Experimental

The yields of the acids reported in Table I were those obtained when the Ivanov reagent, prepared from 0.5 mole of phenylacetic acid dissolved in 300 cc. of benzene and isopropylmagnesium chloride obtained from 1 mole of magnesium, 1.15 moles of isopropyl chloride and 1200 cc. of ether, was allowed to react with 0.55 mole of the required aldehyde or ketone.

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[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. XXIII. Basic Esters of β-Substituted α-Cyclohexyl-β-hydroxypropionic Acids

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α-Cyclohexyl-β-hydroxypropionic acid and sixteen β-substituted α-cyclohexyl-β-hydroxypropionic acids were prepared by hydrogenation of the corresponding α-phenyl-β-hydroxypropionic acids. Hydrochlorides and methobromides of the basic esters of these acids have been described and the antispasmodic activity of some of the compounds has been reported.

Recently, a number of basic esters of β-substituted α-phenyl-β-hydroxypropionic acids have been reported to be potent antispasmodics.[3-6] During this investigation, basic esters of α-cyclohexyl-β-hydroxypropionic acid and β-substituted α-cyclohexyl-β-hydroxypropionic acids have been synthesized. Each α-cyclohexyl acid was prepared by low pressure hydrogenation of the corresponding α-phenyl-β-hydroxypropionic acid[7] in the presence of platinum oxide catalyst.

We know of only two reports which describe the hydrogenation of α-phenyl-β-hydroxy acids or their derivatives to the corresponding α-cyclohexyl compounds: Miescher and Hoffmann[8] hydrogenated catalytically salts of atropine and scopolamine to the corresponding hexahydroatropine and hexahydroscopolamine salts; Raffelson[9] hydrogenated α,α-diphenyl-β-hydroxypropionic acid to α-phenyl-α-cyclohexyl-β-hydroxypropionic acid.

TABLE I

α-CYCLOHEXYL-β-HYDROXYPROPIONIC ACID AND β-SUBSTITUTED α-CYCLOHEXYL-β-HYDROXYPROPIONIC ACIDS, $C_6H_{11}CH(COHRR')COOH$

Compounds 1, 3, 4, 5, 6, 9, 12 and 13 were recrystallized from benzene; 2, 7, 8, 11, 14 and 17 from toluene; 10 from benzene–petroleum ether; 15 from methyl ethyl ketone; 16 from methyl ethyl ketone–petroleum ether (90–100°).

	R	R'	M.p., °C.	Yield,[a] %	Formula	Neut. equiv. Calcd.	Neut. equiv. Found	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	H	H	89–90	90	$C_9H_{16}O_3$	172.2	171.9	62.77	62.69	9.36	9.43
2	H	CH_3	140–142	84	$C_{10}H_{18}O_3$	186.2	186.7	64.49	64.80	9.74	9.56
3	H	C_2H_5	99–101	83	$C_{11}H_{20}O_3$	200.3	200.0	65.97	65.82	10.07	10.43
4	H	C_3H_7	99–100	76	$C_{12}H_{22}O_3$	214.3	213.4	67.25	67.00	10.35	10.23
5	H	i-C_3H_7	119–121	79	$C_{12}H_{22}O_3$	214.3	214.8	67.25	67.55	10.35	10.49
6	H	C_5H_{11}	98–99	88	$C_{14}H_{26}O_3$	242.3	241.5	69.38	69.28	10.81	10.71
7	H	C_6H_{11}[b,c]	184–186	89	$C_{15}H_{26}O_3$	254.4	253.4	70.82	70.63	10.30	10.02
8	H	C_6H_{13}	93–94	81	$C_{15}H_{28}O_3$	256.4	256.1	70.27	70.39	11.01	11.25
9	CH_3	CH_3	107–108	93	$C_{11}H_{20}O_3$	200.3	200.6	65.97	65.76	10.07	10.14
10	CH_3	C_2H_5	89–90	72	$C_{12}H_{22}O_3$	214.3	214.7	67.25	67.46	10.35	10.46
11	CH_3	C_6H_{11}[b,c]	141–143d.	72	$C_{16}H_{28}O_3$	268.4	268.0	71.60	71.35	10.52	10.60
12	C_2H_5	C_2H_5	84–86	82	$C_{13}H_{24}O_3$	228.3	229.1	68.39	68.37	10.59	10.56
13	C_3H_7	C_3H_7	116–118	91	$C_{15}H_{28}O_3$	256.4	255.4	70.27	70.59	11.01	10.97
14	—$CH_2(CH_2)_3CH_2$—		156–157	85	$C_{14}H_{24}O_3$	240.4	239.3	69.97	70.13	10.07	10.09
15	—$CH_2CH(CH_3)$-$(CH_2)_2CH_2$—		142–144	71	$C_{15}H_{26}O_3$	254.4	254.9	70.82	70.63	10.30	10.36
16	—CH_2CH_2CH-$(CH_3)CH_2CH_2$—		159–160	73	$C_{15}H_{26}O_3$	254.4	254.0	70.82	70.83	10.30	10.41
17	—$CH_2(CH_2)_5CH_2$—		147–149	67	$C_{16}H_{28}O_3$	268.4	268.0	71.60	71.53	10.52	10.53

[a] In five instances (compounds 1, 2, 14, 16 and 17) hydrogenation was also carried out at 60–70°; in each case the crude reaction product proved more difficult to purify, and the yield of pure product was lower. [b] Cyclohexyl. [c] This acid was prepared from the corresponding α,β-diphenyl acid by hydrogenation of both aromatic rings. This acid, m.p. 141–143°, was obtained by refluxing the recrystallized hydrogenation product (m.p. 129–132°) with a 100% excess of 2% sodium hydroxide solution, followed by acidification.

(1) This paper represents part of a dissertation submitted by R. H. Cox in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1954.

(2) Sterling-Winthrop Fellow.

(3) A. W. Weston and R. W. DeNet, THIS JOURNAL, **73**, 4221 (1951).

(4) G. R. Treves and F. C. Testa, *ibid.*, **74**, 46 (1952).

(5) F. F. Blicke and H. Raffelson, *ibid.*, **74**, 1730 (1952).

(6) F. F. Blicke and R. H. Cox, *ibid.*, **77**, 5399 (1955).

(7) The α-phenyl-β-hydroxypropionic acids which were hydrogenated have been described previously.[5,6]

(8) K. Miescher and K. Hoffmann, U. S. Patent 2,265,185; *C.A.*, **36**, 1737 (1942).

(9) H. Raffelson, Dissertation, University of Michigan, 1951.

Table II

Hydrochlorides and Methohalides of β-Diethylaminoethyl Esters of β-Substituted α-Cyclohexyl-β-hydroxypropionic Acids,

$$\underset{\displaystyle RR'COH}{C_6H_{11}\underset{|}{C}HCOOCH_2CH_2N(C_2H_5)_2\cdot HCl} \text{ or } CH_3X$$

Compounds 1, 2, 4, 10, 14, 18, 20, 24 and 28 were recrystallized from methyl ethyl ketone; 3 from ethanol–ethyl acetate; 5, 15, 22 and 33 from isopropyl alcohol–ether; 6 from methyl ethyl ketone–ether; 7 and 16 from isopropyl alcohol–methyl ethyl ketone; 8 and 9 from isopropyl alcohol–acetone; 11 and 31 from acetone–ether; 12, 26, 30 and 32 from isopropyl alcohol; 13, 19, 21, 27 and 29 from ethanol–ether; 17 and 23 from acetone; 25 from ethanol–isopropyl alcohol.

	R	R'	Salt	M.p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halogen Calcd.	Halogen Found	Antispasmodic activity; % of atropine sulfate[a]
1	H	H	HCl	92–94[b]	74	$C_{15}H_{30}O_3NCl$	58.52	58.60	9.82	9.95	11.52	11.47	5.9
2	H	H	CH_3Br	92–94[b]		$C_{16}H_{32}O_3NBr$	52.45	52.40	8.81	8.80	21.82	21.79	19.4
3	H	CH_3	CH_3I	92–95		$C_{17}H_{34}O_3NI$	47.77	47.59	8.02	7.97	29.70	29.54	
4	H	C_2H_5	HCl	103–105	59	$C_{17}H_{34}O_3NCl$	60.78	61.07	10.24	10.50	10.55	10.48	7.1
5	H	C_2H_5	CH_3Br	125–126		$C_{18}H_{36}O_3NBr$	54.81	55.16	9.20	9.50	20.27	20.12	23.2
6	H	C_3H_7	HCl	100–102	55	$C_{18}H_{36}O_3NCl$	61.78	61.68	10.37	10.51	10.14	10.14	5.6
7	H	C_3H_7	CH_3Br	121–122		$C_{19}H_{38}O_3NBr$	55.87	55.88	9.38	9.52	19.57	19.43	44.0
8	H	i-C_3H_7	HCl	139–141	66	$C_{18}H_{36}O_3NCl$	61.78	61.72	10.37	10.44	10.14	10.28	3.1
9	H	i-C_3H_7	CH_3Br	190–192[c]		$C_{19}H_{38}O_3NBr$	55.87	55.74	9.38	9.36	19.57	19.46	13.7
10	H	C_5H_{11}	HCl	105–107	80	$C_{20}H_{40}O_3NCl$	63.54	63.56	10.67	10.82	9.38	9.29	1.3
11	H	C_5H_{11}	CH_3Br	101–103		$C_{21}H_{42}O_3NBr$	57.78	58.03	9.70	9.91	18.31	18.10	18.5
12	H	C_6H_{11}[d]	HCl	166–168	80	$C_{21}H_{40}O_3NCl$	64.68	64.53	10.34	10.50	9.09	8.98	2.3
13	H	C_6H_{11}[d]	CH_3Br	135–138		$C_{22}H_{42}O_3NBr$	58.92	58.90	9.44	9.50	17.82	17.78	
14	H	C_6H_{13}	HCl	109–111	68	$C_{21}H_{42}O_3NCl$	64.34	64.43	10.80	10.77	9.04	8.95	0.5
15	H	C_6H_{13}	CH_3Br	100–103		$C_{22}H_{44}O_3NBr$	58.65	58.37	9.85	9.84	17.74	17.65	18.5
16	CH_3	CH_3	HCl	139–141	76	$C_{17}H_{34}O_3NCl$	60.78	61.16	10.21	10.35	10.55	10.47	4.6
17	CH_3	CH_3	CH_3Br	128–130		$C_{18}H_{36}O_3NBr$	54.81	55.02	9.20	9.17	20.27	20.18	14.0
18	CH_3	C_2H_5	HCl	116–117	67	$C_{18}H_{36}O_3NCl$	61.78	61.74	10.37	10.53	10.14	10.08	21.0
19	CH_3	C_2H_5	CH_3Br	142–144		$C_{19}H_{38}O_3NBr$	55.87	55.80	9.38	9.42	19.57	19.36	48.0
20	CH_3	C_6H_{11}[d]	HCl	147–149	66	$C_{22}H_{42}O_3NCl$	65.40	65.44	10.48	10.44	8.77	8.89	
21	CH_3	C_6H_{11}[d]	CH_3Br	194–195[c]		$C_{23}H_{44}O_3NBr$	59.72	59.42	9.59	9.68	17.28	17.15	3.2
22	C_2H_5	C_2H_5	HCl	129–131	68	$C_{19}H_{38}O_3NCl$	62.69	62.62	10.53	10.78	9.74	9.71	6.8
23	C_2H_5	C_2H_5	CH_3Br	150–152		$C_{20}H_{40}O_3NBr$	56.87	56.63	9.54	9.54	18.92	18.78	32.0
24	C_3H_7	C_3H_7	HCl	123–125	67	$C_{21}H_{42}O_3NCl$	64.34	64.48	10.80	10.83	9.04	8.98	0.2
25	C_3H_7	C_3H_7	CH_3Br	183–185		$C_{22}H_{44}O_3NBr$	58.65	58.80	9.85	10.07	17.74	17.59	0.8
26	$-CH_2(CH_2)_3CH_2-$		HCl	176–178	82	$C_{20}H_{38}O_3NCl$	63.89	63.92	10.19	10.42	9.43	9.37	9.5
27	$-CH_2(CH_2)_3CH_2-$		CH_3Br	135–138		$C_{21}H_{40}O_3NBr$	58.05	57.87	9.28	9.41	18.40	18.29	62.0
28	$-CH_2CH(CH_3)(CH_2)_2CH_2-$		HCl	159–161	68	$C_{21}H_{40}O_3NCl$	64.68	64.78	10.34	10.35	9.09	9.01	
29	$-CH_2CH(CH_3)(CH_2)_2CH_2-$		CH_3Br	149–151		$C_{22}H_{42}O_3NBr$	58.92	58.67	9.44	9.65	17.82	17.63	
30	$-CH_2CH_2CH(CH_3)CH_2CH_2-$		HCl	183–185	77	$C_{21}H_{40}O_3NCl$	64.68	64.69	10.34	10.25	9.09	9.16	2.8
31	$-CH_2CH_2CH(CH_3)CH_2CH_2-$		CH_3Br	155–157		$C_{22}H_{42}O_3NBr$	58.92	59.20	9.44	9.42	17.82	17.71	20.6
32	$-CH_2(CH_2)_5CH_2-$		HCl	175–176	74	$C_{22}H_{42}O_3NCl$	65.40	65.18	10.48	10.25	8.77	8.75	1.8
33	$-CH_2(CH_2)_5CH_2-$		CH_3Br	139–142		$C_{23}H_{44}O_3NBr$	59.72	59.49	9.59	9.65	17.28	17.12	7.6

[a] See F. F. Blicke and R. H. Cox, This Journal, **77**, 5399 (1955), footnote 9. [b] A mixture of compound 1 (9 parts) and compound 2 (1 part) melted at 62–82°. [c] Melted with decomposition. [d] Cyclohexyl.

The α-cyclohexyl-β-hydroxypropionic acids which were synthesized are reported in Table I.[10] Two of these acids (compounds 7 and 9) contained a cyclohexyl substituent in the β-position; each compound was prepared from the required α,β-diphenyl-β-hydroxy acid by hydrogenation of both aromatic rings.

Two transformations were carried out which contributed to the confirmation of the structures of the acids. α-Cyclohexyl-β-hydroxypropionic acid (compound 1) was oxidized with alkaline potassium permanganate to the previously reported cyclohexylmalonic acid.[11] α-Cyclohexyl-α-(1-hydroxycyclohexyl)-acetic acid (compound 14) was dehydrated by fusion in the presence of anhydrous copper sulfate; catalytic hydrogenation of the crude dehydration product yielded the known dicyclohexylacetic acid.[12,13]

In addition to the α-cyclohexyl acids prepared, β,β-dicyclohexyl-β-hydroxypropionic acid, a structural isomer of compound 7, was synthesized by hydrogenation of β,β-diphenyl-β-hydroxypropionic acid.[14]

The basic ester hydrochlorides were synthesized by reaction of the required acid and basic alkyl chloride in isopropyl alcohol by a general procedure.[15] The methohalides were obtained by treatment of the ester base, dissolved in ether, with a fourfold excess of the methyl halide.

We observed that in the case of β,β-disubstituted α-phenyl-β-hydroxypropionic acids and the salts of their basic esters, decomposition took place after a period of time at room temperature; evidence of this decomposition was the ketonic odor and the depression of the original melting point. In the case of the α-cyclohexyl analogs described in this paper, no evidence of decomposition, under the same conditions, has been noticed. A study[16] of the base-catalyzed cleavage of β-hydroxy acids has shown definitely that the β-substituted α-phenyl-β-hydroxypropionic acids decompose much more readily than the α-cyclohexyl analogs.

We are indebted to the Sterling–Winthrop Research Institute for the pharmacological data (Table II).

Experimental

α-Cyclohexyl-β-hydroxypropionic Acids. General Procedure.—The required α-phenyl-β-hydroxypropionic acid (0.025 mole), dissolved in about 60 cc. of acetic acid, was hydrogenated under an initial pressure of 50 pounds in the presence of 0.3 g. of platinum oxide catalyst. The catalyst was filtered and the acetic acid was removed under 15 mm. pressure.

In some instances (Table I, compounds 14–17), the solubility of the hydrogenation product was limited to such an extent that some of the product appeared as a crystalline precipitate during the course of the hydrogenation. When the hydrogenation was completed, the precipitated material was dissolved by the addition of either acetone or more acetic acid, and the catalyst was removed.

The two α,β-diphenyl-β-hydroxy acids, which upon hydrogenation yielded compounds 7 and 11, were sparingly soluble in acetic acid; therefore, an appreciable amount of the original acid remained suspended at the beginning of the hydrogenation. This limited solubility did not appear to have any appreciable effect upon the rate or completeness of the hydrogenation.

Oxidation of α-Cyclohexyl-β-hydroxypropionic Acid.—The acid (1.7 g.) was dissolved in a solution of 2.1 g. of sodium carbonate in 20 cc. of water, and 2.5 g. of potassium permanganate was added. The solution was heated on a steam-bath for 20 minutes, cooled in an ice-bath, adjusted to a *p*H of 5.8 with hydrochloric acid and extracted immediately with ether. The cyclohexylmalonic acid (1.2 g., 65%), obtained from the dried ethereal extract, melted at 176–177° dec.[17] after recrystallization from formic acid.

Calcd. for $C_9H_{14}O_4$: neut. equiv., 186.2. Found: neut. equiv., 186.6.

Dehydration of α-Cyclohexyl-α-(1-hydroxycyclohexyl)-acetic Acid Followed by Hydrogenation.—A mixture of 4.8 g. of the finely powdered acid and 7.5 g. of anhydrous copper sulfate was stirred occasionally and heated at 195–200° (bath temperature) for 20 minutes. The organic residue, obtained from the ethereal extract, was dissolved in a mixture of 50 cc. of acetic acid and 50 cc. of acetic anhydride and was hydrogenated in the presence of 0.3 g. of platinum oxide catalyst under an initial pressure of 50 pounds. The product was recrystallized from benzene–petroleum ether (90–100°); the dicyclohexylacetic acid weighed 2.8 g. (62%); m.p. 134–135°.[18]

Calcd. for $C_{14}H_{24}O_2$: neut. equiv., 224.3. Found: neut. equiv., 224.8.

β,β-Dicyclohexyl-β-hydroxypropionic Acid.—This acid was obtained in 81% yield by hydrogenation of β,β-diphenyl-β-hydroxypropionic acid[14] in the manner described above; m.p. 135–137° after recrystallization from toluene.

Anal. Calcd. for $C_{15}H_{26}O_3$: C, 70.82; H, 10.30; neut. equiv., 254.4. Found: C, 70.84; H, 10.00; neut. equiv., 254.9.

β-Piperidinoethyl α-Cyclohexyl-α-(1-hydroxycyclohexyl)-acetate Hydrochloride.—This salt melted at 195–196° after recrystallization from isopropyl alcohol–methyl ethyl ketone; yield 77%.

Anal. Calcd. for $C_{21}H_{38}O_3NCl$: C, 65.01; H, 9.87; N, 3.61; Cl, 9.14. Found: C, 65.07; H, 10.03; N, 3.57; Cl, 9.01.

γ-Dimethylaminopropyl α-Cyclohexyl-α-(1-hydroxycyclohexyl)-acetate Hydrochloride.—This compound melted at 151–153° after recrystallization from isopropyl alcohol–methyl ethyl ketone; yield 64%.

Anal. Calcd. for $C_{19}H_{35}O_3NCl$: C, 63.05; H, 10.02; N, 3.87; Cl, 9.80. Found: C, 62.80; H, 10.09; N, 3.89; Cl, 9.71.

β-Diethylaminoethyl β,β-Dicyclohexyl-β-hydroxypropionate Hydrochloride and Methobromide.—The hydrochloride melted at 126–127° after recrystallization from toluene–petroleum ether (90–100°); yield 73%.

Anal. Calcd. for $C_{21}H_{40}O_3NCl$: C, 64.68; H, 10.34; N, 3.59; Cl, 9.09. Found: C, 64.50; H, 10.35; N, 3.62; Cl, 8.99.

The methobromide melted at 178–179° after recrystallization from isopropyl alcohol–methyl ethyl ketone.

Anal. Calcd. for $C_{22}H_{42}O_3NBr$: C, 58.92; H, 9.44; N, 3.12; Br, 17.82. Found: C, 59.02; H, 9.40; N, 3.17; Br, 17.65.

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(10) The only acid of this type mentioned in the literature[8] is α-cyclohexyl-β-hydroxypropionic acid; however, no description of the acid was reported.

(11) E. Hope and W. H. Perkin, *J. Chem. Soc.*, **95**, 1360 (1909).

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(15) H. Horenstein and H. Pählicke, *ibid.*, **71**, 1644 (1938).

(16) To be published.

(17) Ref. 11, m.p. 176–178° dec.

(18) Ref. 12, m.p. 137°; ref. 13, m.p. 134–135°.