Acknowledgments.—We wish to thank Drs. Richard Tislow and Irving Geller and their associates for the pharmacological evaluations and Dr. Gordon Ellis and his group for the analytical data.

Indanols. IV.[1] Indanoxypropanolamines

SEYMOUR L. SHAPIRO, VINCENT A. PARRINO, ELAINE S. ISAACS, AND LOUIS FREEDMAN

Research Laboratories, U. S. Vitamin & Pharmaceutical Corporation, Yonkers, New York

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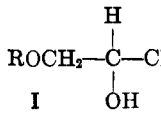
In a series of indanoxypropanolamines, $ROCH_2CHOHCH_2A$, compounds providing the best muscle relaxant activity have been found wherein R is 4-indanyl, and A is a relatively weak basic secondary amino group.

Indanoxypropanolamines of the type (I) have been synthesized and examined as central nervous system depressants. Related compounds have been evaluated as analgesics,[2,3] hypnotics,[4] anticonvulsants,[5,6] and muscle relaxants.[7,8]



I

R = 4 and 5-indanyl
A = dialkylamino substituted aminoalkylamino

The indanoxypropanolamines I (Table I) were obtained in fair

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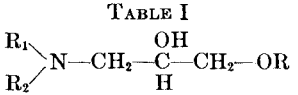
TABLE I



No.	R_1	R_2	M.p. °C.[a,b] or b.p.	Mm.	Yield, %	Formula	Analyses, %[c] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
	R = 4-indanyl											
1	—$(CH_2)_5$—		60–61		15	$C_{17}H_{25}NO_2$	74.1	74.1	9.2	9.3	..	..
2	—$(CH_2)_2$—O—$(CH_2)_2$—		158–164	0.3	49	$C_{16}H_{23}NO_3$	..	..	..	..	5.1	5.1
3	C_3H_5—[d]	C_3H_5—[d]	139–145	0.2	67	$C_{18}H_{25}NO_2$	75.2	75.1	8.8	8.9	4.9	5.2
4	—$(CH_2)_2N(CH_3)$—$(CH_2)_2$—		88–89		53	$C_{17}H_{26}N_2O_2$	70.3	70.0	9.0	9.0	9.7	9.5
5	—$(CH_2)_2N(CH_2CH_2OH)$—$(CH_2)_2$—		184–190	0.2	20	$C_{18}H_{28}N_2O_3$	67.5	67.8	8.8	8.6	..	..
6	—$(CH_2)_2N(C_6H_5)$—$(CH_2)_2$—		74–76		58	$C_{22}H_{28}N_2O_2$	..	..	..	..	8.0	8.3
7	$C_6H_5CH_2$—	CH_3—	174–178	0.2	52	$C_{20}H_{25}NO_2$	77.1	76.9	8.1	8.1	..	..
8	$C_6H_5CH_2$—	$HOCH_2CH_2$—	206–210	0.2	46	$C_{21}H_{27}NO_3$	..	..	..	..	4.1	3.8
9	*d*-$C_6H_5CH_2CHCH_3$—	CH_3—	172–184	0.1	33	$C_{22}H_{29}NO_2$	77.8	77.6	8.6	8.1	4.1	4.3
10	—(1,2)—CH_2—C_6H_4—$(CH_2)_2$—		104–106		49	$C_{21}H_{25}NO_2$	..	..	..	..	4.3	4.2
11	4-Py$(CH_2)_2$—[e]	CH_3—	186–208	0.2	33	$C_{20}H_{27}N_2O_2$	..	..	..	..	8.6	9.0
	R = 5-indanyl											
12	—$(CH_2)_5$—		135–141	0.2	47	$C_{17}H_{25}NO_2$	74.1	74.2	9.2	9.4	..	..
13	C_3H_5—[d]	C_3H_5—[d]	140–148	0.3	41	$C_{18}H_{25}NO_3$	..	..	..	..	4.9	4.7
14	$(CH_3)_2N$—$(CH_2)_2$—	CH_3—	134–142	0.2	39	$C_{17}H_{28}N_2O_2$	69.8	69.9	9.7	9.3	9.6	9.7
15	—$(CH_2)_2NCH_3$—$(CH_2)_2$—		165–168	0.2	46	$C_{17}H_{26}N_2O_2$	70.3	70.4	9.0	8.7	9.7	9.8
16	—$(CH_2)_2N(CH_2CH_2OH)$—$(CH_2)_2$—		180–184	0.2	36	$C_{18}H_{28}N_2O_3$	..	..	..	..	8.8	8.7
17	$C_6H_5CH_2$—	CH_3—	168–174	0.2	53	$C_{20}H_{25}NO_2$	77.1	77.2	8.1	7.8	4.5	4.6
18	*d*-$C_6H_5CH_2CH(CH_3)$—	CH_3—	156–160	0.1	46	$C_{22}H_{29}NO_2$	77.8	77.6	8.6	8.8	4.1	4.0
19	—(1,2)—CH_2—C_6H_4—$(CH_2)_2$—		61–63		29	$C_{21}H_{25}NO_2$	78.0	77.7	7.8	8.1	4.3	4.4
20	2-Py$(CH_2)_2$—[e]	CH_3—	170–182	0.3	50	$C_{20}H_{26}N_2O_2$	..	..	..	..	8.6	8.8
21	4-Py$(CH_2)_2$—[e]	CH_3—	168–185	0.2	37	$C_{20}H_{26}N_2O_2$	..	..	..	..	8.6	8.7

[a] Melting points are not corrected. [b] The solids were recrystallized from hexane. [c] Analyses by Weiler and Strauss, Oxford, England. [d] C_3H_5— is allyl. [e] Py is pyridyl.

yield through condensation of the 3-(4- or 5-indanoxy)-propylene oxides with the secondary amine, which attacks at the less substituted oxiranyl carbon.[9-13]

Reaction of a phenol[1,14] or an amine[15,16] with epichlorohydrin is relatively complex and proceeds through initial condensation at the oxirane ring. In the preparation of the indanoxy propylene oxides, reaction of the indanols with epichlorohydrin gave more than one product. Thus, condensation of 5-indanol with epichlorohydrin afforded, in addition to 51% of 1,2-epoxy-3-(5-indanoxy)-propane, a 20% yield of 3-(5-indanoxy)-2-propen-1-ol, further identified as its dibromo derivative and phenylurethane. Also obtained was a 5% yield of 3-(5-indanoxy)-1,2-propanediol, characterized as its bis-phenylurethane, and a nuclear monobromo derivative, which has been assigned the structure 3-[5-(6-bromoindanoxy)]-1,2-propanediol based on analysis, ultraviolet absorption spectra,[17] and synthetic studies in related systems.[18,19]

Similar condensation with 4-indanol gave 69% of 1,2-epoxy-3-(4-indanoxy)-propane, an 8% yield of product which readily hydrolyzes in dilute base to liberate chloride ions[15] and gives the diol below and which has been assigned the structure 1-chloro-2-hydroxy-3-(4-indanoxy)-propane, as well as a 3% yield of 3-(4-indanoxy)-1,2-propanediol characterized as its monobromo derivative, 3-[4-(7-bromoindanoxy)]-1,2-propanediol.

In the ultraviolet, the propylene oxide, the chlorohydrin, and the diol derived from 4-indanol have spectra similar to 4-methoxyindan,[18] with the bromo derivative of the diol showing bathochromic and hyperchromic effects typical of *p*-bromo substitution in a phenol.[17] The ultraviolet absorption spectrum of 5-indanol is decidedly hyperchromic and bathochromic relative to that of 3,4-dimethylphenol.[18] The compounds 3-(5-indanoxy)-1,2-propanediol, its mono-

(9) N. S. Isaacs and R. E. Parker, *J. Chem. Soc.*, 3497 (1960).
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(12) L. B. Kier and R. B. Penland, *J. Org. Chem.*, **25**, 1865 (1960).
(13) J. K. Addy, R. M. Laird, and R. E. Parker, *J. Chem. Soc.*, 1708 (1961).
(14) O. Stephenson, *ibid.*, 1571 (1954).
(15) J. B. McKelvey, B. G. Webre, and R. R. Benerito, *J. Org. Chem.*, **25**, 1424 (1960).
(16) J. B. McKelvey, B. G. Webre, and E. Klein, *ibid.*, **24**, 614 (1959).
(17) A. Burawoy and J. T. Chamberlain, *ibid.*, 2310 (1952).
(18) S. L. Shapiro, T. Bazga, K. Weinberg, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 3726 (1958).
(19) J. S. Buck, R. A. Cutler, F. C. Nachod, R. G. Powles, R. Rakoczy, T. J. Slauson, and B. F. Tullar, *ibid.*, **79**, 3559 (1957).

bromo derivative, and the dibromo derivative of 3-(5-indanoxy)-2-propen-1-ol retain the spectral influences noted with 5-indanol.[18] Alternatively, 1,2-epoxy-3-(5-indanoxy)-propane and 3-(5-indanoxy)-2-propen-1-ol have maxima similar to 3,4-dimethylphenol, but a strong hypochromic effect prevails.

The pharmacological findings are detailed in Table II.

TABLE II

PHARMACOLOGICAL RESULTS

No.	$LD_{min.}$[a]	M.R.[b]	A.S.[c]	M.A.**[d]	A[e]
1	300		37	41	
2	500	46			
3	750	137	125		
4	500		21		33/170
5	750	165			
7	750	175	100		
9	750		50	26	66/500
10	>1000	195			
11	300	58			50/150
15	750	375			
16	450		200	29	
18	>1000			33	
20	450		140	20	
21[f]	450		150		

[a] $LD_{min.}$ is the minimum lethal dose as established subcutaneously in mice. [b] Muscle Relaxant Test (M.R.)—the muscle relaxant assay (developed by Dr. G. Sisson of these laboratories) utilizes the ability of both centrally and peripherally acting depressants to block tight-rope-walking in mice. At 5 min. intervals from 10 to 30 min., and 60 to 80 min., following subcutaneous injection in varying dosages of the test compound, mice are placed on tight rope and observed for 30 sec. Under these conditions, sham-treated mice will cling to the tight rope for a full 30 sec. during each trial. Mice receiving muscle relaxant drugs fail to cling to the tight rope in proportion to the dose received. From the dose response curve, the ED_{50} in mg./kg. (50% of animals fail to cling to the rope) is calculated and reported above. Six mice are used per test, and each animal is tested 12 times. Control drugs show these ED_{50} (subcutaneous): meprobamate, 66; phenaglycodol, 116. [c] Audiogenic Seizure Test (A.S.)—The audiogenic seizure test was adapted from N. P. Plotnikoff and D. M. Green, *J. Pharmacol. Exptl. Therap.*, 119, 294 (1957). The response of a mouse to the bell alarm is graded as follows: seizure and death, "4"; seizure and convulsion, "3"; jumping, "2"; running, "1"; no abnormal response, "0." The test compounds are administered at a given dosage in mg./kg. s.c. and 90 min. after injection of the drug, the mice are exposed in the chamber with the bell on for 90 sec. Six mice are used in each test and the response of each mouse to the bell alarm is noted, and totalled for the 6 mice. Thus, if at a particular dosage level the drug is com-

pletely effective, all animals will have a 0 response, and the rating will be 0. Under the influence of the drug, the total score for the animals will be lower, *i.e.*, say at 75 mg./kg., it might be 18; subtracting 18 from the control total of 24 yields 6, and 6/24 equals 25% protection. A variety of dosage levels similarly evaluated are plotted and the point giving 50% protection is the ED_{50} in mg./kg. [d] The depression in motor activity (M.A.) was established as described by S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 333 (1957). ** All compounds tested at 100 mg./kg. s.c. except no. 1, tested at 50 mg./kg. [e] The analgesic test (A) was performed following the procedure described by C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954), and results are reported as % analgesia/mg./kg. of compound given s.c. [f] Tremorine ED_{50} = 60 mg./kg., method used as described by S. L. Shapiro, H. Soloway, E. Chodos, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 203 (1959).

Of the molecular parameters evaluated, it is clear that in the muscle relaxant test, the 4-indanoxy substituent is associated with more effective structures than the 5-indanoxy compounds. Apparently, the contribution of a substituent *ortho* to the phenoxy oxygen noted in related systems prevails in this present group of compounds.

An hydroxyl group on carbon *beta* to an amino group materially lowers its basicity.[20,21] In this series, compounds having only one basic site have been designed to provide varying orders of basicity with the piperidino[20] (compounds 1 and 12), being the most basic, and morpholino[20] (compound 2), aralkylamino[22] (compounds 7, 8, 9, 17, and 18), isoquinolino (compounds 10 and 19), the diallyl (compounds 3 and 13), being of lower basicity.

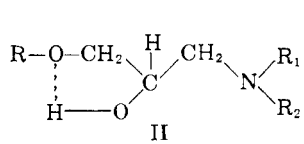
Alternatively, with the substituted aminoalkyl substituents, the accessibility of two nitrogens suggests the N-methylpiperazine analogs (compounds 4 and 15), and the dimethylaminoethyl analog (compound 14), as having the initial protonated site at the terminal nitrogen. In turn, the phenylpiperazine (compound 6) and the pyridylalkyl groups[23] (compounds 11, 20, and 21), would preferably be protonated at the nitrogen joining the trimethylene bridge, while the site of protonation of the hydroxyethylpiperazino compounds (compounds 5 and 16) would not be readily predictable.

Assessing these factors, the data suggest that with the muscle relaxant effect, compounds 2, 11, and 3, which are in the somewhat less basic group, provide the best results. The tendency for muscle

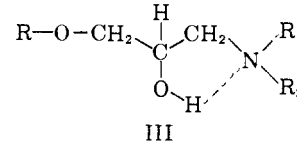
(20) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **78**, 2570 (1956).
(21) M. M. Tuckerman, J. R. Mayer, and F. C. Nachod, *ibid.*, **81**, 92 (1959).
(22) G. Vexlearschi and P. Rumpf, *Compt. rend.*, **236**, 939 (1953).
(23) H. C. Brown and X. R. Mihm, *J. Am. Chem. Soc.*, **77**, 1723 (1955).

relaxant activity to be associated with the less basic molecules suggests a closer parallelism with the noted effectiveness of neutral carbamate type structures.

Another structural feature of these compounds is the relatively minor role of intramolecular hydrogen bonding. Thus structures II and III are hydrogen bonded forms typifying compounds in this series.



II



III

Recent work[24] has indicated that hydrogen bonds forming structures such as III are stronger than those from II. Moreover, as the availability of the unshared *p* electrons on the nitrogen decreases, the strength of the —OH - - - N type bond decreases. Also, the presence of groups *ortho* to the oxygen atom on R would diminish the tendency for hydrogen bonding of the form II.[25,26] The data are suggestive of heightened activity with those structural systems reducing hydrogen bond formation.

Heightened activity in the audiogenic seizure test (compounds 1 and 4) is associated with more basic structures. Interestingly, compounds bearing the purportedly analeptic *d*-α-methylphenethyl group (compounds 9 and 18) showed central nervous system depressant effects.

Experimental[27]

1,2-Epoxy-3-(5-indanoxy)-propane.—A mixture of 134.2 g. (1.0 mole) of 5-indanol, 101.6 g. (1.1 mole) of epichlorohydrin and 67.3 g. (1.2 mole) of potassium hydroxide in 1 l. of water was stirred at 25° for 24 hr. The oil formed was extracted with four 200 ml. portions of chloroform, the chloroform extract washed with water, the chloroform removed and the residue (190 g.) distilled. The product obtained weighed 96.0 g. (51%), b.p. 94–104° (0.4 mm.), n^{20}D 1.5494, λ_{max} (methanol) 278 mμ (ϵ1.11 × 10^3).

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.8; H, 7.4; mol. wt., 190.2. Found: C, 76.5; H, 7.9; mol. wt., 194.0.

3-(5-Indanoxy)-2-propen-1-ol.—The distillation above when continued, yielded

(24) H. J. Freedman, *J. Am. Chem. Soc.*, **83**, 2900 (1961).
(25) G. Baddeley and N. H. P. Smith, *J. Chem. Soc.*, 2516 (1961).
(26) S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 6322 (1959).
(27) Data appearing in tables are not reproduced in Experimental Section.

39 g. (20%) of this product, b.p. 82–111° (0.06 mm.), $n^{20}D$ 1.5488, λ_{max} (methanol), 277 mμ (ϵ 0.92 × 10^3).

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.8: H, 7.4. Found: C, 75.9; H, 7.6.

The *carbanilide* was prepared by treatment under heating with an equivalent of phenyl isocyanate, m.p. 189–190° (from acetonitrile).

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.8; H, 6.2; N, 4.5. Found: C, 73.8; H, 6.4; N, 4.7.

2,3-Dibromo-3-(5-indanoxy)-propanol.—A chilled solution of 3.8 g. (0.02 mole) of 3-(5-indanoxy)-2-propen-1-ol in 10 ml. of chloroform was treated with 3.2 g. (0.02 mole) of bromine, with noted decolorization and exothermic reaction. The chloroform was removed and the residue distilled to give 5.99 g. (86%) of product, b.p. 150–162° (0.25 mm.), $n^{20}D$ 1.5967, λ_{max} (methanol) 286 mμ (ϵ 3.28 × 10^3). On boiling briefly with aqueous sodium hydroxide, a strong bromide ion test was obtained.

Anal. Calcd. for $C_{12}H_{14}Br_2O_2$: C, 41.2; H, 4.0; Br, 45.7. Found: C, 41.4; H, 3.5; Br, 46.0.

3-(5-Indanoxy)-propane-1,2-diol.—The initial distillation next gave 45.6 g. of an oil, b.p. 120–140° (0.06 mm.) which solidified, and on recrystallization (hexane) gave 11.4 g. (5%) of product, m.p. 77–78°, λ_{max} (methanol) 279 mμ (ϵ 2.82 × 10^3).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.2; H, 7.7. Found: C, 69.2; H, 7.8.

On heating with 2 equiv. of phenyl isocyanate, the dicarbanilide was obtained, m.p. 132–133° (ethyl acetate–hexane).

Anal. Calcd. for $C_{26}H_{26}N_2O_5$: C, 69.9; H, 5.9; N, 6.3. Found: C, 69.5; H, 5.8; N, 6.0.

3-[5-(6-Bromoindanoxy)]-propane-1,2-diol.—A solution of 2.6 g. (0.012 mole) of 3-(5-indanoxy)-propane-1,2-diol in 50 ml. of chloroform was treated with 1.6 g. (0.01 mole) of bromine in 10 ml. of chloroform with absorption of bromine, and evolution of hydrogen bromide. Evaporation of the solvent gave 3.81 g. of residue which on recrystallization (ethyl acetate–hexane) yielded 0.6 g. (21%) of product, m.p. 93–94°, λ_{max} (methanol), 285 mμ (ϵ 3.94 × 10^3). The solution from attempted hydrolysis with aqueous sodium hydroxide gave no test for bromide ion.

Anal. Calcd. for $C_{12}H_{15}BrO_3$: C, 50.2; H, 5.3; Br, 27.8; mol. wt., 287.2. Found: C, 50.0; H, 5.3; Br, 27.7; mol. wt., 288.

3-(4-Indanoxy)-propylene Oxide.—A mixture of 134.2 g. (1.0 mole) of 4-indanol, 101.6 g. (1.1 mole) of epichlorohydrin and 67.3 g. (1.2 mole) of potassium hydroxide in 1 l. of water was stirred at 25° for 24 hr. The oil formed was extracted with three 200 ml. portions of chloroform, the chloroform extract washed with water, the chloroform removed and the residue (179 g.) distilled; product obtained, 131 g.) 69%, b.p. 78–100° (0.1–0.2 mm.), $n^{20}D$ 1.5496, λ_{max} (methanol), 267, 275 mμ (ϵ × 10^2, 5.8, 5.3).

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.8; H, 7.4. Found: C, 75.7; H, 7.1.

3-(4-Indanoxy)-2-hydroxypropyl Chloride.—The distillation above, continued, gave 18.1 g. (8%) of product, b.p. 106–110° (0.02 mm.), $n^{20}D$ 1.5331, λ_{max} (methanol) 267, 276 mμ (ϵ × 10^2, 5.8, 5.2).

The product has not been obtained in analytically pure form.

Anal. Calcd. for $C_{12}H_{15}ClO_2$: C, 63.6; H, 6.7; Cl, 15.6. Found: C, 64.5; H, 6.8; Cl, 13.6.

Hydrolysis with aqueous isopropyl alcohol and sodium hydroxide yielded the diol, m.p. 72–73°; it did not depress the melting point of the compound below, mixture m.p. 72–74°.

3-(4-Indanoxy)-propane-1,2-diol.—The residue of the initial condensation solidified (20.5 g.) and after addition of 65 ml. of benzene and 220 ml. of heptane gave 6.2 g. (3%) of product, m.p. 73–74°, λ_{max} (methanol) 267, 276 mμ ($\epsilon \times 10^2$, 6.1, 5.6).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.2; H, 7.7. Found: C, 69.1; H, 7.4.

3-[4-(7-Bromoindanoxy)]-propane-1,2-diol.—Upon bromination following the procedure for the isomeric diol described above, the product, which gave no positive bromide test after boiling with aqueous sodium hydroxide, was obtained in 77% yield, m.p. 110–111° (ethyl acetate–hexane), λ_{max} (methanol), 273, 282 mμ ($\epsilon \times 10^2$, 8.8, 7.5).

Anal. Calcd. for $C_{12}H_{15}BrO_3$: C, 50.2; H, 5.3; Br, 27.8. Found: C, 50.6; H, 5.6; Br, 27.3.

1-(4-Methylpiperazino)-3-(4-indanoxy)-propane-2-ol (Compound 4).—A mixture of 1.5 g. (0.015 mole) of N-methylpiperazine and 1.9 g. (0.01 mole) of 1,2-epoxy-3-(4-indanoxy)-propane in 6 ml. of heptane was heated in an oil-bath, maintained at 100° for a period of 2 hr. When cool, the reaction mixture was washed with 10 ml. of water, the heptane layer separated, the heptane removed and, on scratching, the oily residue solidified. There was obtained 1.95 g. (67.2%) of product, m.p. 83–86°.

1-(N-Methylbenzylamino)-3-(4-indanoxy)-propane-2-ol (Compound 7).—In a manner similar to that described above, and using N-methylbenzylamine as the reactant amine, there was obtained a residual oil which, on distillation, afforded 2.42 g. (52%) of product, b.p. 174–178° (0.2 mm.).

The other compounds in Table I were prepared similarly.

Acknowledgment.—The authors wish to thank Drs. G. Ungar and G. Sisson and their staff for the pharmacological screening of the compounds, and M. Blitz and W. Greenfield for the ultraviolet absorption data.