TABLE II

CHEMICAL PROPERTIES

No. (from Table I)	Yield, %[a]	Mp, °C[b]	Cryst solvent	Formula[c]
11	58[e]	174–175	EtOH	$C_{16}H_{18}N_2O_2$
12	60[d]	201.5–203.5	MeOH	$C_{18}H_{22}N_2O_5$
13	43[e]	213.5–217	MeOH	$C_{17}H_{22}N_2O_4$
18	6.5[f]	109.5–111.5	EtOH–H_2O	$C_{15}H_{17}NO_2$
19	7.1[g]	209–210	Benzene–hexane	$C_{10}H_{13}NO$
20	66[e]	209–210	EtOH	$C_9H_{11}NO$
22	14.5[h]	171–172	MeOH	$C_{11}H_{13}NO_2$
23	25[e]	167–168	EtOH	$C_{12}H_{15}NO_3$
24	88[e]	273–274 dec	DMF–H_2O	$C_{10}H_{11}NO_3$

[a] Based on product melting not less than 2° below maximum obtained. [b] Footnote 3. [c] Prepared as described for **23** from acetoacetbenzylamide (in place of ethyl acetoacetate) and 2,4-pentanedione (in place of 1,3-cyclohexanedione). The solids did not dissolve, so 150 ml more of AcOH and 50 g more of Zn were added. [d] Prepared as described for **23** from acetoacet-3,4,5-trimethoxyanilide[4] (in place of ethyl acetoacetate) and 2,4-pentanedione (in place of 1,3-cyclohexanedione). The nitrosation reaction mixture became very thick and 300 ml more of AcOH and 150 ml more of H_2O was added. The crude product was crystallized from AcOH then from *i*-PrOH and finally from MeOH. [e] Preparation specifically described in the Experimental Section. [f] Prepared as described for **13** from ethyl benzoylacetate (in place of acetoacet-3,4,5-trimethoxyanilide). The crude product was extracted with ether, washed (H_2O), dried (Na_2SO_4), and distilled *in vacuo*. After removing unreacted ethyl benzoylacetate, solid was obtained which was recrystallized first from cyclohexane and then from 75% EtOH. [g] Prepared as described for **13** from 2,4-pentanedione (in place of acetoacet-3,4,5-trimethoxyanilide) and crude 1,2-cyclopentanedione monoxime [A. C. Cope, L. L. Estes, J. R. Emery, and A. C. Haven, *J. Am. Chem. Soc.*, **73**, 1199 (1951)] (in place of 2,3-butanedione 2-oxime). The crude product was recrystallized first from EtOH, with the aid of decolorizing charcoal, and then from benzene–hexane. [h] Prepared as described for **13** from cyclohexane-1,3-dione (in place of acetoacet-3,4,5-trimethoxyanilide) and 2,3,4-pentanetrione 3-monoxime (in place of 2,3-butanedione 2-oxime). [i] All compounds analyzed for C, H, N.

12°. After stirring at <12° for 3 hr and standing at room temperature overnight, a solution of 39 g (0.348 mole) of 1,3-cyclohexane dione in AcOH was added. Then 45 g of Zn dust was added at such a rate that the temperature did not rise above 60°. After stirring for 0.5 hr and refluxing for 3 hr the solution was separated from excess Zn and poured into 3 l. of ice water giving 40.9 g of yellow solid. This was recrystallized first from C_6H_6 and then from EtOH yielding 17.4 g of crystals, mp 167–168°.

4,5,6,7-Tetrahydro-3-methyl-4-oxo-2-indolecarboxylic Acid (24).—A solution of 21.2 g (0.096 mole) of the above ester and 10 g of NaOH in 100 ml of H_2O and 50 ml of EtOH was stirred under reflux for 8 hr, diluted with H_2O, and washed (Et_2O). The aqueous solution was acidified with HCl giving 18.1 g of acid which was recrystallized from DMF–H_2O yielding 16.25 g of crystals, mp 273–274° dec.

4,5,6,7-Tetrahydro-3-methyl-4-oxoindole (20).—Eleven grams (0.057 mole) of the above acid was heated with stirring in a Claisen flask in an oil bath at 266–270° until evolution of CO_2 ceased. The product was then distilled under high vacuum giving 6 g of white solid, mp 208–210°. Recrystallization from EtOH yielded 5.7 g of white crystals, mp 209–210°.

3',4',5'-Trimethoxy-2,4,5-trimethylpyrrole-3-carboxanilide (13).—To a solution of 26.7 g (0.1 mole) of acetoacet-3,4,5-trimethoxyanilide,[4] 13.6 g (0.1 mole) of $NaOAc.3H_2O$, and 10.1 g (0.1 mole) of 2,3-butanedione 2-oxime in 50 ml of AcOH was slowly added with stirring, during 10 min, 17.3 g (0.25 g-atom) of Zn dust. After stirring under reflux for 1.5 hr the mixture was poured into ice water giving 28.3 g of dark solid. This was recrystallized twice from MeOH, with the aid of decolorizing charcoal, yielding 13.4 g of tan crystals, mp 213.5–217°.

(13) Melting points were taken in capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compounds showed no need for correction. Ir spectra were obtained on all pure compounds and were in accordance with the proposed structure. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for these elements or functions were within ±0.4% of theoretical.

(14) From Aldrich Chemical Co., Milwaukee, Wis.

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Some Analogs of 1-*p*-Chlorobenzyl-5-methylindole-3-acetic Acid

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Earlier we reported on the synthesis and biological properties of a series of 2-substituted 1-*p*-chlorobenzyl-5-methylindole-3-acetic acids.[1] Our interest in these compounds stemmed from the α-glycerophosphate dehydrogenase (GPDH) inhibitory activity of 1-*p*-chlorobenzyl-2-ethyl-5-methylindole-3-acetic acid (**40**), an activity which might be of potential value in the chemotherapy of tumors.[1] Since none of the alterations which were made at the 2 position produced any over-all improvement in biological activity, it was decided to synthesize some related compounds having structural modifications at other locations in the molecule. These new compounds (**1**–**9**) and their properties are listed in Table I.

For the synthesis of 1-*p*-chlorobenzyl-2-ethylindole-3-acetic acid (**1**) and 1-*p*-chlorobenzyl-2-ethyl-6-methylindole-3-acetic acid (**2**), 2-ethylindole (**12**)[2] and 2-ethyl-6-methylindole (**13**)[2] were obtained by application of the Madalung[3a] reaction to propiono-*o*-toluidide (**10**)[4] and propiono-*p*-xylidide (**11**).[5] The acetic acid side chains were elaborated by means of the gramine[3b] sequence and the final products were obtained by hydrolysis after N-alkylation of the esters **20** and **21** with *p*-chlorobenzyl chloride. The experimental methods used for obtaining these compounds were essentially the same as those used earlier[1] for the synthesis of similar products. The intermediates obtained during the preparation of **1** and **2** are described in Table II.

An alternative route to **1**, wherein the nitrile **16** was alkylated with *p*-chlorobenzyl chloride to give 1-*p*-chlorobenzyl-2-ethylindole-3-acetonitrile (**16a**) which in turn was hydrolyzed to **1** with base, gave a lower over-all yield because of the low yield in the alkylation step.

Hydrogenolysis of 1-*p*-chlorobenzyl-2-ethyl-5-methylindole-3-acetic acid[1] in the presence of a Raney nickel catalyst gave 1-benzyl-2-ethyl-5-methylindole-3-acetic acid (**3**).

For the synthesis of 1-*p*-chlorobenzyl-2-ethyl-5-methylindole-3-glyoxylic acid (**4**) and its diethylamide

(1) E. Walton, C. H. Stammer, R. F. Nutt, S. R. Jenkins, and F. W. Holly, *J. Med. Chem.*, **8**, 204 (1965).

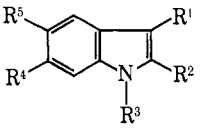
(2) Prepared earlier in lower yield by a different method by R. Quelet and M. Chastrette, *Compt. Rend.*, **249**, 1526 (1959).

(3) W. C. Sumpter and F. M. Miller, "The Chemistry of Heterocyclic Compounds," Vol. 8, A. Weisberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1954: (a) p 15; (b) p 62; (c) p 3.

(4) M. T. Dangyan, *Izv. Akad. Nauk Arm. SSR*, 3 (1944); *Chem. Abstr.*, **40**, 3410[3] (1946).

(5) C. V. Bowens and L. E. Smith, *J. Am. Chem. Soc.*, **62**, 3522 (1940).

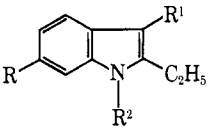
TABLE I



No.	R^1	R^2	R^3	R^4	R^5	Recrystn solvent[b]	Yield,[c] %	Mp, °C	Formula	Analyses
1	CH_2COOH	C_2H_5	$CH_2C_6H_4Cl$-*p*	H	H	A	81	135–138	$C_{19}H_{18}ClNO_2$	C, H, Cl, N
2	CH_2COOH	C_2H_5	$CH_2C_6H_4Cl$-*p*	CH_3	H	A	72	157–168	$C_{20}H_{20}ClNO_2$	C, H, Cl, N
3	CH_2COOH	C_2H_5	$CH_2C_6H_5$	H	CH_3	A	77	146–149	$C_{20}H_{21}NO_2$	C, H, N
4	COCOOK	C_2H_5	$CH_2C_6H_4Cl$-*p*	H	CH_3	B	70		$C_{20}H_{17}ClKNO_3$	C, H, Cl, N
5	$COCON(CH_3)_2$	C_2H_5	$CH_2C_6H_4Cl$-*p*	H	CH_3	A	73	138–140	$C_{22}H_{23}ClN_2O_2$	C, H, Cl, N
6	CH_2COOH	C_2H_5	$CH_2C_6H_4Cl$-*p*	H	CH_3O	A	80	136–138	$C_{20}H_{20}ClNO_3$	C, H, Cl, N
7	CH_3	$(CH_2)_2COOH$	$CH_2C_6H_4Cl$-*p*	H	CH_3O	A	64	130–132	$C_{20}H_{20}ClNO_3$	C, H, Cl, N
8	CH_2COOH	$COCH_3$	$CH_2C_6H_4Cl$-*p*	H	CH_3	A	41	170–175	$C_{20}H_{18}ClNO_3$	C, H, Cl, N
9	CH_2COOH	$COCH_2Cl$	$CH_2C_6H_4Cl$-*p*	H	CH_3	C	36	180–185	$C_{20}H_{17}Cl_2NO_3$	C, H, N
39[a]	CH_2COOH	C_2H_5	H	H	CH_3					
40[a]	CH_2COOH	C_2H_5	$CH_2C_6H_4Cl$-*p*	H	CH_3					

[a] Prepared previously.[1] [b] A, C_6H_6–petroleum ether (bp 30–60°); B, EtOH–H_2O; C, C_6H_6, then Et_2O. [c] From immediate precursor.

TABLE II



No.	R	R^1	R^2	Recrystn solvent[a]	Yield,[b] %	Mp, °C	Formula	Analyses
12	H	H_2	H	A	61	42–44[c]		
13	CH_3	H_2	H	A	73	71–72[d]		
14	H	$CH_2N(CH_3)_2$	H	B	85	117–119	$C_{13}H_{18}N_2$	C, H, N
15	CH_3	$CH_2N(CH_3)_2$	H	C	37	96–98	$C_{14}H_{20}N_2$	C, H, N
16	H	CH_2CN	H	D	82	119–121	$C_{12}H_{12}N_2$	C, H, N
17	CH_3	CH_2CN	H	D	73	77–78	$C_{13}H_{14}N_2$	C, H, N
18	H	CH_2COOH	H	E	78	193–203	$C_{12}H_{13}NO_2$	C, H, N
19	CH_3	CH_2COOH	H	D	90	163–172	$C_{13}H_{15}NO_2$	C, H, N
20	H	CH_2COOCH_3	H	Oil				
21	CH_3	CH_2COOCH_3	H	G	66	61–63	$C_{14}H_{17}NO_2$	C, H, N
22	H	CH_2COOCH_3	$CH_2C_6H_4Cl$-*p*	F	64	99–103	$C_{20}H_{20}ClNO_2$	C, H, Cl, N
23	CH_3	CH_2COOCH_3	$CH_2C_6H_4Cl$-*p*	Oil				

[a] A, petroleum ether (bp 30–60°); B, cyclohexane; C, hexane; D, Et_2O–petroleum ether; E, Me_2CO–petroleum ether; F, Et_2O; G, C_6H_6–petroleum ether. [b] From immediate precursor. [c] Lit.[2] mp 46°. [d] Lit.[2] mp 68°.

(**5**), 1-*p*-chlorobenzyl-2-ethyl-5-methylindole (**24**)[6a] was treated with oxalyl chloride.[6b,c] Decomposition of the intermediate 1-*p*-chlorobenzyl-2-ethyl-5-methylindole-3-glyoxylyl chloride (**25**) with aqueous K_2CO_3 gave the glyoxylic acid as its water-insoluble, alcohol-soluble potassium salt (**4**). Alternatively, treatment of the acid chloride (**25**) with dimethylamine produced the dimethylamide (**5**).

The synthesis of 1-*p*-chlorobenzyl-2-ethyl-5-methoxyindole-3-acetic acid (**6**) was not straightforward. Several attempts to prepare 2-ethyl-5-methoxyindole (**26**) from 4-methoxypropiono-2-toluidide (**27**) by the Madalung[3a] method were unsuccessful. Presumably, cleavage of the methoxy group occurred in the basic medium at the high temperatures required for the reaction. Alternatively, a Fisher[3c] reaction between N-*p*-chlorobenzyl-N-*p*-methoxyphenylhydrazine hydrochloride (**28**) and ethyl 3-propionylpropionate (**29**)[7] gave no isolable amount of the methyl ester of **6**, but, as demonstrated by nmr measurements, produced the isomeric methyl 3-(1-*p*-chlorobenzyl-5-methoxy-3-methylindole-2)propionate (**31**), which on hydrolysis gave the corresponding acid (**7**) in good yield.

The 5-methoxyindole (**6**) was finally synthesized by an indirect route. The unsymmetrical hydrazine hydrochloride (**28**) reacted with 2,3-butanedione (**32**) under Fisher conditions, and methyl 1-*p*-chlorobenzyl-5-methoxy-2-indolyl ketone (**33**) was obtained in satisfactory yield. Wolff–Kishner reduction of the keto function gave 1-*p*-chlorobenzyl-2-ethyl-5-methoxyindole (**26**) on which the acetic acid side chain was developed by the gramine sequence. In this case, both the synthesis of the gramine (**34**) and displacement with cyanide to form the nitrile (**35**) required more strenuous conditions and gave lower yields than did the same sequence applied to indoles unsubstituted at the heteroatom.

The synthesis of the 2-acylindoles (**8**) and (**9**) was accomplished by the acylation of methyl 1-*p*-chlorobenzyl-5-methylindole-3-acetate (**36**)[1] with the appropriate acid chloride. Reaction of **36** with acetyl chloride at 25° for 5 min with zinc chloride as catalyst gave methyl 2-acetyl-1-*p*-chlorobenzyl-5-methylindole-3-acetate (**37**), the acid (**8**) being obtained by alkaline hydrolysis. The corresponding reaction of **36** with

(6) (a) E. Walton, F. W. Holly, and S. R. Jenkins, *J. Org. Chem.*, **33**, 192 (1968); (b) by the method of M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6208 (1954); (c) see also G. Domschke and H. Fürst, *Chem. Ber.*, **94**, 2353 (1961).

(7) J. Cason and E. J. Reist, *J. Org. Chem.*, **23**, 1496 (1958).

chloroacetyl chloride was much more sluggish. In the presence of zinc chloride no reaction was detected after several hours at room temperature, whereas heating at 110° for 5 min gave the desired methyl 2-chloroacetyl-1-*p*-chlorobenzyl-5-methylindole-3-acetate (**38**). Without $ZnCl_2$, **38** was produced from **36** after 5 hr of refluxing with chloroacetyl chloride. The ester (**38**) was converted to the acid (**9**) by ester exchange in acetic acid containing HCl; alkaline hydrolysis was completely unsuccessful.

The end products (**1**–**9**) of these syntheses were tested in several *in vitro* and *in vivo* systems[8] and the results are listed in Table III. None of these new compounds

TABLE III

	—GPDH—		—LDH—		—IC_{50}, μg/ml—	
Compd	$M \times 10^4$	% inhib	$M \times 10^4$	% inhib	*Clostridium feseri*[a]	KB cell culture
1	0.6	50	12.6	0	65	33
2	1.0	50	3.0	0	25	60
3						40
4	4.0	50	12.6	0	52	>100
5	3.2	0	3.2	0	>1000	3.3
6	0.8	50	6.3	0	25	33
7	5.0	0	5.0	0		33
8	2.5	50	6.4	50	153	60
9	2.0	0	2.0	0	58	3.3
39	16.0	0	16.0	0	>1000	>100
40	1.0	50	7.0	0	26	60

[a] Average of two determinations.

showed an appreciable improvement in GPDH inhibitory activity when compared with the lead compound (**40**).[1] Four of the compounds (**5**, **7**, **9**, **39**) were ineffective GPDH inhibitors at the highest levels tested. The 2-acetylindole (**8**) was the only compound in this and the earlier series[1] which showed activity as an inhibitor of lactic acid dehydrogenase (LDH). Some enhancement in cytotoxicity against KB cells was noted in both the glyoxylic acid dimethylamide (**5**) and the 2-chloroacetylindole (**9**). However, neither of these compounds showed any GPDH or LDH inhibitory activity. In the *Clostridium feseri* system, the glyoxylic acid dimethylamide **5** and N-1 unsubstituted derivative **39** were inactive. The 6-methylindole **2** and the 5-methoxyindole **6** had activities comparable with the lead compound **40** in this and the other test systems. In preliminary tests in animal tumor systems, compounds **1**, **4**, **9**, and **39** showed no more than a very low and not always reproduced activity against Sarcoma 180.

Experimental Section[9]

1-*p*-Chlorobenzyl-2-ethylindole-3-acetonitrile (16a).—A solution of 4 g of **16** in 22 ml of dry DMF was added dropwise at 0° to a stirred suspension of 0.99 g of NaH (a 55% mineral oil dispersion). After the addition was complete, the mixture was warmed to 25° for 20 min and cooled to 0° and 3.7 g of *p*-chlorobenzyl chloride was added. After stirring at 25° for 4 hr, the reaction mixture was poured into 200 ml of ice and water and extracted with four 150-ml portions of ether. The ether extracts were washed (H_2O), saturated NaCl) and concentrated to 6.2 g of oil which was chromatographed on 120 g of acid-washed alumina in C_6H_6–cyclohexane (1:2). Fractions containing product (R_f 0.73, dle) were pooled and concentrated to a crystalline (1.3 g) residue which when recrystallized (C_6H_6–C_6H_{14}) gave 750 mg (11%) of **16a**, mp 116–119°. *Anal.* ($C_{19}H_{17}ClN_2$) C, H, N.

1-*p*-Chlorobenzyl-2-ethylindole-3-acetic Acid (1). From 16a.—A 700-mg sample of **16a** was hydrolyzed in aqueous-ethanolic KOH, and the crude product was extracted into ether which when concentrated gave 620 mg of **1**. Recrystallization gave 530 mg (70%) of **1**, mp 134–138°.

1-Benzyl-2-ethyl-5-methylindole-3-acetic Acid (3).—A solution of 2.0 g (5.5 mmoles) of **40**[1] in 100 ml of EtOH was treated with 6.05 ml of 1 *N* NaOH and 1 tablespoon of Raney Ni and shaken at 75° in H_2 at about 2.46 kg/cm² for 16 hr. The mixture was filtered and the filtrate was concentrated to dryness. The residue was acidified with dilute HCl and extracted with $CHCl_3$. Concentration of the $CHCl_3$ gave 1.9 g of crude product, which when recrystallized yielded 1.3 g of **3**.

Potassium 1-*p*-Chlorobenzyl-2-ethyl-5-methylindole-3-glyoxylate (4).—A solution of 2.4 g of 1-*p*-chlorobenzyl-2-ethyl-5-methylindole (**24**)[6] in 25 ml of dry ether was treated dropwise at 0° with a solution of 3 ml of oxalyl chloride in 15 ml of dry Et_2O and stirred for about 2 hr. Excess cold aqueous $KHCO_3$ was added; the layers were separated and the ether layer was washed ($KHCO_3$). The combined aqueous solutions were acidified and the oily free acid was extracted (Et_2O), dried, and concentrated. A residual 3 g of product was obtained as an oil which could not be crystallized. On the addition of half-saturated $KHCO_3$ solution, the oil dissolved and quickly reprecipitated as a crystalline water-insoluble K salt. When this material was washed with ether a yellow impurity was removed and 2.36 g of purified **4** was obtained.

1-*p*-Chlorobenzyl-2-ethyl-5-methylindole-3-glyoxylic Acid Dimethylamide (5).—1-*p*-Chlorobenzyl-2-ethyl-5-methylindole-3-glyoxylyl chloride in ether, prepared as in the synthesis of **4** from 6 g of **24**, was added to 100 ml of cold, stirred 25% Me_2NH in H_2O. The ether layer was separated and the aqueous layer was extracted with two 200-ml portions of $CHCl_3$. The combined organic layers were washed three times with water and concentrated. Recrystallization of the residue gave 6.1 g of **5**.

N-*p*-Chlorobenzyl-N-*p*-methoxyphenylhydrazine Hydrochloride (28).—A mixture of 144 g (0.83 mole) of *p*-methoxyphenylhydrazine hydrochloride, 1 l. of toluene, and 108.5 g (150 ml) of Et_3N was heated (75–80°) for 1 hr and 84.7 g (0.53 mole) of *p*-chlorobenzyl chloride was added. After being stirred 24 hr at 75°, $Et_3N^+H \cdot Cl^-$ was filtered off and washed (Et_2O). The filtrate and washings were concentrated to 500 ml and 140 ml of *i*-PrOH containing 15 g of HCl was added. After being cooled for 1 hr the solid was removed and washed (Et_2O). The yield of **28**, mp 140–146°, was 117 g (74%). *Anal.* ($C_{14}H_{16}Cl_2N_2O$) C, H, Cl, N.

3-[2-(1-*p*-Chlorobenzyl-5-methoxy-3-methylindole)]propionic Acid (7).—To a solution of 71.8 g (0.24 mole) of **28** in 1 l. of EtOH was added 38 g (0.24 mole) of ethyl β-propionylpropionate,[7] the reaction mixture was refluxed for 8 hr and cooled, and the precipitated NH_4Cl was removed. The filtrate was concentrated and the residual oil, dissolved in $CHCl_3$, was washed three times with water and dried. Concentration gave 96 g of an oil which showed one major and three minor components on tlc. Purification of the crude oil by chromatography on acid-washed alumina in ether–hexane (1:3) gave 52.4 g (57%) of ethyl 3-[2-(1-*p*-chlorobenzyl-5-methoxy-3-methylindole)]propionate (**31**) which was essentially one component as shown by tlc on alumina in benzene–hexane (1:1).

Hydrolysis of 48.5 g (0.126 mole) of **31** in 960 ml of EtOH, 6 g of NaOH, and 360 ml of water gave eventually 41 g of white solid which when recrystallized (benzene–petroleum ether (bp 30–60°)) gave 29 g of **7**, mp 130–132°.

Methyl 1-*p*-Chlorobenzyl-5-methoxy-2-indolyl Ketone (33).—A solution of 18 g (0.60 mole) of **28** and 6.2 g (0.72 mole) of 2,3-butanedione in 200 ml of *i*-PrOH was refluxed for 2.5 hr and cooled and a small amount of NH_4Cl was removed. The filtrate was concentrated to dryness, and the residue was dissolved in a mixture of 200 ml of H_2O and 100 ml of Et_2O. The aqueous layer was washed with three 200-ml portions of ether and the ether extracts were washed with 500 ml of dilute HCl, two 50-ml portions of water, and 50 ml of saturated NaCl. The dried ($MgSO_4$) ether solution was concentrated and the residual oil

(8) The rationale and methodology for conducting these tests were presented earlier.[1]

(9) Microanalyses were performed by Mr. R. N. Boos and his associates. Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. All melting points were determined on a micro hot stage and are corrected. Solvent concentrations were carried out at reduced pressure in a rotary evaporator.

was chromatographed in C_6H_6 on 100 g of acid-washed alumina. Elution with C_6H_6 gave 14 g of oil which was crystallized by the addition of 150 ml of hexane. Recrystallization (C_6H_6–petroleum ether) gave 6.0 g (32%) of **33**, mp 110–111°. *Anal.* ($C_{18}H_{16}ClNO_2$) C, H, Cl, N.

1-*p*-Chlorobenzyl-2-ethyl-5-methoxyindole (26).—A mixture of 1.16 g (3.7 mmoles) of **33**, 10 ml of diethylene glycol, 1.0 ml of hydrazine hydrate (85% aqueous), and 0.70 g of KOH was heated to about 160–180° for 2 hr, cooled to 100°, and poured onto ice. The cold mixture was extracted with three portions of ether. The ether extracts were washed (H_2O, dilute HCl, saturated NaCl) and concentrated to 1.17 g of residual oil. The oil was chromatographed on 5 g of acid-washed alumina in benzene and gave 1.05 g of oil which, when crystallized from 2 ml of C_6H_6 and 8 ml of petroleum ether, gave 700 mg (63%) of **26**, mp 91–92°. *Anal.* ($C_{18}H_{18}ClNO$) C, H, Cl, N.

1-*p*-Chlorobenzyl-2-ethyl-5-methoxygramine (34).—By a procedure similar to that used for the synthesis of **14**, 31.3 g (0.104 mole) of **26** was converted into 27.4 g of crude **34**. Recrystallization from 150 ml of hexane gave 18.6 g (50%) of **34**, mp 92–94°. *Anal.* ($C_{21}H_{25}ClNO$) C, H, Cl, N.

1-*p*-Chlorobenzyl-2-ethyl-5-methoxyindole-3-acetonitrile (35).—By the procedure used for the synthesis of **16**, 15.7 g (44 mmoles) of **34** was converted with MeI to the methiodide which when treated with KCN gave 9.7 g of crude **35** along with 7.8 g of recovered starting methiodide. Chromatography of the crude product on alumina in benzene followed by crystallization from C_6H_6–petroleum ether gave 3.9 g (52% based on starting methiodide not recovered) of **35**, mp 108–110°. *Anal.* ($C_{20}H_{19}ClN_2O$) C, H, Cl.

1-*p*-Chlorobenzyl-2-ethyl-5-methoxyindole-3-acetic Acid (6).—By hydrolysis with hot aqueous–ethanolic KOH, 3.9 g of **35** was converted into 3.9 g of crude **6**. Recrystallization gave 3.3 g of **6**.

Methyl 2-Acetyl-1-*p*-chlorobenzyl-5-methylindole-3-acetate (37).—To 1 g of methyl 1-*p*-chlorobenzyl-5-methylindole-3-acetate[1] and 0.5 g of fused $ZnCl_2$ was added 10 ml of AcCl and the light yellow mixture was stirred at room temperature for 5 min and poured onto ice. The semisolid obtained was extracted into 100 ml of $CHCl_3$ and washed twice with 10% $KHCO_3$ and several times with water. Concentration of the $CHCl_3$ gave 1 g of solid. Recrystallization from Et_2O (25 ml) gave 0.52 g (45%) of **37**, mp 125–128°. *Anal.* ($C_{21}H_{20}ClNO_3$) C, H, Cl, N.

2-Acetyl-1-*p*-Chlorobenzyl-5-methylindole-3-acetic Acid (8).—Three grams of **37** was hydrolyzed in hot aqueous–ethanolic KOH. Recrystallization of the crude product gave 1.2 g of **8**.

Methyl 2-Chloroacetyl-1-*p*-chlorobenzyl-5-methylindole-3-acetate (38).—Methyl 1-*p*-chlorobenzyl-5-methylindole-3-acetate[1] (1 g) dissolved in 10 ml of chloroacetyl chloride was refluxed for 5 hr with stirring. The dark brown solution was poured onto ice, and an oil separated. The aqueous mixture was extracted twice with $CHCl_3$, and the combined $CHCl_3$ extracts were washed (H_2O) until neutral and dried ($MgSO_4$). The solvent was removed and the residual oil solidified after the addition of a few drops of petroleum ether. The solid was recrystallized from Et_2O–petroleum ether and 0.4 g (33%) of **38**, mp 110–112°, was obtained. *Anal.* ($C_{21}H_{19}Cl_2NO_3$) C, H, Cl, N.

2-Chloroacetyl-1-*p*-chlorobenzyl-5-methylindole-3-acetic Acid (9).—To a suspension of 300 mg of **38** in 3 ml of glacial AcOH was added 0.2 ml of concentrated HCl and the mixture was refluxed for 11 hr. The solvent was removed and the residue was dissolved in ether and washed (H_2O) until neutral. Concentration of the dried ether solution gave a residue (280 mg) of product. Recrystallization left 105 mg of **9**.

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Synthesis and Biological Activity of Some 3-Substituted Amino-1-carbamoyl- and -thiocarbamoylpyrrolidines

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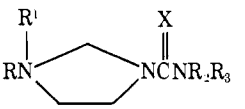
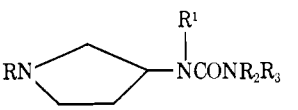
This paper describes the synthesis and pharmacological properties of a series of 3-amino-1-carbamoyl- and -thiocarbamoylpyrrolidines (I). These compounds are structurally related to the 1-substituted 3-pyrrolidinylureas (II), some of which show CNS depressant activity.[1]



I, X = O, S



II

Chemistry.—The carbamoyl- and thiocarbamoylpyrrolidines (Table I) were prepared by the reaction of the 3-substituted aminopyrrolidines with (1) alkyl or aryl isocyanates, (2) potassium cyanate, (3) substituted carbamoyl chlorides, or (4) alkyl or aryl isothiocyanates. The general procedure for the preparation of the intermediate 3-aminopyrrolidines has been reported.[2] The preparation of compounds not previously described is given in the Experimental Section.

Pharmacology.—These carbamoylpyrrolidines, when tested in the general behaviorial screen in mice,[3] showed mainly CNS depression. Several compounds showed activity in the fighting mice test.[4] Compounds **5**, **8**, **11**, **19**–**21** blocked the aggressive behavior of at least two of the five mice tested at a dose of 20 mg/kg ip. The acute intraperitoneal LD_{50} estimates (mouse) of these compounds ranged from 500 to 1800 mg/kg.

Three compounds (**8**, **20**, **21**) also suppressed the toxic effect of amphetamine in aggregated mice[5] at a dose of 10 mg/kg ip and in the anesthetized dog produced a transient lowering of the blood pressure. None of these compounds was effective in protecting against thiosemicarbazide-induced convulsions in mice.[6]

Experimental Section

General procedures, in most instances, are given below for the preparation of the compounds described in this paper. Analyses, yields, and physical properties are recorded in Table I and significant variations in the procedure are noted in the table footnotes. Temperatures are uncorrected. Microanalyses were by Micro-Tech Laboratories, Inc., Skokie, Ill.

3-Amino-1-carbamoylpyrrolidines. Procedure 1. By Reaction of 3-Aminopyrrolidine and Alkyl or Aryl Isocyanates.—

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