7.13	7.00	9.44	9.28	10.80	10.65

[a] Fumaric acid salt. [b] Hydrochloride.

TABLE V
DERIVATIVES OF 5,6-DIHYDRO-11H-BENZO[*a*]CARBAZOLE



No.	X	M.p., °C.	Yield, %	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
1	CN	156–157	71.1	$C_{19}H_{16}N_2$	83.79	83.63	5.92	6.05	10.29	10.27
2	CH_2NH_2	302–304[a]	70.6	$C_{19}H_{21}ClN_2$	72.94	72.98	6.77	6.80	8.96	8.91
3	CO_2CH_3	118–119	89.5	$C_{20}H_{19}NO_2$	78.66	78.66	6.27	6.43	4.59	4.60
4	$CONHCH_3$	169–170	84.9	$C_{20}H_{20}N_2O$	78.91	78.98	6.62	6.45	9.21	9.08
5	CH_2NHCH_3	200–201[a]	88.3	$C_{20}H_{23}ClN_2$	75.49	75.21	7.09	7.13	8.57	8.60

[a] Hydrochloride.

marized in Scheme I. The intermediates and products are shown in Tables IV and V.

Pharmacology.[9]—The N-aminoalkyl derivatives of II, III, IV, V, and VI prepared in the course of this investigation were submitted to a preliminary pharmacologic assessment for general stimulation, depression, and autonomic activity. Compounds which exhibited activity in this test were tested for antimorphine[10] and antireserpine[11] activity. Some of the results are shown in Table VI.

The compounds possessing the most significant activity were those of types II and III, *i.e.*, the derivatives of 1,3,4,5-tetrahydrothiopyrano[4,3-*b*]indole and 5,6-dihydro-11H-benzo[*a*]carbazole. In type II, antireserpine effects predominated over antimorphine, while in type III this order was reversed. N-Dimethylaminoethyl-1,3,4,5-tetrahydrothiopyrano[4,3-*b*]indole (Table VI, **10**) was found to have antireserpine activity equal to imipramine and little antimorphine effect. N-Piperidinoethyl-5,6-dihydro-11H-benzo[*a*]carbazole (Table VI, **11**) exhibited an antimorphine effect twice that of imipramine but showed only slight activity in the antireserpine test. Both of these compounds markedly potentiated the stimulation caused by amphetamine in the self-stimulation test[12] used to screen for antidepressant activity.

Experimental[13]

Materials.—The polycyclic indoles (II, III, V, and VI) were obtained from the appropriate ketone and phenylhydrazine in the manner described in the literature cited. 2,3-Pentamethylene-1H-benz[*g*]indole (IV, R = H), hitherto unreported, was obtained in 18% yield by essentially the procedure used for 5,6-dihydro-11H-benzo[*a*]carbazole[3] (III, R = H).

Alkylation Procedure.—The dialkylaminoalkyl derivatives of systems II, III, IV, V, and VI were obtained in the following manner.

A 500-ml. flask fitted with a stirrer, dropping funnel, and reflux condenser protected by a drying tube was charged with dimethylformamide (100 ml.). Sodium hydride (5.0 g., 0.10 mole, of a 52% dispersion in mineral oil) was then added. A solution of polycyclic indole (0.1 mole) in dimethylformamide

(9) Pharmacological testing was carried out by Dr. R. Tislow, Dr. M. Gluckman, Dr. L. Stein, and associates of these laboratories.

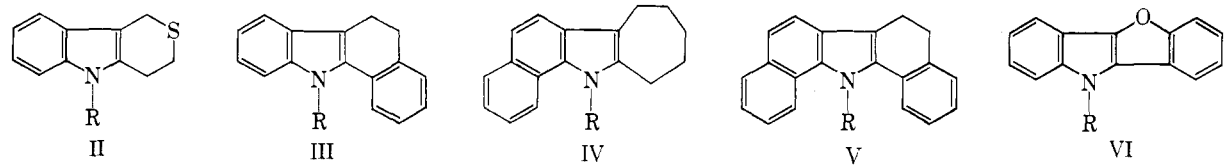
(10) C. H. Holten, *Acta pharmacol. toxicol.*, **13**, 113 (1957).

(11) B. Rubin, M. H. Malone, M. H. Waugh, and J. C. Burke, *J. Pharmacol. Exptl. Therap.*, **120**, 125 (1957).

(12) L. Stein and J. Seifter, *Science*, **134**, 286 (1961).

(13) Melting points were taken in open capillary tubes in a Thomas-Hoover apparatus and are corrected. Boiling points are not corrected.

TABLE VI
PHARMACOLOGICAL RESULTS[a]



II III IV V VI

No.	Compd. type	R	ED_{50}, mg./kg. vs. morphine	ED_{50}, mg./kg. vs. reserpine	D.m.a.,[b] mg./kg.
1	II	$Me_2NCH_2CH_2CH_2$	240	180	100
2	III	$Me_2NCH_2CH_2CH_2$	160	188	50
3	IV	$Me_2NCH_2CH_2CH_2$	>200	>400	200
4	V	$Me_2NCH_2CH_2CH_2$	>400	>400	400
5	VI	$Me_2NCH_2CH_2CH_2$	240	>800	100
6	II	$C_4H_8NOCH_2CH_2$	115	220	>400
7	II	$C_4H_8NCH_2CH_2$	382	210	400
8	II	$(C_2H_5)_2NCH_2CH_2$	Synergistic	15	400
9	II	$Me_2NCH(CH_3)CH_2$	>127	120	127
10	II	$Me_2NCH_2CH_2$	>400	42	200
11	III	$C_5H_{10}NCH_2CH_2$	91	390	50
12	III	$C_4H_8NCH_2CH_2$	375	430	127
13	III	$Et_2NCH_2CH_2$	>400	>400	40
14	III	$Me_2NCH(CH_3)CH_2$	40	>400	127
15	III	$NH_2CH_2CH_2CH_2$	>127	>127	127
16	Imipramine[c]		258	40	40

[a] Mice, *p.o.* The values reported are minimum doses producing activity; > means the compound was inactive up to indicated dose. [b] Decreased motor activity. [c] Used as standard.

was added dropwise, with stirring. The mixture was stirred at 30–35° for 1 hr. A solution of freshly distilled dialkylaminoalkyl chloride (0.1 mole) in dimethylformamide was added and the mixture was stirred 18 hr. at 25–30°. The reaction mixture was poured into ice–water (600 ml.) and acidified with concentrated HCl. The solution was extracted with ether to remove nonbasic components and then made alkaline with aqueous NaOH. The product was extracted with ether, and the extract was washed with saline and dried over Na_2SO_4. After removal of the drying agent, the base was converted to the salt with dry HCl.

1,3,4,5-Tetrahydrothiopyrano[4,3-*b*]indole-5-propionitrile (VIIa).—A 200-ml. three-necked flask fitted with thermometer, stirrer, addition funnel, and condenser protected by a drying tube was charged with 1,3,4,5-tetrahydrothiopyrano[4,3-*b*]indole (12.5 g., 0.066 mole), benzene (90 ml.), and trimethylbenzylammonium methoxide (0.3 ml. of a 40% solution in methanol). The mixture was warmed to 50° and acrylonitrile (3.9 g., 0.073 mole) was added. After the exothermic reaction subsided, the mixture was heated under reflux for 3 hr., then cooled to room temperature. A solid separated from the solution and was collected on a funnel, washed with cold benzene, and dried. Recrystallization from ethanol–acetone gave 10.9 g. (68.5%) of product, m.p. 152–154°.

5,6-Dihydro-11H-benzo[*a*]carbazole-11-propionitrile (VIIb).—Treatment of 109.7 g. (0.5 mole) of 5,6-dihydro-11H-benzo[*a*]-carbazole (III, R = H) with acrylonitrile (29.2 g., 0.55 mole) in the manner described for VIIa afforded 96.8 g. (71.1%) of nitrile, m.p. 155–157°, after recrystallization from ethanol–acetone.

1,3,4,5-Tetrahydrothiopyrano[4,3-*b*]indole-5-propionic Acid (XIIa).—A 200-ml. flask was charged with VIIa (3.0 g., 0.0124 mole), 90% ethanol (60 ml.), and NaOH (3.2 g., 0.08 mole). The mixture was heated under reflux for 27 hr. and then concentrated to dryness. The residue was dissolved in boiling water (125 ml.), decolorized with Norit A, and filtered hot. The filtrate was acidified to pH 1 with concentrated HCl (15 ml.). On cooling, the product crystallized and was collected by filtration. Recrystallization from aqueous methanol afforded 2.56 g. of product (78%), m.p. 157–158.5°.

Ethyl 1,3,4,5-Tetrahydrothiopyrano[4,3-*b*]indole-5-propionate (XIIIa).—A mixture of XIIa (8.7 g., 0.033 mole), ethanol (30 ml.), benzene (30 ml.), and concentrated H_2SO_4 (5 ml.) was stirred and heated under reflux for 5 hr. After standing overnight, the mixture was poured onto ice (100 g.). The layers were separated, using a separatory funnel. The aqueous phase was extracted with ether and combined with the benzene layer. The combined extracts were washed with sodium carbonate (10 ml. of a 10% aqueous solution), then with saline, and were dried over anhydrous $MgSO_4$. The solvents were removed under vacuum, leaving a solid product (9.5 g.), m.p. 78–81°. Recrystallization from methanol gave an analytical sample, m.p. 80–82°.

Methyl 5,6-Dihydro-11H-benzo[*a*]carbazole-11-propionate (IXb).—Anhydrous HCl was passed into a stirred suspension of VIIb (20.4 g., 0.075 mole) in absolute methanol (400 ml.) for 4 hr., resulting in a clear solution. After standing overnight, the solution was treated with 1.5 ml. of water and heated under reflux 2 hr. The reaction mixture was cooled and the precipitate was collected by filtration, washed with methanol, and dried. A second crop was obtained by concentrating the filtrate to a small volume. The combined solid was recrystallized from hot methanol, yielding 20.5 g. (89.5%) of product, m.p. 118–119°.

N-Methyl-1,3,4,5-tetrahydrothiopyrano[4,3-*b*]indole-5-propionamide (Xa).—A solution of XIIIa (8.0 g., 0.028 mole) in benzene (60 ml.) containing liquid methylamine (15 ml.) was sealed in a pressure flask and allowed to stand at room temperature 3 days. The reaction mixture was then transferred to an evaporating dish and concentrated to dryness on a steam bath. The solid residue was recrystallized from heptane–benzene, yielding 5.2 g. (68.7%) of product, m.p. 140.5–143°. An analytical sample prepared by further recrystallization from heptane–benzene had m.p. 142.5–143.5°.

N-Methyl-5,6-dihydro-11H-benzo[*a*]carbazole-11-propionamide (Xb).—A solution of IXb (15 g., 0.049 mole) in 75 ml. of methylene dichloride was mixed with a saturated methanolic solution of methylamine (75 ml.) and sealed in a pressure bottle. After 3 days at room temperature, the contents of the bottle were transferred to a beaker and the solid was collected on a Büchner funnel, washed with methanol, and dried. Recrystallization from hot methanol yielded 12.7 g. (84.9%) of Xb, m.p. 169–170°.

5-(3-Aminopropyl)-1,3,4,5-tetrahydrothiopyrano[4,3-*b*]indole (VIIIa).—A 1-l. three-necked flask fitted with a stirrer, addition funnel, and condenser protected by a drying tube was charged with anhydrous ether (200 ml.) and $LiAlH_4$ (2.5 g., 0.065 mole). To the well-stirred suspension was added a solution of VIIa (7.1 g., 0.03 mole) in warm benzene (150 ml.). The reaction mixture was stirred and heated under reflux for 3 hr. and then cooled to room temperature. Water (12 ml.) was added drop-

wise, with vigorous stirring. After the addition was completed, the mixture was stirred 2 hr. and filtered. The filter cake was washed with benzene and ether, and the filtrate was concentrated under vacuum, yielding 7.1 g. (98.2%) of an oil. The oil was dissolved in acetone (100 ml.) and added to a hot solution of fumaric acid (3.5 g.) in acetone (300 ml.), precipitating the fumarate salt of VIIIa. Recrystallization from acetone–methanol afforded 2.8 g. of product, m.p. 190–191°.

11-(3-Aminopropyl)-5,6-dihydro-11H-benzo[*a*]carbazole (VIIIb).—Reduction of VIIb (13.6 g., 0.05 mole) with $LiAlH_4$ (2.9 g., 0.08 mole) in the manner described for VIIIa afforded 12.1 g. of crude product. This was distilled, yielding 9.75 g. (71%) of product, which was collected at 218–228° (0.6 mm.). Treatment of the base in ethanol with an ethanolic solution of HCl gave the hydrochloride. Recrystallization from methanol yielded a product with m.p. 302–304°.

5-(3-Methylaminopropyl)-1,3,4,5-tetrahydrothiopyrano[4,3-*b*]indole (XIa).—A 1-l. three-necked flask fitted as above was charged with anhydrous ether (250 ml.) and $LiAlH_4$ (2.2 g., 0.06 mole). To this was added, with stirring, a warm solution of Na (4.7 g., 0.017 mole) in benzene (150 ml.). The reaction mixture was stirred at room temperature for 5 hr. Water (5 ml.) was added slowly and the mixture was allowed to stand overnight. The precipitate was filtered from the solution and washed well with ether. The combined filtrate and washings were washed with saline and dried over anhydrous $MgSO_4$. The solvent was removed, leaving 2.1 g. of base (50%), which was dissolved in absolute ethanol (20 ml.) and acidified with an ethanolic solution of HCl. Anhydrous ether was added until the solution became turbid. On cooling the solution, the hydrochloride crystallized out and was collected on a funnel, washed with ether, and dried. Recrystallization from ethanol afforded 1.7 g. (62%) of XIa, m.p. 190–192°.

11-(3-Methylaminopropyl)-5,6-dihydro-11H-benzo[*a*]carbazole (Xb).—Reduction of Xb (11.7 g., 0.38 mole) with $LiAlH_4$ (5 g., 0.13 mole) was carried out as described for Xa, yielding 10.5 g. (88.3%) of crude base. Conversion to the hydrochloride afforded 8.5 g. (74.8%), m.p. 200–201.5°.

Synthesis and Microbiological Properties of 3-Amino-3,4-dihydro-1-hydroxycarbostyril[1]

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3-Amino-3,4-dihydro-1-hydroxycarbostyril, synthesized by the catalytic hydrogenation of *o*-nitrophenylalanine hydrochloride, was compared with some structurally related compounds as growth inhibitors in several microbiological assays. Of these compounds, 3-amino-3,4-dihydro-1-hydroxycarbostyril inhibits the growth of *Escherichia coli*, *Leuconostoc dextranicum*, and *Lactobacillus arabinosus* at concentrations of 2 γ/ml. for each microorganism. In general, only a partial and noncompetitive reversal of 3-amino-3,4-dihydro-1-hydroxycarbostyril toxicity by certain protein hydrolysates and histidine was observed for each test organism, which suggests that other substituted derivatives of 3-amino-3,4-dihydrocarbostyrils may produce potent and noncompetitive antagonists.

In contrast to the strictly competitive-like response observed with phenylalanine in reversing the toxicity of *o*-aminophenylalanine for *Escherichia coli*, a noncompetitive reversal of the inhibitory effects of 3-amino-3,4-dihydrocarbostyril was demonstrated with phenylalanine for *E. coli* and *Leuconostoc dextranicum*.[3] In view of the biological results of 3-amino-3,4-dihydrocarbostyril with bacteria,[3] and its previously reported physiological activity,[4] further investigations with other substituted derivatives of 3-amino-3,4-dihydrocarbostyril seem warranted in an effort to produce noncompetitive antagonists as potential chemotherapeutic agents. Accordingly, a related derivative, 3-amino-3,4-dihydro-1-hydroxycarbostyril, was prepared and subsequently found to inhibit growth of several microorganisms, and only partial reversal of the inhibitions could be achieved with certain protein hydrolysates and with histidine. The method of synthesis as well as a preliminary report on its biologically antagonistic properties are herein presented.

Experimental[5]

Organic Syntheses. Ethyl 2-Acetamido-2-(*o*-nitrobenzyl)cyanoacetate.—To a solution of 10 g. of ethyl acetamidocyanoacetate in 100 ml. of magnesium-dried ethanol containing 1.35 g. of sodium was added 10.1 g. of *o*-nitrobenzyl chloride and the solution was allowed to reflux for 3 hr. Sodium chloride was removed by filtration from the hot reaction mixture, and the filtrate was cooled overnight to yield 16 g. of crude material. Recrystallization from ethanol–water gave 15 g. of product, m.p. 150–151°.

Anal. Calcd. for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95. Found: C, 54.81; H, 4.80.

Hydrolysis of Ethyl 2-Acetamido-2-(*o*-nitrobenzyl)cyanoacetate.—A 10-g. sample of ethyl 2-acetamido-2-(*o*-nitrobenzyl)-cyanoacetate was hydrolyzed in the presence of 100 ml. of concentrated HCl for 5 hr. to yield 6.95 g. of *o*-nitrophenylalanine hydrochloride, m.p. 219–220° dec. (lit.[6] m.p. 222–223°).

A 4.0-g. sample of ethyl 2-acetamido-2-(*o*-nitrobenzyl)cyanoacetate was hydrolyzed in the presence of 4.0 g. of sodium carbonate for 6 hr. Acidification of the reaction mixture with hydrochloric acid and subsequent cooling yielded a crystalline material. Recrystallization from ethanol gave about 1 g. of N-acetyl-*o*-nitrophenylalanine, m.p. 205–206°.

Anal. Calcd. for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.79. Found: C, 52.24; H, 5.23.

3-Amino-3,4-dihydro-1-hydroxycarbostyril Hydrochloride.—A 5.0-g. sample of *o*-nitrophenylalanine hydrochloride dissolved in 50% methanol (pH 1.5) was hydrogenated under 3.66 kg./cm.^{2} of hydrogen pressure in the presence of 200 mg. of platinum black for 5 hr. The hydrogenated solution, after removal of the catalyst, showed a pH of 3.6. Reduction in volume of the filtrate *in vacuo* yielded a residue which was recrystallized from ethanol–water to yield 1.2 g. of product, m.p. 258–263° dec.

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(2) Taken in part from the M.S. Thesis of Ok Hi Park Choun, Abilene Christian College, August, 1963.

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(5) All melting points were determined by the capillary technique and are corrected. The paper chromatograms were determined by the ascending techniques using the solvents indicated, and the spots were developed with ninhydrin reagent. The ultraviolet spectra were determined on a Bausch and Lomb Spectronic 505 spectrophotometer using water as solvent. The authors are indebted to D. Howell and D. Tharp for the elemental analyses.

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