A solution of S-ethyl 3,4-dihydro-2,4-dioxo-3-methyl-1(2H)-pyrimidinecarbothioate (0.10 g., 0.00047 mole) in 20 ml. of distilled water was heated on a steam bath for 5 hr. Evaporation of the water left a white residue which was first treated with ether to extract any starting material. Extraction with ethyl acetate gave 0.05 g. (86%) of 3-methyluracil, m.p. 179°. A mixture melting point with analyzed material prepared from 2-thiouracil by the method of Brown, *et al.*,[1] showed no depression. The infrared spectra were superimposable.

Tribenzoyl-2,4-diaminopyrimidine.[8]—To 10 ml. of water solution containing 0.8 g. (0.02 mole) of NaOH and 1.0 g. (0.0091 mole) of 2,4-diaminopyrimidine was added dropwise 2.5 ml. (0.025 mole) of benzoyl chloride. After stirring at room temperature overnight, the aqueous solution was decanted from a yellow gum which was made granular by stirring with methanol. Recrystallization from methanol gave 2 g. (53%) of white product, m.p. 230–231°.

Anal. Calcd. for $C_{25}H_{18}N_2O_3$: C, 71.08; H, 4.30; N, 13.27. Found: C, 70.84; H, 4.21; N, 13.52.

2-Pyrimidylphthalimide.—A test tube containing a well-ground mixture of 2-aminopyrimidine (0.95 g., 0.01 mole) and phthalic anhydride (1.48 g., 0.01 mole) was heated at 140° for 90 min. After cooling, the solid was extracted with ethanol, ethyl acetate, and acetone. Recrystallization from ethyl acetate gave white crystals of product (0.54 g.), m.p. 120°. The yield was 65% based on the 2-aminopyrimidine used (0.6 g. was recovered).

Anal. Calcd. for $C_{12}H_7N_3O_2$: C, 63.99; H, 3.13; N, 18.61. Found: C, 64.12; H, 3.05; N, 18.57.

Ascending Paper Chromatography.—Several pyrimidinecarbamates and thiolcarbamates were chromatographed to test for homogeneity, using a 5:3 mixture of 1-butanol and 5 *N* acetic acid at room temperature. Each gave only a single dark spot, observed under ultraviolet light. Values of the ratio R_f pyrimidine-R_f adenine, using adenine as internal standard, were as follows: **1**, 1.29; **3**, 1.58; **4**, 1.67; **5**, 1.54; **6**, 1.54; **7**, 1.66; **8**, 1.62; **10**, 1.74; **11**, 1.58; **12**, 1.35; **13**, 1.60; **14**, 1.54; **15**, 1.54; **16**, 1.10; **17**, 1.54.

Acyltryptamines. IV.[1] Azepino[5,4,3-*cd*]indoles

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5-Acetyl-8-chloro-1,2,3,4-tetrahydro-1-oxo-β-carboline (IIb) was obtained from the cyclization of 2,3-piperidinedione 3-[(3-acetyl-6-chlorophenyl)hydrazone], prepared by coupling diazotized 3-acetyl-6-chloroaniline with 3-carboxy-2-piperidone. The chlorine substituent was used to block the undesired cyclization at C-6. Acid treatment of 4-acetyl-2-carboxy-7-chlorotryptamine, obtained from the alkaline hydrolysis of IIb, gave 9-chloro-3,4-dihydro-6-methyl-1H-azepino[5,4,3-*cd*]indole (IVa) and the corresponding 2-carboxylic acid (IVb). Catalytic reduction of IV resulted in removal of chlorine followed by saturation of the C=N bond. Acylation of IVa with acetic anhydride gave 5-acetyl-9-chloro-3,4,5,6-tetrahydro-6-methylene-1H-azepino[5,4,3-*cd*]-indole (VII) which was hydrolyzed to 7-chloro-4,N-diacetyltryptamine (VIII). Treatment of IV with KBH_4 or $LiAlH_4$ resulted in reduction of the C=N bond without loss of chlorine. Other reactions included N-1 and N-5 alkylation and conversion of the carboxyl substituent at C-2 to carbethoxy, hydroxymethyl, trimethoxybenzoyloxymethyl, piperidinocarbonyl, and piperidinomethyl groups. A limited pharmacological evaluation of the azepinoindoles failed to uncover any significant effects at nontoxic dose levels.

Previous studies in this laboratory on the synthesis of acyltryptamines[2] showed that 4-acetyl-2-carboxytryptamine is readily cyclized to a derivative of azepino[5,4,3-*cd*]indole. This finding suggested an investigation of some of the chemical and pharmacological properties of this novel nucleus.

According to our previous communication, cyclization of the (*m*-acetylphenyl)hydrazone of 2,3-piperidinedione resulted in a mixture consisting of approximately three parts of 7-acetyl-1,2,3,4-tetrahydro-1-oxo-β-carboline[3] and one part of 5-acetyl-1,2,3,4-tetrahydro-1-oxo-β-carboline (IIa) (Chart I). This unfavorable proportion limited the availability of azepinoindole since only the 5-acyl isomer (IIa) can be utilized for its synthesis. For this reason, it was decided to prevent the formation of the undesirable isomer by the use of a chloro substituent as a removable blocking group. Accordingly, diazotized 3-acetyl-6-chloroaniline was coupled with 3-carboxy-2-piperidone to give 2,3-piperidinedione 3-[(3-acetyl-6-chlorophenyl)hydrazone] (I). Cyclization of I in refluxing formic acid gave the desired 5-acetyl-β-carboline derivative IIb in high yield. Alkaline hydrolysis of IIb resulted in the formation of 5-acetyl-2-carboxy-7-chlorotryptamine (III), which on refluxing for 100 hr. in hydrochloric acid–acetic acid mixture gave 9-chloro-3,4-dihydro-6-methyl-1H-azepino[5,4,3-*cd*]indole (IVa) and the corresponding 2-carboxylic acid (IVb) in a ratio of approximately 1:3. The rate of decarboxylation is apparently decelerated by the negative effect of chlorine upon the electron density at the indole nitrogen.[4] In contrast, the decarboxylation of the corresponding chlorine-free acid was completed within 6 hr.[2]

The effects of chlorine were also noticeable in other phases of this sequence. For example, when the coupling reaction was carried out in normal fashion, complete conversion to an unidentified, amorphous red product took place. This was avoided by lowering the pH of the reaction mixture to 1–2 from the usual 3–4.

After fulfilling its function by directing the cyclization of the hydrazone in the desired manner, the chlorine was removed by catalytic hydrogenation over palladium on carbon. Interrupting the reduction of IVa after the uptake of 1 mole of hydrogen permitted the isolation of 3,4-dihydro-6-methyl-1H-azepino[5,4,3-*cd*]indole (V) described in part II of this series.[2] If the reduction were allowed to proceed to completion, satura-

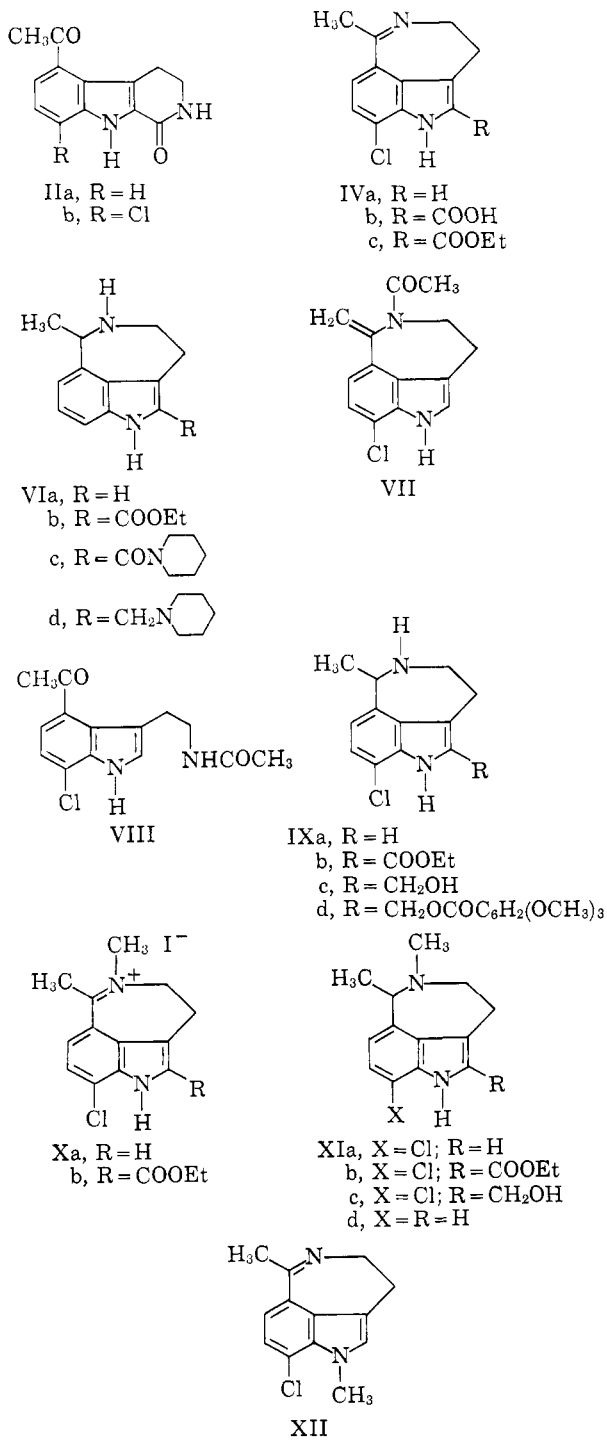
(1) Paper III in this series: M. von Strandtmann, C. Puchalski, and J. Shavel, Jr., *J. Med. Chem.*, **7**, 141 (1964).

(2) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *ibid.*, **6**, 719 (1963).

(3) The generally accepted β-carboline nomenclature takes precedence over the systematic name, 1H-pyrido[3,4-*b*]indole, according to A. M. Patterson, L. T. Capell, and D. F. Walter, "The Ring Index," 2nd Ed., American Chemical Society, Washington, D. C., 1960.

(4) Protonation of the nitrogen is the first step in the decarboxylation of indole-2-carboxylic acids, according to R. A. Abramovitch, *J. Chem. Soc.*, 881 (1956).

CHART I



tion of the C=N bond took place. The infrared spectrum of the resulting tetrahydroazepinoindole (VIa) no longer showed the C=N bond at 1630 cm.$^{-1}$ displayed by the parent compound IVa; the ultraviolet spectrum exhibited bands typical of the indole chromophore.

Acetylation of IVa with acetic anhydride in pyridine gave the enamide VII, which opened on mild acidic hydrolysis[5] to give 4,N-diacetyl-7-chlorotryptamine (VIII). The infrared spectrum of VII displayed bands at 895–905 (overtone at 1820 cm.$^{-1}$) and at 1607 cm.$^{-1}$ which are characteristic of the out-of-plane deformation of a methylene group and of the stretching vibration of a conjugated vinyl group.[6] Alkaline hydrolysis of the amide VIII resulted in recyclization to the parent azepinoindole IVa. It is noteworthy that such a cyclization did not take place in the course of the alkaline hydrolysis of the cyclic amides IIa and IIb.

Reduction of IVa with $LiAlH_4$ or KBH_4 resulted in saturation of the C=N bond with retention of chlorine to give IXa.

Methylation of the azepine nitrogen by treatment of IVa with methyl iodide followed by reduction of the resulting quaternary salt Xa gave the tertiary amine XIa. Methylation of the indole nitrogen to give XII was accomplished by refluxing IVa with dimethyl carbonate in the presence of sodium hydride.[7]

Attempts at dehydrogenation of IVa by heating with mercuric acetate, palladium black, or chloranil were unsuccessful.

The ester IVc, obtained by Fischer esterification of the azepinoindole-2-carboxylic acid IVb, was subjected to a series of reactions analogous to those described for the parent nucleus, such as quaternization (Xb), reduction of the C=N bond without (IXb and XIb) and with (VIb and XId) removal of chlorine. In the course of this work the ester function was converted to hydroxymethyl (IXc and XIc), trimethoxybenzoyloxymethyl (IXd), piperidinocarbonyl (VIc), and piperidinomethyl (VId) groups.

Of interest here is the reaction of the amino alcohol IXc with trimethoxybenzoyl chloride in pyridine which gave, as the only isolable material, a small amount of O-acylated rather than N-acylated product. The basic properties of this compound (IXd) and its infrared spectrum, which showed an ester band at 1710 cm.$^{-1}$ and no bands in the amide region, left no doubt as to the identity of this compound.

The infrared spectra of the esters IVc, VIb, IXb, Xb, and XIb showed carbonyl bands in the 1690–1705-cm.$^{-1}$ region, whereas the amide band of VIc was found at 1600 cm.$^{-1}$. This lowering of the C=O stretching frequency reflects the electron release by the indole nucleus at the 2-position.[8]

Summary of Pharmacological Data.—Concurrent with the dose-range studies in mice the gross effects of the drug on behavior, autonomic and central nervous systems, reflexes, muscle tone, and motor coordination were evaluated. No significant effects were observed at nontoxic doses. At toxic or lethal levels all of the compounds tested produced moderate to marked stimulation of the central nervous system, as was evidenced by Straub tail, increased startle response, tremors, and twitches with clonic and clonic-tonic convulsions. These symptoms were accompanied by exophthalmus and sometimes (VIb, IXa, and XIa) by thick salivation. The onset of action was rapid, and deaths usually occurred within 5–15 min. of drug administration. The central effects of compounds VIc, VId, and IXc ($ALD_{50} \geqq 200$) were relatively less in-

(5) This method of ring opening is an adaptation of a procedure applied for cleavage of various 1-methyl-3,4-dihydroisoquinolines by A. Brossi, J. Wuersch, and O. Schnider, *Chimia* (Aarau), **12**, 114 (1958).

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 60.

(7) This method will be described in detail in one of our forthcoming publications.

(8) The ν_{CO} of 2-acetyl-3-methylindole occurs at 1631 cm.$^{-1}$ according to J. A. Ballantine, C. B. Barret, R. J. S. Beer, B. G. Boggiano, S. Eardley, B. E. Jennings, and A. Robertson, *J. Chem. Soc.*, 2227 (1957). An analogous lowering of the carbonyl frequency of the 2-position of the pyrrole ring has been described by P. Mirrone and V. Lorenzelli, *Ann. chim.* (Rome), **48**, 72 (1958), and by U. Eisner and R. L. Erskine, *J. Chem. Soc.*, 971 (1958).

TABLE I:

No.		X	R	A	B	LD_{50},[a] mg./kg. p.o.	Analgesia: mg./kg. p.o.	Analgesia: % protection	Cardiovascular effects: mg./kg. i.v.	Cardiovascular effects: Blood pressure,[b] mm.	Cardiovascular effects: min.	Response to ref. agents[c] and remarks
V[d]	>C—N—	H	H		H	75	35	0	0.1	↑ <20	>30	Potentiates DMPP
IVa	>C═N—	Cl	H		H	25	5	20	2	↓ <20	<10	Blocks EPI, *nor*-EPI; potentiates DMPP; tremors at higher dose
									10	↓ 80	22	
IVc	>C═N—	Cl	H		COOEt	180						
XII	>C═N—	Cl	CH_3		H	175	100[e]	67				
Xa[f]	>C═N$^+$<	Cl	H	CH_3	H	>1000			10	↓ <20	<10	Blocks EPI
VIa	>C—N<	H	H	H	H	150	50	20	2	No effect		Blocks EPI, ACH, DMPP, carotid occlusion
IXa	>C—N<	Cl	H	H	H	75	50	30	1	↓ <20	<10	Blocks ACH; potentiates DMPP
XIa	>C—N<	Cl	H	CH_3	H	75	25	0	1	↓ <20	10–30	Blocks histamine, DMPP, carotid occlusion
IXc	>C—N<	Cl	H	H	CH_2OH	375	150	10				
VIb	>C—N<	H	H	H	COOEt	100			3	↓ <20	>30	Blocks EPI, *nor*-EPI; potentiates DMPP
VIc	>C—N<	H	H	H	CON	200	100	0				
VId	>C—N<	H	H	H	CH_2N	400			10	No effect		

[a] Approximate LD_{50}. [b] Change in blood pressure, fall (↓) or rise (↑). [c] Epinephrine (EPI), norepinephrine (*nor*-EPI), 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP), acetylcholine (ACH). [d] This previously described compound (ref. 2) is included for purpose of comparison. [e] This dose proved lethal to 4 out of 10 mice. [f] Poor absorption from gastrointestinal tract.

tense. The quaternary salt Xa was completely inactive because of poor absorption.

Several of the compounds (IVa, VIa, and IXa) possess analgesic properties, as was suggested by their ability to protect mice from the "writhing-syndrome" induced by phenylquinone.[9] However, this lead was not pursued further because of the narrow margin of safety.

The cardiovascular evaluation in anesthetized dogs[10] failed to uncover significant effects at nontoxic doses. At 10 mg./kg. i.v., IVa produced a blood pressure fall of 80 mm., which required 22 min. to return to normal.

Compounds VIa–d and IX did not reverse endotoxin-induced lung inflammation in mice[11] to a significant degree. Similar absence of antiinflammatory properties was shown by IVa and IVc in the cotton pellet test.[12]

The pharmacological results are summarized in Table I. Compounds not included in the table received no pharmacological evaluation.

Experimental[13]

2,3-Piperidinedione 3-[(3-Acetyl-6-chlorophenyl)hydrazone] (I).—A mixture of 85.5 g. (0.5 mole) of 3-carbethoxy-2-piperidone and 30 g. of KOH in 1 l. of water was incubated over night at 30°, filtered, chilled to 0°, treated with 50 ml. of 6 *N* HCl, and added at 0° to a freshly prepared diazonium salt solution. The latter was obtained by diazotizing at 0–5° a mixture of 84.75 g. (0.5 mole) of 3-amino-4-chloroacetophenone, 205 ml. of concentrated HCl, and 750 ml. of water with a solution of 36.25 g. (0.51 mole) of sodium nitrite in 125 ml. of water. The mixture was stirred at 10° for 5 hr. The precipitated product was filtered, washed with water, and recrystallized from 95% ethanol; m.p. 184–186°; yield 78%; λ_{max} mμ (ε) 239.5 (21,200), 254–261 plateau (10,000), 334 (21,600); ν_{max} 1500 (ms), 1570 (s), 1600 (ms), 1655 (ms), 1675 (ms), 1690 (ms), 3150 (ms), 3250 (ms) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{14}ClN_3O_2$: C, 55.82; H, 5.04; Cl, 12.68; N, 15.02. Found: C, 55.60; H, 5.34; Cl, 12.60; N, 15.18.

5-Acetyl-8-chloro-1,2,3,4-tetrahydro-1-oxo-β-carboline (IIb).—A solution of 62 g. of compound I in 310 ml. of 88% formic acid was refluxed for 24 hr. and concentrated *in vacuo*. The concentrate was chilled, and the precipitated product was collected on a filter and washed with cold formic acid; m.p. 219–230°, yield 40 g. (69%). An analytical sample was obtained by recrystallization from absolute ethanol; m.p. 234–236°; λ_{max} mμ (ε) 226 (21,650), 255 (17,400), 322 (11,950); ν_{max} 1550 (m), 1670 (ms), 1695 (s), 3100 (m), 3200 (ms), 3450 (m) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{11}ClN_2O_2$: C, 59.43; H, 4.22; Cl, 13.50; N, 10.66. Found: C, 59.37; H, 4.44; Cl, 13.38; N, 10.36.

4-Acetyl-2-carboxy-7-chlorotryptamine (III).—A mixture of 40 g. of IIb, 100 g. of KOH, 480 ml. of ethanol, and 360 ml. of water was refluxed for 18 hr. After removal of the ethanol *in vacuo*, the residue was treated with 480 ml. of water. The solution was chilled and adjusted to *ca.* pH 6 with glacial acetic acid. On scratching, a heavy yellow precipitate formed, which was collected on a filter and washed with cold water; slow charring above 240°, yield 41 g. (95%). An analytical sample was obtained by recrystallization from 50% ethanol; slow charring above 250°; λ_{max} mμ (ε) 218.5 (23,000), 258 (16,100), 347 (7200), 408 (7080); ν_{max} 1550 (m), 1610 (m), 1680 (m), 3400 (m) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; N, 9.98. Found: C, 55.50; H, 4.75; N, 9.81.

(9) E. A. Siegmund, A. Cadmus, and G. Lu, *J. Pharmacol. Exptl. Therap.*, **119**, 184 (1957).

(10) For the description of the method see ref. 2.

(11) E. C. Herrmann, Jr., C. Engle, and P. L. Perlman, *Am. J. Physiol.*, **197**, 803 (1959).

(12) R. Meier, W. Schuler, and P. Desaulles, *Experientia*, **6**, 469 (1950).

(13) Melting points were determined on a Mel Temp melting point apparatus with an aluminum block and are uncorrected. Infrared spectra were recorded on a Baird spectrograph, Model No. 455, as Nujol mulls. Ultraviolet spectra were determined on a Beckman DK-1 spectrophotometer in 95% ethanol.

9-Chloro-3,4-dihydro-6-methyl-1H-azepino[5,4,3-*cd*]indole (IVa) and 9-Chloro-3,4-dihydro-6-methyl-1H-azepino[5,4,3-*cd*]-indole-2-carboxylic Acid Hydrochloride (IVb).—A mixture of 41 g. of III, 1230 ml. of 20% HCl, and 492 ml. of glacial acetic acid was refluxed for 100 hr. The solution was chilled, and the precipitated IVb was collected on a filter and recrystallized from boiling water; m.p. >360; yield 19 g.; λ_{max} mμ (ε) 221 (22,180), 248 (12,180), 267 (15,650), 346 (7950), 397 (8250); ν_{max} 1300 (s), 1550 (m), 1645 (ms), 1710 (s), 3050 (ms), 3150 (ms) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{11}ClN_2O_2 \cdot HCl$: C, 52.19; H, 3.71; Cl, 23.71; N, 9.36. Found: C, 52.19; H, 3.83; Cl, 23.80; N, 9.10.

The filtrate was adjusted in the cold to pH 12 with 40% KOH solution, and the precipitated IVa was collected on a filter, washed with cold water, and recrystallized from 50% ethanol; m.p. 208–211°; yield 6.5 g.; λ_{max} mμ (ε) 245 (24,620), 339 (6400); ν_{max} 805 (ms), 1100 (s), 1170 (ms), 1250 (ms), 1505 (m), 1555 (ms), 1630 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{11}ClN_2$: C, 65.90; H, 5.07; Cl, 16.22; N, 12.81. Found: C, 65.93; H, 5.24; Cl, 16.19; N, 12.71.

Ethyl 9-Chloro-3,4-dihydro-6-methyl-1H-azepino[5,4,3-*cd*]-indole-2-carboxylate (IVc).—A suspension of 23 g. of IVb in 3 l. of absolute ethanol was brought to reflux by passing in dry HCl for 4 hr. with stirring. Reflux was maintained for an additional 4 hr. by gentle heating with continued HCl addition. On standing at room temperature for 18 hr., a heavy crystalline precipitate formed. After chilling, the product was filtered, washed with and recrystallized from absolute ethanol; m.p. 229–234°; yield 24.5 g. (97%); λ_{max} mμ (ε) 225.5 (20,750), 249 (13,200), 263 (14,050), 343 (9290), 387 (7900); ν_{max} 1030 (ms), 1105 (ms), 1155 (s), 1195 (ms), 1235 (s), 1280 (s), 1535 (ms), 1615 (ms), 1700 (ms) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{15}ClN_2O_2 \cdot HCl$: C, 55.06; H, 4.93; Cl, 21.67; N, 8.56. Found: C, 55.22; H, 5.12; Cl, 21.67; N, 8.26.

3,4-Dihydro-6-methyl-1H-azepino[5,4,3-*cd*]indole (V).—A solution of 1.08 g. (0.005 *M*) of IVa in 20 ml. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 50 mg. of 10% palladium on carbon until 137 ml. (0.005 *M*) of hydrogen had been taken up. The mixture was filtered, and the filtrate was evaporated *in vacuo*. The solid residue was treated with hot water and filtered. The aqueous filtrate was made basic in the cold with 40% KOH, and the crystalline precipitate was filtered, washed with cold water, and recrystallized twice from absolute ethanol, m.p. 274–279°, yield 11%.

***dl*-3,4,5,6-Tetrahydro-6-methyl-1H-azepino[5,4,3-*cd*]indole (VIa).**—A solution of 0.736 g. of V in 75 ml. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 50 mg. of 10% palladium on carbon. The reduction mixture was filtered, and the filtrate was evaporated *in vacuo*. The white crystalline residue was recrystallized from absolute ethanol for analysis; m.p. 200–205°; yield 80%; λ_{max} mμ (ε) 225.5 (31,900), 284 (6720); ν_{max} 745 (s), 785 (m), 1155 (m), 1170 (m), 1620 (mw), 3300 (m) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.15; H, 7.82; N, 15.01.

Direct hydrogenation of 4.75 g. of IVa by the above method gave an 82% yield of VIa hydrochloride which melted at 267–273°.

Anal. Calcd. for $C_{12}H_{14}N_2 \cdot HCl$: C, 64.71; H, 6.79; Cl, 15.92; N, 12.58. Found: C, 64.46; H, 6.97; Cl, 15.81; N, 12.38.

Ethyl *dl*-3,4,5,6-Tetrahydro-6-methyl-1H-azepino[5,4,3-*cd*]-indole-2-carboxylate (VIb).—This compound was prepared from 5 g. of IVc analogously to the above described hydrogenation of VIa. After evaporation of the solvent, the residue was taken up in 250 ml. of water and made basic in the cold with 40% KOH solution. The precipitated product was filtered, washed with cold water, and recrystallized from ethanol; m.p. 172–174°; yield 90%; λ_{max} mμ (ε) 233 (21,200), 300 (18,200); ν_{max} 750 (ms), 1025 (ms), 1100 (ms), 1170 (ms), 1260 (ms), 1535 (m), 1695 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.97; H, 6.84; N, 10.79.

***dl*-3,4,5,6-Tetrahydro-6-methyl-2-piperidinocarbonyl-1H-azepino[5,4,3-*cd*]indole (VIc).**—A solution of 10 g. of VIb in 100 ml. of piperidine was treated with 5 ml. of ethanolic HCl and refluxed for 7 days. The reaction mixture was diluted to 1000 ml. with ice water and extracted with five 100-ml. portions of chloroform. The combined extracts were washed several times with water, dried (Na_2SO_4), and evaporated to dryness *in vacuo*. The residue was recrystallized from absolute ethanol; m.p. 221–223°; yield 83%; λ_{max} mμ (ε) 224 (29,400), 294 (12,200); ν_{max} 755 (m), 1270 (m), 1595 (ms), 3150 (m) cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{23}N_3O$: C, 72.69; H, 7.79; N, 14.13. Found: C, 72.39; H, 7.82; N, 14.25.

***dl*-3,4,5,6-Tetrahydro-6-methyl-2-piperidinomethyl-1H-azepino[5,4,3-*cd*]indole (VId).**—This compound was obtained from 5 g. of VIc by a method analogous to the preparation of IXc. The analytical sample was obtained by recrystallization from absolute ethanol; m.p. 171–174°; yield 23%; λ_{max} mμ (ε) 228.5 (33,800), 285.5 (8800); ν_{max} 745 (s), 860 (m), 1095 (ms), 1170 (m), 3300 (m) cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{25}N_3$: C, 76.28; H, 8.89; N, 14.83. Found: C, 76.17; H, 9.10; N, 14.76.

5-Acetyl-9-chloro-3,4,5,6-tetrahydro-6-methylene-1H-azepino-[5,4,3-*cd*]indole (VII).—A solution of 10 g. of IVa in 2.5 ml. of pyridine and 25 ml. of acetic anhydride was heated on a steam bath for 1 hr. The mixture was chilled, and the yellow crystalline precipitate was filtered and recrystallized from absolute ethanol; m.p. 236–239°; yield 9.5 g. (80%); λ_{max} mμ (ε) 224 (22,400), 242 (16,700), 321 (9100); ν_{max} 800 (ms), 895–905 (doublet ms), 990 (w), 1085 (s), 1410 (ms), 1500 (m), 1550 (m), 1605 (ms), 1630 (s), 1820 (w), 3150 (ms) cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{13}ClN_2O$: C, 64.49; H, 5.02; Cl, 13.60; N, 10.74. Found: C, 64.27; H, 5.25; Cl, 13.73; N, 10.55.

4-Acetyl-7-chloro-N-acetyltryptamine (VIII).—A solution of 8 g. of VII in 10 ml. of water and 10 ml. of 3 *N* HCl was warmed on a steam bath for 3 hr. The mixture was cooled and made basic with NH_4OH. The precipitated oily product crytallized on standing. It was filtered, washed with water, and recrystallized from absolute ethanol; m.p. 144–147°; yield 8 g.; λ_{max} mμ (ε) 242 (23,900), 314 (7350); ν_{max} 1170 (ms), 1235 (ms), 1610 (ms), 1620 (ms), 1675 (ms), 3300 (ms) cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{15}ClN_2O_2$: C, 60.32; H, 5.42; Cl, 12.72; N, 10.05. Found: C, 60.08; H, 5.66; Cl, 12.82; N, 10.28.

A mixture of 1 g. of VIII, 8 ml. of water, 12 ml. of ethanol, and 2.5 g. of KOH was refluxed for 18 hr. On concentration *in vacuo*, a crystalline product was obtained which was identified by melting point and infrared spectrum as 9-chloro-3,4-dihydro-6-methyl-1H-azepino[5,4,3-*cd*]indole (IVa).

***dl*-9-Chloro-3,4,5,6-tetrahydro-6-methyl-1H-azepino[5,4,3-*cd*]indole (IXa).**—A solution of 3.75 g. of IVa in 125 ml. of methanol was treated with 3.75 g. of KBH_4 and stirred for 2.5 hr. After evaporation of the methanol *in vacuo*, the solid residue was triturated with water, filtered, washed with water, and recrystallized from absolute ethanol; m.p. 152–154°; yield 3 g. (80%); λ_{max} mμ (ε) 228 (33,000), 291.5 (7100), 301 (6550); ν_{max} 785 (ms), 800 (ms), 1075 (ms), 1090 (ms), 1165 (ms), 1620 (m), 3350 (ms) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{13}ClN_2$: C, 65.30; H, 5.94; Cl, 12.69; N, 16.07. Found: C, 65.52; H, 5.82; Cl, 12.65; N, 16.13.

Ethyl *dl*-9-Chloro-3,4,5,6-tetrahydro-6-methyl-1H-azepino-[5,4,3-*cd*]indole-2-carboxylate (IXb).—This compound was prepared from IVc by a procedure analogous to that of IXa; m.p. 126–129°; yield 50%; λ_{max} mμ (ε) 239.5 (27,800), 297 (18,400); ν_{max} 1190 (ms), 1285 (ms), 1540 (mw), 1695 (ms) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{17}ClN_2O_2$: C, 61.53; H, 5.85; Cl, 12.11; N, 9.57. Found: C, 61.69; H, 5.72; Cl, 12.19; N, 9.45.

***dl*-9-Chloro-3,4,5,6-tetrahydro-6-methyl-1H-azepino[5,4,3-*cd*]indole-2-methanol (IXc).**—A mixture of 8 g. of IVc, 250 ml. of dry tetrahydrofuran, and 8 g. of $LiAlH_4$ was refluxed for 6 hr. Excess $LiAlH_4$ was destroyed by the cautious addition of water. The mixture was filtered, and the insolubles were extracted several times with hot tetrahydrofuran. The combined filtrates and washings were evaporated *in vacuo*. The solid residue was recrystallized from absolute ethanol; m.p. 215–218°; yield 43%; λ_{max} mμ (ε) 231.5 (30,400), 290 (7160); ν_{max} 1005 (s), 1050 (ms), 1105 (ms), 1300 (ms), 1510 (m), 3150 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{15}ClN_2O$: C, 62.27; H, 6.03; Cl, 14.14; N, 11.17. Found: C, 62.53; H, 6.32; Cl, 14.13; N, 10.90.

***dl*-9-Chloro-3,4,5,6-tetrahydro-6-methyl-1H-azepino[5,4,3-*cd*]indole-2-methanol 3,4,5-Trimethoxybenzoate (IXd).**—A solution of 1 g. of IXc in 20 ml. of pyridine was added in the cold to a solution of 1.4 g. of 3,4,5-trimethoxybenzoyl chloride in 5 ml. of pyridine. After 1 hr. in the cold, the solution was filtered and treated with 250 ml. of anhydrous ether. The gummy precipitate was filtered and dissolved in glacial acetic acid. Treatment of this solution with ice and 40% KOH gave a crystalline precipitate. This was filtered and recrystallized from

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} 1090 (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 (9800), 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 $C_{13}H_{13}ClN_2 \cdot HCl$: 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,

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