IIc, and this is primarily because of the interaction of the oxygen with the nearby hydrogen atom.

EXPERIMENTAL

5α,6α-Epoxycholestane. Cholesterol was converted to cholesteryl chloride[16] m.p. 96–98° with thionyl chloride. Reduction of the chloride with sodium and alcohol[17] gave cholest-5-ene, m.p. 89–91°. To 25 g. of this olefin in 150 ml. of ether was added dropwise a slight excess of monoperphthalic acid[18] in ether. The solution was allowed to stand for 3 hr., during which time additional monoperphthalic acid was added as indicated by testing with starch-iodide paper. The reaction mixture was then poured into water, the ether layer was separated, washed with water, dilute sodium bicarbonate solution and water. The ether was evaporated and the epoxide was crystallized from absolute ethanol, wt. 17.7 g., m.p. 76–76.2°.

Coprostan-6-one. The rearrangement of the epoxide was carried out with boron trifluoride–etherate [19] The chromatography was carried out using Merck acid-washed alumina which had been washed well with distilled water and activated by heating at 110° for 24 hr. Crystallization of the product from methanol gave the ketone, m.p. 132–133°.

Cholestan-6-one. The procedure used was the same as that described for the preparation of coprostan-6-one, except the material was chromatographed on basic alumina; yield 35%, m.p. 98–99°.

Coprostan-4-one.[20] This compound was obtained by rearrangement of the 4α,5α-epoxide,[19] needles, m.p. 104–106.5.° The purest sample used for the rotatory dispersion measurements had a m.p. of 108–109°.

Cholestane-4-one.[20] Sodium borohydride, 0.095 g., was dissolved in 5 ml. of diglyme, and to the stirred solution was added cautiously 0.212 g. of anhydrous aluminum chloride followed by 2.0 g. of Δ^4-cholestene. After 4 hr. the mixture was poured into water and the product was extracted with ether. The ether solution was washed with water and dilute bicarbonate solution. The ether was evaporated and to the residue was added 50 ml. of 2*N* sodium hydroxide in aqueous methanol followed by 5 ml. of 30% hydrogen peroxide. The solution was stirred for 15 min., diluted with water and extracted with ether. The ether extracts were washed with water, acidified potassium iodide solution, dilute sodium bicarbonate, and water. The solvent was evaporated and the residue was taken up in 75 ml. of acetic acid. A solution of 0.5 g. of chromium trioxide in 90% acetic acid was added and the mixture was allowed to stand for 5 hr. Benzene was then added and the mixture was stirred for 3 hr. The benzene layer was separated, washed with bicarbonate solution and water, and the benzene was evaporated. Chromatography of the residual oil on basic alumina gave .43 g. of product, m.p. 96–99.5°.

The same compound was obtained by chromatography of coprostan-4-one on basic alumina. The purest sample used for the rotatory dispersion measurements had a m.p. of 95.5–96°.

Rotatory dispersion measurements. The equipment and general procedure was described earlier.[7a] The curves for the compounds were all in reasonable agreement with those reported in the literature.[15] For the present equilibration studies rotations of the 6-ketones were measured at 318 mμ and those of the 4-ketones at 315 mμ utilizing a xenon light source. Equilibrium was approached from both sides by letting each compound stand 24 hr. in 0.4*N* potassium hydroxide solution in methanol. No change in the equilibrium point occurred after an additional 24 hr. The equilibrium point for the 4-ketones was 99.1 ± 2% *trans*, while that for the 6-ketones was 88.4 ± 2% *trans*.

DETROIT 2, MICH.

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[16] H. Schmid and K. Kagi, *Helv. Chem. Acta.*, **33**, 1582 (1950).

[17] J. Mauthner and W. Suida, *Monatsh.*, **17**, 579 (1896).

[18] L. F. Fieser, *Experiments in Organic Chemistry*, 3rd ed., revised, D. C. Heath, Boston, p. 329.

[19] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596 (1957).

[20] The authors are also indebted to Dr. Carl Djerassi, Stanford University, for samples of this compound.

[CONTRIBUTION FROM THE DEPARTMENTS OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF KANSAS AND UNIVERSITY OF WISCONSIN]

Stereochemistry of the Cyclization of the Half-Esters of Diarylitaconic Acid

E. E. SMISSMAN, P. S. PORTOGHESE, AND R. A. MODE

Received April 3, 1961

The stereochemistry of the products obtained by the Stobbe condensation of 3,4-methylenedioxy-3′,4′,5′-trimethoxybenzophenone with dimethyl succinate and the dihydro-Stobbe products is proven. The conformational implications derived by a study of the cyclization of the dihydro-Stobbe products are discussed.

In the course of our investigation of certain lignans derived from podophyllin (*Podophyllum peltatum*) we wanted to prepare a quantity of 3-carbomethoxy-4-(3′,4′,5′-trimethoxyphenyl)-6,7-methylenedioxy-1-tetralone (Va), previously synthesized by Walker[1] and Gensler.[2]

From the Stobbe condensation of 3,4-methylenedioxy-3′,4′,5′-trimethoxybenzophenone with dimethyl succinate, we have isolated half-esters of diarylitaconic acid, Ia and Ib. Catalytic hydrogenation to the dihydro half-esters IIIa and IIIb and subsequent cyclization *via* the acid chloride afforded the respective tetralones, Va and Vb.

The tetralone, Va, which we prepared melted 5° higher than the reported[2] compound. This prompted us to investigate the geometry of the Stobbe isomers as well as the structures of the cyclized products Va and Vb. Heating Ib in the presence of acetic anhydride and anhydrous sodium acetate produced 1-acetoxy-3-carbomethoxy-4-(3′,4′,5′-trimethoxyphenyl)-6,7-methylenedioxynaphthalene,

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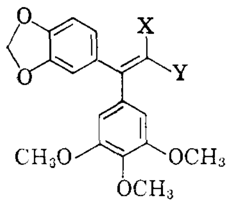
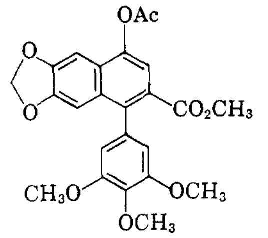
[1] G. N. Walker, *J. Am. Chem. Soc.*, **75**, 3390 (1953).

[2] W. J. Gensler, C. M. Samour, S. Y. Wang, and F. Johnson, *J. Am. Chem. Soc.*, **82**, 1714 (1960).

II,[3] in good yield. Alkaline permanganate oxidation of II gave 3,4,5-trimethoxybenzoic acid, VI. The oxidation product VI indicated that ring closure proceeded only by cyclization into the methylenedioxyphenyl ring. This is in agreement with the structure of Stobbe isomer Ib. On this basis the alternate geometric structure Ia was assigned.



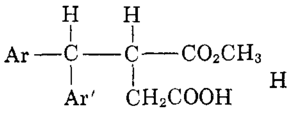
I



II

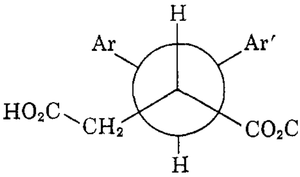
(a) $x = CO_2CH_3$, $Y = CH_2{-}CO_2H$
(b) $x = CH_2CO_2H$, $Y = CO_2CH_3$

Since catalytic hydrogenation proceeds with *cis* addition, the diasterioisomeric dihydro-Stobbe products have structures IIIa and IIIb. An examination of the Newman projection formulas for both isomers suggests that the geometry of the most energetically favorable transition state in the cyclization process will be similar to conformations IVa and IVb. On this basis we predicted IVa would cyclize into the methylenedioxyphenyl ring to yield the tetralone Va and that similar compelling conformational forces would operate in IVb to afford the structure Vb. These conclusions were borne out by the oxidation products, trimethoxybenzoic acid, VI, and trimethoxyphthalic anhydride, VII, which were obtained from Va and Vb respectively. Thus, it is of interest that the incipient *o*-methoxy group in IVb did not prevent the approach of the acylonium ion in the formation of tetralone, Vb. Gensler[2] has found that the anhydride, VIII, yielded the indanone, IX, as the exclusive product. In this case, though there is a possibility of two reaction products (IX or the acid corresponding to Vb), steric compression exerted by the methoxyl groups will be large enough to favor the formation of the indanone, IX. The conditions under which we conducted the cyclization of IVb precluded the formation of the indanone IX. Compound Vb exhibited an infrared absorption at 5.96 μ which is consistent with an α-tetralone system.[4] Further evidence for the *trans*-3-carbomethoxy-4-aryl groups in Va and Vb was furnished when the compounds were recovered unchanged upon prolonged treatment with base. If the groups were oriented in a *cis* manner, epimerization at C-3 would have occurred.[5,6]



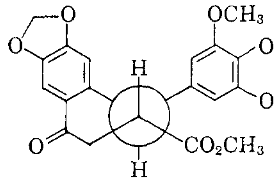
$\mathrm{Ar{-}\overset{H}{\underset{Ar'}{C}}{-}\overset{H}{\underset{CH_2COOH}{C}}{-}CO_2CH_3}$

III

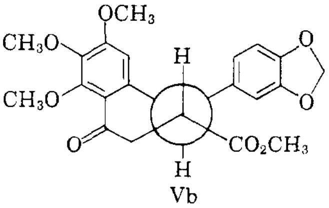


IV

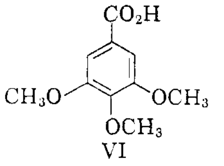
(a) Ar = 3,4-methylenedioxyphenyl
Ar′ = 3′,4′,5′-trimethoxyphenyl
(b) Ar = 3′,4′,5′-trimethoxyphenyl
Ar′ = 3,4-methylenedioxyphenyl



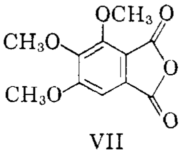
Va



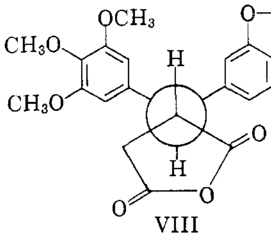
Vb



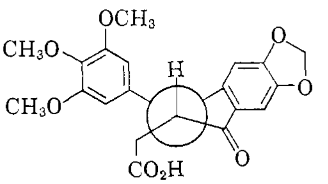
VI



VII



VIII



IX

EXPERIMENTAL

3,4-Methylenedioxy-3′,4′,5′-trimethoxydiphenylitaconic acid monomethyl ester (Ia and Ib). The procedure used was similar to that of Johnson and Miller.[7] A total of 16.2 g. (0.41 g.-atom) of potassium was added in divided portions to anhydrous *t*-butyl alcohol (390 ml.). After the potassium had dissolved, 80.5 g. (0.44 mole) of dimethyl succinate was added to the solution. A portion of this mixture (50 ml.) was added to the reaction flask containing 3,4-methylenedioxy-3′,4′,5′-trimethoxybenzophenone[3] 24.3 g., (0.077 mole). The remainder was added with continuous stirring over a period of 2 hr. at 60°. The mixture was then heated at the same temperature for an additional 5 hr. After cooling, 1:1 hydrochloric acid was added to acidify the solution. The *t*-butyl alcohol was removed from the mixture *in vacuo* and the remaining aqueous solution extracted with several portions of ethyl acetate. The organic phase was washed with distilled water and extracted with 5% sodium bicarbonate solution. The combined bicarbonate extracts were acidified

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(3) F. G. Baddar, L. S. El-Assal, and V. B. Baghos, *J. Chem. Soc.*, 1714 (1955).

(4) D. Lednicer and C. R. Hauser, *J. Am. Chem. Soc.*, **80**, 3409 (1958).

(5) G. N. Walker, *J. Am. Chem. Soc.*, **75**, 3393 (1953).

(6) A. W. Schrecker and J. L. Hartwell, *J. Am. Chem. Soc.*, **75**, 5916 (1953).

(7) W. S. Johnson and M. W. Miller, *J. Am. Chem. Soc.*, **72**, 511 (1950).

and the resulting oil extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated to dryness. The weight of the solid acid residue was 33.1 g. (100% crude yield).

The crude mixture was dissolved in boiling ethyl acetate. After cooling the solution to room temperature, it was maintained at 5° for 12 hr. The crude Stobbe isomer Ia (10.1 gm.), m.p. 160–178° was collected by filtration. After four recrystallizations from ethyl acetate the melting point was 188–189°. Further recrystallization failed to alter the melting point.

Anal. Calcd. for $C_{22}H_{22}O_9$: C, 61.39; H, 5.15. Found: C, 61.26; H, 5.22.

The infrared absorption spectrum showed bands at 5.79 μ (unconjugated ester) and 5.90 μ (α,β unsaturated acid). The ultraviolet absorption $\lambda_{\max}^{C_2H_5OH}$ 295, mμ ε 12,120.

The mother liquor containing Stobbe isomer Ib was concentrated and 12.5 g. of crude Ib (m.p. 140–146°) crystallized from the solute. After several recrystallizations from ethyl acetate the melting point of Ib was 147–148.5°.

Anal. Calcd. for $C_{22}H_{22}O_9$: C, 61.39; H, 5.15. Found: C, 61.14; H, 5.23.

The infrared spectrum was almost identical to that of Ia. The ultraviolet absorption showed $\lambda_{\max}^{C_2H_5OH}$ 297, ε 13,000.

1-Acetoxy-3-carbomethoxy-4-(3',4',5'-trimethoxyphenyl)-6,7-methylenedioxynaphthalene (II). The Stobbe isomer, Ib, (2.18 g., 0.005 mole) was cyclized by refluxing for 5 hr. in 25 ml. of acetic anhydride containing 0.53 g. (0.006 mole) of anhydrous sodium acetate. After cooling to room temperature the excess acetic anhydride was decomposed with a solution of sodium carbonate. The solid which separated was extracted with ethyl acetate, washed with sodium carbonate solution, and with water. After drying over anhydrous magnesium sulfate the ethyl acetate extract was concentrated to 20 ml. Upon standing overnight at 0–5°, there was obtained 1.91 g. (84%) of crystalline product, m.p. 205–206°. Further recrystallization did not alter the melting point.

Anal. Calcd. for $C_{24}H_{22}O_9$: C, 63.43; H, 4.88. Found: C, 63.74; H, 5.04.

The infrared spectrum showed carbonyl absorption bands at 5.70 μ and 5.81 μ.

3,4-Methylenedioxy-3',4',5'-trimethoxybenzhydrylsuccinic acid monomethyl ester (IIIa and IIIb). One gram (2.3 moles) of Stobbe isomer Ia was dissolved in 50 ml. of glacial acetic acid containing 10 drops of 70% perchloric acid. After addition of 0.2 g. of 10% palladium on charcoal the mixture was stirred at room temperature at a pressure of 1 atm. of hydrogen until a theoretical amount of hydrogen was absorbed. The hydrogenation mixture was filtered and sodium bicarbonate was added to neutralize the perchloric acid. Most of the glacial acetic acid was removed *in vacuo*. Water was added and the mixture extracted several times with ethyl acetate. After drying the ethyl acetate extracts over magnesium sulfate, the ethyl acetate was removed and the oily residue, after crystallization from benzene–petroleum ether (b.p. 60–68°) yielded 0.76 g. (76%) of IIIa, m.p. 143–145.° After several recrystallizations from ethyl acetate the melting point was 145–146.5°. The compound was converted to its dimethyl ester, m.p. 92.5–93.5°.

Anal. Calcd. for $C_{23}H_{26}O_9$: C, 61.87; H, 5.87. Found: C, 61.80, 61.89; H, 5.82, 6.17.

The infrared spectrum in chloroform showed bands at 5.76 μ (ester) and 5.82 μ (acid). The ultraviolet absorption exhibited a maximum at 289 mμ, ε 4900.

One gram (2.3 mmoles) of Stobbe isomer Ib was hydrogenated using the above procedure. Several recrystallizations from benzene–petroleum ether afforded 0.70 g. (70%) of dihydro Stobbe compound (IIIb), m.p. 86–89°.

Anal. Calcd. for $C_{22}H_{24}O_9$: C, 61.10; H, 5.59. Found: C, 60.85; H, 5.60.

The infrared spectrum included bands at 5.77 μ (ester) and 5.82 μ (carboxyl group). The ultraviolet absorption in ethanol showed a maximum at 287 mμ, ε 4600.

Hydrogenation of Ia and Ib in ethyl acetate also gave rise to IIIa and IIIb respectively. The rates of hydrogenation appeared to be enhanced when conducted in acid medium.

3-Carbomethoxy-4-(3',4',5-trimethoxyphenyl)-6,7-methylenedioxy-1-tetralone (Va). Enough 0.5*N* sodium hydroxide was added to 3.4 g. (0.008 mole) of dihydro Stobbe compound IIIa to produce a pink color with phenolphthalein. This solution was lyophyllized and the fluffy sodium salt heated at 60° *in vacuo* for 24 hr. Dry benzene (50 ml.) was added to the lyophyllized material and the mixture cooled in ice. Four drops of pyridine was added to the mixture followed by 2.5 ml. (0.029 mole) of oxalyl chloride.[8] After standing for 5 min. the excess oxalyl chloride was removed *in vacuo* and an additional quantity of dry benzene was added to bring the total volume to 50 ml. The chilled benzene mixture was treated with 1.6 ml. (0.014 mole) of stannic chloride. An orange complex immediately developed. After standing in an ice bath for an additional 10 min., the product was poured into a mixture of 50 g. of ice and 50 ml. of concd. hydrochloric acid. The mixture was extracted three times with ethyl acetate. The organic phase was washed with concentrated hydrochloric acid, water, and sodium bicarbonate solution. After drying over anhydrous magnesium sulfate the extract was evaporated to 25 ml. On cooling to room temperature there was obtained 1.72 g. (52%) of fluffy needles, m.p. 183–183.5.°

Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.85; H, 5.52.

The infrared spectrum showed bands at 5.78 μ (ester) and 5.98 μ (tetralone).

3-Carbomethoxy-4-(3',4'-methylenedioxyphenyl)-6,7,8-trimethoxy-1-tetralone (Vb). The dihydro Stobbe compound IIIb (4.7 g., 0.011 mole) was cyclized employing the above procedure. After several unsuccessful attempts at crystallization the oily tetralone was passed through a silicic acid–chloroform chromatographic column. The chloroform eluant was evaporated to an oil which crystallized from benzene-ether (2.09 g., 46%), m.p. 134–135°. After three recrystallizations the compound melted at 135.5–136.5°. No change in melting point was observed on further recrystallization.

Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.30; H, 5.47.

The infrared spectrum exhibited bands at 5.75 and 5.96 μ.

Oxidation of 1-acetoxy-3-carbomethoxy-4-(3',4',5'-trimethoxyphenyl)-6,7-methylenedioxynaphthalene (II). The naphthalene compound (0.50 g., 0.0011 mole) was heated on a steam bath with 10 ml. of 1*N* sodium hydroxide until the solution was clear, after which a 4% potassium permanganate solution was slowly added with stirring and continued heating until the permanganate color persisted for at least 10 min. After cooling, the mixture was filtered, acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The organic phase was dried with anhydrous sodium sulfate and evaporated to a brown solid residue. This solid was found too impure to be crystallized directly and was chromatographed on a silicic acid–chloroform column. The first fraction eluted from the column crystallized on evaporation of the chloroform. Recrystallization from ether–petroleum ether afforded crystals, m.p. 167–168°. Admixture with authenic sample of 3,4,5-trimethoxybenzoic acid gave no depression in melting point, 168.5–169.5°. The infrared spectrum of the degradation product was superimposable with that of 3,4,5-trimethoxybenzoic acid.

Oxidation of 3-carbomethoxy-4-(3',4',5'-trimethoxyphenyl)-6,7-methylenedioxy-1-tetralone, (Va). The tetralone, Va, (0.50 g., 0.0012 mole) was oxidized in a manner identical to the oxidation of II. In this case the solid residue was crystallized without the aid of absorption chromatography. Recrystallization from ether–petroleum ether gave needles melting at 169–170°. On admixture with 3,4,5-trimethoxy-

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[8] A. L. Wilds and C. H. Shunk, *J. Am. Chem. Soc.*, **72**, 2388 (1950).

benzoic acid no depression in melting point was observed, m.p. 170–171°. The infrared spectra were also superimposable.

Oxidation of 3-carbomethoxy-4-(3′,4′-methylenedioxyphenyl) 6,7,8-trimethoxy-1-tetralone, (Vb). The oxidations of 0.5 g. (0.0012 mole) of tetralone, Vb, was conducted in a manner identical to the oxidation of compound II. Difficulties were encountered in the purification of the oily oxidation product as it resisted all attempts at purification by fractional crystallization and column chromatography. Sublimation of the oil at 100°/0.01 mm. afforded a quantity of crystalline material. Recrystallization from ether gave needles, m.p. 144–146°, which did not depress the melting point of 3,4,5-trimethoxyphthalic anhydride on admixture. The infrared spectra were superimposable.

Attempted epimerization of 3-carbomethoxy-4-(3′,4′,5′-trimethoxyphenyl) - 6,7 - methylenedioxy - 1 - tetralone, (Va). The tetralone (0.20 g.) was dissolved in 5 ml. of dry pyridine and heated for 24 hr. at 100°. The pyridine was removed and after crystallization from ethyl acetate, 0.19 g. of tetralone, m.p. 183–183.5°, was recovered. When admixed with starting material no melting point depression was observed.

Attempted epimerization of 3-carbomethoxy-4-(3′,4′-methylenedioxyphenyl)-6,7,8-trimethoxy-1-tetralone, (Vb). The tetralone IVb (0.20 g.) was subjected to the same conditions as compound IVa. The material was crystallized from benzene-ether. The recovered tetralone, 0.18 g., m.p. 135–135.5° produced no melting point depression when admixed with starting material.

Acknowledgment. We wish to thank the National Science Foundation for a grant in support of this work.

LAWRENCE, KAN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, EVANS CHEMICAL LABORATORY, THE OHIO STATE UNIVERSITY]

The *ortho*-Claisen Rearrangement. V. The Products of Rearrangement of Allyl *m*-X-Phenyl Ethers[1]

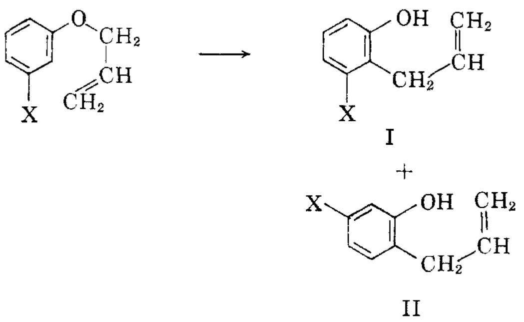
WILLIAM N. WHITE AND CARL D. SLATER[2,3]

Received January 5, 1961

Isotope dilution analysis has been applied to determine the percentages of 2-allyl-5-X-phenol formed during the Claisen rearrangement of six allyl *m*-X-phenyl ethers.

The effect of substituents on the rearrangement of allyl aryl ethers has been investigated extensively.[4–7] These studies have led to a definition of the stereochemical[7] and electrical[6] nature of the transition state of this rearrangement. However, the isomerization of allyl *m*-X-phenyl ethers has not been systematically examined, and the scanty information which is available[5] indicates these compounds may behave somewhat anomalously. Therefore, it seemed probable that an investigation of the Claisen rearrangement of allyl *m*-X-phenyl ethers would lead to information more clearly delineating the electronic character of this reaction.

As a first phase of this study, it was deemed desirable to determine the distribution of isomers resulting from reaction of an allyl *m*-X-phenyl ether. This question has been investigated only superficially in the past. Previous results are summarized in Table I.



In the case of the methoxy, hydroxy and trifluoromethyl substituents the structure of the product indicated was established. The yields, however, are not sufficiently high to exclude the possibility of significant quantities of the other isomer having been formed, but lost in the work-up. Some work with allyl *m*-acetamidophenyl ether is interesting in this respect. Arnold and co-workers[8] report that only the 5-acetamido product was obtained. The structure was proven and its melting point was given as 160.5–162°. On the other hand, Budesinsky and Rockova[9] performed the rearrangement under identical condi-

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[1] This investigation was supported by research grant NSF-G7345 from the National Science Foundation.

[2] Monsanto Fellow, 1959–60; Ethyl Corp. Fellow, 1958–59.

[3] From the thesis submitted by Carl D. Slater in partial fulfillment of the requirements for the Doctor of Philosophy Degree at the Ohio State University.

[4] W. N. White, D. Gwynn, R. Schlitt, C. Girard, and W. Fife, *J. Am. Chem. Soc.*, **80**, 3271 (1958).

[5] H. Goering and R. R. Jacobson, *J. Am. Chem. Soc.*, **80**, 3278 (1958).

[6] W. N. White and W. K. Fife, *J. Am. Chem. Soc.*, **83**, 3846 (1961).

[7] (a) E. N. Marvell and J. L. Stephenson, *J. Org. Chem.*, **25**, 676 (1960); (b) A. W. Burgstahler, *J. Am. Chem. Soc.*, **82**, 4681 (1960); (c) W. N. White and B. E. Norcross, *J. Am. Chem. Soc.*, **83**, 1968 (1961); (d) L. D. Huestis and L. J. Andrews, *J. Am. Chem. Soc.*, **83**, 1963 (1961).

[8] R. T. Arnold, J. McCool, and E. Schultz, *J. Am. Chem. Soc.*, **64**, 1023 (1942).

[9] Z. Budesinsky and R. Rockova, *Chem. Listy*, **48**, 427 (1954); *Chem. Abstr.*, **49**, 3880 (1955).