absolute ethanol: m.p. 90–94°; yield 15%; λ_{max} mμ (ε) 215 (53,100), 275 (18,000); ν_{max} 1130 (s), 1220 (s), 1325 (ms), 1415 (m), 1505 (m), 1590 (m), 1710 (ms), 3150 (mw), 3350 (mw) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{25}ClN_2O_5 \cdot 0.5C_2H_5OH$: C, 61.60; H, 6.03; Cl, 7.58; N, 5.99. Found: C, 61.51; H, 5.80; Cl, 7.33; N, 5.88.

9-Chloro-3,4-dihydro-6-methyl-1H-azepino[5,4,3-*cd*]indole Methiodide (Xa).—A solution of 5 g. of compound IVa in 100 ml. of absolute ethanol was treated with 15 ml. of methyl iodide and refluxed for 1 hr. After chilling, the precipitated yellow crystals were filtered and washed with and recrystallized from absolute ethanol; m.p. 251–253°; yield 74%; λ_{max} mμ (ε) 215 (32,100), 340 (5200), 405 (6125); ν_{max} 1000 (ms), 1290 (ms), 1535 (ms), 1615 (ms), 3150 (ms) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{14}ClIN_2$: C, 43.29; H, 3.91; I, 35.19; N, 7.77. Found: C, 43.52; H, 3.70; I, 35.28; N, 7.53.

Ethyl 9-Chloro-3,4-dihydro-6-methyl-1H-azepino[5,4,3-*cd*]-indole-2-carboxylate Methiodide (Xo).—This compound was prepared from 5 g. of IVc by the same method as Xa. The analytical sample was obtained by recrystallization from 95% ethanol; m.p. 260–265°; yield 87%; λ_{max} mμ (ε) 222 (35,000), 250 (12,400), 271 (14,800), 346 (8900), 390 (10,000); ν_{max} 1125 (ms), 1240 (ms), 1310 (ms), 1550 (m), 1630 (ms), 1705 (ms), 3300 (ms) cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{18}ClIN_2O_2$: C, 44.41; H, 4.19; N, 6.47. Found: C, 44.53; H, 4.30; N, 6.51.

***dl*-9-Chloro-3,4,5,6-tetrahydro-5,6-dimethyl-1H-azepino-[5,4,3-*cd*]indole (XIa).**—This compound was prepared from 4.5 g. of Xa by the same method as IXa: m.p. 179–181°; yield 85%; λ_{max} mμ (ε) 227 (33,700), 290.5 (7100), 301 (6665); ν_{max} 1085 (vs), 1135 (s), 1510 (m), 1565 (mw), 1615 (m) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{15}ClN_2$: C, 66.52; H, 6.44; Cl, 15.11; N, 11.93. Found: C, 66.73; H, 6.39; Cl, 15.09; N, 11.90.

Ethyl *dl*-9-Chloro-3,4,5,6-tetrahydro-5,6-dimethyl-1H-azepino-[5,4,3-*cd*]indole-2-carboxylate (XIb).—This compound was prepared from 3 g. of Xb by the same method as IXa. The analytical sample was obtained by recrystallization from methanol: m.p. 99–101°; yield 87%; λ_{max} mμ (ε) 237.5 (30,000), 297 (19,900); ν_{max} 805 (m), 1110 (m), 1260 (ms), 1530 (mw), 1705 (ms), 3350 (m) cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{19}ClN_2O_2$: C, 62.64; H, 6.24; Cl, 11.56; N, 9.13. Found: C, 62.80; H, 6.44; Cl, 11.64; N, 9.24.

***dl*-9-Chloro-3,4,5,6-tetrahydro-5,6-dimethyl-1H-azepino-[5,4,3-*cd*]indole-2-methanol (XIc).**—This compound was prepared from 5 g. of Xb by the same method as IXc. The analytical sample was obtained by recrystallization from absolute ethanol; m.p. 206–210°; yield 55%; λ_{max} mμ (ε) 229.5 (3900), 290 (8000); ν_{max} 785 (ms), 990 (m), 1005 (ms), 1110 (s), 1290 (ms), 3150 (ms) cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{17}ClN_2O$: C, 63.51; H, 6.47; Cl, 13.39; N, 10.58. Found: C, 63.66; H, 6.72; Cl, 13.22; N, 10.36.

***dl*-3,4,5,6-Tetrahydro-5,6-dimethyl-1H-azepino[5,4,3-*cd*]indole (XId).**—This compound was prepared from 0.5 g. of XIa by the same method as VIb. The analytical sample was obtained by recrystallization from absolute ethanol: m.p. 207–210°; λ_{max} mμ (ε) 225 (30,800), 284 (6400); ν_{max} 740 (s), 990 (m), 1035 (m), 1065 (m), 1130 (m), 1160 (ms), 1415 (m) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.96; H, 8.13; N, 13.94.

9-Chloro-3,4-dihydro-1,6-dimethyl-1H-azepino[5,4,3-*cd*]-indole Hydrochloride (XII).—A mixture of 5 g. of IVa, 5 g. of sodium hydride suspension in oil (55%), 50 ml. of dimethyl carbonate, and 300 ml. of dry tetrahydrofuran was refluxed under protection from moisture for 40 hr. and poured with stirring into a mixture of 250 g. of ice and 50 ml. of glacial acetic acid. After evaporation of the organic solvents *in vacuo*, the volume of the concentrate was doubled by addition of water. After filtration of the mixture through diatomaceous earth, the filtrate was made basic with 40% KOH and extracted with five 100-ml. portions of chloroform. The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The oily residue was taken up in a small amount of absolute ethanol and treated with ethanolic HCl. The resulting heavy precipitate was filtered, washed, and recrystallized from absolute ethanol: m.p. 280–282°; yield 56%; λ_{max} mμ (ε) 234 (19800), 260 (14,400), 343 (4000), 411 (610.0); ν_{max} 955 (m), 1075 (m), 1180 (m), 1270 (s), 1535 (ms), 1605 (mw), 1640 (ms) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{15}ClN_2 \cdot HCl$: C, 58.00; H, 5.24; Cl, 26.34; N, 10.42. Found: C, 58.10; H, 5.55; Cl, 26.55; N, 10.63.

Attempts at Dehydrogenation of IVa.—(a) A mixture of IVa (1 g.) and palladium black (0.5 g.) was refluxed in cymene (50 ml.) for 100 hr. (b) A solution of IVa (0.5 g.) in 5% acetic acid (15 ml.) was treated with mercuric acetate (1.2 g.) and heated on a steam bath (80–90°) for 4 hr. (c) A mixture of IVa (1 g.) and chloranil (1.5 g.) was refluxed in xylene for 4 hr.

Upon working up, by conventional methods, batches a and b gave starting material, whereas batch c yielded an intractable black resin.

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1-*p*-Chlorobenzyl-5-methylindole-3-acetic Acid. Some 2-Substituted Derivatives

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1-*p*-Chlorobenzyl-5-methylindole-3-acetic acid and its 2-methyl, -ethyl, -propyl, and -phenyl derivatives have been synthesized as potential antitumor agents and have been tested in several biological systems.

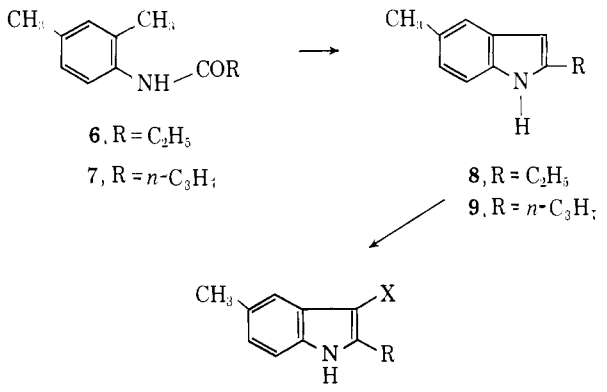
During the course of work directed toward finding inhibitors of lactate dehydrogenase (LDH),[1] 1-*p*-chlorobenzyl-2-ethyl-5-methylindole-3-acetic acid (**1**), although a poor inhibitor of LDH, was found to be an effective inhibitor of α-glycerophosphate dehydrogenase (GPDH). In addition, it was cytotoxic to cells in culture and inhibited the growth of an anaerobic bacterium. The very low levels of GPDH observed in nearly all malignant tissues[2] make inhibitors of this enzyme of some interest in cancer chemotherapy.

(1) A rationale for the interest in inhibitors of LDH as potentially useful materials in the chemotherapy of cancer has been presented: G. E. Boxer and T. M. Devlin, *Science*, **134**, 1495 (1961).

(2) A. Delbrück, H. Schimassek, K. Bartsch, and T. Bücher, *Biochem. Z.*, **331**, 207 (1959); H. Holzer, P. Glogner, and G. Sedlmayr, *ibid.*, **330**, 59 (1958); G. E. Boxer and C. E. Shonk, *Cancer Res.*, **20**, 85 (1960); E. J. Ciaccio, D. L. Keller, and G. E. Boxer, *Biochem. Biophys. Acta*, **37**, 191 (1960).

since suppression of residual capacity for α-glycerophosphate synthesis might prevent synthesis of essential phospholipids by the malignant cell. In view of these activities, the synthesis of a few close relatives of 1-*p*-chlorobenzyl-2-ethyl-5-methylindole-3-acetic acid was undertaken. This paper describes variations of the substituent at the 2-position; the compounds which were prepared include the 2-proteo (**2**), -methyl (**3**), -propyl (**4**), and -phenyl (**5**) analogs of the 2-ethyl compound (**1**).

For the synthesis of the indoles **1** and **4**, the requisite 2-ethyl-5-methylindole (**8**)[3] and 5-methyl-2-propylindole (**9**) were prepared by means of the Madalung[4a] method. The xylidides (**6** and **7**) were made from 2,4-xylidine and the appropriate acid anhydrides by conventional methods. The acetic acid side chains were completed by application of the well-known gramine[4b] sequence.



6, R = C_2H_5
7, R = *n*-C_3H_7
8, R = C_2H_5
9, R = *n*-C_3H_7

10, X = $CH_2N(CH_3)_2$; R = C_2H_5
11, X = $CH_2N(CH_3)_2$; R = *n*-C_3H_7
12, X = $CH_2N^+(CH_3)_3I^-$; R = *n*-C_3H_7
13, X = CH_2CN; R = *n*-C_3H_7
14, X = CH_2COOH; R = C_2H_5
15, X = CH_2COOH; R = *n*-C_3H_7
16, X = CH_2COOCH_3; R = C_2H_5
17, X = CH_2COOCH_3; R = *n*-C_3H_7

In the 2-ethyl series, the cyanide displacement was done directly on the gramine homolog, and the resulting nitrile, without being isolated, was hydrolyzed to the acetic acid (**14**), but in only 22% yield.

The propylgramine (**11**), however, was converted to the quaternary salt (**12**) which reacted with cyanide ion at a much lower temperature (avoiding partial hydrolysis to the amide), and the isolated nitrile (**13**) was hydrolyzed cleanly to the acetic acid (**15**) in an overall yield of about 50%. The improved yield and easier purification of products in the latter sequence justified the additional operations.

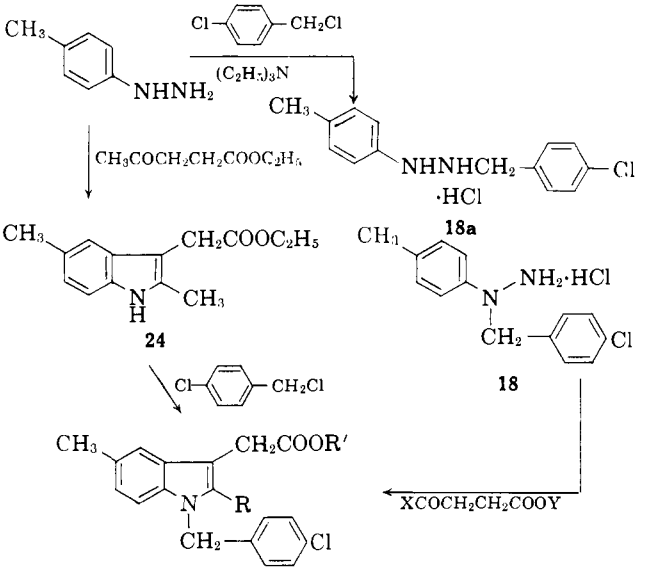
Aralkylation of the indole nitrogen anion, prepared from the esters **16** and **17** and sodium hydride, in N,N-dimethylformamide with *p*-chlorobenzyl chloride proceeded smoothly, and alkaline hydrolysis of the intermediate esters gave the desired products **1** and **4**.

For preparing the 2-proteo (**2**), 2-methyl (**3**), and 2-phenyl (**5**) analogs, reaction of N-*p*-tolyl-N-*p*-chlorobenzylhydrazine hydrochloride (**18**) with the appropriate β-acylpropionic acid or ester in a conventional Fisher indole[4c] synthesis was used.

(3) Prepared previously by another method by R. Quelot and M. Chastelle, *Compt. rend.*, **249**, 1526 (1959).

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

The hydrazine (**18**) was prepared by alkylation of *p*-tolylhydrazine with *p*-chlorobenzyl chloride in the presence of triethylamine. The product was a mixture consisting of about 80% of the desired compound (**18**) and about 20% of a second component, presumably N-*p*-tolyl-N'-*p*-chlorobenzylhydrazine hydrochloride (**18a**). The presence of the by-product (**18a**) offers no problem as it is incapable of undergoing a Fisher-type ring closure and its strongly basic properties provide a means for its easy removal from the indoles.



22, R = CH_3; R' = C_2H_5
23, R = H; R' = CH_3
1, R = C_2H_5; R' = H
2, R = R' = H
3, R = CH_3; R' = H
4, R = *n*-C_3H_7; R' = H
5, R = C_6H_5; R' = H

19, X = H; Y' = CH_3
20, X = CH_3; Y' = H
21, X = C_6H_5; Y' = H

The 2-methylindole (**3**) was also synthesized *via* a Fisher reaction between *p*-tolylhydrazine and ethyl levulinate. The intermediate ester **24** was aralkylated in the usual manner with *p*-chlorobenzyl chloride. Hydrolysis of the ester **22** with sodium hydroxide led to the isolation of **3** as its water-insoluble sodium salt.

The end products of these syntheses were tested in several *in vitro* and *in vivo* systems. The results of these tests are indicated in Table I. The dehydrogenase inhibitory activity[5] of these materials was meas-

TABLE I

1-*p*-CHLOROBENZYL-5-METHYLINDOLE-3-ACETIC ACID

2-Substituent	$M \times 10^4$ — % inhibition —GPDH—	—LDH—	*Clostridium feseri* IC_{50}, γ/ml.[a]	KB cell culture IC_{50}, γ/ml.[a]
2-Ethyl (**1**)	1.0 — 50	20 — 0	26	60
2-Proteo (**2**)	8.0 — 50	13 — 0	105	25
2-Methyl (**3**)	1.0 — 50	4.0 — 0	64	
			85	50
2-Propyl (**4**)	0.32 — 50	6.3 — 0	20	
			29	50
2-Phenyl (**5**)	0.08 — 50	6.3 — 50	>1000	30

[a] Concentration resulting in 50% inhibition of growth.

(5) For the methods used for measuring the enzyme inhibitory activity see E. I. Ciaccio, G. E. Boxer, T. M. Devlin, and R. Ford, *Cancer Res.*, submitted for publication.

ured against both lactate dehydrogenase and α-glycerophosphate dehydrogenase. The increased inhibitory activity of the 2-phenylindole (**5**) against GPDH should be noted; however, a corresponding increase of activity in any of the other test systems was by no means dramatic and in some cases an actual diminution of activity was noted. It can be seen that the GPDH-inhibitory activity of these compounds varies directly with the size of the 2-substituent, the 2-phenylindole (**5**) being the most active and the 2-proteo analog (**2**) the least active.

Although the cytotoxicity of the 2-ethylindole (**1**) was first determined with Walker 256 cells, this system was no longer available at the time the analogs were made, and cytotoxicity was determined using KB cells.[6] It can be seen readily that the level of activity of **1** against Walker 256 cells (1 γ/ml.) was not attained with KB cells nor were any of the new materials appreciably active in the KB system. It would appear that the changes in the 2-substitutent have little effect on the KB cell inhibitory activity of these compounds.

It has been shown[7] that a number of antitumor agents are also good inhibitors of certain anaerobic bacteria. With this in mind the indoles were tested against *Clostridium feseri* ATCC 10092. In this system, the 2-phenyl analog (**5**) shows no activity. The 2-ethyl (**1**) and 2-propyl (**4**) derivatives appear to be the most active; however, the 2-proteo (**2**) and 2-methyl (**3**) analogs are only slightly less active.

When tested in animal tumor systems, 1-*p*-chlorobenzyl-2-ethyl-5-methylindole-3-acetic acid (**1**) showed a low but not always reproducible activity against Sarcoma 180 and Carcinoma 755. Preliminary testing of the analogs indicated that no improvement was obtained by replacement of the 2-ethyl with other substituents.

Experimental[8]

N-*p*-Chlorobenzyl-N-*p*-tolylhydrazine Hydrochloride (18). A solution of 26 g. (0.131 mole) of *p*-tolylhydrazine hydrochloride (Aldrich) in 150 ml. of toluene was treated with 21.7 g. (0.215 mole, 30 ml.) of triethylamine and heated at 75–80° for 1 hr. A solution of 17 g. (0.106 mole) of *p*-chlorobenzyl chloride in 50 ml. of toluene was added during 20 min. and heating and stirring were continued for about 24 hr. The reaction mixture was cooled, and the precipitated triethylammonium chloride was filtered and washed with toluene. The toluene solution was concentrated under reduced pressure to a volume of 100 ml. and treated with 28 ml. of 3 *N* HCl in 2-propanol. The solution was cooled and the crystals which formed were removed and dried. A total of 19.7 g. (66%) of N-*p*-chlorobenzyl-N-*p*-tolylhydrazine hydrochloride, m.p. 156–176°,[9] was obtained.

Anal. Calcd. for $C_{14}H_{16}Cl_2N_2$: C, 59.37; H, 5.69; Cl, 25.04; N, 9.89. Found: C, 59.35; H, 5.49; Cl, 24.50; N, 9.59.

Methyl 1-*p*-Chlorobenzyl-5-methylindole-3-acetate (23).—To a solution of 35.4 g. (0.125 mole) of N-*p*-chlorobenzyl-N-*p*-tolylhydrazine hydrochloride (**18**) in 500 ml. of methanol was added 16 g. (0.138 mole) of 3-carbomethoxypropionaldehyde.[10] The reaction mixture was refluxed for 29 hr. After concentration of the methanol solution to 350 ml. and cooling in an ice bath, 21.3 g. of white solid was obtained. The solid was dissolved in ether, and the ether solution was washed twice with water and dried ($MgSO_4$). Removal of the solvent at reduced pressure gave 16.2 g. (39.5%) of **23**: m.p. 104–105°; λ_{max}^{MeOH} 302.5 mμ (ε 4818), 292 (5638), 278 (6851), 223 (42,614).

Anal. Calcd. for $C_{19}H_{18}ClNO_2$: C, 69.61; H, 5.53; Cl, 10.82; N, 4.27. Found: C, 69.68; H, 5.73; Cl, 10.30; N, 3.95.

1-*p*-Chlorobenzyl-5-methylindole-3-acetic Acid (2).—Hydrolysis of the methyl ester (**23**) in aqueous-alcoholic potassium hydroxide gave the acid **2**, m.p. 174–177°, in 74% yield; λ_{max}^{MeOH} 302 mμ (ε 4831), 292 (5961), 278 (6585), 223 (38,906).

Anal. Calcd. for $C_{18}H_{16}ClNO_2$: C, 68.93; H, 5.14; Cl, 11.30; N, 4.46. Found: C, 69.30; H, 5.47; Cl, 11.04; N, 4.14.

1-*p*-Chlorobenzyl-2,5-dimethylindole-3-acetic Acid (3).—A solution of 9.9 g. (28 mmoles) of 80% N-*p*-chlorobenzyl-N-*p*-tolylhydrazine hydrochloride (**18**) and 3.25 g. (28 mmoles) of levulinic acid in 100 ml. of acetic acid was heated at 100° for 4 hr. The reaction mixture was concentrated to dryness at reduced pressure, and the residue was dissolved in 250 ml. of methylene chloride and washed with 100 ml. of 1 *N* HCl and three 100-ml. portions of water. The methylene chloride solution was concentrated to dryness, and the residue was crystallized from 200 ml. of hot methylene chloride by the addition of 400 ml. of petroleum ether (b.p. 30–60°). The colored product (5.6 g., m.p. 180–185° dec.) was dissolved in 300 ml. of hot methylene chloride. The solution was filtered through a pad of decolorizing carbon, and the pale yellow filtrate was concentrated on the steam bath to 200 ml. Dilution with 400 ml. of petroleum ether gave 3.5 g. (42%) of product, m.p. 180–185° dec. For analysis **3** was dried at reduced pressure and 110°: λ_{max}^{MeOH} 290 mμ (ε 7640), 278 (7760), 226 (37,400); λ_{sh}^{MeOH} 300 mμ (ε 6000).

Anal. Calcd. for $C_{19}H_{18}ClNO_2$: C, 69.62; H, 5.53; N, 4.27. Found: C, 69.54; H, 5.26; N, 4.40.

Ethyl 2,5-Dimethylindole-3-acetate (24).—A solution of 39.5 g. (0.25 mole) of *p*-tolylhydrazine hydrochloride and 23 ml. (0.25 mole) of levulinic acid (**20**) in 500 ml. of 1.4 *N* alcoholic HCl was refluxed for 3 hr. The ammonium chloride which precipitated was removed, and the filtrate was concentrated at reduced pressure. The residue was diluted with 100 ml. of water and extracted with four 100-ml. portions of ether. The ether extract was washed with 50 ml. of dilute HCl, four 100-ml. portions of 10% $KHCO_3$, and four 100-ml. portions of water. The ether solution was concentrated at reduced pressure and the residual oil crystallized on standing. Recrystallization from hexane gave 23 g. of crude product, m.p. 39–40°.

A 7.2-g. portion of the product was chromatographed on a short column of acid-washed alumina in benzene–ether (9:1). Concentration of the eluate gave a residual oil (6.5 g.) which was crystallized from 5 ml. of ether and 25 ml. of petroleum ether to give 5.3 g. (30%) of **24**, m.p. 48–49°: λ_{max}^{MeOH} 297 mμ (ε 5620), 286 (7200), 279 (7100), 225 (29,100).

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.82; H, 7.71; N, 6.05.

Sodium 1-*p*-Chlorobenzyl-2,5-dimethylindole-3-acetate.—A solution of 11.5 g. (0.05 mole) of ethyl 2,5-dimethylindole-3-acetate (**24**) in 50 ml. of dry dimethylformamide was added dropwise over a 10-min. period to a cold suspension of 2.38 g. (0.052 mole) of sodium hydride (as a 55% emulsion in mineral oil) in 50 ml. of dry dimethylformamide. The mixture was stirred at room temperature for 1 hr. and cooled to 5°, and 8.3 g. (0.052 mole) of *p*-chlorobenzyl chloride was added dropwise. The suspension was stirred at room temperature overnight, then added to 200 g. of ice–water and extracted three times with ether. The combined ether layers were extracted twice with 10% $KHCO_3$ solution and washed twice with water. The ether was removed at reduced pressure. The residue was chromatographed on 200 g. of acid-washed alumina. Elution with benzene–cyclohexane (1:4) yielded 3.0 g. (17%) of crystalline ethyl 1-*p*-chlorobenzyl-2,5-dimethylindole-3-acetate (**22**) which was not further purified but used in the next step. The infrared spectrum of the product showed a band at 5.8 (C=O) and no band at 2.9 μ (–NH). An additional 5 g. of product contaminated with starting indole (–NH band at 2.9 μ) was also obtained from the column.

A solution of 3 g. (8.5 mmoles) of ethyl 1-*p*-chlorobenzyl-2,5-

(6) The procedure for the KB assays is described by C. O. Gitterman, E. L. Dulaney, E. A. Kaczka, G. W. Campbell, D. Hendlin, and H. B. Woodruff, *Cancer Res.*, **24**, 440 (1964).

(7) T. W. Bradner and D. A. Clarke, *ibid.*, **18**, 299 (1958); J. H. DiPaolo and R. Rosenfield, *ibid.*, **18**, 1214 (1958); J. G. Cappuccino, M. George, P. C. Merker, and G. S. Tarnowski, *ibid.*, **24**, 1243 (1964).

(8) Microanalyses were performed by Mr. R. N. Boos and his associates and the ultraviolet spectral measurements were done by Mr. E. A. MacMullin and his associates. All melting points were determined on a micro hot stage and are corrected. T.l.c. stands for thin layer chromatography.

(9) The broad melting point is best explained by assuming the product to be contaminated with the N,N′ isomeric product. The n.m.r. spectrum shows the presence of about 20% of a second component of very similar structure.

(10) E. Mosettig and R. Mozingo, *Org. Reactions*, **4**, 371 (1948).

dimethylindole-3-acetate (**22**) in 50 ml. of ethanol was treated with 0.36 g. (9.0 mmoles) of NaOH in 11 ml. of water, and the mixture was refluxed for 2 hr. The solvents were removed at reduced pressure, and the residue was dissolved in 50 ml. of hot water. When the solution was cooled to room temperature, the sodium salt of the product crystallized. The suspension was extracted once with ether. The aqueous layer was heated to dissolve the solid, and the solution was filtered and cooled. The very fine solid was filtered in the cold room, and 1.9 g. (65%) of sodium 1-*p*-chlorobenzyl-2,5-dimethylindole-3-acetate was obtained; λ_{max}^{EtOH} 300 mμ (ϵ 5220), 292 (6100), 284 (5890), 226 (28,800).

Anal. Calcd. for $C_{19}H_{17}ClNNaO_2$: C, 65.40; H, 4.91; N, 4.02. Found: C, 65.33; H, 5.03; N, 4.10.

2-Ethyl-5-methylindole (**8**).—A suspension of 421 g. (moist with the petroleum ether used to remove the mineral oil) of 90% sodamide (mineral oil dispersion) in 3 l. of N,N-diethylaniline was stirred under nitrogen and treated portionwise with 257 g. (1.45 moles) of 2,4-propionoxylidide.[11] The mixture was heated carefully to reflux during 1 hr. and heated at 200° for 3 hr. The reaction mixture was cooled to 90°, 1 l. of water was added (carefully at first) to decompose any unreacted sodamide, and it was kept at 25° for 16 hr.; 400 ml. of water was added, and the mixture was extracted with one 3-l. and two 1.5-l. portions of ether. The combined ether layers were washed with 3 *N* HCl until the washings were strongly acidic, and then with 500 ml. each of water and saturated NaCl. The dried ether layer was concentrated at reduced pressure to a residual solid (193 g.). The infrared spectrum of the product did not have a band at 6.0 μ (-CONH-), indicating the reaction was complete. Recrystallization from 3 l. of petroleum ether gave a total of 154 g. (67%) of **8**, m.p. 78–83° (lit.[3] m.p. 81°).

2-Ethyl-5-methylgramine (**10**).—A solution of 100 g. (0.68 mole) of 2-ethyl-5-methylindole (**8**) in 450 ml. of dioxane was added dropwise to a stirred solution of 25.5 g. (0.85 mole) of formaldehyde (69 ml. of 37% aqueous), 38.3 g. (0.85 mole) of dimethylamine (155 ml. of 25% aqueous), 450 ml. of glacial acetic acid, and 450 ml. of dioxane at a temperature maintained below 0°. After the addition was complete, the reaction mixture was allowed to warm to room temperature over a period of 16 hr. It was diluted with 3.5 l. of water, treated with 20 g. of Darco, and filtered. The filtrate was made basic (~pH 12) with 10 *N* KOH. The mixture was kept at 0° for several hours, and the solid (107 g., m.p. 101–105°) was removed. A 40-g. portion of the crude product was dissolved in 600 ml. of ether and extracted into one 800-ml. and two 150-ml. portions of 10% HCl. The acidic layer was washed with ether and made basic with solid NaOH while being cooled.

The oil which separated was extracted into three 300-ml. portions of ether which in turn were washed with saturated NaCl. The residue (39.4 g.) obtained after removal of the ether was recrystallized from about 400 ml. of hexane. The recovery of **10**, m.p. 101–105°, was 34.4 g. (63% over-all).

Anal. Calcd. for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 78.12; H, 9.14; N, 13.23.

2-Ethyl-5-methylindole-3-acetic Acid (**14**).—A solution of 26.9 g. (0.125 mole) of 2-ethyl-5-methylgramine (**10**) and 50 g. (0.77 mole) of KCN in 200 ml. of ethanol and 100 ml. of water was refluxed for 3 days. The solution was cooled, acidified with concentrated HCl, and warmed on the steam bath in the hood while a vigorous stream of nitrogen was passed through for about 10 min. After being cooled, the mixture was treated with 40 g. of KOH. The mixture was refluxed for 16 hr. and diluted to 1 l. with water. After being extracted with three 150-ml. portions of chloroform, the aqueous phase was acidified with 60 ml. of concentrated HCl. The acidic solution was extracted with four 150-ml. portions of chloroform. Combined extracts were dried and concentrated to 9 g. of crude product. Recrystallization from 75 ml. of benzene gave 6.0 g. (22%) of **14**, m.p. 148–153°.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.89; H, 6.93; N, 6.85.

1-*p*-Chlorobenzyl-2-ethyl-5-methylindole-3-acetic Acid (**1**).—2-Ethyl-5-methylindole-3-acetic acid (**14**) (5.8 g., 0.027 mole) was converted into methyl 2-ethyl-5-methylindole-3-acetate (**16**) by means of methanolic HCl.

A solution of the ester **16** in 10 ml. of dry dimethylformamide was added to a suspension of 1.3 g. (0.03 mole) of sodium hydride (as a 55% emulsion in mineral oil) in 25 ml. of dry dimethylformamide. The mixture, cooled in an ice bath, was stirred until the evolution of hydrogen ceased. A solution of 3.7 ml. (0.03 mole) of *p*-chlorobenzyl chloride in 10 ml. of dry dimethylformamide was added in 10 min., and the stirring was continued for 16 hr. at room temperature. The reaction mixture was concentrated at reduced pressure, and the residue was distributed between ether and 0.25 *N* NaOH. The ether layer was washed with 0.25 *N* HCl and with saturated $NaHCO_3$. Concentration of the dried ether layer gave 8.5 g. of crude product. The intensity of the band at 2.95 μ (-NH) in the infrared spectrum indicated that the product contained about 25% of the unalkylated starting material. This was removed by chromatography on 150 g. of acid-washed alumina using benzene–hexane (1:1) as the eluting solvent. About 4.7 g. of methyl 1-*p*-chlorobenzyl-2-ethyl-5-methylindole-3-acetate having no absorption at 2.95 μ (-NH) in its infrared spectrum was obtained; λ_{max}^{neat} 5.85 μ (-$COOCH_3$).

The ester prepared above was dissolved in 25 ml. of methanol, 10 ml. of 30% NaOH was added, and the solution was refluxed for 2 hr. The reaction solution was concentrated to about 20 ml., cooled, and diluted with 20 ml. of water. The precipitated solid was removed, washed with water, and dried. It weighed 2.4 g., λ_{max}^{Nujol} 6.1–6.4 μ (-COO^-). The infrared spectrum as well as analytical results indicated that this material was sodium 1-*p*-chlorobenzyl-2-ethyl-5-methylindole-3-acetate.

Anal. Calcd. for $C_{20}H_{19}ClNNaO_2$: C, 66.03; H, 5.26; Cl, 9.75; N, 3.85. Found: C, 66.10; H, 5.78; Cl, 9.71; N, 4.00.

A small sample of the sodium salt was triturated with 6 *N* HCl and the insoluble residue was dried and recrystallized twice from cyclohexane. 1-*p*-Chlorobenzyl-2-ethyl-5-methylindole-3-acetic acid, m.p. 147–149°, was obtained; λ_{max}^{Nujol} 5.86 μ (-COOH); λ_{max}^{MeOH} 225 mμ (ϵ 30,500), 240 (6650), 282 (6450), 300 (5540).

Anal. Calcd. for $C_{20}H_{20}ClNO_2$: C, 70.28; H, 5.90; Cl, 10.40; N, 4.10. Found: C, 69.83; H, 6.13; Cl, 10.43; N, 4.25.

2,4-Butyroxylidide (**7**).—A solution of 121 g. (1 mole) of 2,4-xylidine in 350 ml. of dry pyridine was stirred and treated dropwise with 180 g. (1.14 moles) of butyric anhydride. The solution was cooled periodically to keep the temperature at 25°. After 120 g. of the butyric anhydride had been added, a precipitate separated from solution. The thick mixture was stirred for 2 hr., then added to 2 l. of ice–water. After being stirred for 30 min., the solid was filtered and washed three times with water. The dried product, m.p. 101–109°, weighed 154 g. (81%). This material was satisfactory for use in the next step. Recrystallization of 4 g. from ether gave 3.1 g. of analytically pure **7**, m.p. 109–111°, λ_{sh}^{EtOH} 273 mμ (ϵ 690), λ_{max}^{EtOH} 231 mμ (ϵ 7280).

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.37; H, 8.96; N, 7.32. Found: C, 75.37; H, 8.72; N, 7.16.

5-Methyl-2-propylindole (**9**).—A suspension of 165 g. (moist with the petroleum ether used to remove the mineral oil) of 90% sodamide (mineral oil dispersion) in 1400 ml. of N,N-diethylaniline was stirred under nitrogen and treated portionwise with 150 g. (0.78 mole) of 2,4-butyroxylidide (**7**). The mixture was heated slowly to 180–190° during 2 hr., and the temperature was maintained at 180–190° for an additional 2 hr. The reaction mixture was cooled to about 50°, and the excess sodium hydride was carefully decomposed by the dropwise addition of 700 ml. of water. The organic phase was extracted into one 1500-ml. portion and the 700-ml. portions of ether. The combined ether layers were washed with four 700-ml. portions of cold 4 *N* HCl, 500 ml. of water, and 500 ml. of saturated NaCl. The ether solution was dried and concentrated to 131 g. of residual solid, m.p. 61–70°. Bands at 6.0 μ (-CONH-) in the infrared spectrum (chloroform) indicated that not all of the starting material had cyclized.

The impure product was reheated as above with an additional 65 g. of sodamide in 650 ml. of N,N-diethylaniline. A similar work-up gave 114.2 g. of product, m.p. 67–70°. Recrystallization from 1.5 l. of petroleum ether gave 38 g. (28%) of **9**: m.p. 74–75°; λ_{max}^{EtOH} 295 mμ (ϵ 5360), 284 (7530), 274 (7930), 223 (29,000).

Anal. Calcd. for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09. Found: C, 82.84; H, 8.60; N, 7.90.

Reworking the crystallization mother liquors gave an additional 49 g. of good quality **9**. The total yield was 63%.

5-Methyl-2-propylgramine (**11**).—A solution of 10 g. (0.059 mole) of 5-methyl-2-propylindole (**9**) in 60 ml. of dioxane was added dropwise to a stirred mixture of 60 ml. of dioxane, 60 ml.

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

of acetic acid, 3.3 g. (0.073 mole) of dimethylamine (13.2 ml. of 25% aqueous), and 2.2 g. (0.073 mole) of formaldehyde (5.95 ml. of 37% aqueous) at about 0° over a period of 1.5 hr. The reaction mixture was kept at room temperature for about 16 hr., and the clear yellow solution was diluted with 500 ml. of water. A small amount of yellow gum which precipitated was removed by filtration. The filtrate was made basic with 140 ml. of cold 10 *N* KOH. The solid which precipitated was filtered, washed with water until neutral, and dried. The product, m.p. 107–111°, suitable for the next step amounted to 12.5 g. (92%). For analysis it was recrystallized from 50 ml. of ether by the addition of 100 ml. of petroleum ether, and 7.1 g. of **11**: m.p. 109–111°, was obtained; λ_{max}^{MeOH} 295 mμ (ε 5730), 284 (7550), 276 (7660).

Anal. Calcd. for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 77.94; H, 9.43; N, 11.71.

5-Methyl-2-propylindole-3-acetonitrile (13).—A solution of 66.1 g. (0.287 mole) of 5-methyl-2-propylgramine (**11**) in the minimum volume of ether was added dropwise during 15 min. to 400 ml. of stirred methyl iodide at 3°. The mixture was stirred for 6 hr. at 0° and then allowed to warm to room temperature overnight. The pink solid was filtered and washed well with ether.

The dried methiodide was added to 183 g. of KCN in 1.4 l. of water. The mixture was heated to 80° in 20 min. with stirring and kept at that temperature for 2 hr. The mixture was cooled and the lumpy product was filtered and washed twice with water. To break up the solid, it was dissolved in 200 ml. of ethanol and added dropwise to 1 l. of stirred cold water. Product (57.7 g.) melting at 98–102° was obtained. Recrystallization from ether–petroleum ether gave 41.5 g. (68%) of **13**: m.p. 105–106°; λ_{max}^{MeOH} 296 mμ (ε 5730), 286 (7750), 277 (7880), 226 (33,200).

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 78.89; H, 7.45; N, 13.39.

Hydrolysis of **13** in aqueous–alcoholic KOH gave **5-methyl-2-propylindole-3-acetic acid (15)**, m.p. 144–149°, in 82% yield.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 73.03; H, 7.18; N, 6.20

The acid **15** in methanolic HCl was converted into **methyl 5-methyl-2-propylindole-3-acetate (17)**, m.p. 78–79°, in 91% yield; λ_{max}^{MeOH} 297 mμ (ε 6110), 287 (7700), 280 (7630), 225 (31,650).

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.24; H, 7.51; N, 5.65.

1-*p*-Chlorobenzyl-5-methyl-2-propylindole-3-acetic Acid (4).—Methyl 5-methyl-2-propylindole-3-acetate (**17**) was converted into the acid (**4**) by essentially the same process used for the preparation of the 2-ethylindole (**1**). The product **4**, m.p. 143–149°, was obtained in an over-all yield of 30%; λ_{sat}^{MeOH} 300 mμ (ε 5960); λ_{max}^{MeOH} 290 mμ (ε 7550), 273 (7650), 226 (36,800).

Anal. Calcd. for $C_{21}H_{22}ClNO_2$: C, 70.88; H, 6.23; Cl, 9.96; N, 3.94. Found: C, 70.80; H, 6.25; Cl, 9.90; N, 3.60.

1-*p*-Chlorobenzyl-5-methyl-2-phenylindole-3-acetic Acid (5).—A mixture of 9.9 g. (28 mmoles) of 80% N-*p*-chlorobenzyl-N-*p*-tolylhydrazine hydrochloride (**18**) and 5.0 g. (28 mmoles) of 3-benzoylpropionic acid (**21**) in 140 ml. of acetic acid was heated on the steam bath for 4 hr. The reaction solution was concentrated to dryness at reduced pressure. The residue in 200 ml. of methylene chloride was washed with one 200-ml. portion of 2 *N* HCl and three 100-ml. portions of water. The dried ($MgSO_4$) methylene chloride layer was concentrated, and the residue was crystallized from 150 ml. of methylene chloride by adding 300 ml. of petroleum ether. The solid (4 g., m.p. 180–195°) was recrystallized twice from 200 ml. of methylene chloride and 400 ml. of petroleum ether. The product (3.4 g., 31%, m.p. 204–207°) would not give completely satisfactory elemental analyses because of contamination with a small amount of solvent (CH_2Cl_2) which was not removed at 100° and reduced pressure. Recrystallization of this material from 80 ml. of hot acetone by adding 50 ml. of petroleum ether gave 2.9 g. of **5**, m.p. 205–208°, λ_{max}^{MeOH} 300 mμ.

Anal. Calcd. for $C_{24}H_{20}ClNO_2$: C, 73.94; H, 5.17; Cl, 9.09; N, 3.59. Found: C, 73.89; H, 5.13; Cl, 9.07; N, 3.86.

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Thio Analogs of Carisoprodol (N-Isopropyl-2-methyl-2-propyl-1,3-propanediol Dicarbamate)

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Two thio analogs of carisoprodol, 3-carbamoxy-2-methyl-2-propylpropyl N-isopropylthiocarbamate and 2-methyl-2-propyl-3-thiocarbamoxypropyl N-isopropylcarbamate, and two thio analogs of meprobamate, 3-carbamoxy-2-methyl-2-propylpropyl thiolcarbamate and 2-methyl-2-propylpropyl 1,3-bis(dithiocarbamate), were synthesized.

Carisoprodol, N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate (**1**), was first synthesized by Berger and Ludwig.[2] It has found wide application as a muscle relaxant.[3] Meprobamate, 2-methyl-2-propyl-1,3-propanediol dicarbamate (**2**), was first synthesized by Ludwig and Piech[4] and is a well-known tranquilizer. Recently,[5] the synthesis of two thio analogs (**3** and **4**) of meprobamate was published. We now wish to report the synthesis of 3-carbamoxy-2-methyl-2-propylpropyl N-isopropylthiocarbamate (**13**) and 2-methyl-2-propyl-3-thiocarbamoxypropyl N-isopropylcarbamate (**12**), thio analogs of carisoprodol, and 3-carbamoxy-2-

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