was hydrogenated[10] in the presence of 0.3 g. of palladium-on-charcoal (5%) catalyst[17] under an initial pressure of 30 pounds until the required amount of hydrogen had been absorbed. The residue, obtained after removal of the catalyst and the solvent, was mixed with 500 cc. of 48% hydrobromic acid and was stirred and refluxed for 48 hours. The mixture was poured into ice-water, the layers were separated and the aqueous layer was extracted with ether. The combined organic layer and ether extract were washed with water and then extracted with sodium bicarbonate solution. The alkaline solution was washed with ether, cooled in an ice-bath and made strongly acidic with dilute sulfuric acid. The oily precipitate was separated and the aqueous layer was extracted with ether. From the combined dried oil and extract, 31 g. of product was obtained, b.p. 208–210° (732 mm.). *Anal.* Calcd. for $C_7H_{14}O_2$: neut. equiv., 130.2. Found: neut. equiv., 131.2. The infrared spectrum was identical with that of the product V obtained from crotonic acid and isopropylmagnesium chloride.

The amide (m.p. and mixed m.p. 137–138°) and the anilide (m.p. and mixed m.p. 110–111°) were prepared from the acid chloride.

α-(1-Hydroxycyclohexyl)-β-isopropylbutyric Acids (VI).—Crotonic acid (17.2 g.), dissolved in 400 cc. of ether, was added slowly to isopropylmagnesium chloride prepared from 10.7 g. of magnesium, 50 cc. of isopropyl chloride and 100 cc. of ether. After the addition of a solution of 23.5 g. of cyclohexanone in 100 cc. of ether, the mixture was refluxed for 4 hours. The material was poured into cold ammonium chloride solution and treated in the usual manner. Strong acidification of the aqueous layer yielded a white solid (18.2 g.) which was triturated with 150 cc. of ice-cold petroleum ether (30–40°). The material was extracted with 200 cc. of boiling petroleum ether (90–100°) and then filtered. After this process had been repeated, the residue (8.9 g.) was recrystallized from methyl ethyl ketone; m.p. 194–196° dec.

Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59; neut. equiv., 228.3. Found: C, 68.10; H, 10.41; neut. equiv., 227.8.

The combined petroleum ether extracts were refrigerated whereupon 6.4 g. of product precipitated, m.p. 131–135° dec. after recrystallization from petroleum ether (90–100°).

Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59; neut. equiv., 228.3. Found: C, 68.23; H, 10.69; neut. equiv., 227.3.

α-(Phenylcarbamyl)-β-isopropylbutyric Acid (VII).—After the preparation of isopropylmagnesium chloride from 5.4 g. of magnesium, 25 cc. of isopropyl chloride and 50 cc. of ether, the solution was stirred and 8.6 g. of crotonic acid, dissolved in 300 cc. of benzene, was added. The mixture was refluxed for 18 hours, a solution of 14.4 g. of phenyl isocyanate in 50 cc. of benzene was added and the mixture was refluxed for 4 hours. The material was poured into an ice-cold solution of 20 cc. of concentrated sulfuric acid in 250 cc. of water. The aqueous layer was extracted with ether, the extract was combined with the organic layer, the solution was washed with water and then extracted with 400 cc. of 10% potassium carbonate solution. The alkaline extract was washed with ether, cooled in an ice-bath, stirred and 15 cc. of concentrated sulfuric acid dissolved in 150 cc. of water was added. The gummy precipitate was extracted with ether and the solvent was removed from the dried extract under an air jet. The residue was washed with cold petroleum ether (30–40°) and crystallized from 150 cc. of benzene; yield 9.0 g. The product sintered at 128° and melted at 134° dec. after recrystallization from benzene.

Anal. Calcd. for $C_{14}H_{19}O_2N$: C, 67.44; H, 7.68; N, 5.62; neut. equiv., 249.3. Found: C, 67.34; H, 7.84; N, 5.56; neut. equiv., 247.8.

When the acid (1.5 g.) was heated for 1 hour in an oil-bath (200°), a gas was evolved. The solidified residue, β-isopropylbutyranilide, was recrystallized from petroleum ether (90–100°); yield 1.0 g., m.p. and mixed m.p. 110–111°.

ANN ARBOR, MICH.

(17) Purchased from Wilkens-Anderson Company, Chicago, Ill.

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

Antispasmodics. XXII. β-Diethylaminoethyl Esters of β-Substituted α-Phenyl-β-hydroxypropionic Acids

BY F. F. BLICKE AND R. H. COX[1,2]

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Eighteen salts of β-diethylaminoethyl β-substituted α-phenyl-β-hydroxypropionates have been described. The required acids were obtained by the Ivanov reaction. The antispasmodic activity has been reported.

A number of investigators[3–5] have shown that basic alkyl esters of β-substituted α-phenyl-β-hydroxypropionic acids are potent antispasmodics. The required acids were obtained from phenylacetic acid by the use of the Ivanov reaction.

During this investigation, we prepared a number of β-substituted α-phenyl-β-hydroxypropionic acids (Table I) by interaction of the Ivanov reagent, $C_6H_5CH(MgCl)COOMgCl$, with the following aldehydes and ketones: hexaldehyde,[6] anisaldehyde, 2-methyl- and 3-methylcyclohexanone, cycloöctanone,[7] propiophenone and 2-acetylthiophene. By the Horenstein and Pählicke procedure[8] some of the acids were converted into hydrochlorides of their β-diethylaminoethyl esters; a variety of quaternary bromides of the esters were also prepared (Table II).

An attempt to obtain β-diethylaminoethyl α,β-diphenyl-β-hydroxyvalerate from the required acid and β-diethylaminoethyl chloride, by the Horenstein and Pählicke process, yielded only β-diethylaminoethyl phenylacetate and propiophenone. β-Diethylaminoethyl α-phenyl-α-(1-hydroxycyclooctyl)-acetate was obtained in 73% yield from the required acid and the basic alkyl halide; however, a small amount of cycloöctanone was present in the reaction mixture which showed that some cleavage of the acid or ester had occurred.

When α-phenyl-α-(1-hydroxycyclohexyl)-acetic acid was distilled under 15 mm. pressure, cyclohexanone was present in the distillate; however, the bulk of the acid distilled unchanged.

(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) Purchased from Matheson, Coleman and Bell, Norwood, Ohio.

(7) F. F. Blicke, J. Azuara, N. Doorenbos and E. B. Hotelling, *ibid.*, **75**, 5418 (1953).

(8) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1644 (1938).

TABLE I

β-SUBSTITUTED α-PHENYL-β-HYDROXYPROPIONIC ACIDS, $C_6H_5CH(COHRR')COOH$

Compound 1 was recrystallized from benzene; 2 from butanol–toluene; 3 from ethanol–petroleum ether (60–70°); 4 from ethanol–methyl ethyl ketone; 5 and 6 from methyl ethyl ketone; 7 from toluene.

	R	R′	M.p., °C.	Yield, %	Formula	Neut. equiv. Calcd.	Neut. equiv. Found	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	H	C_5H_{11}	110–111	53	$C_{14}H_{20}O_3$	236.3	236.3	71.16	71.17	8.53	8.65
2	H	4-$CH_3OC_6H_4$	139–140[a,b,c]	71	$C_{16}H_{16}O_4$	272.3	272.0	70.57	70.50	5.92	6.09
3	CH_3	2-C_4H_3S[d]	162–163[a]	37	$C_{14}H_{14}O_3S$	262.3	262.0	64.09	64.30	5.38	5.35
4	C_2H_5	C_6H_5	197–198[a]	35	$C_{17}H_{18}O_3$	270.3	270.1	75.53	75.40	6.71	6.95
5	—CH(CH₃)(CH₂)₃CH₂—		126–129	39	$C_{15}H_{26}O_3$	248.3	247.4	72.55	72.61	8.12	8.13
6	—CH₂CH(CH₃)(CH₂)₂CH₂—		194–195	74	$C_{15}H_{26}O_3$	248.3	249.0	72.55	72.68	8.12	8.20
7	—CH₂(CH₂)₅CH₂—		162–163	77	$C_{16}H_{22}O_3$	262.3	262.3	73.26	73.42	8.45	8.36

[a] Melted with decomposition. [b] D. Ivanov and N. I. Nicolov (*Bull. soc. chim.*, [4] **51**, 1325 (1932)), m.p. 136.5° dec. [c] The acid (yield 71%, m.p. 139–140° dec.) was recrystallized from ethanol–petroleum ether (90–100°) and then it melted at 148–150° dec. After another recrystallization, it melted at 160–162° dec. Finally, after further recrystallization from ethanol, an acid was obtained which melted at 168–170° dec.; yield 9%. *Anal.* Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92; neut. equiv., 272.3. Found: C, 70.60; H, 6.30; neut. equiv., 273.2. Undoubtedly, the described behavior is due to the presence of diastereoisomers. [d] 2-Thienyl. After several weeks at room temperature, this acid had darkened and had acquired a strong odor characteristic of 2-acetylthiophene.

TABLE II: SALTS OF β-DIETHYLAMINOETHYL β-SUBSTITUTED α-PHENYL-β-HYDROXYPROPIONATES, $C_6H_5CH(COHRR')COOCH_2CH_2N(C_2H_5)_2\text{-}R''X$

Compound 1 was recrystallized from isopropyl alcohol–methyl ethyl ketone; 2 and 4 from benzene–ether; 3 and 5 from isopropyl alcohol–ether; 6, 7, 8, 10, 11, 13, 14, 15, 16 and 18 from ethanol–ether; 9 from ethanol; 12 and 17 from acetone.

	R	R′	R″X	M.p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Halogen Calcd.	Halogen Found	Anti-spasmodic activity[f]
1	H	C_3H_7	CH_3Br[a]	135–136		$C_{19}H_{32}O_3NBr$	56.71	56.42	8.02	8.04	3.48	3.52	19.86	19.78	100.0
2	H	C_5H_{11}	HCl	106–107	80	$C_{20}H_{34}O_3NCl$	64.59	64.47	9.21	9.19	3.77	3.79	9.53	9.47	
3	H	C_5H_{11}	CH_3Br	101–103		$C_{21}H_{36}O_3NBr$	58.60	58.76	8.43	8.64	3.25	3.26	18.57	18.41	
4	H	C_6H_{13}	HCl[b]	102–103	68	$C_{21}H_{36}O_3NCl$	65.35	65.30	9.40	9.46	3.63	3.60	9.18	9.11	5.4
5	H	C_6H_{13}	CH_3Br	111–113		$C_{22}H_{38}O_3NBr$	59.45	59.11	8.62	8.59	3.15	3.14	17.98	17.84	53.0
6	—$CH_2(CH_2)_3CH_2$—		C_2H_5Br[c]	175–176		$C_{22}H_{36}O_3NBr$	59.72	59.36	8.20	8.58	3.17	3.14	18.06	18.00	118.2
7	—$CH_2(CH_2)_3CH_2$—		CH_2=$CHCH_2Br$	152–154		$C_{23}H_{35}O_3NBr$	60.78	60.62	8.00	8.14	3.08	3.04	17.58	17.52	70.5
8	—$CH_2(CH_2)_3CH_2$—		$C_6H_5CH_2Br$	172–174[d]		$C_{27}H_{38}O_3NBr$	64.28	64.31	7.59	7.72	2.78	2.75	15.84	15.85	28.0
9	—$CH_2(CH_2)_3CH_2$—		$C_6H_5COCH_2Br$	200–202[d]		$C_{28}H_{38}O_4NBr$	63.16	63.02	7.19	7.05	2.63	2.58	15.01	14.94	33.3
10	—$CH(CH_3)(CH_2)_3CH_2$—		HCl	158–160	59	$C_{21}H_{34}O_3NCl$	65.69	65.80	8.93	8.92	3.65	3.62	9.23	9.27	11.5
11	—$CH(CH_3)(CH_2)_3CH_2$—		CH_3Br	190–192[d]		$C_{22}H_{36}O_3NBr$	59.71	59.54	8.21	8.24	3.17	3.15	18.06	17.90	32.4
12	—$CH_2CH(CH_3)(CH_2)_2CH_2$—		HCl	150–152	52	$C_{21}H_{34}O_3NCl$	65.69	65.78	8.93	9.00	3.65	3.70	9.23	9.16	
13	—$CH_2CH(CH_3)(CH_2)_2CH_2$—		CH_3Br	195–196		$C_{22}H_{36}O_3NBr$	59.71	59.97	8.21	8.32	3.17	3.15	18.06	18.00	27.5
14	—$CH_2CH(CH_3)(CH_2)_2CH_2$—		CH_2=$CHCH_2Br$	143–145		$C_{24}H_{38}O_3NBr$	61.53	61.27	8.18	8.35	2.99	2.91	17.06	17.00	16.7
15	—$CH_2CH_2CH(CH_3)CH_2CH_2$—		CH_3Br[c]	194–196		$C_{22}H_{36}O_3NBr$	59.71	59.93	8.21	8.25	3.17	3.15	18.06	18.00	80.4
16	—$CH_2CH_2CH(CH_3)CH_2CH_2$—		CH_2=$CHCH_2Br$	153–155		$C_{24}H_{38}O_3NBr$	61.53	61.27	8.18	8.21	2.99	2.92	17.06	17.01	47.6
17	—$CH_2(CH_2)_5CH_2$—		HCl	144–146	73	$C_{22}H_{36}O_3NCl$	66.35	66.03	9.18	9.10	3.52	3.64	8.91	8.97	40.8
18	—$CH_2(CH_2)_5CH_2$—		CH_3Br	153–158		$C_{23}H_{39}O_3NBr$	60.51	60.68	8.39	8.46	3.07	3.15	17.51	17.45	52.9

[a] The hydrochloride has been reported.[3] [b] The required acid has been described (D. Ivanov and N. I. Nicolov, *Bull. soc. chim.*, [4] **51**, 1325 (1932)). [c] The hydrochloride,[3–5] the methiodide[4] and methobromide[5] have been reported. [d] Melted with decomposition. [e] The hydrochloride and methiodide have been reported.[4] We obtained the required acid in 69% yield although the previously reported yield[4] was only 20%. [f] Expressed as % of atropine sulfate.

The antispasmodic activity of the compounds in Table II, based on that of atropine sulfate, was determined at the Sterling–Winthrop Research Institute.[9]

(9) The concentration of atropine sulfate, determined from dose response curves, which is expected to reduce by 50% the height of the contracture of the isolated rabbit ileum induced by 1:1,000,000 acetylcholine (effective concentration$_{50}$ or EC$_{50}$), usually falls within the range of 1:50,000,000 to 1:70,000,000. However, the sensitivity of intestinal strips is so variable that, in a given test, it is not uncommon to find the maximum effective dilution is much greater or much less than the range mentioned above.

In order to obtain valid data with respect to the activity of a compound in comparison with the activity of atropine, the procedure, described by F. P. Luduena and A. M. Lands (*J. Pharmacol. Exp. Therap.*, **110**, 282 (1954)), was adopted. When a compound was tested for activity, the same segments of the intestine were used to determine the EC$_{50}$ for atropine sulfate. The EC$_{50}$ found for atropine sulfate divided by the EC$_{50}$ found for the compound tested, multiplied by 100, gave the activity of the compound in terms of per cent. of atropine sulfate activity. For example

$$\% \text{ Activity of the compd. tested (X)} = \frac{1/50{,}000{,}000 \text{ (EC}_{50} \text{ of At.S.)}}{1/25{,}000{,}000 \text{ (EC}_{50} \text{ of X)}} \text{ times } 100 = 50\%$$

based on atropine sulfate (At.S.)

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.

ANN ARBOR, MICH.

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

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

BY F. F. BLICKE AND R. H. COX[1,2]

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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.