phic activities as manifested by changes in the weights of the ventral prostate, seminal vesicles, and levator ani. Interpretation of results obtained by this type of routine assay is necessarily very limited in scope because changes in histology and vital organs were not determined. Nevertheless, the fact that I was shown to be more active than testosterone may reflect rapid transportation of the compound across the lipid barrier and rapid cleavage to testosterone.

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Some Alkylideneaminooxyalkanoic Acids and Derivatives[1a]

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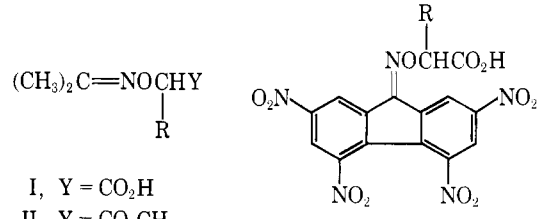
In view of the interest in alkylideneaminooxyacetic acids and their esters as potential therapeutic agents[2] and because of the use of alkylideneaminooxypropionic acids[3,4] in processes of optical resolution[3,5] and determination of absolute configuration,[6] we have now prepared additional homologs and their derivatives (I–IV) in this series. Several of these compounds have been tested for antitumor activity in the screening program of the Cancer Chemotherapy National Service Center. None of the compounds tested exhibited sufficient antitumor activity in a specific test system to meet the acceptance criteria of the CCNSC Protocols. Data on the screening tests are presented in Table I. Recrystallization from benzene of compounds IVb and IVc gives excellent products which are stable to drying *in vacuo* at moderate temperatures and which are 1:1 molecular compounds with the solvent. Benzene is lost if drying is conducted at higher temperatures.



I, Y = CO_2H
II, Y = CO_2CH_3
III, Y = CH_2OH

IV

a, R = CH_3
b, R = C_2H_5
c, R = $CH_3(CH_2)_3$

TABLE I
SUMMARY OF ANTICANCER SCREENING DATA[a]

Compd	Test[b] system	Dose, mg/kg	T/C,[c] %
Ib	SA	125	71
	LE	100	96
	LL	25[d]	103
	KB[e]		
Ic	SA	125	54
	LE	100	100
	LL	100	69
	KB[e]		
IIa	SA	125	115
	91	100	71
	LE	100	94
	KB[e]		
IIb	SA	60[f]	160
	LE	50	110
	LL	50	113
IIc	SA	125	109
	LE	100	101
	LL	100	102
IIIa	SA	125	66
	91	100	83
	LE	100	104
	KB[e]		
IIIc	SA	125	93
	91	100	121
	LE	100	109
	KB[e]		

[a] We are indebted to N. H. Greenberg of the Drug Evaluation Branch, CCNSC, National Cancer Institute, for assistance in interpretation of these data. For testing procedures and criteria for activity see *Cancer Chemotherapy Rept.*, **25**, 1 (1962). [b] SA = Sarcoma 180, LL = Lewis lung carcinoma, LE = L1210 lymphoid leukemia, 91 = S91 Cloudman melanoma, KB = tissue culture. [c] For LE, ratio of mean survival times of test animals to control animals. For other test systems, ratio of tumor weights of test animals to control animals. [d] Toxic in dosage of 100 mg/kg; survivors 0/6. [e] $ED_{50} > 0.01$ μg/ml. [f] Toxic in dosage of 125 mg/kg; survivors 3/6.

Experimental Section[7]

2-(Isopropylideneaminooxy)alkanoic Acids (I).—The procedure followed that used by Newman and Lutz[3] for the synthesis of Ia. From 500 g of 2-bromobutyric acid (Distillation Products Industries) and 219 g of acetoxime was obtained a liquid, bp 81–100° (0.5 mm), which crystallized on being dissolved in 50 ml of 30–60° petroleum ether–acetone (4:1, v/v) and cooling; yield 118 g (25%) of Ib, obtained as prisms, mp 48–52°, raised to 54.5–55.5° on repeated recrystallization from the same solvent.

Anal. Calcd for $C_7H_{13}NO_3$: C, 52.81; H, 8.23; N, 8.80. Found: C, 52.81; H, 8.18; N, 8.80.

Similarly 2-bromohexanoic acid was converted to Ic and crystallized from petroleum ether–acetone (5:3, v/v) to give prisms (13% yield), mp 41–43.5°, raised to 42–43.5° on recrystallization from petroleum ether alone.

Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.61; H, 9.13; N, 7.78.

Methyl 2-(Isopropylideneaminooxy)alkanoates (II).—The procedure followed that used by Klemm, Stalick, and Bradway[6] for

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the synthesis of IIa. From 0.4–0.5 mole of acids Ib and Ic were obtained 80–85% yields of liquid esters IIb [bp 88–92° (12 mm)] and IIc [bp 101–112° (12 mm)], respectively. For analyses the crude esters were redistilled several times at reduced pressure and center constant-boiling fractions were collected; $n^{23}D$ 1.4295 for IIb, 1.4335 for IIc; infrared bands (neat) at 1775 ± 5 (strong, C=O) and 1666 ± 2 cm^{-1} (weak, C=N).

Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found for IIb: C, 55.55; H, 8.67; N, 7.82. Calcd for $C_{10}H_{19}NO_3$: C, 59.67; H, 9.52; N, 6.96. Found for IIc: C, 59.23; H, 9.46; N, 6.72.

2-(Isopropylideneaminooxy)-1-alkanols (III).—To an ice-cold solution of 22 g (0.127 mole) of ester IIb in 500 ml of anhydrous ether was added, in five portions and with stirring, 3.4 g (0.089 mole) of solid $LiAlH_4$. The reaction mixture was stirred 1 hr longer, allowed to stand at room temperature overnight, and then processed in the same fashion as used in the preparation of IIIa,[6] yield 14.3 g (78%) of IIIb, bp 83–86° (13 mm). After four more distillations an analytical sample was obtained; significant infrared bands (neat) at 3450 (OH) and 1640 cm^{-1} (C=N).

Anal. Calcd for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 57.97; H, 10.54; N, 9.34.

Likewise from 50 g (0.25 mole) of ester IIc and 6.4 g (0.17 mole) of $LiAlH_4$ was obtained 34.9 g (80%) of IIIc, bp 93–105° (21 mm). After three more distillations there resulted an analytical sample, bp 113–113.5° (13 mm), $n^{23}D$ 1.4455, significant infrared bands (neat) at 3390 (OH) and 1630 cm^{-1} (C=N).

Anal. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.09. Found: C, 62.07; H, 10.90; N, 7.66.

2-(2,4,5,7-Tetranitro-9-fluorenylideneaminooxy)alkanoic Acids (IV).—The procedure followed that used by Newman and Lutz[3] for synthesis of IVa. A mixture of 23.1 g of 2,4,5,7-tetranitrofluorenone, 15.4 g of Ib, 2.5 g of *p*-toluenesulfonic acid, and 175 ml of glacial acetic acid was refluxed, cooled, and diluted with water. The precipitate was washed with dilute acetic acid, dissolved in 80 ml of propionic acid, and reprecipitated by addition of an equal volume of water to this hot solution; yield 24.8 g (84%) of IVb, mp 166–169°. For analysis, IVb was converted to the **IVb–benzene molecular compound** (by repeated recrystallization from benzene), obtained as pale yellow prisms or powder, mp 126–127°, stable to drying for 8 hr at 25° (0.1 mm).

Anal. Calcd for $C_{17}H_{11}N_5O_{11}\cdot C_6H_6$: C, 51.21; H, 3.18; N, 12.99. Found: C, 51.20; H, 3.11; N, 13.02.

Similarly Ic was converted to IVc (90% yield), mp 211.5–216°. Four recrystallizations from benzene gave yellow prisms of **IVc–benzene molecular compound,** mp 216–217.5°, stable to drying for 30 hr at 56° (0.05 mm).

Anal. Calcd for $C_{19}H_{15}N_5O_{11}\cdot C_6H_6$: C, 52.82; H, 3.72; N, 12.32. Found: C, 52.68; H, 3.93; N, 12.16.

Compounds Affecting the Central Nervous System. II. Substituted 1,2,3,4-Tetrahydropyrido[4,3-*b*]indoles

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The 1,2,3,4-tetrahydropyrido[4,3-*b*]indole (γ-carboline) ring system, in contrast to the β-carboline nucleus, has been little investigated as a source of biologically active compounds. N_2 quaternary salts of this ring system were investigated[2] as potential curarizing agents, some of them having a potency of about one-fifth that of *d*-tubocurarine. Hörlein[3] prepared 5-alkyl-, substituted alkyl-, arylalkyl-, and aryl-γ-carbolines, some of which were claimed to have antihistaminic activity. In particular 2-methyl-5-benzyl-1,2,3,4-tetrahydropyrido[4,3-*b*]indole (mebhydrolin) was shown to have prolonged antihistaminic activity[4] with little sedative effect in man.[5]

No reports have appeared on the effect of γ-carbolines on the central nervous system, and, following our interest in the activity of 1-arylalkyl-4-piperidones,[6] the effect of replacing the oxygen function and 3-alkyl group in these compounds by an indole nucleus to give 1,2,3,4-tetrahydro-γ-carbolines was investigated.

2-Substituted 1,2,3,4-tetrahydro-γ-carbolines were prepared by condensation of the corresponding substituted 4-piperidone with phenylhydrazine hydrochloride in ethanolic hydrochloric acid.[3,7] When 1-substituted phenylhydrazines were used in this reaction the corresponding 2,5-disubstituted 1,2,3,4-tetrahydro-γ-carbolines were obtained. 5-Alkyl- and 5-dialkylaminoalkyl-1,2,3,4-tetrahydro-γ-carbolines were obtained by condensation of the appropriate 2-substituted 1,2,3,4-tetrahydro-γ-carboline with an alkyl halide in the presence of sodamide.[3] The parent compound, 1,2,3,4-tetrahydropyrido[4,3-*b*]indole, was prepared from 4-piperidone hydrochloride and phenylhydrazine hydrochloride, reaction with 2-diethylaminoethyl chloride giving 2-(2-diethylaminoethyl)-1,2,3,4-tetrahydropyrido[4,3-*b*]indole.

The spectra are, as would be expected, similar to the corresponding alkylindoles,[8–11] having a broad, partially resolved peak in the ultraviolet at 270–280 mμ (log ϵ_{max} 3.5–4.0) and a further peak at 225–230 mμ (log ϵ_{max} 4.5–4.8).

Biological Activity.—The pharmacological tests used to investigate the activity of these compounds on the central nervous system have been described in the preceding paper of this series.[6] 2-Methyl-1,2,3,4-tetrahydro[4,3-*b*]indole and its 8-bromo derivative blocked the conditioned avoidance response in rats (ED_{50} values 20 and 25 mg/kg, respectively). The LD_{50} values of the compounds were 430 and 370 mg/kg, respectively. The activity of chlorpromazine under similar experimental conditions was 10 and 200 mg/kg, respectively. These two compounds also had analgesic activity in the hot-plate test in mice (ED_{50} values 30 and 60 mg/kg, respectively). Replacement of the methyl group in the 2-position by ethyl, benzyl, phenethyl, and 2-diethylaminoethyl led to less active compounds. This contrasted with the parent piperidones where optimium activity was found with 1-arylalkyl-3-alkyl-4-piperidones.[6]

Substitution of the hydrogen atom on the indole nitrogen atom by alkyl, arylalkyl, aryl, or dialkylaminoalkyl gave compounds with no significant activity in the pharmacological tests employed in this study. Thus for activity in the conditioned avoidance response

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