from absolute alcohol gave colorless, transparent needles, m.p. 177.5–177.8° (efferv.) (immersed at room temperature), 171–173° (efferv.) (immersed at 150°), $[\alpha]^{20}_{\mathrm{D}}$ −165° (*c* 0.43, pyridine). The resolidified material melted at 167–170° and showed no depression on admixture with desoxypicropodophyllin.

Anal. Calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81; 3-OCH_3, 22.36. Found: C, 63.39; H, 5.88; OCH_3, 22.61.

Recrystallization of the crude hydroxy acid from hot dilute ethanol, followed by drying at room temperature, gave colorless, fine needles, m.p. 171–172° (efferv.).

Anal. Calcd. for $C_{22}H_{24}O_8 \cdot {}^1/_2H_2O$: C, 62.11; H, 5.92. Found: C, 61.97; H, 5.63.

Desoxypodophyllotoxin (I).—Hydrogen was bubbled through a mixture of 2.79 g. of podophyllotoxin chloride,[2] 0.28 g. of 5% palladium–barium sulfate catalyst[16] and 28 cc. of anhydrous toluene, which was stirred and boiled under reflux. The rate of hydrogen chloride evolution, which was measured by titration with *N* sodium hydroxide,[3] became slow at the end of three hours; therefore another 0.28 g. of catalyst was added and the reaction continued for three hours. The catalyst was removed (Celite), washed with hot chloroform, and the combined filtrate and washings evaporated. Addition of hexane to the oil, and chilling, provided 2.55 g. (99%) of pale tan solid, m.p. 163–165°. The crude material was recrystallized from ethanol, further purified by chromatography on alumina and elution with chloroform, then recrystallized from 50% ethanol, from methanol, and finally from ethanol to yield large, colorless, glistening prisms, m.p. 167.8–168.8°, $[\alpha]^{20}_{\mathrm{D}}$ −115° (*c* 0.50, chloroform), $[\alpha]^{20}_{\mathrm{D}}$ −181° (*c* 0.61, pyridine). The melting point was unchanged after further recrystallization. There was no mixed melting point depression with silicicolin, and the infrared spectra of the two substances were identical.

Anal. Calcd. for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.62; H, 5.66.

Desoxypicropodophyllin (I).—A mixture of 200 mg. of desoxypodophyllotoxin, 400 mg. of anhydrous sodium acetate and 3 cc. of absolute ethanol was refluxed for 17 hours, then diluted with 15 cc. of hot water to yield 187 mg. (93%) of tiny, colorless, electrified needles, m.p. 170.4–172.0°. Recrystallization from 30% ethanol gave material melting at 170.7–172.0°, $[\alpha]^{21}_{\mathrm{D}}$ +32° (*c* 0.50, chloroform), $[\alpha]^{21}_{\mathrm{D}}$ +43° (*c* 0.52, pyridine). Mixed m.p. determination and the infrared spectra proved the identity of the compound with silicicolin-B.

Anal. Calcd. for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.54; H, 5.46.

This compound was also prepared in 48% yield by refluxing 135 mg. of desoxypodophyllotoxin with 1.25 cc. of ethanol, 0.5 cc. of water and 0.025 cc. of piperidine for one hour, and diluting with 4 cc. of water; m.p. 170.5–172.0°, $[\alpha]^{20}_{\mathrm{D}}$ +33.5° (*c* 0.49, chloroform).

Desoxypodophyllic Acid.—A solution prepared by boiling 500 mg. of desoxypodophyllotoxin with 500 mg. of sodium hydroxide, 4 cc. of water and 2 cc. of ethanol for five minutes was diluted with 10 cc. of water, cooled in ice and, after addition of 10 cc. of chloroform, acidified with shaking by the addition of 7 cc. of 2 *N* hydrochloric acid. The colorless, crystalline hydroxy acid (518 mg., 95%) was collected and washed with cold water and chloroform; m.p. 161–163° (dec., rapid heating). Recrystallization by dissolving in a small amount of ethanol, and diluting with chloroform, then with water, yielded material which, after drying in air, contained one molecule of water of crystallization and melted with effervescence at 161–162° when immersed at 150° (heating rate 2°/min.), $[\alpha]^{20}_{\mathrm{D}}$ −160° (*c* 0.52, pyridine). The resolidified material remelted at 170–172° and did not depress the melting point of desoxypicropodophyllin.

Anal. Calcd. for $C_{22}H_{24}O_8 \cdot H_2O$: C, 60.82; H, 6.03. Found: C, 60.80; H, 6.13.

Acknowledgment.—The authors wish to express their sincere appreciation to Professor Nathan L. Drake, University of Maryland, for a sample of his desoxypicropodophyllin,[6] and to Dr. Léo Marion, National Research Council, Canada, for a sample of cicutin.

BETHESDA, MARYLAND

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[16] Baker and Co., Inc., Newark, N. J.

[CONTRIBUTION FROM THE RESEARCH INSTITUTE, MONTREAL GENERAL HOSPITAL]

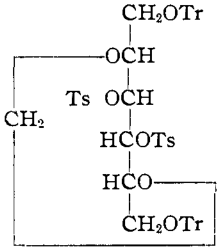
Epoxy Glycitols. I. Synthesis and Properties of 3,4-Anhydro-2,5-methylene-1,6-ditrityl-D-talitol (= D-Altritol)

BY SAMUEL B. BAKER[1] AND GABRIEL KOHANYI

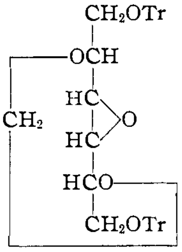
RECEIVED NOVEMBER 18, 1952

An anhydro hexitol derivative has been synthesized in which the anhydro group was of the ethylene oxide type and which was on two secondary carbon atoms rather than on a primary and a secondary atom. This anhydro glycitol was found to be unusually stable to alkali and a methylene acetal group on the same molecule was found to be very labile to acid.

Recent interest in anhydro glycitols has led us to describe our investigations on the possibility of synthesizing monoepoxy sugar alcohols in which the epoxy rings are substituted on the secondary alcohol positions of hexitols and their derivatives. This publication describes the results of the work on the synthesis and properties of 3,4-anhydro-2,5-methylene-1,6-ditrityl-D-talitol (I). The latter compound (I) was prepared by two methods, namely, by the action of sodium methoxide in methanolic chloroform and by saponification with alcoholic potassium hydroxide of 2,5-methylene-3,4-ditosyl-1,6-ditrityl-D-mannitol (II). Inasmuch as mannitol has end-to-end symmetry the tosyl groups on C-3 and C-4 are equivalent and it is therefore immaterial which tosyloxy group is removed in the formation of the epoxy ring.



II



I

A relatively concentrated solution of alcoholic potassium hydroxide was found necessary to convert II to I and, as expected, the anhydride proved to be unusually stable to the action of alkali. In this it resembles 1,2–5,6-diisopropylidene-D-talitol which Bladon and Owen[2] found to be unaffected by

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[1] To whom inquiries should be addressed.

[2] P. Bladon and L. N. Owen, *J. Chem. Soc.*, 605 (1950).

0.2 N methanolic sodium methoxide. In contrast to these 3,4-anhydrohexitols, methyl 2,3-anhydro-4,6-benzylidene-α-D-alloside undergoes scission of the ethylene oxide ring when treated with aqueous potassium hydroxide.[3] The question of the relative stability of similarly located epoxy rings in glycoses and in glycitols will be the subject of a future communication.

The action of various acidic reagents on 3,4-anhydro-2,5-methylene-1,6-ditrityl-D-talitol was also studied. With boiling 10% hydrochloric acid the trityl groups were quantitatively removed, the ethylene oxide ring cleaved and the methylene bridge (at least in part) hydrolyzed.[4] Crystalline D-mannitol was isolated from the reaction mixture in 27% yield; methyleneation of the mother liquor afforded 2,4-3,5-dimethylene-D-iditol which was further characterized through its diacetate and dibenzoate. The physical properties of these D-iditol derivatives agreed with the corresponding ones of the L-iditol series prepared by Hann and Hudson.[5]

The anhydro talitol (I) was found to be labile to other acidic reagents. Acetyl bromide in anhydrous medium removed the trityl groups as trityl bromide and cleaved the anhydro ring to yield an amorphous product containing bromine. Debromination with silver acetate in boiling acetic acid converted this to 1,3,4,6-tetraacetyl-2,5-methylene-D-mannitol; the analogous D-iditol which was presumably formed could not be isolated.

Boiling 80% acetic acid also attacked the anhydro talitol (I). Aside from a quantitative yield of tritanol, the only crystalline product isolated was a minute amount of D-mannitol. The major reaction product was a sirup which, from its behavior with lead tetraacetate, appeared to have the composition of a 2,5-methylenehexitol.

Experimental

2,5-Methylene-1,6-ditrityl-D-mannitol.—2,5-Methylene-D-mannitol[6] (100 g.) and freshly prepared triphenylchloromethane (320 g.) were dissolved in anhydrous pyridine (1000 cc.). The reaction mixture was allowed to stand for 72 hours at 40°. Water (50 cc.) was added dropwise to dissolve the separated pyridinium chloride and the homogeneous yellow solution was then added to cold water (4000 cc.). A colorless oil separated and it was triturated until stiff. The product solidified and after it was broken up it was filtered and washed with water to remove most of the pyridine. A fraction of the air-dried material, on recrystallization from ethyl acetate, melted at 82–84°, but it resolidified and then melted at 202–203°. The material was probably solvated. The remainder of the crude product was then dried at 100° *in vacuo* and on recrystallization from a mixture of acetone–petroleum ether it melted at 202–203°. The yield was 265 g. (76%) and the rotation was $[\alpha]^{25}\mathrm{D}$ −10° (pyridine, c 9.3764, l 2).

Anal. Calcd. for $C_{45}H_{42}O_6$: C, 79.65; H, 6.19. Found: C, 79.59; H, 6.21.

A sample (0.3016 g.) of the above was dissolved in 50.0 ml. of 0.0225 M lead tetraacetate in glacial acetic acid. The solution was then diluted to 100.0 ml. with acetic acid in a volumetric flask. Analysis of 10-cc. aliquots after 90 minutes and 24 hours indicated that 0.26 and 0.98 mol. equiv. lead tetraacetate were consumed.

3,4-Diacetyl-2,5-methylene-1,6-ditrityl-D-mannitol.—2,5-Methylene-1,6-ditrityl-D-mannitol (10 g.) was dissolved in anhydrous pyridine (20 cc.). The solution was cooled to −15° and acetic anhydride (20 cc.) was added. The solution was allowed to stand at 22° and after about two hours crystallization occurred. After standing overnight at 22°, the crystalline mass was triturated with cold water (200 cc.), filtered, and washed with water. The crude air-dried material was recrystallized twice from hot acetone yielding 9.6 g. (84%) of glistening hexagonal plates melting at 250–250.5° and rotating $[\alpha]^{22}\mathrm{D}$ 44.7° ($CHCl_3$, c 8.386, l 2).

Anal. Calcd. for $C_{49}H_{46}O_8$: C, 77.16; H, 6.03; CH_3CO, 11.3. Found: C, 77.09; H, 6.09; CH_3CO, 11.3.

The compound, above (5 g.) was suspended in acetic anhydride (50 cc.) and pure redistilled acetyl bromide (3 g.) was added. The mixture was agitated for one hour, during which time the crystalline substance dissolved and trityl bromide separated. The excess acetyl bromide was then removed *in vacuo* at 35°. The cooled (−10°) mixture was filtered and the theoretical yield of trityl bromide (4.1 g.) was obtained. The filtrate was added to cold water and the sirup was dissolved in chloroform. The chloroform solution was washed with bicarbonate solution and then dried over sodium sulfate. The sirup obtained on solvent removal was dissolved in a small volume of 99% ethanol. On cooling, needles (1.8 g.) separated which melted at 115–118°. A mixed melting point determination with authentic 1,3,4,6-tetraacetyl-2,5-methylene-D-mannitol[6] showed no depression.

3,4-Dibenzoyl-2,5-methylene-1,6-ditrityl-D-mannitol.—2,5-Methylene-1,6-ditrityl-D-mannitol (5 g.) was dissolved in anhydrous pyridine (10 cc.). Benzoyl chloride (2 cc.) was added and the mixture allowed to stand overnight at 22°. The solution, containing crystalline pyridinium chloride, was added to cold water and the gummy mass solidified after four hours. The solid was broken up, filtered and washed with water. The air-dried product was dissolved in acetone and the acetone solution decolorized with charcoal. After filtration, the filtrate was made slightly turbid with petroleum ether. Cooling and scratching caused precipitation of rectangular plates. Further recrystallization from acetone–petroleum ether yielded 5.5 g. (84%) melting at 113–114°, rotating $[\alpha]^{21}\mathrm{D}$ −30.7° ($CHCl_3$, c 8.552, l 2).

Anal. Calcd. for $C_{59}H_{50}O_8$: C, 79.91; H, 5.64; C_6H_5CO, 23.7. Found: C, 79.84; H, 5.73; C_6H_5CO, 23.6.

2,5-Methylene-3,4-ditosyl-1,6-ditrityl-D-mannitol (II).—2,5-Methylene-1,6-ditrityl-D-mannitol (100 g.) was dissolved in anhydrous pyridine (250 cc.). *p*-Toluenesulfonyl chloride (62 g.) was added and the solution allowed to stand at 40° for five days. The reaction mixture, containing crystalline pyridinium chloride, was cooled to 5° and added to a large volume of cold water. The sirupy mass solidified and after it was broken up it was filtered and washed repeatedly with water. The crude air-dried material was recrystallized twice from butanol-1 yielding 81.5 g. (57%) melting at 130–132°. A sample was recrystallized from a large volume of ether and the melting point was 131–132° and rotation $[\alpha]^{22}\mathrm{D}$ −20.8° ($CHCl_3$, c 6.9068, l 2).

Anal. Calcd. for $C_{59}H_{54}S_2O_{10}$: C, 71.80; H, 5.47; S, 6.49. Found: C, 71.63; H, 5.52; S, 6.5.

3,4-Anhydro-2,5-methylene-1,6-ditrityl-D-talitol. Method A.—2,5-Methylene-3,4-ditosyl-1,6-ditrityl-D-mannitol (II) (10 g.) was dissolved in anhydrous chloroform (100 cc.). Sodium (0.4 g.) dissolved in anhydrous methanol (20 cc.) was added and the solution allowed to stand until neutral to phenolphthalein (4 days). The precipitated sodium *p*-toluenesulfonate was removed by filtration and the filtrate concentrated to dryness. The resulting sirup was dissolved in ether and crystalline substance separated. On standing an additional crop separated. The total precipitate was then recrystallized from ethanol, yielding 3.5 g. of unchanged starting material as indicated by a mixed melting point determination. The residual sirup was then dissolved in anhydrous ethanol. A crystalline product separated and on recrystallization from a large volume of ethanol it weighed 2.2 g. and melted at 180–186°. The obviously impure material was recrystallized from a hot ethyl acetate–petroleum ether solution. A further recrystallization from dioxane did not raise the melting point above 194–196° and it rotated $[\alpha]^{22}\mathrm{D}$ −78.5° ($CHCl_3$, c 2.626, l 2).

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[3] N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **63**, 1727 (1941).

[4] Hydrolysis of the 2,5-methylene ring in 1,3-2,5-4,6-trimethylene-D-mannitol has been observed by H. G. Fletcher, Jr., and H. W. Diehl, THIS JOURNAL, **74**, 3797 (1952). E. J. Bourne, G. T. Bruce and L. F. Wiggins, *J. Chem. Soc.*, 2708 (1950), noted a parallel hydrolysis with 1,3-2,5-4,6-triethylidene-D-mannitol.

[5] R. M. Hann and C. S. Hudson, THIS JOURNAL, **67**, 602 (1945).

[6] A. T. Ness, R. M. Hann and C. S. Hudson, *ibid.*, **65**, 2215 (1943).

Method B.—2,5-Methylene-3,4-ditosyl-1,6-ditrityl-D-mannitol (II) (50 g.) was added to a solution made up of potassium hydroxide (25 g.), water (25 cc.) and ethanol (2500 cc.). The mixture was refluxed for two days on the steam-bath. During the first four hours most of the solid material had dissolved and then crystallization began. The mixture was then concentrated to about 1000 cc., water (1000 cc.) was added and the cooled mixture was filtered. The residue was washed with water until the washings were neutral. The air-dried product was then recrystallized twice from dioxane yielding 27.7 g. (83%) and rotating $[\alpha]^{22}\text{D}$ −78.3° ($CHCl_3$, *c* 3.721, *l* 2) and melting at 195–196°. This compound was found to be identical with that obtained by method A by a mixed melting point determination.

Anal. Calcd. for $C_{45}H_{40}O_5$: C, 81.81; H, 6.06; $(C_6H_5)_3COH$, 78.9. Found: C, 81.69; H, 6.11; $(C_6H_5)_3COH$, 77.4.

A glycol group was shown to be absent since a benzene solution of lead tetraacetate was not reduced after 18 hours at 23°.

A sample (3 g.) was dissolved in an acetylation mixture consisting of pyridine (15 cc.) and acetic anhydride (15 cc.). The solution was added to cold water after standing for two days at 22°. The starting material was recovered unchanged as indicated by melting point and rotation. Therefore hydroxyl groups were not present in the talitol derivative.

Effect of Acetyl Bromide on 3,4-Anhydro-2,5-methylene-1,6-ditrityl-D-talitol (I).—The latter compound (25 g.) was suspended in acetic anhydride (75 cc.). Freshly distilled acetyl bromide (22 cc.) was added and the mixture agitated for one hour during which time the talitol derivative dissolved and trityl bromide separated. The excess acetyl bromide was removed by distillation *in vacuo* at 35° and the mixture after being cooled to −15° was filtered to remove trityl bromide (24 g.). The acetic anhydride was then removed by distillation *in vacuo* and the thick sirup triturated with a paste of potassium bicarbonate. Chloroform and water were added and the neutral chloroform solution was dried over anhydrous sodium sulfate. The solvent was removed completely and the sirup was found to contain organic bromide by decomposition of a small quantity of sirup with boiling alcoholic potassium hydroxide, followed by cautious acidification of the alkaline solution with nitric acid and addition of 2% silver nitrate. The remainder of the sirup was therefore dissolved in glacial acetic acid (200 cc.) and silver acetate (25 g.) added. The mixture was refluxed for one hour when a filtered aliquot indicated the absence of bromide. The mixture was filtered and the filtrate concentrated at 40° *in vacuo* to about 25 cc. Saturated aqueous potassium bicarbonate was added to remove the remaining acetic acid and the sirup dissolved in chloroform. The chloroform solution was dried over anhydrous sodium sulfate and after filtration the solvent was removed completely. The sirupy residue was dissolved in a small volume of 99% ethanol and the solution was decolorized with charcoal. The colorless filtrate was seeded with several crystals of 1,3,4,6-tetraacetyl-2,5-methylene-D-mannitol and on prolonged cooling a crop of crystals was obtained, melting at 113–116°. Recrystallization from ethanol raised the melting point to 115–117° and the yield was 2.6 g. This was found to be 1,3,4,6-tetraacetyl-2,5-methylene-D-mannitol by a mixed melting point determination with an authentic sample. The residues from the separation and recrystallization of the mannitol derivative were redissolved in 99% ethanol and treated with charcoal to remove a slight coloration. Crystallization did not occur and other solvents were employed without success. It was probable that 1,3,4,6-tetraacetyl-2,5-methylene-D-iditol was present in the sirup but it could not be crystallized.

Action of Alcoholic Potassium Hydroxide on 3,4-Anhydro-2,5-methylene-1,6-ditrityl-D-talitol (I).—A solution of potassium hydroxide (5 g.) in 95% ethanol (500 cc.) was added to 3,4-anhydro-2,5-methylene-1,6-ditrityl-D-talitol (5 g.). The mixture was heated under reflux on the steam-bath for 24 hours. Carbon dioxide was bubbled through the solution and the total mixture concentrated to dryness. The solid residue was extracted with hot water to remove carbonate and then filtered. The residue was thoroughly washed with hot water and the air-dried product weighing 4.8 g. had melted at 194–196°. The melting point was not depressed when a sample of the recovered product was admixed with authentic 3,4-anhydro-2,5-methylene-1,6-ditrityl-D-talitol (I).

Action of 80% Acetic Acid on 3,4-Anhydro-2,5-methylene-1,6-ditrityl-D-talitol (I).—The latter compound (10 g.) was heated under reflux for two hours with 80% acetic acid (100 cc.). The solution was cooled and mixed with cold water (200 cc.). The mixture was allowed to stand overnight to complete the separation of tritanol which was removed by filtration. The yield of tritanol was quantitative (7.8 g.). The filtrate was concentrated to dryness *in vacuo* and the residual acetic acid removed by repeated distillation of ethanol. The glassy sirup was dissolved in absolute ethanol and a trace of color removed with charcoal. Several crystals separated on prolonged cooling and after drying the melting point was 164–166°. A mixed melting point determination with a sample of D-mannitol showed no depression. This was therefore an indication that acidic conditions not only removed the trityl groups but also cleaved the anhydro ring and hydrolyzed, to some extent, the methylene acetal. The remainder of the glassy sirup after solvent removal was broken up. The yield was 2.6 g. (89%).

A sample (0.1061 g.) of the amorphous material was dissolved in acetic acid (25 cc.), by prolonged agitation, in a volumetric flask. Lead tetraacetate in glacial acetic acid (50 ml. of 0.0525 *M* solution) was added and the solution then made up to 100 ml. with acetic acid. Aliquots (5 ml.) were removed and analyzed after 0.5, 1, 3, 24 and 48 hours. Based on the assumption that the material present was a methylenehexitol, 0.6, 0.65, 0.78, 0.98, 1.01 molecular equivalents of lead tetraacetate were consumed by the times indicated.

Action of 10% Hydrochloric Acid on 3,4-Anhydro-2,5-methylene-1,6-ditrityl-D-talitol (I).—The anhydride (20 g.) was suspended in 10% aqueous hydrochloric acid (250 cc.). The mixture was boiled vigorously under reflux for two hours and the separated tritanol removed by filtration. The filtrate was then refluxed for an additional four hours and then distilled to remove formaldehyde that was obtained from hydrolysis of the methylene acetal. The volume (70 cc.) of distillate was replaced by an equal volume of water and this process was repeated six times when the sensitive dimethone test for formaldehyde was weak. The solution was then concentrated under reduced pressure to half volume. Water (500 cc.) was added and the solution was neutralized cautiously with lead carbonate and the lead chloride removed by filtration. The filtrate was agitated for one hour with silver carbonate (25 g.) to remove the remaining chloride ions and after filtration silver and lead ions were removed by bubbling hydrogen sulfide through the solution. The slightly yellow solution was decolorized with charcoal and then concentrated to dryness under reduced pressure. The resulting colorless sirup was dissolved in hot ethanol from which, on cooling, crystals of D-mannitol separated in a yield of 1.5 g. (27.2% of theoretically possible hexitol) melting at 165–166°. A mixed melting point determination with authentic D-mannitol was not depressed. The ethanolic filtrate containing D-iditol could not be made to crystallize and therefore it was concentrated to a thick sirup and dissolved in concentrated hydrochloric acid (15 cc.) and formaldehyde (15 cc.). The solution was slowly concentrated in a vacuum desiccator until a solid residue remained. Water (5 cc.) was added and the mixture was filtered and washed once with cold water (10 cc.). The yield was 1.4 g. and the product melted with partial decomposition at 260–262° and rotated $[\alpha]^{22}\text{D}$ −36.1° (H_2O, *c* 0.3, *l* 2). Hann and Hudson[5] reported a melting point of 264–266° and a rotation in water of +39.2° for 2,4–3,5-dimethylene-L-iditol.

1,6-Diacetyl-2,4–3,5-dimethylene-D-iditol.—A portion (0.25 g.) of the presumed 2,4–3,5-dimethylene-D-iditol was suspended in a mixture of acetic anhydride (8 cc.) and anhydrous sodium acetate (0.5 g.). The mixture was heated to boiling and kept at the boiling point for five minutes and then allowed to stand until the temperature decreased to 22°. Cold water (5°) (50 cc.) was added and after one hour the crystalline product was removed by filtration and washed with about 5 cc. of cold water. The air-dried material was recrystallized twice from ethanol yielding 0.26 g. (72%) which melted at 218–219° and rotated $[\alpha]^{22}\text{D}$ 4.0° ($CHCl_3$, *c* 0.84, *l* 2). Hann and Hudson[5] reported a melting point of 219–220° and $[\alpha]^{20}\text{D}$ −3.9° ($CHCl_3$) for the enantiomorph, 1,6-diacetyl-2,4–3,5-dimethylene-L-iditol.

1,6-Dibenzoyl-2,4–3,5-dimethylene-D-iditol.—This latter was prepared from 0.25 g. of 2,4–3,5-dimethylene-D-iditol, above, employing the method Hann and Hudson reported[5] for the preparation of the enantiomorph. The yield obtained after two recrystallizations from acetone was 0.32 g. (65%). It melted at 242–243° and rotated $[\alpha]^{22}_{D}$ −39.1° ($CHCl_3$, c 0.904, l 2). The reported[5] melting point and rotation for the enantiomorph were 242–243° and $[\alpha]^{20}_{D}$ +38.6° ($CHCl_3$), respectively.

Acknowledgments.—The authors are indebted to the Sugar Research Foundation, New York, for a grant in aid of this work to this Institute.

MONTREAL, CANADA

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

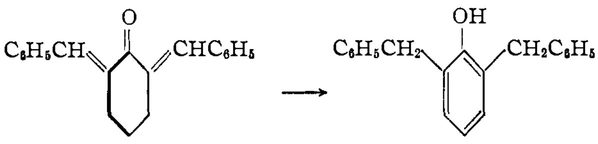
Tropolones by Isomerization. I. 3,7-Dibenzyltropolone[1]

BY NELSON J. LEONARD AND GENE C. ROBINSON[2]

RECEIVED OCTOBER 27, 1952

A new synthesis of tropolones is here described, represented by the isomerization of 3,7-dibenzylidene-1,2-cycloheptanedione to 3,7-dibenzyltropolone with hydrogen bromide–acetic acid. The generation of the tropolone nucleus was demonstrated in the physical and chemical properties of the product. Moreover, the structure of the substituted tropolone was verified by an independent synthesis proceeding through 3,7-dibenzyl-1,2-cycloheptanedione. Certain evidence bearing on the mechanism of the conversion has been accumulated by a study of variations in the reaction conditions and by the behavior of possible bromine-containing intermediates.

The consideration of tropolone as an aromatic system[3] and the known aromatization of 2,6-dibenzylidenecyclohexanone (I) to 2,6-dibenzylphenol (II) by means of hydrogen bromide–acetic acid[4,5]

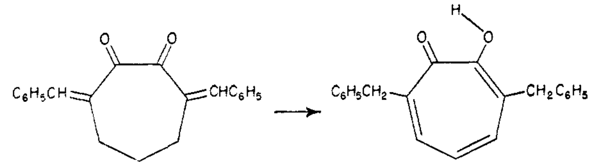


I

II

IIa, OAc in place of OH

suggested that 3,7-dibenzyltropolone (IV) might be obtained similarly from 3,7-dibenzylidene-1,2-cycloheptanedione (III). We have indeed been able to effect the isomerization of III to IV by hydrogen bromide in acetic acid, thus providing a new route for the synthesis of substituted tropolones.



III

IV

The intermediate in the seven-membered ring aromatization, 3,7-dibenzylidene-1,2-cycloheptanedione (III), was obtained by condensation of benzaldehyde with 1,2-cycloheptanedione in ethanol solution containing piperidine. This yellow compound, m.p. 189–190°, had ultraviolet (Fig. 1) and infrared (Fig. 2) absorption spectra characteristic of the α,β-unsaturated carbonyl systems present. Conversion to a colorless isomer, m.p. 118–119°, was effected in 46% yield by treatment of III with hydrogen bromide in acetic acid at 60°. The ultraviolet absorption spectrum of the product (Fig. 1) was similar to that of representative tropolones.[6] The infrared absorption spectrum in chloroform solution (Fig. 2) showed a peak at 2990 cm.$^{-1}$, the form of which was characteristic of a strongly bonded hydroxyl group, and at 1605 cm.$^{-1}$, indicative of the carbonyl in a tropolone.[7,8] Finally, the dark green color obtained with alcoholic ferric chloride solution was characteristic of a tropolone.[6] All of the accumulated evidence thus indicated that the structure of the isomerization product of 3,7-dibenzylidene-1,2-cycloheptanedione (III) was 3,7-dibenzyltropolone (IV).

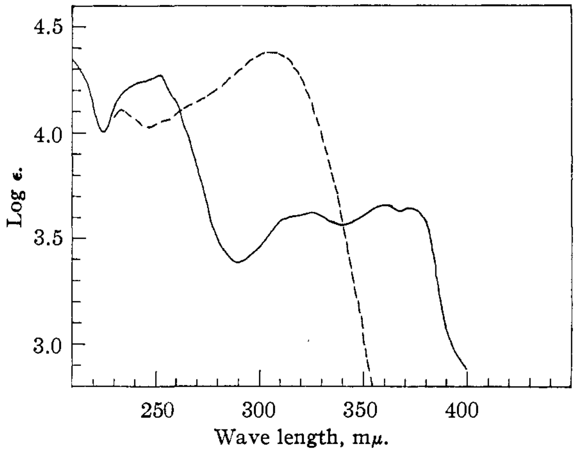


Fig. 1.—Ultraviolet absorption spectra: ———, 3,7-dibenzyltropolone; - - - 3,7-dibenzylidene-1,2-cycloheptanedione (in cyclohexane).

A study of the isomerization conditions was undertaken to obtain evidence bearing on the mechanism of the conversion. The isomerization is not induced by acid alone, since perchloric, sulfuric and hydrochloric acid in acetic acid were ineffectual in bringing about the conversion. The temperature employed seemed to be a critical factor governing the yield, and the optimum reaction temperature was about 60°. The reaction time appeared not to be as critical a factor, but the best yield was obtained after about 11 hours. The singular effec-

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(1) Presented at the 122d National Meeting of the American Chemical Society, Altantic City, N. J., September 15, 1952.

(2) Monsanto Chemical Company Fellow 1951–1952.

(3) M. J. S. Dewar, *Nature*, **155**, 50 (1945).

(4) R. Weiss and J. Ebert, *Monatsh.*, **66**, 399 (1935).

(5) We have found that the procedure of Weiss and Ebert[4] can be simplified by conducting the isomerization at atmospheric pressure in an open vessel. Addition of acetic anhydride to the hydrogen bromide–acetic acid provides for the formation of 2,6-dibenzylphenyl acetate (IIa) in excellent yield.

(6) J. W. Cook and J. D. Loudon, *Quart. Revs.*, **5**, 99 (1951).

(7) H. P. Koch, *J. Chem. Soc.*, 512 (1951).

(8) G. P. Scott and D. S. Tarbell, THIS JOURNAL, **72**, 240 (1950).