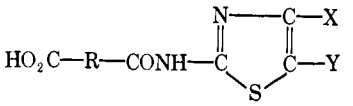
TABLE III
AMIC ACIDS



Compd	Starting acid	X	Y	Mp, °C	Formula	Analysis[d]	Yield, %
33	Maleic	H	H	153–154[a]	$C_7H_6N_2O_3S$	C, H, N	83
34	3,3-Dimethylglutaric	H	H	181–182[a]	$C_{10}H_{14}N_2O_3S$	C, H, N	91
35	3,4,5,6-Tetrachlorophthalic	H	H	183[a]	$C_{11}H_4Cl_4N_2O_3S$	C, H, Cl, N	62
36	Succinic	H	H	196–197[a]	$C_7H_8N_2O_3S$	C, H, N	88
37	Cyclohexane-1,2-dicarboxylic	H	H	193–194[a]	$C_{11}H_{14}N_2O_3S$	C, H, N	38
38	4-Cyclohexene-1,2-dicarboxylic	H	H	173–175[a]	$C_{11}H_{12}N_2O_3S$	C, H, N	51
39	3,4,5,6-Tetrabromophthalic	H	H	193[a]	$C_{11}H_4Br_4N_2O_3S$	C, H, Br, N	60
40	3-Nitrophthalic	H	NO_2	202–203[a]	$C_{11}H_6N_4O_7S$	C, H, N	81
41	3,6-Endoxycyclohexane-1,2-dicarboxylic	Naphtho[2,3-*d*][b]		270–272[a]	$C_{19}H_{16}N_2O_4S$	C, H, N	87
42	3,6-Endoxycyclohexane-1,2-dicarboxylic	6-Ethoxybenzo[c]		202–203[a]	$C_{17}H_{18}N_2O_5S$	C, H, N	52

[a] With decomposition. [b] From 2-amino[2,3-*d*]naphthothiazole. [c] From 2-amino-6-ethoxybenzothiazole. [d] See Table I, footnote *h*

TABLE IV
BIOLOGICAL DATA[a]

Compd	Dose, mg/kg	Survivors	% T/C[b]
16	160	6/6	21
	160	4/6	40
	160	6/6	*c*
	160	4/7	48
	160	5/6	51
	160	5/6	35
22	400	5/6	36
	400	2/6	*c*
	400	5/6	25
	400	5/7	26
	400	5/6	27
	400	6/6	46
	400	6/6	62

[a] Test system in all cases was Lewis lung carcinoma, with each test animal receiving a single daily injection for 11 days, the surviving animals being sacrificed on the 12th day. [b] Ratio of survival time of test animals to control animals, where 42% is considered acceptable. [c] Test data not reported.

Appropriate compounds were submitted to and screened under the auspices of the Cancer Chemotherapy National Service Center[5] in the primary rodent screens. Most of the compounds were also assayed for growth inhibitory activity against the KB cell line in tissue culture. In most cases the screens showed little activity in the following test systems: Sarcoma 180, Adenocarcinoma 755, L1210 lymphoid leukemia, Dunning leukemia, S91 Cloudman melanoma, Lewis lung carcinoma, and KB tissue culture. However, compounds **16** and **22** showed considerable activity in the screen against Lewis lung carcinoma. These significant data are summarized in Table IV.

Experimental Section

N-(2-Thiazolyl)-7-oxabicyclo[2.2.1]heptane-2,3-dicarboximide (17). Method A.—A mixture of 13.4 g (0.08 mole) of 3,6-endoxycyclohexane-1,2-dicarboxylic acid anhydride and 8.1 g (0.08 mole) of 2-aminoethiazole was dissolved in 100 ml of xylene and refluxed for 4 hr. After cooling, the product crystallized and was recrystallized (EtOH), yield 7.5 g, 38%, final mp 187–188°.

Method B.—An intimate mixture of 8.4 g (0.05 mole) of 3,6-endoxycyclohexane-1,2-dicarboxylic acid anhydride and 5 g (0.05 mole) of 2-aminothiazole was heated at 180° for 30 min. The temperature was raised to 220° and maintained for 10 min. After pouring the oil into water, the crude product which solidified was dried. Two recrystallizations (EtOAc) (charcoal) gave 5.6 g (43%) of analytically pure product, mp 187–188°.

Method C. 1-Cyclohexanecarboxylic Acid 2-(2-Thiazolyl)-amide (37).—A solution of 7.7 g (0.05 mole) of 1,2-cyclohexanedicarboxylic anhydride in CH_2Cl_2 was added 5 g (0.05 mole) of refluxing 2-aminothiazole. After 1 hr, the solvent was removed *in vacuo*, and the residue was washed (hot EtOAc). The crude product, 7.4 g, was dried, mp 179–182°. Two recrystallizations (MeOH) yielded 4.9 g (39%) of pure amic acid, mp 193–194° dec.

Acknowledgment.—The authors wish to thank Dr. Harry Wood of the National Cancer Institute for making the results of the screening data available.

(5) *Cancer Chemotherapy Rept.*, **1**, 43 (1959).

Some Hydrogenated Dibenz[*e*,*g*]isoindoline Derivatives

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Received September 2, 1967

For many years we have been interested in isoindoline types of compounds[2,3] and their pharmacological properties. Among these properties in particular have been the ganglionic blocking and hypotensive activity as well as their cytotoxicity. We now wish to report a small group of dibenz[*e*,*g*]isoindoline derivatives and some of their biological properties.

The key intermediate in our synthesis was the anhydride I, which was readily obtained from 1,1′-octahydrobiphenyl by means of the Diels–Alder reaction.[4] Preparation of the desired compounds was carried out by the reaction of the anhydride with an appropriate dialkylaminoalkylamine to produce an amic acid which on heating at 200° cyclized to yield the imide II. This product could be distilled easily and was reduced readily

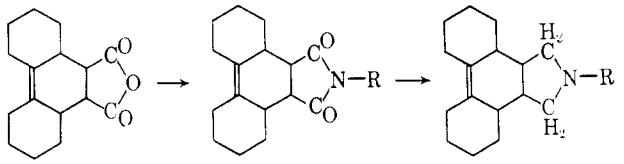
(1) Deceased, June 1967.

(2) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, **75**, 4911 (1953).

(3) C. H. Grogan and L. M. Rice, *J. Med. Chem.*, **6**, 802 (1963).

(4) E. E. Gruber and R. Adams, *J. Am. Chem. Soc.*, **57**, 2555 (1935).

by means of lithium aluminum hydride to the base III in high yield. The product was stable to distillation



I II III

and was converted into the hydrochloride and methiodide salts.

The dihydrochloride of base III (R = dimethylaminopropyl) when screened against KB tissue culture cells was active at about 10 μg/ml. None of the compounds showed any activity against L1210 lymphoid leukemia. The dimethiodide of III (R = dimethylaminopropyl) produced ganglionic blockage when tested on the nictitating membrane of the cat and gave a moderate reduction of blood pressure in an anesthetized dog.

Experimental Section[5]

N-(3-Dimethylaminopropyl)-1,2,3,4,5,6,7,8,8a,9,10,10a-dodecahydro-9,10-phenanthrenedicarboximide (II, R = dimethylaminopropyl).—To 5 g (0.0192 mole) of finely powdered anhydride I was added, with shaking, 2.5 g (excess) of 3-dimethylaminopropylamine. After the initial reaction the mixture was heated at 180–200° for 30 min. The product distilled as a viscous glass, bp 210–220° (0.07 mm), yield 5 g (76%). *Anal.* ($C_{21}H_{32}N_2O_2$) C, H, N.

The monomethiodide, prepared in the usual manner, melted at 208–210°. *Anal.* ($C_{22}H_{35}IN_2O_2$) I.

N-(3-Dimethylaminopropyl)-3a,3b,4,5,6,7,8,9,10,11,11a,11b-dodecahydrodibenz[*e,g*]isoindoline (III, R = dimethylaminopropyl).—To a solution of 9 g of $LiAlH_4$ hydride in 1 l. of anhydrous ether, the imide II dissolved in 1 l. of anhydrous ether was added rapidly with vigorous stirring and the mixture was refluxed 4 hr. While stirring, the reaction mixture was decomposed by the dropwise addition of H_2O (36 ml) and the stirring was continued for an additional 3 hr. After standing overnight the solution was filtered and the inorganic cake was washed (dry Et_2O). The solution was dried (Na_2SO_4), the solvent was removed, and the residual oil was distilled, bp 160–170° (0.07 mm). The distillate weighed 3.3 g (80%). *Anal.* ($C_{21}H_{36}N_2$) C, H, N.

The dihydrochloride prepared in the usual manner after recrystallization from EtOH–Me_2CO melted at 305–306° (put in bath at 290°). *Anal.* ($C_{21}H_{38}Cl_2N_2$) Cl, N.

The dimethiodide was prepared in EtOH by refluxing with excess MeI and diluting with 3 vol. of EtOAc. After recrystallization from EtOH–Me_2O with a trace of ether the crystals melted at 240–242° dec. *Anal.* ($C_{23}H_{42}I_2N_2$) I, N.

N-(2-Dimethylaminoethyl)-3a,3b,4,5,6,7,8,9,10,11,11a,11b-dodecahydrodibenz[*e,g*]isoindoline (III, R = dimethylaminoethyl) was prepared as outlined above except that the imide was not distilled. The crude imide was dissolved in ether and reduced ($LiAlH_4$), bp 155–160° (0.05 mm). *Anal.* ($C_{20}H_{34}N_2$) C, H, N.

The dihydrochloride, prepared in the usual way, melted at 259–260° dec. *Anal.* ($C_{20}H_{36}Cl_2N_2$) Cl.

The dimethiode prepared as described above melted at 241–242° dec. *Anal.* ($C_{22}H_{40}I_2N_2$) I.

N-(3-Morpholinopropyl)-3a,3b,4,5,6,7,8,9,10,11,11a,11b-dodecahydrodibenz[*e,g*]isoindoline (III, R = morpholinopropyl) was prepared as above from 5 g of the anhydride without isolation of the imide. It boiled at 180–190° (0.07 mm) and weighed 4.1 g. *Anal.* ($C_{23}H_{38}N_2O$) C, H, N.

The dihydrochloride when recrystallized from EtOH–Et_2O melted at 286–289°. *Anal.* ($C_{23}H_{40}Cl_2N_2O$) Cl, N.

The dimethiodide was prepared in MeOH and precipitated with EtOAc. When recrystallized from EtOH–ether it melted at 246–248°. *Anal.* ($C_{25}H_{44}I_2N_2O$) I, N.

(5) Melting points were determined with a Thomas–Hoover apparatus and are corrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.3% of the theoretical values.

The Ethyl Homologs of 2,4,5-Trimethoxyphenylisopropylamine

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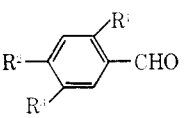
Received January 18, 1967
Revised Manuscript Received August 23, 1967

Of the six possible 1-(trimethoxyphenyl)-2-aminopropanes (trimethoxyamphetamines),[1] the 2,4,5 isomer (IIa) was the most potent as a psychotomimetic agent,[2,3] and it serves in this present report as the reason for the synthesis of the seven possible ethyl homologs. These have been prepared by routes which preclude isomer contamination. In preliminary observations only the 4-monoethoxy isomer IIe exceeds IIa in psychotomimetic potency.

Experimental Section

The 2-ethoxy homolog (IIb) was prepared by the Claisen rearrangement of allyl 3,4-dimethoxyphenyl ether as described earlier.[1] The remaining isomers (IIc–h) employed the three separate 3,4-dialkoxyphenols obtained by the peracetic acid oxidation of the appropiate aldehyde. The synthesis of 2,4-dimethoxy-5-ethoxyphenylisopropylamine (IIe) is typical. The malononitrile derivatives were prepared as described earlier.[1] The microanalyses of all new compounds in Tables I and II are listed in Table III; melting points were determined on a Kofler Heizbank and are corrected.

TABLE I



			Mp, °C	
R^1	R^2	R^3	ArCHO	ArCH=C(CN)$_2$
H	OCH_3	OCH_3	45[a]	147[b]
H	OCH_3	OC_2H_5	50[c]	142
H	OC_2H_5	OCH_3	60[d]	141
H	OC_2H_5	OC_2H_5	Oil[e]	105[f]
OCH_3	OCH_3	OC_2H_5	108[g]	136
OCH_3	OC_2H_5	OCH_3	109[h]	172
OCH_3	OC_2H_5	OC_2H_5	89	157
OC_2H_5	OCH_3	OC_2H_5	111	158
OC_2H_5	OC_2H_5	OCH_3	99	173
OC_2H_5	OC_2H_5	OC_2H_5	95[i]	170

[a] L. Gattermann [*Ann.*, **357**, 313 (1907)] reported mp 43–44°. [b] H. Kauffmann [*Ber.*, **52**, 1422 (1919)] reported mp 147°. [c] E. Spath and E. Bernhauer [*ibid.*, **58**, 200 (1925)] reported mp 150–151°. [d] F. Tiemann [*ibid.*, **8**, 1127 (1875)] reported mp 64–65°. [e] Obtained from the Eastman Kodak Co. [f] R. P. Mariella and J. M. Bauer [*J. Org. Chem.*, **23**, 120 (1958)] reported mp 104–104.5°. [g] F. S. H. Head and A. Robertson [*J. Chem. Soc.*, 2434 (1930)] reported mp 110°. [h] Lit.[g] mp 110°. [i] W. Will [*Ber.*, **16**, 2106 (1883)] reported mp 95°.

1,3-Dimethoxy-4-ethoxybenzene.—To a solution of 4-ethoxy-3-methoxyphenol in MeOH (14 g in 20 ml) was added a solution of 5.3 g of KOH in MeOH (100 ml), followed by MeI (11.9 g). The mixture was refluxed for 2 hr, quenched with 3 vol of H_2O, and made strongly basic with 5% NaOH. Extraction with ether and evaporation of the pooled extracts yielded the title ether as a clear oil, 9.7 g, $n^{25}D$ 1.5210.

(1) A. T. Shulgin, *J. Med. Chem.*, **9**, 445 (1966).
(2) A. T. Shulgin, *Experientia*, **20**, 366 (1964).
(3) C. Naranjo, T. Sargent, and A. T. Shulgin, unpublished data.