

barium salts prepared by precipitation with barium chloride.

**Dry Distillation of Barium Salts.**—Six parts of barium ionylidene acetate, thoroughly mixed with 5 parts of barium formate and an equal volume of "140 mesh" silica, or powdered soft glass, was heated for two hours on a metal bath at 150° under 2 mm. pressure. The distillation was then completed on a sand-bath or over an open flame. The distillate was rectified, and the fraction collected below 100° under 1.3 mm. pressure equaled about one-fourth of the weight of the barium ionylidene acetate used. An identical product was obtained by similar distillation in the absence of barium formate. The fractionated oil showed the elementary composition of ionone.

**Derivatives of Carbonyl Compounds.**—The 2,4-dinitrophenylhydrazones, the 4-phenylsemicarbazones, and the

TABLE II

Melting points of derivatives of	2,4-Dinitrophenylhydrazone	4-Phenylsemicarbazone	p-Chlorobenzoylhydrazone
(a) $\alpha$ -Ionone	143	183-184	214-215
(b) $\beta$ -Ionone	125-127	160-162	218-219
(c) Carbonyl cpd. from " $\alpha$ -ionylidene acetate"	143	181-182	214-215
(d) Carbonyl cpd. from " $\beta$ -ionylidene acetate"	143	180-182	213-214
Mixture (c) and (d)	143	180-182	212-214
Mixture (c) and (a)	143	181-182	214
Mixture (a) and (b)	112-115	148-150	207-208
Davies' "aldehyde"	Not prep.	181-185	202-203

TABLE III

	Carbonyl cpd. Fraction b. p. 90-92° 1 mm.		2,4-Dinitrophenylhydrazone			4-Phenyl-semicarbazone	p-Chlorobenzoylhydr.
	C	H	C	H	N	N	Cl
Calculated for $C_{15}H_{22}O$	83.6	10.1	63.3	6.5	14.1	11.9	9.6
Calculated for $C_{15}H_{20}O$	81.7	10.4	61.3	6.5	15.1	12.0	10.4
Found	81.4	10.4	62.0	6.6	15.2	13.0	10.4

p-chlorobenzoylhydrazones were prepared from the reaction products of both the  $\alpha$ - and  $\beta$ -ionone series, and also from  $\alpha$ - and  $\beta$ -ionone themselves. The dinitrophenylhydrazones were prepared in glacial acetic acid, the others in ethanol containing a few drops of acetic acid. Their melting points and mixed melting points are summarized in Table II, their elementary analyses in Table III. The data confirm that the reaction products in both instances are of the composition  $C_{15}H_{20}O$ , and that they are identical with each other and with  $\alpha$ -ionone.

### Summary

The carbonyl compound which Davies, Heilbron, *et al.*,<sup>5</sup> obtained from the so-called barium  $\beta$ -ionylidene acetate by dry distillation with barium formate was found to be identical with  $\alpha$ -ionone. The same cleavage occurs in the case of barium  $\alpha$ -ionylidene acetate.

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## cis- and trans-8-Methyl-1-hydrindanone<sup>1</sup>

BY W. E. BACHMANN AND S. KUSHNER<sup>2</sup>

8-Methyl-1-hydrindanone (VI), which is of interest because it contains the structural features of the C and D rings of most of the sex hormones, has been prepared by a number of investigators<sup>3-8</sup> by several different methods. Of the two possible forms, *cis* and *trans*, only one and the same form was obtained in all of the syntheses. At first this form was considered to be the *trans* form, but more recently the *cis* configuration has been assigned to it tentatively by Linstead, Millidge and Walpole.<sup>9</sup> We have now prepared this *cis* form by another procedure and have also succeeded in preparing the *trans* form.

(1) Presented before the Organic Division at the Ninth Organic Symposium, Ann Arbor, Michigan, December 29, 1941.

(2) From the Ph.D. dissertation of S. Kushner.

(3) Chuang, Tien and Ma, *Ber.*, **69**, 1494 (1936).

(4) Kon, Linstead and Simons, *J. Chem. Soc.*, 814 (1937).

(5) Robinson and Walker, *ibid.*, 1160 (1937).

(6) Elliott and Linstead, *ibid.*, 660 (1938).

(7) Burnop and Linstead, *ibid.*, 720 (1940).

(8) Nenitzescu and Przemelsky, *Ber.*, **74**, 676 (1941).

(9) Linstead, Millidge and Walpole, *J. Chem. Soc.*, 1140 (1937).

The *cis* form was prepared by the same procedures which were employed in the synthesis of equilenin<sup>10</sup> and related compounds.<sup>11</sup> Chuang, Tien and Huang<sup>12</sup> had prepared 2-methyl-2-carboxycyclohexane-1-acetic acid (III) from 2-carboethoxycyclohexanone. We have made some improvements in the yields of some of the intermediates and have varied the procedures in certain steps. The product obtained through the Reformatsky reaction from 2-carboethoxycyclohexanone and ethyl bromoacetate was dehydrated and hydrolyzed to a mixture of two isomeric unsaturated acids, which probably possess the structures I and II, although there is a possibility that they are geometrical isomers of I. Both unsaturated acids gave III on reduction with Adams platinum catalyst. In addition to the

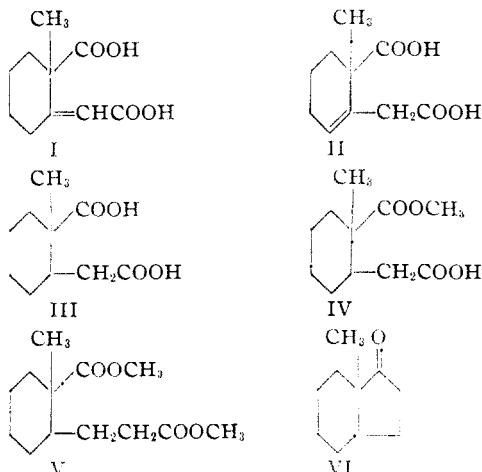
(10) Bachmann, Cole and Wilds, *THIS JOURNAL*, **62**, 824 (1940).

(11) See Bachmann, Kushner and Stevenson, *ibid.*, **64**, 674 (1942), for the most recent article in this series.

(12) Chuang, Tien and Huang, *Ber.*, **68**, 866 (1935).

*cis* form (m. p. 164°)<sup>3,4</sup> which was the chief product, there was obtained a small amount of the *trans* form (m. p. 173–174°) of III from one of the unsaturated acids. The structure—not the configuration—of the *trans* form follows from its formation from the same unsaturated acid which gave rise to the *cis* form; its melting point corresponded to that of the *trans* form (m. p. 174–175°) which Linstead and co-workers<sup>13</sup> prepared by two different methods.

The chloride of the *cis* form of the acid ester IV was converted to the dimethyl ester of 2-methyl-2-carboxycyclohexylpropionic acid (V) by means of the Arndt-Eistert synthesis. This ester was cyclized by sodium methoxide and the resulting cyclic  $\beta$ -keto ester was hydrolyzed and decarboxylated to yield the desired *cis*-8-methyl-1-hydrindanone (VI). The over-all yield of the ketone from the acid ester was 43%.



The same procedure was employed on the *trans* form of IV in order to obtain *trans*-8-methyl-1-hydrindanone. The chief problem was the preparation of the starting acid. The reduction of the unsaturated acid (I or II) gave too small an amount to be of practical use. For its preparation we turned to the readily available 1-methyl-2-cyclohexene-1,2-dicarboxylic acid (VII) of Linstead and Millidge.<sup>13</sup> By pressure hydrogenation of the sodium salt of this acid in the presence of Raney nickel, the *trans* form (according to Linstead and Millidge) of the corresponding saturated acid (VIII) was obtained readily in 80% yield. This procedure is simpler and gave better results than that employed by Linstead

and Millidge, who hydrogenated the dimethyl ester of the reduced acid in the presence of Adams catalyst (which required six days for completion) and heated the resulting mixture of the *cis* and *trans* forms of the saturated esters with potassium in order to increase the proportion of the *trans* ester.

The acid ester of the *trans* 2-methylcyclohexane-1,2-dicarboxylic acid was converted to the dimethyl ester of the *trans* form of III through the Arndt-Eistert synthesis. Considerable difficulty was experienced in this synthesis, particularly when thionyl chloride was used to prepare the acid chloride; the yields of product



fluctuated between 10 and 50%. Consistent results were obtained when oxalyl chloride was used in place of thionyl chloride and the conditions were carefully controlled. By hydrolysis of the resulting dimethyl ester, the *trans* form of the dicarboxylic acid III was obtained. It proved to be identical with the acid which had been obtained in small amount by reduction of the unsaturated acid (I or II).

*trans*-8-Methyl-1-hydrindanone was obtained in an over-all yield of 53% from *trans* form of the acid ester IV as a liquid with a camphoraceous odor. It yielded a crystalline semicarbazone and oxime which differed from the corresponding derivatives of the *cis* form. Although we believe the compounds to have the structures assigned to them, further work will be done to confirm them when circumstances permit. It is planned to prepare *cis*- and *trans*-9-methyl-1-decalone from the intermediates described here. It should be possible to prepare them by lengthening the propionic acid side chain to the butyric acid group through the Arndt-Eistert synthesis and then cyclize the resulting products.

### Experimental

**Ethyl 1-Hydroxy-2-methyl-2-carboethoxycyclohexane-1-acetate.**—2-Carboethoxycyclohexanone was methylated to give 2-methyl-2-carboethoxycyclohexanone by the procedure of Chuang, Tien and Huang.<sup>12</sup> We found it necessary to employ 160 cc. of methanol instead of 60 cc. reported by them to dissolve the sodium methoxide from 18.4 g. of sodium.

(13) (a) Hibbit and Linstead, *J. Chem. Soc.*, 470 (1936); (b) Hibbit, Linstead and Millidge, *ibid.*, 476 (1936); (c) Linstead and Millidge, *ibid.*, 478 (1936).

Inasmuch as our yield of product in the Reformatsky reaction was twice what has been reported,<sup>12</sup> the details of the procedure are given. To 50 g. of granulated zinc (20-mesh, previously treated with dilute hydrochloric acid, washed with water and acetone, and dried) and a few crystals of iodine in 200 cc. of dry benzene (thiophene-free) and 200 cc. of anhydrous ether were added 20.4 g. of 2-methyl-2-carboethoxycyclohexanone and 13.5 cc. of ethyl bromoacetate, and the mixture was refluxed on a water-bath. Five additions of 50 g. of zinc and a trace of iodine were made at forty-five-minute intervals and an additional 13.5 cc. of ethyl bromoacetate was introduced after the second addition of zinc. During the six hours of refluxing, the mixture was frequently shaken vigorously in order to keep the zinc free of addition product.

The mixture was cooled, the addition product was dissolved by adding acetic acid and methanol, the clear solution was decanted from the zinc into water, and the mixture was acidified with acetic acid. The ether-benzene layer was separated from the aqueous solution, the latter was extracted with benzene and the combined organic solutions were washed with water and then with dilute ammonium hydroxide until no more color was removed. The product obtained from the dried solution was distilled under reduced pressure. The distillate consisted of 3 g. of unsaturated ester (b. p. 140-170° (18 mm.)), produced by dehydration of some of the Reformatsky ester, and 23.5 g. of the Reformatsky ester (b. p. 173-177° (18 mm.)), which represents a total yield of 88%.

**Preparation of the Unsaturated Acids (I and II).**—The aforementioned Reformatsky ester was dehydrated by its reaction with thionyl chloride in pyridine according to the procedure described.<sup>12</sup> To a solution of 9.6 g. of potassium hydroxide in 100 cc. of anhydrous methanol was added 15.1 g. of the dehydrated ester and the whole was refluxed for twelve hours or longer. The mixture was cooled and the insoluble potassium salt which had precipitated was filtered from the solution. On treatment with cold dilute hydrochloric acid the salt yielded the free acid as an oil, which was taken up in ether; the solution was saturated with salt and extracted twice with ether. Evaporation of the dried ether solutions yielded 5.01 g. of crystalline  $\alpha$ -acid; m. p. 96-102°. After two recrystallizations from xylene-petroleum ether this unsaturated dicarboxylic acid formed stout colorless plates; m. p. 101.8-103.5°. The acid dissolves readily in hot water (3 cc. per g.); from the cooled solution it crystallizes slowly.

*Anal.* Calcd. for C<sub>10</sub>H<sub>14</sub>O<sub>4</sub>: C, 60.6; H, 7.1; neutral equivalent, 99. Found: C, 60.6; H, 7.0; neut. eq., 99.5.

The alcoholic filtrate was evaporated and the residual salts were dissolved in 100-150 cc. of water. Neutral material was extracted with ether, the aqueous solution was concentrated to 30 cc., 10 g. of sodium hydroxide and 10 g. of potassium hydroxide were dissolved in the solution with cooling and the mixture was allowed to stand for twelve hours. From the salt which precipitated from the solution, 1.61 g. of impure  $\alpha$ -acid was obtained; from the solution 3.05 g. of impure  $\beta$ -acid was obtained by acidification. After sublimation at 150° (0.005 mm.) it crystallized from acetone-petroleum ether as fine white clusters; m. p. 170.5-173.8°.

*Anal.* Calcd. for C<sub>10</sub>H<sub>14</sub>O<sub>4</sub>: C, 60.6; H, 7.1; neutral equivalent, 99. Found: C, 60.8; H, 7.3; neut. eq., 99.5.

The second crop (1.61 g.) of  $\alpha$ -acid, which was somewhat dark, was purified by triturating it with petroleum ether containing just enough acetone and benzene to dissolve the dark oily impurities but not the crystals. The latter were filtered off and dissolved in benzene-petroleum ether, the solution was boiled with Norite, filtered and evaporated and the product was reevaporatively distilled at 150-160° (0.005 mm.) or recrystallized from ether and petroleum ether in order to obtain it pure enough for catalytic reduction; m. p. 97-101°.

***cis*-2-Methyl-2-carboxycyclohexane-1-acetic Acid (III).**—A mixture of 2.5 g. of the  $\alpha$ -unsaturated acid, 40 cc. of glacial acetic acid and 50 mg. of Adams platinum catalyst was shaken under a slight pressure of hydrogen; hydrogenation was complete in one hour. The reduced acid (m. p. 138-153°) obtained from the solution was dissolved in 10% aqueous sodium hydroxide and the solution was concentrated while warm by a stream of air to precipitate the sodium salt of the acid. The salt was filtered off and treated with hydrochloric acid; after one recrystallization from xylene-petroleum ether the acid melted at 161.5-163° (reported,<sup>8</sup> 163-164°), a small amount of *trans* acid was isolated from the mother liquor; m. p. 173-174°. The yield of purified *cis* acid was about 80%. If the unsaturated acid is not pure, a longer time and frequent renewal of the catalyst are required for complete hydrogenation.

The same acid was obtained by hydrogenation of the  $\beta$ -unsaturated acid; the purified  $\beta$ -acid absorbed one mole of hydrogen in fifteen minutes. After one recrystallization of the crude reduced acid it melted at 159.8-161.2°; a mixture of it and the reduced acid above melted at 160-162.6°.

***cis*-2-Methyl-2-carbomethoxycyclohexane-1-acetic Acid (IV).**—Five grams of the crude acid (m. p. 132-148°) obtained above was converted to its dimethyl ester by means of diazomethane and the ester was refluxed with 23.57 cc. of 1.06 *N* aqueous sodium hydroxide in 75 cc. of methanol for two and one-half hours. After removal of the methanol, the residue was dissolved in water, the solution was extracted with ether in order to remove any unreacted ester, and the aqueous solution was poured with stirring into iced dilute hydrochloric acid. The mixture was saturated with salt and the acid ester was extracted with ether; from the dried solution 5.12 g. of the acid ester was obtained as a waxy solid. It was dissolved in low boiling petroleum ether and the solution kept in a refrigerator for twelve hours; from the solution the acid ester separated; m. p. 54.5-60°; yield, 3 g. A melting point of 59-60° was reported for the melting point of the acid ester obtained by catalytic reduction of the unsaturated acid ester.<sup>12</sup>

***cis*-8-Methyl-1-hydrindanone.**—To a cold solution of 3 g. of the aforementioned acid ester in 15 cc. of dry benzene was added 3 drops of pyridine and then 4.5 cc. of purified thionyl chloride with constant swirling of the mixture. After one-half hour the mixture was kept at 40° for ten minutes and then the solvent was removed under reduced pressure. Five cc. of dry benzene was added to the

residual acid chloride and removed by a second evaporation. A solution of the acid chloride in 15 cc. of dry benzene was then added dropwise (through a small cotton plug in the side arm of the flask) to a cold, dried solution of diazomethane which had been prepared from 10 g. of *N*-nitroso-*N*-methylurea in 150 cc. of ether.

After five hours, the solvents were removed under reduced pressure, and 50 cc. of reagent methanol and 0.5 g. of silver oxide (Mallinckrodt U. S. P. grade) were added to the liquid diazoketone. After the mixture had been refluxed on a water-bath for one-half hour, an additional 0.2 g. of silver oxide was added and refluxing was continued for one-half hour. The solution was boiled with Norite and Filter-Cel, filtered and evaporated in a stream of air and finally under reduced pressure. The liquid dimethyl ester of *cis*-2-methyl-2-carboxycyclohexane-1- $\beta$ -propionic acid (V) was dissolved in 50 cc. of dry benzene and cyclized by sodium methoxide according to the procedure described.<sup>13</sup> The cyclic keto ester which was obtained possessed a slight camphor-like odor; it gave a deep blue color with an alcoholic solution of ferric chloride.

A mixture of the crude 2-carbomethoxy-8-methyl-1-hydrindanone, 15 cc. of acetic acid, 7 cc. of concentrated hydrochloric acid and 1.5 cc. of water was refluxed for one hour. The cooled solution was neutralized by means of iced dilute ammonium hydroxide and the ketone was salted out and extracted with ether. By distillation 0.86 g. of *cis*-8-methyl-1-hydrindanone (b. p. 121–123° (45–47 mm.)) was obtained, which solidified in the receiver to a camphoraceous solid. A cooled sample was pressed on a cool porous plate; the colorless solid melted at 38.2–39.5° (reported, 33–34°, 34°, 39.5°). The semicarbazone after several crystallizations from methanol formed colorless needles; m. p. 212–213° when heated rather slowly and 224–225° when heated rapidly (reported, 213°, 221–222°, 224.5°).

The oxime crystallized from aqueous alcohol in colorless needles, m. p. 85.5–87°.

*Anal.* Calcd. for C<sub>10</sub>H<sub>17</sub>ON: N, 8.4. Found: N, 8.5.

***trans*-2-Methylcyclohexane-1,2-dicarboxylic Acid.**—A solution of the potassium acid salt of 2-methyl-1-cyclohexene-1,2-dicarboxylic acid prepared from 15 g. of the acid<sup>13c</sup> in 300 cc. of water and 1.5 g. of Raney nickel catalyst was hydrogenated at 125–150° at 1800–2000 pounds pressure for six hours. The cooled solution was filtered onto iced concentrated hydrochloric acid. The precipitated acid weighed 11.17 g.; m. p. 212.6°. On standing, the filtrate deposited an additional 0.68 g. of the acid; m. p. 214–214.3° (reported,<sup>13c</sup> 210°). The mother liquor after being saturated with salt yielded 2.68 g. of acid (m. p. 191–197°) when extracted with ether.

***trans*-2-Methyl-2-carbomethoxycyclohexane-1-carboxylic Acid (VIII).**—The dimethyl ester prepared from 3.55 g. of the acid by means of diazomethane was refluxed with 18.8 cc. of 1.02 *N* potassium hydroxide and 60 cc. of methanol for twelve hours. The methanol was removed by distillation, the residue was dissolved in water and the solution was extracted with ether to remove unreacted dimethyl ester (0.49 g.). By acidification of the aqueous solution, saturation with salt and extraction with ether 3.32 g. of the acid ester was isolated as an oil which crystallized when cooled and scratched; m. p. 67–82°. After

two recrystallizations from petroleum ether containing a few drops of benzene a sample of the acid ester melted at 90–91.5° with previous softening.

*Anal.* Calcd. for C<sub>10</sub>H<sub>16</sub>O<sub>4</sub>: C, 60.0; H, 8.1. Found: C, 60.4; H, 8.1.

***trans*-2-Methyl-2-carboxycyclohexane-1-acetic Acid (III).**—Five cc. of oxalyl chloride was added to 5 g. of the aforementioned acid ester (m. p. 67–82°) dissolved in 50 cc. of dry benzene. After two hours at room temperature, the solvent and excess oxalyl chloride were removed under reduced pressure; a few cc. of benzene were added and the evaporation repeated. A solution of the acid chloride in 10 cc. of benzene was added dropwise to a cold solution of diazomethane which had been prepared from 37 g. of *N*-nitrosomethylurea and 350 cc. of anhydrous ether, and dried and distilled. After the addition, the solution was allowed to warm to room temperature. After a total time of one and three-quarters hours, the solvent was removed under reduced pressure at room temperature. A solution of the liquid diazoketone in 50 cc. of methanol was added to a flask in which a mixture of 1 g. of silver oxide and 50 cc. of anhydrous methanol had been refluxed for thirty minutes to form a silver mirror. When the mixture was heated, nitrogen was evolved; after bubbling through a mercury trap had ceased, an additional 0.2 g. of silver oxide was added and refluxing was continued for twelve hours. The product obtained by filtration and removal of the methanol was heated with a mixture of 25 cc. of 45% potassium hydroxide solution and 25 cc. of methanol for four to six hours, the methanol was removed, the solution was acidified and the organic acid, after being salted out, was extracted with ether. The acid obtained by removal of the ether crystallized when scratched with a glass rod; it was digested with petroleum ether and acetone and the mixture filtered; weight, 1.67 g.; m. p. 140–153°. From the filtrate an additional 1.04 g. of the acid was isolated. After sublimation and one recrystallization from petroleum ether–acetone, a sample of the acid formed short colorless rods; m. p. 175–177.8°. Mixed with the acid (m. p. 173–174°) obtained by reduction of I (or II) it melted at 173–176°.

*Anal.* Calcd. for C<sub>11</sub>H<sub>18</sub>O<sub>4</sub>: C, 60.0; H, 8.1. Found: C, 60.1; H, 8.1.

***trans*-8-Methyl-1-hydrindanone (VI).**—The dimethyl ester prepared from 1.31 g. of recrystallized *trans* acid (m. p. 172–175°) and diazomethane was heated with 10 cc. of methanol and 5.15 cc. of 1.19 *N* sodium hydroxide for twenty hours. By titration of the excess of alkali and isolation of only a trace of unreacted dimethyl ester, it was shown that the 1.28 g. of acid ester was about 98% pure.

A mixture of 3 g. of the liquid acid ester, 10 cc. of benzene and 3 cc. of oxalyl chloride was allowed to stand for two hours; during the first quarter hour a vigorous reaction took place. After moderate warming for fifteen minutes, the benzene and oxalyl chloride were removed as described previously. Three hours at room temperature were allowed for the reaction between the acid chloride and the diazomethane (from 15 g. of *N*-methylnitrosourea and 150 cc. of ether), and twelve hours for the reaction between the diazoketone and methanol in the presence of silver oxide.

The liquid dimethyl ester of *trans*-2-methyl-2-carboxycyclohexane-1- $\beta$ -propionic acid (V) obtained by evaporation of the filtered methanol solution was then cyclized in the same way as the *cis* isomer, seven hours being allowed for the reaction. The cyclic keto ester gave a bluish-violet color with an alcoholic solution of ferric chloride. Hydrolysis of the keto ester and decarboxylation was carried out as described and the *trans*-8-methyl-1-hydrindanone was obtained as a colorless liquid with a camphor-like odor by distillation at 116–120° at 35 mm.; weight, 1.14 g. On redistillation it boiled at 108–109° at 20 mm.;  $n_{25}^{25}$  1.4807.

*Anal.* Calcd. for  $C_{10}H_{16}O$ : C, 78.9; H, 10.6. Found: C, 78.8; H, 10.3.

The semicarbazone after recrystallization from *n*-butyl alcohol melted at 234° when the melting point tube was placed in the bath at 190°. A mixture of the semicarbazones of *cis*- and *trans*-8-methyl-1-hydrindanones melted at 206–208°.

*Anal.* Calcd. for  $C_{11}H_{19}ON_3$ : N, 20.0. Found: N, 20.1.

The oxime after recrystallization from aqueous alcohol melted at 113–115.5°. Mixed with the oxime of the *cis* cyclic ketone it melted at 74–90°.

*Anal.* Calcd. for  $C_{10}H_{17}ON$ : N, 8.4. Found: N, 8.2.

### Summary

The synthesis of the *cis* and *trans* forms of 8-methyl-1-hydrindanone from cyclohexanone is described. The *cis* and *trans* forms of 2-methyl-2-carboxycyclohexane-1-acetic acid were prepared, the acetic acid side chain was lengthened to a propionic acid group through the Arndt-Eistert synthesis and the esters of the resulting products were cyclized by the Dieckmann method.

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## Synthetic Mydriatics. III

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Although atropine is the most outstanding mydriatic of the ester type, it is known that certain esters, simpler than the alkaloid in structure, produce strong mydriasis.<sup>3</sup> These esters, like atropine, represent combination of a basic alcohol with an arylhydroxy aliphatic acid. The basic alcohol may be as simple as  $\beta$ -dimethylaminoethanol, or somewhat more complex such as  $\beta, \beta$ -dimethyl- $\gamma$ -piperidinopropanol. The acid may be a substituted acetic or propionic acid.

Hitherto, no systematic study has been made to determine which basic alcohols and arylhydroxy acids are most suitable for the preparation of esters which possess mydriatic properties. During this investigation fifty-two products have been synthesized which represent combinations of phenylhydroxyacetic (mandelic), diphenylhydroxyacetic (benzolic),  $\alpha$ -phenyl- $\alpha$ -hydroxypropionic (atrolactic),  $\alpha$ -phenyl- $\beta$ -hydroxypropionic (tropic),  $\beta$ -phenyl- $\alpha$ -hydroxypropionic,  $\beta$ -phenyl- $\beta$ -hydroxypropionic or  $\beta, \beta$ -diphenyl- $\beta$ -hydroxypropionic acid with one of fourteen different basic alcohols.

The esters were obtained by interaction of the phenylhydroxy acid with the required basic alkyl halide according to the procedure of Horenstein and Pählicke.<sup>4</sup>

The compounds, in the form of hydrochlorides, hydrobromides, phosphates or methobromides, were tested by Dr. John G. Beall for mydriatic and local anesthetic activity by surface application of freshly-prepared 2% aqueous solutions to the rabbit's cornea. The pharmacological data are reported in Table I, column I.

It was found that most of the esters which are strong mydriatics are also strong local anesthetics. With the possible exception of compound 34,  $\beta, \beta$ -dimethyl- $\gamma$ -dimethylaminopropyl  $\alpha$ -phenyl- $\alpha$ -hydroxypropionate (27) was the only strongly active mydriatic found which did not produce local anesthesia. In view of the high activity of compound 27, it seems strange that compound 28, the next higher homolog,<sup>5</sup> should have been found to be completely inactive. The strong local anesthetics, compounds 22, 23, 48, 51 and 52, do not dilate the pupil.

Since tropyl mandelate (homatropine) is an

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(2) Lilly Endowment Fellow.

(3) (a) Blicke and Maxwell, *THIS JOURNAL*, **64**, 428 (1942); (b) **64**, 431 (1942).

(4) Horenstein and Pählicke, *Ber.*, **71**, 1654 (1938).

(5) Probably in the strict sense of the term, the next higher homolog of a compound which contains the dimethylamino group would be the corresponding methylethylamino, and not the diethylamino derivative.