Indanols V

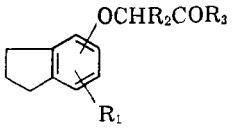
Indanoxyacetic Acid Derivatives

By SEYMOUR L. SHAPIRO†, THEODORE BAZGA, and LOUIS FREEDMAN

Indanoxyacetic acid derivatives (I) yielded compounds with adrenergic blocking and potentiating effects, tranquilizing activity, and anti-inflammatory activity. Of particular interest was the hypocholesteremic effect with α-(indan-4-oxy)butyric acid.

In the preceding paper, indanoxy ethers (1) were projected as simple structural analogs (2, 3) of steroids and related compounds.

Herein, we evaluate indanoxyacetic acid analogs of the type I



I

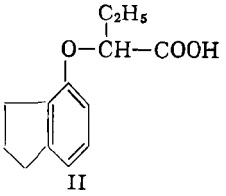
which were varied as shown in Table I. Such structures show formal analogies to the α-biphenylbutyric acids evaluated as hypocholesteremic agents by Garattini and co-workers (4), as well as the auxins (5).

Group variation, as for example R_1 as benzyl and *p*-chlorobenzyl, provided enhanced lipid solubility (6) whereas employment of R_2 from hydrogen through *n*-butyl assessed structures with increasing molecular crowding about the carboxyl group (7). The R_3 group, in turn, was inspected as the indanoxyacetic acids and derived amides and dialkylaminoalkylamides.

Reaction of the appropriate indanol with the substituted ethyl-α-bromoacetate in refluxing acetone (8), employing anhydrous potassium carbonate as an acid binder, gave the ester I, $R_3 = OC_2H_5$. The esters were hydrolyzed to the corresponding acids or converted to the amides.

On oral administration, cholesterolytic activity (8) was noted as follows: compound No./$LD_{min.}$ mg./Kg. s.c./oral dosage mg./Kg., for 3 days/% reduction in serum cholesterol at end of three days: 54/750/250/37; 55/1000/200/31; 56/300/100/51; 57/500/166/none; 58/450/150/none; 12/750/250/12. The 5-position isomer of compound 55, compound 14 ($LD_{min.}$ 500 mg./Kg.) showed 18% reduction in cholesterol after three daily doses at 30 mg./Kg. s.c. Compound 54 afforded lasting hypotension whereas compounds 55 and 56 were without effect on blood pressure (9).

The high order of hypocholesteremia obtainable with compound 56 (II), in the absence of hypotensive activity



II

has suggested additional explorations associated with the steric factor at R_2, along with the influence of substituents *ortho* to the phenoxy oxygen.

Other pharmacological effects of interest were noted as follows: potentiation of adrenaline (compounds 21, 22, 25, 31, and 39), and adrenergic block (compounds 68 and 69); ganglionic block (compound 68); reduction in motor activity (compounds 23, 25, and 72); significant inhibition of mescaline scratch test, with no inhibition of motor activity (compounds 29, 69, and 76); anti-inflammatory effects (compounds 31 and 77).

EXPERIMENTAL[1]

Ethyl α-(Indan-4-oxy)butyrate. (Compound 44).—A mixture of 26.8 Gm. (0.2 mole) of 4-indanol, 39 Gm. (0.2 mole) of ethyl α-bromobutyrate, and 27.6 Gm. (0.2 mole) of anhydrous potassium carbonate in 80 ml. of acetone was stirred and heated under reflux for 4 hours. When cool, the solid was removed by filtration and the filtrate diluted with 250 ml. of ice water and extracted with three 100-ml. portions of ether. The ethereal extracts were combined, washed successively with *N* sodium hydroxide and water, and then dried (anhydrous magnesium sulfate). After filtration, the ether was removed and the residue distilled to give 24 Gm. (48%) of product, b.p. 114–118° at 0.2 mm.

N - Diethylaminoethyl - α - (indan - 4 - oxy)-butyric Acid Amide. (Compound 69.)—A mixture

[1] Typical experimental procedures are given.

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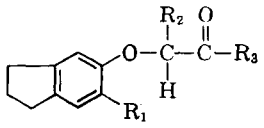
TABLE I.—INDANOXYACETIC ACID DERIVATIVES



No.	R_1	R_2	M.p., °C.[a] B.p., °C. (mm. Press.)	Formula	Analysis, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
				R_3 = —OC_2H_5[b]						
1	H	H	118–120 (0.15)	$C_{13}H_{16}O_3$	70.9	70.8	7.3	8.0	...	...
2	H	CH_3–	110–116 (0.25)	$C_{14}H_{18}O_3$	71.8	72.2	7.7	7.9	...	...
3	H	C_2H_5—	104–110 (0.09)	$C_{15}H_{20}O_3$	72.6	73.1	8.1	8.3	...	...
4[c]	H	*n*-C_3H_7—	134 (0.09)	$C_{16}H_{20}O_3$	72.6	72.7	8.1	8.2	...	...
5	H	*i*-C_3H_7—	110–116 (0.1)		...	...	...	...	...	...
6	$C_6H_5CH_2$—	H	168–178 (0.1)	$C_{20}H_{22}O_3$	77.4	77.4	7.1	7.0	...	...
7	$C_6H_5CH_2$—	CH_3	164–168 (0.4)		...	...	...	...	...	...
8	$C_6H_5CH_2$—	C_2H_5—	170–180 (0.5)		...	...	...	...	...	...
9	*p*-$ClC_6H_4CH_2$—	H	188–194 (0.16)		...	...	...	...	...	...
10	*p*-$ClC_6H_4CH_2$—	CH_3—	176–182 (0.2)	$C_{21}H_{23}ClO_3$	70.3	70.4	6.4	6.5	...	...
11	*p*-$ClC_6H_4CH_2$—	C_2H_5—	184–190 (0.05)		...	...	...	...	...	...
				R_3 = —OH						
12[d]	H	H	159–160 (C)	$C_{11}H_{12}O_3$	68.7	69.1	6.3	6.4	...	...
14	H	C_2H_5—	84–85 (A)	$C_{13}H_{16}O_3$	70.9	71.0	7.3	7.4	...	...
15	H	*n*-C_3H_7—	71–72 (A)	$C_{14}H_{18}O_3$	71.8	72.0	7.7	7.8	...	...
16	H	*i*-C_3H_7—	88–90 (A)	$C_{14}H_{18}O_3$	71.8	71.6	7.7	7.5	...	...
17	*p*-$ClC_6H_4CH_2$—	H	135–136 (B)	$C_{18}H_{17}ClO_3$	68.2	68.3	5.4	5.5	11.2[e]	11.2
18	*p*-$ClC_6H_4CH_2$—	CH_3	125–128 (C)	$C_{19}H_{19}ClO_3$	68.9	68.8	5.7	6.0	10.7[e]	10.6
19	*p*-$ClC_6H_4CH_2$—	C_2H_5—	155–157 (A)	$C_{20}H_{21}ClO_3$	69.6	70.0	6.1	5.9	10.2[e]	10.4
				R_3 = —$NHCH_2CH_2C_6H_5$						
20	H	H	97–98 (B)	$C_{19}H_{21}NO_2$	77.3	77.6	7.2	7.2	4.7	4.5
21	H	CH_3—	62–63 (A)	$C_{20}H_{23}NO_2$	77.6	77.7	7.5	7.3	...	...
22	H	C_2H_5—	64 (B)	$C_{21}H_{25}NO_2$	78.0	78.2	7.8	7.3	4.3	4.2
23	$C_6H_5CH_2$—	C_2H_5—	208–214 (0.04)	$C_{28}H_{31}NO_2$	...	...	...	...	3.4	3.3
24	*p*-$ClC_6H_4CH_2$—	C_2H_5—	85–90 (D)	$C_{28}H_{30}ClNO_2$	75.1	75.1	6.8	6.9	3.1	3.2
				R_3 = —$NHCHCH_3CH_2C_6H_5$[f]						
25	H	CH_3—	121–122 (B)	$C_{21}H_{25}NO_2$	78.0	77.9	7.8	7.9	4.3	4.3
26	H	C_2H_5—	130–131 (B)	$C_{22}H_{27}NO_2$	78.3	78.4	8.1	7.9	4.2	4.0
27	$C_6H_5CH_2$—	C_2H_5—	234–244 (0.2)	$C_{29}H_{33}NO_2$	81.5	81.7	7.8	7.3	...	...
				R_3 = —$NH(CH_2)_2N(C_2H_5)_2$						
28	H	H	166–176 (0.25)	$C_{17}H_{26}N_2O_2$	70.3	70.0	9.0	9.0	9.6	9.5
29	H	CH_3—	160–166 (0.08)	$C_{18}H_{28}N_2O_2$	71.0	70.6	9.3	9.2	9.2	9.5
30	H	C_2H_5—	166 (0.28)	$C_{19}H_{30}N_2O_2$	...	...	...	...	8.8	9.0
31	$C_6H_5CH_2$—	C_2H_5—	202–212 (0.12)	$C_{26}H_{36}N_2O_2$	76.4	76.5	8.9	8.8	6.9	6.7
32	*p*-$ClC_6H_4CH_2$—	C_2H_5—	224 (0.05)	$C_{26}H_{35}ClN_2O_2$	70.4	71.0	7.9	7.9	...	...
				R_3 = —$NH(CH_2)_3N(CH_3)_2$						
33	H	H	178–180 (0.46)	$C_{16}H_{24}N_2O_2$	69.5	69.9	8.7	8.9	...	...
34[g]	H	H	120–122 (E)	$C_{22}H_{27}N_5O_9$	52.3	52.3	5.4	5.3	...	...
35	H	C_2H_5—	160–164 (0.02)	$C_{18}H_{28}N_2O_2$	71.0	70.8	9.3	9.2	9.2	9.1
36	*p*-$ClC_6H_4CH_2$	C_2H_5—	226 (0.09)	$C_{26}H_{33}ClN_2O_2$	70.0	69.9	7.8	7.9	...	...
				R_3 = —$NH(CH_2)_3N(C_2H_5)_2$						
37	H	CH_3—	164–176 (0.11)	$C_{19}H_{30}N_2O_2$	...	...	...	...	8.8	9.2
38[g]	H	CH_3—	101–103 (E)	$C_{25}H_{32}N_6O_9$	54.8	54.5	6.1	6.0	...	...
39	H	C_2H_5—	172 (0.03)	$C_{20}H_{32}N_2O_2$	72.3	72.6	9.7	9.7	8.4	8.3
40	$C_6H_5CH_2$—	C_2H_5—	212–216 (0.06)	$C_{27}H_{38}N_2O_2$	...	...	...	...	6.6	6.3
41	*p*-$ClC_6H_4CH_2$—	C_2H_5—	216–218 (0.05)	$C_{27}H_{37}ClN_2O_2$	70.9	71.0	8.2	7.9	...	...
				R_3 = —OC_2H_5[b]						
42	H	H	112–116 (0.28)	$C_{13}H_{16}O_3$	70.9	70.9	7.3	7.6	...	...
43	H	CH_3—	104–110 (0.18)	$C_{14}H_{18}O_3$	71.8	72.3	7.7	7.9	...	...
44	H	C_2H_5—	114–118 (0.2)	$C_{15}H_{20}O_3$	72.6	73.3	8.1	8.3	...	...
45[c]	H	*n*-C_3H_7—	132 (0.4)	$C_{16}H_{20}O_3$	72.6	73.4	8.1	8.1	...	...
46	H	*i*-C_3H_7—	120 (0.1)	$C_{16}H_{22}O_3$	73.3	73.8	8.5	8.1	...	...
47	H	*n*-C_4H_9—	154 (0.3)	$C_{17}H_{24}O_3$	73.9	73.9	8.8	8.6	...	...
48	$C_6H_5CH_2$—	H	182–192 (0.03)		...	...	...	...	...	...
49	$C_6H_5CH_2$—	CH_3—	163–170 (0.19)	$C_{21}H_{24}O_3$	77.8	78.2	7.5	7.4	...	...
50	$C_6H_5CH_2$—	C_2H_5—	178–190 (0.3)		...	...	...	...	...	...
51	*p*-$ClC_6H_4CH_2$—	H	172–180 (0.08)		...	...	...	...	...	...
52	*p*-$ClC_6H_4CH_2$—	CH_3—	178–181 (0.2)		...	...	...	...	...	...
53	*p*-$ClC_6H_4CH_2$—	C_2H_5—	190–198 (0.3)		...	...	...	...	...	...
				R_3 = —OH						
54[h]	H	H	187–188 (C)	$C_{11}H_{12}O_3$	68.7	68.9	6.3	6.0	...	...
55	H	CH_3—	105–106 (A)	$C_{12}H_{14}O_3$	69.9	69.6	6.8	7.0	...	...
56	H	C_2H_5—	111–112 (A)	$C_{13}H_{16}O_3$	70.9	70.8	7.3	7.5	...	...
57	H	*n*-C_3H_7—	107–108 (A)	$C_{14}H_{18}O_3$	71.7	71.7	7.7	7.9	...	...
58	H	*n*-C_4H_9—	108–109 (A)	$C_{15}H_{20}O_3$	72.6	72.7	8.1	8.0	...	...
59	$C_6H_5CH_2$—	CH_3—	91–92 (A)	$C_{19}H_{20}O_3$	77.0	77.3	6.8	6.9	...	...
60	*p*-$ClC_6H_4CH_2$—	CH_3—	102–104 (A)	$C_{19}H_{19}ClO_3$	68.9	69.1	5.7	6.0	10.7[e]	11.1
61	*p*-$ClC_6H_4CH_2$—	C_2H_5—	116–117 (A)	$C_{20}H_{21}ClO_3$	69.6	69.4	6.1	6.3	10.3[e]	10.2
				R_3 = —$NHCH_2CH_2C_6H_5$						
62	H	H	82–84 (F)	$C_{19}H_{21}NO_2$	77.3	77.0	7.2	7.3	4.7	4.9
63	H	CH_3—	75–76 (B)	$C_{20}H_{23}NO_2$	77.6	77.9	7.5	7.6	4.5	4.6
64	H	C_2H_5—	77–79 (B)	$C_{21}H_{25}NO_2$	78.0	77.6	7.8	7.7	...	...
				R_3 = —$NHCHCH_3CH_2C_6H_5$[f]						
65	H	CH_3—	180–182 (0.18)	$C_{21}H_{25}NO_2$	78.0	78.2	7.8	8.2	4.3	4.2
66	H	C_2H_5—	136–137 (B)	$C_{22}H_{27}NO_2$	78.3	78.7	8.1	7.8	4.2	4.2

TABLE I.—(*continued*)

No.	R_1	R_2	M.p., °C.[a] B.p., °C. (mm. Press.)	Formula	Analysis, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
				R_3 = —$NH(CH_2)_2N(Et)_2$						
67	H	H	166–172 (0.16)	$C_{17}H_{26}N_2O_2$	70.3	70.0	9.0	9.1	9.6	9.6
68	H	CH_3—	170–172 (0.04)	$C_{18}H_{28}N_2O_2$	71.0	71.1	9.3	9.2	9.2	9.1
69	H	C_2H_5—	156–158 (0.12)	$C_{19}H_{30}N_2O_2$	...	...	...	...	8.8	9.0
70	$C_6H_5CH_2$—	H	200–208 (0.08)	$C_{24}H_{32}N_2O_2$	75.8	75.9	8.5	8.4	7.4	7.4
71	$C_6H_5CH_2$—	C_2H_5—	204–210 (0.1)	$C_{26}H_{36}N_2O_2$	76.4	75.9	8.9	8.8	6.9	6.5
				R_3 = —$NH(CH_2)_3N(CH_3)_2$						
72	H	C_2H_5—	172 (1.0)	$C_{18}H_{28}N_2O_2$	71.0	71.1	9.3	9.4	...	...
73	*p*-$ClC_6H_4CH_2$—	C_2H_5—	226 (0.09)	$C_{26}H_{33}ClN_2O_2$	70.0	69.9	7.8	7.9	...	...
				R_3 = —$NH(CH_2)_3N(C_2H_5)_2$						
74	H	H	170–174 (0.12)	$C_{18}H_{28}N_2O_2$	71.0	71.4	9.3	9.5	9.2	9.0
75	H	CH_3—	184 (0.6)	$C_{19}H_{30}N_2O_2$	...	...	...	...	8.8	8.4
76	H	C_2H_5—	176–180 (0.18)	$C_{20}H_{32}N_2O_2$	72.3	72.2	9.7	9.6	8.4	8.5
77	$C_6H_5CH_2$—	C_2H_5—	224 (0.18)	$C_{27}H_{38}N_2O_2$	...	...	...	...	6.6	6.6
78	*p*-$ClC_6H_4CH_2$—	C_2H_5—	240–250 (0.18)	$C_{27}H_{37}ClN_2O_2$	70.9	70.9	8.2	8.0	...	...

[a] Melting points are not corrected. Recrystallizing solvents: A, hexane; B, ethanol-water; C, ethanol; D, methanol; E, water; F, acetonitrile. [b] The esters in some instances were used directly without analyses. Average yield was about 50%. [c] Compound is methyl ester. [d] Reported Koelsch, C. F., and Scheiderbauer, R. A., *J. Am. Chem. Soc.*, **65**, 2311(1943), m.p. 154–155°. [e] Chlorine analysis. [f] Derived from *d*-α-methylphenethylamine. [g] Picrate of preceding compound. [h] Reported Kruber, O., and Schmieden, W., *Ber.*, **72B**, 653(1939); m.p. 182°.

of 3.7 Gm. (0.015 mole) of ethyl α-(indan-4-oxy)-butyrate and 15 ml. of diethylaminoethyl amine was heated under reflux for 8 hours, and on distillation gave 3.12 Gm. (66%) of product, b.p. 156–158° at 0.12 mm.

α-(Indan-4-oxy)butyric Acid. (Compound 56.)—A mixture of 22 Gm. (0.088 mole) of ethyl α-(indan-4-oxy)butyrate and 50 ml. of 3 *N* sodium hydroxide was heated under reflux for 2 hours. When cool, and after acidifying with hydrochloric acid, product was extracted with three 100-ml. portions of ether which, on evaporation, gave 18.5 Gm. (95%) of product.

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Melting and Freezing Behavior of Methyl Stearate

By A. P. SIMONELLI† and T. HIGUCHI

Investigations into the mechanism and kinetics of melting and crystallization of the stable form of methyl stearate as followed by changes in its specific volume have shown that: (*a*) the melting behavior was a sensitive function of its immediate history in a manner not associated with polymorphic transitions, (*b*) the thermodynamic equilibrium point was apparently displaced by stirring and that this displacement was proportional to the rate of stirring, (*c*) the rate of crystal growth for the present system was governed largely by the intrinsic rate of two-dimensional nucleation of a crystal plane, and (*d*) the rate of melting was a function of heat transport at higher temperature potentials. The extreme sensitivity of the method used allows the measurement of phase changes where they were of the order of parts per million and enabled the study under very small temperature potentials.

THE RESULTS of an investigation on the rates of melting and freezing are presented. These changes are often of great fundamental importance in altering the appearance of some and the rates of release of other pharmaceutical dosage forms. Although they are extremely common and apparently simple phenomena, relatively little effort seems to have been directed towards the construction of a clear and comprehensive picture of the underlying principles. Past studies in this area have been largely confined to metallic organic or simple organic systems which involve comparatively small entropy changes upon melt-

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