ethanolic filtrate and the ester was hydrolyzed by refluxing for 4 hr. The ethanol was removed (water pump), water was added and the mixture was extracted with ether to remove unsaponified material. Acidification of the alkaline solution with hydrochloric acid precipitated an oily mixture of acids which was taken up in ether. After drying and distillation of the ether, the residue weighed 8.4 g.

In order to separate unreacted starting material from the desired propionic acid, the crude mixture was subjected to cyclization with anhydrous hydrogen fluoride. Under these conditions the acetic acid is quantitatively cyclized (see below) to give a neutral ketone (0.6 g.), and the propionic acid (7.3 g.) remains unchanged. Thus, the yield of uncyclized recrystallized ***trans*-2-phenylcyclopentanepropionic acid** was 6.7 g., m.p. 77–78° (from petroleum ether). Nunn and Rapson[7] report m.p. 77–78°.

Anal. Calcd. for $C_{14}H_{18}O_2$: neut. equiv., 218.3. Found: neut. equiv., 216.

Cyclization of 2-Phenylcyclopentanepropionic Acid.—2-Phenylcyclopentanepropionic acid (1.92 g.) was dissolved in dry benzene (10 ml.) and thionyl chloride (3 ml.) was added. The acid chloride after removal of the solvents (as above) was taken up in carbon disulfide (25 ml.) and aluminum chloride (1.35 g.) was added in one portion. The mixture was refluxed for 3 hr. and allowed to stand overnight. After decomposition with dilute hydrochloric acid and extraction with ether, the solvents were removed and the residual ketone was evaporatively distilled. The ***trans*-1,2,3,6,7,8,9,10-octahydro-6-oxo-4,5-benzazulene** (IV), crystallized on trituration with petroleum ether, m.p. 66–67° (from petroleum ether) (1.34 g., 75% yield). Nunn and Rapson[7] report m.p. 65.5–67° for this ketone.

Anal. Calcd. for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.01; H, 8.16.

The semicarbazone was prepared by the pyridine method, m.p. 202–203° (from ethyl acetate). Nunn and Rapson[7] report m.p. 202–204°.

Anal. Calcd. for $C_{15}H_{19}N_3O$: N, 16.33. Found: N, 16.07.

Cyclization of 3-Oxo-2-phenylcyclopentaneacetic Acid.—3-Oxo-2-phenylcyclopentaneacetic acid (10 g.) was dissolved in anhydrous hydrogen fluoride (100 g.) and the solution was allowed to stand for 3 hr. The hydrogen fluoride was removed and potassium carbonate solution was added (foaming!). Ether extraction afforded the neutral tricyclic diketone, ***trans*-3,6-dioxo-4,5-benzhydrindane** (V) (3.5 g.), m.p. 133–134° (from methanol); infrared absorption: 1745 cm.$^{-1}$ (alicyclic C=O), 1686 cm.$^{-1}$ (acetophenone C=O).

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.26; H, 6.19.

The major portion of the starting material was recovered from the alkaline solution of its potassium salt and could be recycled. However, the yield of ketone was in no case higher than the above even when a large excess of hydrogen fluoride was used, or when a longer contact time was employed.

The dioxime, prepared by the pyridine method formed short colorless needles, m.p. 206° dec. (from methanol).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13. Found: C, 67.76; H, 6.06.

The orange-red **2,4-dinitrophenylhydrazone**, was prepared in the usual way, m.p. 187–188° (from ethanol).

Anal. Calcd. for $C_{19}H_{16}N_4O_5$: N, 14.73. Found: N, 15.13.

Cyclization of 2-Phenylcyclopentaneacetic Acid.—The acid (10 g.), cyclized with anhydrous hydrogen fluoride (100 g.) and worked up as above, afforded the tricyclic monoketone, ***trans*-6-oxo-4,5-benzhydrindane (VI)** (8.5 g.), m.p. 87.5–88.5° (from methanol); infrared absorption: 1675 cm.$^{-1}$ (benzoyl C=O).

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.29; H, 7.67.

Mousseron, *et al.*,[10] reported m.p. 79–82° for this ketone.

The oxime, prepared by the pyridine method formed colorless prismatic needles, m.p. 181° (from methanol).

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.91; H, 7.32; N, 6.74.

The orange **2,4-dinitrophenylhydrazone** had m.p. 242–244° (from ethanol). Mousseron, *et al.*,[10] reported m.p. 241–243° for this compound.

Anal. Calcd. for $C_{19}H_{18}N_4O_4$: N, 15.29. Found: N, 15.20.

REHOVOTH, ISRAEL

[CONTRIBUTION FROM CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Colchicine Studies. II. Synthesis of 2-(2',3',4'-Trimethoxyphenyl)-cyclohept-2-enone

BY DAVID GINSBURG[1]

RECEIVED MARCH 8, 1954

Various routes for the synthesis of 2-(2',3',4'-trimethoxyphenyl)-cyclohept-2-enone are described. As expected, this ketone acts as an acceptor in the Michael condensation.

In view of our interest in the synthesis of colchicine analogs,[2] the synthesis of 2-(2',3',4'-trimethoxyphenyl)-cyclohept-2-enone (IIb) was undertaken.

When cycloheptane-1,2-dione was treated with phenylmagnesium bromide it was possible to isolate 2-hydroxy-2-phenylcycloheptanone (Ia) which was characterized as the highly crystalline semicarbazone. The ketol was dehydrated by treatment with moderately concentrated sulfuric acid and gave the known 2-phenylcyclohept-2-enone (IIa).[2] It is of interest to note that it was not possible to obtain in strongly acid solution, the 2,4-dinitrophenylhydrazone, m.p. 116–117°, previously described although this may be obtained with Brady reagent and an alcoholic solution of the α,β-ethylenic ketone. The low-melting form was convertible to the high-melting form by means of strong acid in ethanolic solution.

Similarly, when cycloheptane-1,2-dione was treated with 2,3,4-trimethoxyphenyllithium, and the resulting mixture was fractionated in a high vacuum, it was possible to isolate 2-hydroxy-2-(2',3',4'-trimethoxyphenyl)-cycloheptanone (Ib) as a viscous oil which showed the presence of an alcoholic function (2.91 μ) and a ketonic function (5.95 μ), in its infrared absorption spectrum. However, it was not possible to dehydrate this ketol to the desired α,β-ethylenic ketone.

The ketone was ultimately obtained by selenium

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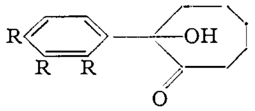
(2) D. Ginsburg and R. Pappo, THIS JOURNAL, **75**, 1094 (1953).

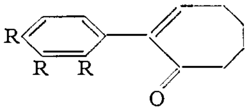
dioxide oxidation of 1-(2',3',4'-trimethoxyphenyl)-cycloheptene.[2] When the oxidation was carried out in acetic acid, the major product was 2-(2',3',4'-trimethoxyphenyl)-cyclohept-2-en-1-ol acetate, accompanied by the corresponding allylic alcohol and a small amount of the desired ketone. The liquid acetate was saponified and the resulting allylic alcohol could be oxidized with either aluminum *t*-butoxide in the presence of acetone or (in lower conversion) with active manganese dioxide.[3]

Alternatively, when selenium dioxide oxidation of the cycloheptene was carried out in aqueous dioxane solution, a somewhat higher proportion of ketone was obtained. The reaction mixture containing the ketone accompanied by allylic alcohol and unreacted olefin was refluxed with hydroxylamine hydrochloride in pyridine solution. After formation of the oxime of the ketonic fraction, the mixture was distilled with superheated steam. The oxime was not volatile and remained behind; acid hydrolysis then afforded the desired ketone. The allylic alcohol was separated from unreacted olefin through benzoylation followed by steam distillation. The benzoate was not volatile and the starting material could be obtained from the distillate. None of these preparative procedures were satisfactory from the point of view of direct conversion. Recycling, however, made available a sufficient quantity of 2-(2',3',4'-trimethoxyphenyl)-cyclohept-2-enone for further synthesis.

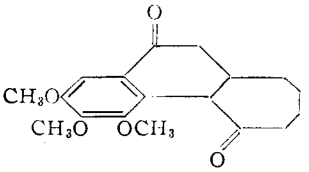
As anticipated, the α,β-ethylenic ketone acted as an acceptor in the Michael condensation and reacted with compounds containing active methylene groups. With diethyl malonate, for example, a liquid adduct was obtained. Upon acid hydrolysis and decarboxylation, followed by cyclization with anhydrous hydrogen fluoride, the expected tricyclic diketone III was obtained.



Ia, R = H
b, R = OCH_3



IIa, R = H
b, R = OCH_3



III

Experimental[4]

2-Hydroxy-2-phenylcycloheptanone.[5]—To phenylmagnesium bromide prepared from bromobenzene (15.7 g.) and magnesium (2.5 g.) in dry ether (50 ml.) was added cycloheptane-1,2-dione[6] (6.0 g.) with stirring and ice cooling, over a period of 1.5 hr. The mixture was allowed to stand overnight and was then decomposed with saturated ammonium chloride solution. After removal of the ether and a forerun, **2-hydroxy-2-phenylcycloheptanone** was obtained (6.2 g., 63%), b.p. 160–165° at 3 mm. The product was an oil which solidified on long standing in the refrigerator. It was characterized as the beautifully crystalline **semicarbazone**, m.p. 197–198° (from ethanol).

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.33; N, 16.08. Found: C, 64.16; H, 7.27; N, 16.00.

2-Phenylcyclohept-2-enone.—A mixture of the above ketol (5 g.), ethanol (50 ml.) and 50% sulfuric acid (5 ml.) was refluxed for 4 hr. After dilution and ether extraction, 2-phenylcyclohept-2-enone (3.8 g., 83%), b.p. 142–143° at 5 mm., was obtained; infrared absorption: 5.97 μ (C=O). The **2,4-dinitrophenylhydrazone** isolated directly from the above reaction mixture before its final work up had m.p. 181° dec. (from ethanol).

Anal. Calcd. for $C_{19}H_{18}N_4O_4$: C, 62.28; H, 4.95; N, 15.29. Found: C, 62.10; H, 5.07; N, 15.25.

This derivative is identical with the high melting form described by Ginsburg and Pappo,[2] m.p. 180–181° dec. The form melting at 116–117° may be converted into the high melting form by recrystallization from ethanol containing a sufficient amount of 50% sulfuric acid.

2-Hydroxy-2-(2',3',4'-trimethoxyphenyl)-cycloheptanone.—Pyrogallol trimethyl ether (168 g.) was metalated as described previously[2] and to the solution of the lithium derivative, cycloheptane-1,2-dione (59 g.) in ether (100 ml.) was added with stirring and ice-cooling, over a period of 4.5 hr. The mixture was poured into water after standing overnight. After removal of the ether and a lower boiling forerun, the **ketol** was obtained, b.p. 190–200° at 1 mm. (29 g.).

Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.01; H, 7.91.

Conditions similar to those used for the dehydration of the unmethoxylated ketol and other, more stringent, dehydration conditions failed to give the α,β-ethylenic ketone. Some demethylation occurred under acid conditions.

Selenium Dioxide Oxidation of 1-Phenylcycloheptene.—A mixture of the olefin[2] (25.8 g.), selenious acid (9.8 g.), glacial acetic acid (30 ml.) and acetic anhydride (5 ml.) was refluxed for 7–8 hr. After cooling, and dilution with water, the mixture was neutralized with cold sodium carbonate solution and extracted with ether. Distillation afforded a forerun (7.3 g.), b.p. 105–150° at 6 mm., and a fraction, b.p. 150–160° at 6 mm. (21.4 g.), whose infrared absorption spectrum indicated that it was largely 2-phenylcyclohept-2-en-1-ol acetate.

2-Phenylcyclohept-2-enone.—The acetate was saponified by refluxing for 4 hr. with excess alcoholic potassium hydroxide. The allylic alcohol thus obtained (17.5 g.) was dried over magnesium perchlorate, and oxidized in the usual way with acetone (200 ml.) and aluminum *t*-butoxide (38 g.) in benzene solution (600 ml.). After the usual workup, 2-phenylcyclohept-2-enone (13 g., 46%) was obtained. Its 2,4-dinitrophenylhydrazone, m.p. 181° dec., caused no m.p. depression on admixture with the derivative described above.

Selenium Dioxide Oxidation of 1-(2',3',4'-Trimethoxyphenyl)-cyclohexene.—From the olefin (12.4 g.), selenious acid (6.5 g.) in refluxing dioxane (7 hr.) after similar work-up, 2-(2',3',4'-trimethoxyphenyl)-cyclohex-2-enone, m.p. 54–57° (6.2 g., 47%) was obtained directly after seeding a heptane solution of the crude product with an authentic sample.[2] Recrystallization yielded material (5.3 g., 40%), m.p. and mixed m.p. 61–62° (from heptane).

Selenium Dioxide Oxidation of 1-(2',3',4'-Trimethoxyphenyl)-cycloheptene. (a) **In Acetic Acid.**—A mixture of the olefin[2] (13.1 g.) selenious acid (3.3 g.), glacial acetic acid (15 ml.) and acetic anhydride (3 ml.) was treated as described above. The crude acetate was obtained; infrared absorption: 5.82 μ (acetate C=O), 5.99 μ (very weak, unsaturated C=O). It was similarly saponified and oxidized by the Oppenauer method.

2-(2',3',4'-trimethoxyphenyl)-cyclohept-2-enone, b.p. 180–185° at 0.05 mm., was obtained as an oil (5.3 g., 38%); infrared absorption: 5.99 μ (C=O).

The **semicarbazone** had m.p. 174–175° dec. (from aqueous ethanol).

Anal. Calcd. for $C_{17}H_{25}N_3O_4$: C, 60.88; H, 7.51; N, 12.53. Found: C, 60.42; H, 7.12; N, 12.42.

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(3) *Cf.* O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, 2190 (1953). We are indebted to Dr. Franz Sondheimer and Syntex, S.A., for a generous quantity of this material.

(4) Melting points and boiling points are uncorrected.

(5) We are indebted to Dr. R. Pappo for the first preparation of this compound.

(6) R. W. Vander Haar, R. C. Voter and C. V. Banks, *J. Org. Chem.*, **14**, 837 (1949).

The brick-red **2,4-dinitrophenylhydrazone** had m.p. 121–123° dec. (from nitromethane).

Anal. Calcd. for $C_{22}H_{26}N_4O_7$: N, 12.22. Found: N, 12.48.

(b) **In Dioxane.**—The olefin (13.1 g.), selenious acid (6.5 g.) and dioxane (10 ml.) were refluxed for 8 hr. After the usual work-up, the crude product whose infrared spectrum showed that it contained both the allylic alcohol and the desired α,β-ethylenic ketone [2.92 μ (OH), 5.99 μ (C=O)], was dissolved in pyridine (50 ml.) and hydroxylamine hydrochloride (10 g.) and absolute ethanol (10 ml.) were added. The mixture was refluxed for 4 hr. and then subjected to steam distillation. The crude oxime of the desired ketone remained behind. Refluxing the oxime with dilute hydrochloric acid for 4 hr. and ether extraction afforded the ketone whose semicarbazone (6.4 g., 38%), had m.p. 174–175° dec. and was identical with the product described above.

Benzoylation of the portion volatile with steam, with an equal weight of benzoyl chloride in a tenfold weight of pyridine, permitted separation of the allylic alcohol from a small amount of unreacted olefin.

Steam distillation of the benzoylation mixture afforded only the olefin (1.6 g.) as the volatile fraction. The benzoate could be saponified with excess ethanolic potassium hydroxide and the resulting crude allylic alcohol (4.7 g.) could be oxidized further either by the Oppenauer method or the method described below.

Oxidation of 2-(2′,3′,4′-Trimethoxyphenyl)-cyclohept-2-en-1-ol with Active Manganese Dioxide.—The alcohol (1 g.), b.p. 170–173° at 5 mm., was dissolved in chloroform (25 ml.) and the solution was shaken with active manganese dioxide[3] for 24 hr. at room temperature. After removal of the inorganic material by filtration and the chloroform by distillation under vacuum, the residue was treated with semicarbazide hydrochloride in ethanol-pyridine. The semicarbazone of 2-(2′,3′,4′-trimethoxyphenyl)-cyclohept-2-enone (410 mg., 34%), m.p. and mixed m.p. 174–175°, was obtained.

1,2,3-Trimethoxy-6,6a,7,8,9,10,11,11a-octahydro-5,11-dioxo-5H-cyclohept[a]naphthalene. (a) Michael Condensation.—The conditions used were analogous to those previously described.[7] The ketone IIb (5 g.), ethyl malonate (8 g.) and potassium *t*-butoxide (prepared from 0.14 g. of potassium and 3 ml. of *t*-butyl alcohol) afforded after acid saponification and decarboxylation as described,[7] **3-oxo-2-(2′,3′,4′-trimethoxyphenyl)-cycloheptaneacetic acid** (4.4 g., 72%), as an oil.

Anal. Calcd. for $C_{18}H_{24}O_6$: neut. equiv., 336.4. Found: neut. equiv., 330.

(b) **Cyclization.**—The above acid (3.4 g.) was dissolved in anhydrous hydrogen fluoride. The tricyclic diketone III formed colorless needles (2.6 g., 81%), m.p. 110° (from petroleum ether).

Anal. Calcd. for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.59; H, 6.61.

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(7) D. Ginsburg and R. Pappo, *J. Chem. Soc.*, 938 (1951).

CAMBRIDGE 38, MASS.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Configuration of α-Methoxyadipic Acid

BY DONALD S. NOYCE AND JAMES H. CANFIELD

RECEIVED APRIL 5, 1954

α-Methoxyadipic acid has been prepared and resolved. From ethyl γ-chlorobutyrate and sodio-dimethylmalonate, there was obtained diethyl α-carboethoxyadipate, which by bromination, decarboxylation and replacement with methoxyl afforded α-methoxyadipic acid. (+)α-Methoxyadipic acid afforded (+)2-methoxy-1,6-hexanediol on reduction with lithium aluminum hydride, whose bis-tosylate on further reduction afforded (+)2-methoxyhexane, which has been configurationally related to glyceraldehyde.

Current interest in the absolute configuration of broad series of natural products has produced a great deal of progress in recent years.[1–4] We have been interested in effecting a direct chemical relationship between the sugars (glyceraldehyde) and the monoterpenes. Such a relationship involving the common reference compound (−)*cis*-3-hydroxycyclohexanecarboxylic acid (I) has been undertaken. The degradation of (−)-I to (+)3-methylcyclohexanone (II) has been reported previously,[5] and more recently the degradation of (−)-I to (−)α-methoxyadipic acid (III).[6] The present report is concerned with the last stage of the stereochemical interrelationship, that of relating (−)α-methoxyadipic acid to glyceraldehyde.

For the preparation of III the method reported by von Braun and Meyer[7] for the preparation of α-bromoadipic acid (IV) has been used with some modification. Treatment of γ-butyrolactone with ethanolic hydrogen chloride afforded ethyl γ-chlorobutyrate (V) in 91% yield. When V was allowed to react with sodiomalonic ester, catalyzed by sodium iodide,[8] diethyl α-carboethoxyadipate (VI) was obtained in 73% yield. VI was hydrolyzed to the malonic acid, which was treated with one mole of bromine, and decarboxylated to afford α-bromoadipic acid (IV). Esterification of IV with diazomethane and treatment with sodium methoxide in methanol afforded dimethyl α-methoxyadipate (VII), which was thence hydrolyzed to α-methoxyadipic acid (*dl*-III).

The resolution of III proved reasonably tedious. Using the cinchonidine salt, the (−)-form concentrated in the head fractions, and after several crystallizations, nearly completely resolved (−)-III was obtained after cleavage of the salt. This material proved to be identical with that obtained previously by the degradation of (−)-I,[6] by comparison of the infrared spectra of the Nujol mulls, whereas the spectrum of *dl*-III differed in details.

Reduction of (−)-III afforded (−)2-methoxy-1,6-hexanediol ((−)-VIII). Formation of the bis-*p*-toluenesulfonate and reduction with lithium alu-

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(1) A. Fredga, "The Svedberg Memorial Volume," Almquist and Wiksells, Boktryckeri, Upsala, 1944. p. 261; see also *Acta Chem. Scand.*, **1**, 361 (1947).

(2) S. Bergstrom, A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **32**, 3, 1613, 1617, 2003 (1949).

(3) W. G. Dauben, D. F. Dickel, O. Jeger and V. Prelog, *ibid.*, **36**, 325 (1953).

(4) A. Furst, O. Jeger, R. B. Woodward, *et al.*, THIS JOURNAL, **76**, 314 (1954).

(5) D. S. Noyce and D. B. Denney, *ibid.*, **74**, 5912 (1952).

(6) D. S. Noyce and D. B. Denney, *ibid.*, **76**, 768 (1954).

(7) J. von Braun and F. Meyer, *Ber.*, **74**, 19 (1941).

(8) U. S. Patent 2,415,261; *C. A.*, **41**, 3119 (1947).