3β,23-Dihydroxy-23,23-diphenylnor-5,16-choladiene (XX).—The ester (XV) was converted to the diphenylcarbinol (XX) using the procedure given for the preparation of (VI). The crude product was recrystallized from methanol to give fine needles melting at 148–150° with bubbling; $[\alpha]^{26}D$ −50.3° (2% in $CHCl_3$). The analytical sample after drying in a vacuum-oven over phosphorus pentoxide at 55° for one hour contained methanol of solvation.

Anal. Calcd. for $C_{35}H_{44}O_2 \cdot {}^1/_2CH_3OH$: C, 83.15; H, 9.04. Found: C, 83.23; H, 8.93.

The methanol was removed by drying a sample at 100° for 18 hours at 10 μ pressure: m.p. 144.4–145.5° with bubbling.

Anal. Calcd. for $C_{35}H_{44}O_2$: C, 84.63; H, 8.93. Found: C, 84.22, 84.53; H, 9.30, 9.13.

The ethanol solvate melted at 140–143° with bubbling; $[\alpha]^{26}D$ −50.1° (2% in $CHCl_3$).

Anal. Calcd. for $C_{35}H_{44}O_2 \cdot {}^1/_2C_2H_5OH$: C, 83.19; H, 9.12. Found: C, 83.03; H, 8.92.

3β-Acetoxy-23,23-diphenylnor-5,16,22-cholatriene (XXI).—The diphenylcarbinol (XX) was dehydrated and the 3-hydroxyl acetylated by the method of Whitman and Schwenk.[21]

(21) B. Whitman and E. Schwenk, THIS JOURNAL, 68, 1865 (1946).

A mixture of 2.07 g. of the carbinol (XX), 20 cc. of acetic acid and 8.0 cc. of acetic anhydride was cooled to 10° and 0.20 cc. of perchloric acid (72%) C.P. was added with external cooling. The mixture was shaken gently until complete solution was obtained, allowed to stand at 15–20° for 30 minutes, poured into ice-water and filtered. The crude dry product, 2.05 g., m.p. 154.5–156.5°, was crystallized from methanol and then ethanol to give 1.60 g. of plates melting at 161.5–162.0°; $[\alpha]^{22}D$ −13.0° (2% in $CHCl_3$). The ultraviolet adsorption $\lambda_{max.}^{ethanol}$ 250 mμ was log ε 4.2.

Anal. Calcd. for $C_{37}H_{44}O_2$: C, 85.33; H, 8.52. Found: C, 85.42; H, 8.80.

Acknowledgment.—We wish to thank Dr. W. B. Tarpley and Miss C. Vitiello of our Chemical Research Division, for furnishing the infrared data and interpretations given in this paper. We are indebted to N. M. Murrill for preparing methyl 3β-acetoxynor-5-cholenate from 3β-acetoxy-23-diazonor-5-cholene-22-one.

BLOOMFIELD, NEW JERSEY RECEIVED JUNE 21, 1951

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SCHIEFFELIN & CO.]

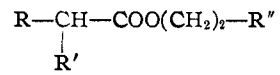
Basic Esters and Quaternary Derivatives of β-Hydroxy Acids as Antispasmodics[1]

BY GINO R. TREVES AND FRANK C. TESTA

A series of basic esters of (1-hydroxycycloalkyl)-arylacetic acids is described. Eighteen new compounds were synthesized and isolated as hydrochlorides and quaternary methiodides. Preliminary work done in our pharmacological laboratory shows that several members of our series possess neurotropic activity comparable to that of atropine and musculotropic activity of the order of magnitude of papaverine.

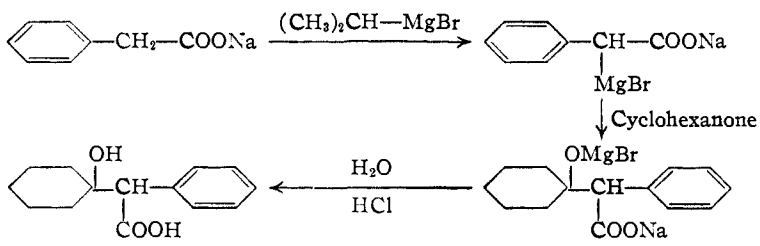
In recent years, a large number of basic esters of various hydroxy acids have been prepared and tested for pharmacological action. Among them, esters of tropic, benzilic, mandelic and substituted glycolic acids have been shown to possess high antispasmodic activity.

In a search for new and better antispasmodic agents, a series of alkylaminoalkyl and N-piperidinoalkyl esters of (1-hydroxycycloalkyl)-arylacetic acids were synthesized. These can be represented by the general structure



R is a 1-hydroxycycloalkyl group
R′ is a phenyl or a 4-methoxyphenyl group
R″ is a substituted amino group or a 1-piperidyl group

Six acids, five of which are new, were used for the syntheses of the esters. For purpose of comparison, the structural formulas of tropic acid (I), the "acid moiety" of atropine, and of (1-hydroxycyclohexyl)-phenylacetic acid (II), one of our acids, are shown above. It is observed that the carbon attached to the primary hydroxy group in I becomes part of a cyclohexyl ring in II and that the hydroxy group assumes in our structure a position angular to the ring. The acids were prepared by a modification of a method devised by Ivanoff and Spassoff.[2] The procedure exemplified for the preparation of (1-hydroxycyclohexyl)-phenylacetic acid is



Sodium phenylacetate was added to an ethereal solution of isopropylmagnesium bromide. Evolution of propane occurred with the formation of the intermediate sodium phenylacetate magnesium bromide. The addition of cyclohexanone in ether, followed by hydrolysis, produced the desired β-hydroxy acid. Table I shows the structures of the acids with their melting points, yields, and carbon hydrogen analyses.

By treating a solution of the sodium salts of the acids with the hydrochlorides of β-chloroethylalkylamines and β-chloroethyl-N-piperidine in isopropyl alcohol, eighteen new esters were synthesized and isolated as hydrochlorides. The quaternary methiodides were obtained by converting these hydrochlorides to the free bases and treating them with methyl iodide.

Tables II and III show the hydrochlorides and methiodides along with melting points, carbon–hydrogen analyses and antispasmodic activities.

(1) Presented at the Cleveland Meeting of the Division of Medicinal Chemistry, American Chemical Society, April, 1951.

(2) D. Ivanoff and A. Spassoff, *Bull. soc. chim.*, [4] 49, 375 (1931).

TABLE I

$$R-CH(COOH)-R'$$

Comp.	R	R'	M.p., °C. (cor.)	Yield, %	Formula	Analyses,[a] % Carbon Calcd.	Carbon Obsd.	Hydrogen Calcd.	Hydrogen Obsd.
1[d]	1-Hydroxycyclopentyl	C_6H_5–	100–101	62	$C_{12}H_{16}O_3$	70.9	70.61	7.27	6.89
2[e]	1-Hydroxycyclohexyl	C_6H_5–	143–144	60	$C_{14}H_{18}O_3$	71.6	72.00	7.74	7.77
3[b,d]	1-Hydroxy-4-methylcyclohexyl	C_6H_5–	177–178	20	$C_{15}H_{20}O_3$	72.55	72.58	8.12	7.86
4[e]	1-Hydroxycyclopentyl	p-$CH_3OC_6H_4$–	132–134	54	$C_{14}H_{18}O_4$	67.2	67.5	7.20	7.30
5[e]	1-Hydroxycyclohexyl	p-$CH_3OC_6H_4$–	154–155	45	$C_{15}H_{20}O_4$	68.16	68.21	7.63	7.90
6[e]	1-Hydroxy-4-methylcyclohexyl	p-$CH_3OC_6H_4$–	162–164	25	$C_{16}H_{22}O_4$	69.04	68.86	7.97	7.78

[a] All the analyses reported in this paper were performed by the Schwarzkopf Microanalytical Laboratory, Middle Village, N. Y. [b] The compound reported here is the high-melting isomer. [c] Crystallized from dilute methanol. [d] Crystallized from ethylene dichloride–petroleum ether mixture. [e] Crystallized from benzene.

TABLE II

$$R-CH(COO(CH_2)_2-R''\cdot HCl)-R'$$

Comp.	R	R'	R''[a]	M.p., °C. (cor.)	Formula	Analyses. % Carbon Calcd.	Carbon Obsd.	Hydrogen Calcd.	Hydrogen Obsd.	Antispasmodic activity AcCh	Antispasmodic activity $BaCl_2$
7[b]	1-Hydroxycyclopentyl	C_6H_5–	$(CH_3)_2N$–	139	$C_{17}H_{26}O_3NCl$	62.39	62.18	7.97	8.23	++	++
8[c]	1-Hydroxycyclopentyl	C_6H_5–	$(C_2H_5)_2N$–	135–136	$C_{19}H_{30}O_3NCl$	64.1	64.47	8.49	8.13	++	+
9	1-Hydroxycyclopentyl	C_6H_5–	$C_5H_{10}N$–	138–139	$C_{20}H_{30}O_3NCl$	64.94	65.23	8.18	8.24	++	+
10	1-Hydroxycyclohexyl	C_6H_5–	$(CH_3)_2N$–	139–141	$C_{18}H_{28}O_3NCl$	63.34	63.67	8.21	8.28	++	++
11	1-Hydroxycyclohexyl	C_6H_5–	$(C_2H_5)_2N$–	136–137	$C_{20}H_{32}O_3NCl$	65.04	65.32	8.67	8.53	++	++
12	1-Hydroxycyclohexyl	C_6H_5–	$C_5H_{10}N$–	176–177	$C_{21}H_{32}O_3NCl$	66.03	66.14	8.13	8.35	++	++
13	1-Hydroxy-4-methylcyclohexyl	C_6H_5–	$(CH_3)_2N$–	153–154	$C_{19}H_{30}O_3NCl$	64.4	64.2	8.19	8.29	++	+++
14	1-Hydroxy-4-methylcyclohexyl	C_6H_5–	$(C_2H_5)_2N$–	154–155	$C_{21}H_{34}O_3NCl$	65.8	65.38	8.87	8.72	++	+++
15	1-Hydroxy-4-methylcyclohexyl	C_6H_5–	$C_5H_{10}N$–	194–195	$C_{22}H_{34}O_3NCl$	66.88	67.07	8.65	8.46	++	++
16	1-Hydroxycyclopentyl	p-$CH_3OC_6H_4$–	$(CH_3)_2N$–	172	$C_{18}N_{28}O_4NCl$	60.5	60.42	7.84	7.52	+	+
17	1-Hydroxycyclopentyl	p-$CH_3OC_6H_4$–	$(C_2H_5)_2N$–	118–119	$C_{20}H_{32}O_4NCl$	62.24	62.20	8.34	8.44	+	+
18	1-Hydroxycyclopentyl	p-$CH_3OC_6H_4$–	$C_5H_{10}N$–	138–139	$C_{21}H_{32}O_4NCl$	63.37	63.57	8.15	7.99	+	+
19	1-Hydroxycyclohexyl	p-$CH_3OC_6H_4$–	$(CH_3)_2N$–	157–158	$C_{19}H_{30}O_4NCl$	61.36	61.61	8.13	7.86	+	+
20	1-Hydroxycyclohexyl	p-$CH_3OC_6H_4$–	$(C_2H_5)_2N$–	152–154	$C_{21}H_{34}O_4NCl$	63.05	62.79	8.56	8.16	+	+
21	1-Hydroxycyclohexyl	p-$CH_3OC_6H_4$–	$C_5H_{10}N$–	192–105	$C_{22}H_{34}O_4NCl$	64.13	64.06	8.13	8.34	+	+
22	1-Hydroxy-4-methylcyclohexyl	p-$CH_3OC_6H_4$–	$(CH_3)_2N$–	167–168	$C_{20}H_{32}O_4NCl$	62.24	61.96	8.35	8.25	+	++
23	1-Hydroxy-4-methylcyclohexyl	p-$CH_3OC_6H_4$–	$(C_2H_5)_2N$–	131–133	$C_{22}H_{36}O_4NCl$	63.81	63.86	8.78	8.95	+	++
24	1-Hydroxy-4-methylcyclohexyl	p-$CH_3OC_6H_4$–	$C_5H_{10}N$–	161–162	$C_{23}H_{34}O_4NCl$	64.84	65.09	8.52	8.57	+	+

[a] $C_5H_{10}N$– is a 1-piperidyl group. [b] This compound is identical to 75 GT as referred to by B. S. Priestley and M. M. Medine in *Am. J. Ophthalmol.*, 34, 572 (1951). [c] This compound is identical with 92 GT as referred to in the article by D. Bovet and V. G. Longo in *J. Pharm. Exp. Ther.*, 102, 22 (1951).

TABLE III

$$R-CH(COO(CH_2)_2-R''\cdot CH_3I)-R'$$

Comp.	R	R'	R''[a]	M.p., °C. (cor.)	Formula	Analyses, % Carbon Calcd.	Carbon Obsd.	Hydrogen Calcd.	Hydrogen Obsd.	Antispasmodic activity AcCh
25	1-Hydroxycyclopentyl	C_6H_5–	$(CH_3)_2N$–	130–131	$C_{19}H_{30}O_3NI$	49.88	49.82	6.74	6.53	+++
26	1-Hydroxycyclopentyl	C_6H_5–	$(C_2H_5)N$–	142–143	$C_{20}H_{32}O_3NI$	52.06	52.04	6.99	6.85	++++
27	1-Hydroxycyclopentyl	C_6H_5–	$C_5H_{10}N$–	103–106	$C_{21}H_{32}O_3NI$	53.27	53.38	6.81	6.79	++
28	1-Hydroxycyclohexyl	C_6H_5–	$(CH_3)_2N$–	158–159	$C_{19}H_{30}O_3NI$	51.01	50.61	6.76	6.78	+++
29	1-Hydroxycyclohexyl	C_6H_5–	$(C_2H_5)_2N$–	139–141	$C_{21}H_{34}O_3NI$	53.05	52.92	7.17	6.88	+++
30	1-Hydroxycyclohexyl	C_6H_5–	$C_5H_{10}N$–	110–112	$C_{22}H_{34}O_3NI$	54.20	54.39	7.03	6.83	++
31	1-Hydroxy-4-methylcyclohexyl	C_6H_5–	$(CH_3)_2N$–	92–93	$C_{20}H_{32}O_3NI$	52.05	52.06	7.00	7.53	+
32	1-Hydroxy-4-methylcyclohexyl	C_6H_5–	$(C_2H_5)_2N$–	158–159	$C_{22}H_{36}O_3NI$	54.06	53.91	7.66	7.47	+++
33	1-Hydroxy-4-methylcyclohexyl	C_6H_5–	$C_5H_{10}N$–	157–160	$C_{23}H_{36}O_3NI$	55.08	54.80	7.23	7.39	++
34	1-Hydroxycyclopentyl	p-$CH_3OC_6H_4$	$(CH_3)_2N$–	129–131	$C_{19}H_{30}O_4NI$	49.25	49.47	6.54	6.58	+
35	1-Hydroxycyclopentyl	p-$CH_3OC_6H_4$	$(C_2H_5)_2N$–	98–101	$C_{21}H_{34}O_4NI$	51.32	51.18	6.99	6.90	+
36[b]	1-Hydroxycyclopentyl	p-$CH_3OC_6H_4$	$C_5H_{10}N$–	75–76	$C_{22}H_{34}O_4NI$	52.47	52.42	6.68	6.64	+
37	1-Hydroxycyclohexyl	p-$CH_3OC_6H_4$	$(CH_3)_2N$–	165–166	$C_{20}H_{32}O_4NI$	50.31	50.22	6.77	6.90	+
38	1-Hydroxycyclohexyl	p-$CH_3OC_6H_4$	$(C_2H_5)_2N$–	179–180	$C_{22}H_{36}O_4NI$	52.27	52.48	7.12	7.34	+
39	1-Hydroxycyclohexyl	p-$CH_3OC_6H_4$	$C_5H_{10}N$–	131–133	$C_{23}H_{36}O_4NI$	53.38	53.53	7.01	6.98	+
40[c]	1-Hydroxy-4-methylcyclohexyl	p-$CH_3OC_6H_4$	$(CH_3)_2N$–	85–100	$C_{21}H_{34}O_4NI$	51.32	51.44	6.99	7.16	+
41	1-Hydroxy-4-methylcyclohexyl	p-$CH_3OC_6H_4$	$(C_2H_5)_2N$–	195–196	$C_{23}H_{38}O_4NI$	53.10	53.01	7.32	7.40	+
42	1-Hydroxy-4-methylcyclohexyl	p-$CH_3OC_6H_4$	$C_5H_{10}N$–	165–167	$C_{24}H_{38}O_4NI$	54.23	54.53	7.2	7.05	+

[a] $C_5H_{10}N$– is a 1-piperidyl group. [b] On drying at 56° *in vacuo*, the compound melted and lost about 3.9% of its weight. The analysis was performed on this material. [c] This product is a mixture of isomers.

Pharmacology

The antispasmodic activity recorded in Table II and III represents the ability of the compounds to produce 75% or better relaxation of the isolated rabbit ileum made spastic with acetylcholine or barium chloride. It will suffice here to state that a ++++ grading against acetylcholine-induced spasm represents an activity about equal to that

of atropine and that +++ against barium chloride indicates an activity about equal to that of papaverine.

Intravenous acute toxicities determined in mice for the most active compounds showed that, in general, the quaternary methiodides are approximately four times more toxic than the corresponding hydrochlorides. The LD_{50} for the tertiary hydrochlorides ranged between 50–80 mg./kg., whereas the quaternaries showed LD_{50} of 11–25 mg./kg.

Fast and complete mydriasis of relatively short duration was produced by several compounds following local application in the rabbit eye.

Anesthetic properties of short duration were also exhibited by several tertiary hydrochlorides on the rabbit cornea. Quaternary compounds were not effective.

A detailed discussion of the pharmacological investigation will be published elsewhere.

Experimental

The examples below illustrate the procedures used for the preparation of the acid intermediates (see Table I) and of the hydrochlorides and methiodides of the esters (see Tables II and III).

(1-Hydroxycyclohexyl)-phenylacetic Acid.—To a Grignard reagent prepared from 2.4 g. (0.1 mole) of magnesium turnings and 12.3 g. (0.1 mole) of isopropyl bromide in 75 cc. of anhydrous ether, 9.1 g. (0.058 mole) of sodium phenyl acetate was added. The mixture was refluxed for one-half hour after the evolution of gas ceased. Then 5.7 g. (0.058 mole) of cyclohexanone in 50 cc. of anhydrous ether was added dropwise and the mixture refluxed for one hour. The reaction product was decomposed with ice-cold dilute hydrochloric acid solution, and the ether layer was separated and extracted with 200 cc. of 5% sodium hydroxide solution. The free acid which was obtained on acidification, was washed with hot water and recrystallized from dilute methanol. There was obtained 7.5 g. (60%) of product, m.p. 143–144°.

β-Diethylaminoethyl (1-Hydroxycyclohexyl)-phenylacetate Hydrochloride.—To a solution of 2.3 g. (0.1 mole) of sodium in 150 cc. of isopropyl alcohol, 23.4 g. (0.1 mole) of (1-hydroxycyclohexyl)-phenylacetic acid was added followed by 17.5 g. (0.1 mole) of β-chloroethyldiethylamine hydrochloride. The mixture was refluxed for 16 hours, filtered and the solvent removed under reduced pressure on the steam-bath. The residue was washed with anhydrous ether and recrystallized from an ethyl acetate–ethanol mixture. The white crystals obtained weighed 23.2 g. (63%) and melted at 136–137°.

It was often found necessary to purify the compounds by converting the hydrochlorides to the free bases with alkali. The hydrochlorides were then reobtained by passing a stream of hydrogen chloride through ethereal solutions of the free bases. The precipitates thus formed were filtered off and recrystallized from the proper solvents.

β-Diethylaminoethyl (1-Hydroxycyclohexyl)-phenylacetate Methiodide.—Five grams of β-diethylaminoethyl (1-hydroxycyclohexyl)-phenylacetate hydrochloride, 100 cc. of ether and 25 cc. of a concentrated solution of sodium bicarbonate were vigorously stirred for 15 minutes. The ether layer was separated, dried over anhydrous potassium carbonate and filtered. The ether solution was then evaporated to dryness, the residue dissolved in 25 cc. of ethanol and an excess of methyl iodide (3.7 g.) added. After allowing the solution to stand at room temperature for a few hours, the alcohol and excess methyl iodide were driven off on the steam-bath under reduced pressure. The residue was dissolved in a mixture of ethyl acetate and ethanol, from which 5.4 g. (83%) of crystalline material melting at 139–141° was obtained.

NEW YORK 3, N. Y. RECEIVED JUNE 7, 195

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

The Basic Isomerization of Allyl Aryl Sulfides to Propenyl Aryl Sulfides[1a]

BY D. S. TARBELL AND M. A. McCALL

A series of allyl aryl sulfides has been shown to isomerize readily on treatment with base to the corresponding propenyl aryl sulfides. The structures have been established in most cases by catalytic reduction of both isomers to the *n*-propyl aryl sulfides, as well as by consideration of the infrared and ultraviolet spectra. The compounds studied are the allyl derivatives of thiosalicylic and 3,5-dichlorothiosalicylic acids, allyl 2-pyridyl sulfide and allyl phenyl sulfide. The latter has been shown to isomerize to a mixture of *cis*- and *trans*-propenyl phenyl sulfides, which have been separated as the sulfilimines by chromatography. The usefulness of hydrogenolysis of sulfilimines to regenerate the parent sulfides has been demonstrated. The mechanism of the isomerization of the allyl sulfides is believed to involve a removal of a proton to form an anion stabilized by contributions from forms with a decet of electrons around sulfur.

The present work was undertaken as part of a general comparison of the cleavage of carbon–sulfur and carbon–oxygen bonds in analogous compounds.[1b] It seemed that a study of the behavior on heating of allyl aryl sulfides should yield results of value in this connection, because the thermal rearrangement of the allyl aryl ethers (Claisen rearrangement) has been studied intensively.[2] In the only previous study on allyl aryl sulfides, Hurd and Greengard[3] found that allyl phenyl and allyl *p*-tolyl sulfides rearranged very much more slowly than the corresponding oxygen compounds to give small yields of the allylthiophenols. Since it is known[4] that compounds such as I undergo rearrangement (with loss of carbon dioxide) much more rapidly than the ethers which lack the carboxyl group, it appeared that compounds of the type II should be suitable for the purpose we had in mind. During the preparation of the allyl compound II, we observed that it was readily isomerized by base into the propenyl sulfide. This behavior, which appears to be general, forms the subject of the present paper.

3,5-Dichlorothiosalicylic acid (VIII) was obtained from methyl 3,5-dichloro-2-aminobenzoate[5] in 70% yield by the Leuckart xanthate reaction.[6]

(1) (a) Presented at the 118th Meeting of the American Chemical Society, Chicago, Ill., Sept. 7, 1950. (b) Earlier papers on this topic: Harnish and Tarbell, THIS JOURNAL, **70**, 4123 (1948); Rylander and Tarbell, *ibid.*, **72**, 3021 (1950); Wilson and Tarbell, *ibid.*, **72**, 5200 (1950). For a review of the cleavage of the carbon-sulfur bond, see D. S. Tarbell and D. P. Harnish, *Chem. Revs.*, **49**, 1 (1951).

(2) For a review, see "Organic Reactions," Vol. II, John Wiley and Sons, New York, N. Y., pp. 1–48.

(3) Hurd and Greengard, THIS JOURNAL, **52**, 3356 (1930).

(4) (a) Claisen and Eisleb, *Ann.*, **401**, 21 (1913); Claisen, *ibid.*, **418**, 69 (1918); (b) Tarbell and Wilson, THIS JOURNAL, **64**, 607 (1942).

(5) Freundler, *Bull. soc. chim.*, **49**, 606 (1911).

(6) *Cf. Org. Syntheses*, **27**, 81 (1947).