[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

Elimination Reactions of Bicyclic Quaternary Salts. III. γ-Tropolone from Some Appropriately Substituted Tropanes

BY J. MEINWALD AND O. L. CHAPMAN[1]

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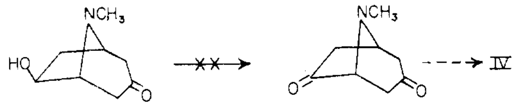
Some unsuccessful efforts to prepare γ-tropolone (IV) *via* 6β-hydroxytropinone (V) are described briefly. The base degradation of teloidinone methobromide (VII) has been found to give IV in fair yield. The degradation of a number of closely related compounds also has been studied; 6β,7β-dimethoxytropinone methobromide (X) was found to yield γ-tropolone methyl ether (XI) almost quantitatively. These results, coupled with Heusner's excellent synthesis of X and the known acid hydrolysis of XI to IV, open practical, preparative routes to both γ-tropolone and its methyl ether.

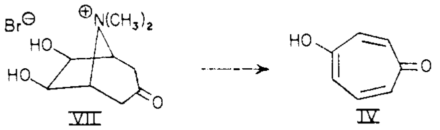
Recent studies on the elimination reactions of tropinone methiodide (I)[2] and 6β-hydroxytropinone methiodide (II)[3] to give a mixture of cycloheptadienones and tropone (III), respectively, have made it clear that tropane derivatives may serve as quite flexible precursors for a variety of troponoid compounds. In connection with an interest in studying some reactions of γ-tropolone (IV), we have investigated several possible synthetic routes to IV starting from appropriate bicyclic precursors.[4]

The first attack on this problem involved the oxidation of 6β-hydroxytropinone (V) to the corresponding ketone VI, the methiodide of which should be readily convertible to IV by a process consisting of two β-elimination reactions followed by enolization. This attack was never effectively launched, as a result of our inability to accomplish the requisite oxidation of V to VI. A large number of experiments using (1) chromic oxide under a variety of conditions, (2) the Oppenauer method or (3) N-bromoacetamide resulted either in the recovery of unchanged starting material or else in the formation of products which could not be characterized.[5] This approach was abandoned, therefore, in favor of a study of the elimination reactions of the equally attractive precursor, teloidinone methobromide (6β,7β-dihydroxytropinone methobromide, VII).[6]



V VI

The initial experiments with VII were encouraging, and have been reported in a preliminary communication.[7] A 45% yield of γ-tropolone could be observed to form in dilute, basic solution, according to the equation shown below. However, on a preparative scale, the isolable yield was only half as good.[7] This study has therefore been extended, and we now wish to report the course of the elimination reactions of the methobromides of teloidinone acetonide (VIII), 6β-hydroxy-7β-methoxytropinone (IX) and 6β,7β-dimethoxytropinone (X). Table I summarizes the outcome of these experiments. The data for teloidinone methobromide have been included for completeness. The yields are based on the intensity of the 360 mμ absorption maximum of the γ-tropolone anion.[4]



VIII IV

TABLE I

Compound	Conditions	Yield of γ-tropolone, %
Teloidinone methobromide (VII)	1, $NaHCO_3$ in H_2O	45
Teloidinone methobromide (VII)	2, $Ba(OH)_2$ in H_2O (dil.)	45
Teloidinone methobromide (VII)	3, $Ba(OH)_2$ in H_2O (concd.)	24
Teloidinone methobromide (VII)	4, Anhydrous pyridine	23
Teloidinone acetonide methobromide (VIII)	1, $NaHCO_3$ in H_2O	41
Teloidinone acetonide methobromide (VIII)	2, $NaHCO_3$ in H_2O, then acid	41
6β-Hydroxy-7β-methoxytropinone methobromide (IX)	1, $NaHCO_3$ in H_2O	48
6β-Hydroxy-7β-methoxytropinone methobromide (IX)	2, $NaHCO_3$ in H_2O, then acid	66
6β,7β-Dimethoxytropinone methobromide (X)	1, $NaHCO_3$ in H_2O	~100[a]
6β,7β-Dimethoxytropinone methobromide (X)	2, $NaHCO_3$ in H_2O, then acid	91

[a] γ-Tropolone methyl ether.

Degradation of the acetonide VIII gave γ-tropolone directly, albeit in yields which were no better than those obtained using VII. Some improvement could be realized in the case of the monomethoxy compound IX, where the initial yield could be increased by mild acid hydrolysis of the product. In this instance, it is apparent that γ-tropolone methyl ether (XI) is formed along with VI. This is in no way surprising, and simply indicates that the methoxyl and hydroxyl groups are lost with roughly comparable ease. Degradation of X, the last case studied, yields γ-tropolone methyl ether (XI) nearly quantitatively. This reaction has made possible the preparation of XI

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[1] American Viscose Fellow, summer 1956; Procter and Gamble Fellow, 1956-1957; Dow Chemical Co. Fellow, summer 1957.

[2] J. Meinwald, S. L. Emerman, N. C. Yang and G. Büchi, THIS JOURNAL, **77**, 4401 (1955).

[3] E. E. van Tamelen, P. Barth and F. Lornitzo, *ibid.*, **78**, 5442 (1956).

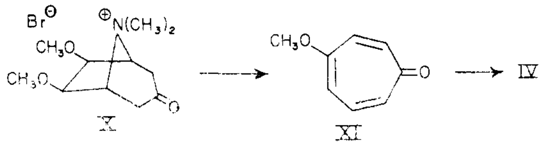
[4] The first synthesis of IV was achieved by T. Nozoe, T. Mukai, Y. Ikegama and T. Toda, *Chemistry & Industry*, 66 (1955). Shortly thereafter, R. S. Coffey, R. B. Johns and A. W. Johnson, *ibid.*, 658 (1955), completed another synthesis.

[5] In the interest of brevity, details of these attempts have been omitted.

[6] Teloidinone is available by total synthesis using the Robinson–Schöpf "biosynthetic" technique. The procedure leading to teloidinone was first developed by C. Schöpf and W. Arnold, *Ann.*, **558**, 109 (1947). A more convenient preparation is described by J. C. Sheehan and B. M. Bloom, THIS JOURNAL, **74**, 3825 (1952).

[7] J. Meinwald and O. L. Chapman, *ibid.*, **78**, 4816 (1956).

in quantity, since X is readily available by the method of Heusner.[8] In view of the ready acid hydrolysis of XI to IV,[9] X appears to be the precursor of choice for either γ-tropolone or its methyl ether.



Acknowledgment.—The authors are deeply indebted to Dr. Alex Heusner, C. H. Boehringer Sohn, Germany, for a sample of 6β-hydroxy-7β-methoxytropinone as well as for a generous gift of 6β,7β-dimethoxytropinone methobromide. They also wish to thank the Research Corporation for the partial support of this research program through a Frank Gardner Cottrell grant.

Experimental

Oxidations of 6β-Hydroxytropinone (V).—Ten experiments were carried out in an attempt to obtain VI. The chromic acid oxidations were worked up by making the solutions basic with potassium carbonate, saturating the basic solution with salt, and continuously extracting with ether. The Oppenauer and N-bromoacetamide oxidations were worked up in the usual manner with the final step being the same as for the chromic acid oxidations. The oxidations of 6β-hydroxytropinone methiodide were worked up by adding acetone to precipitate the inorganic material, filtering, and evaporating the aqueous acetone to dryness.

Teloidinone Acetonide Methobromide (VIII).—Teloidinone acetonide[10] (0.9 g.) in 10 ml. of methanol was treated with excess methyl bromide. After standing overnight in the refrigerator, the solution was evaporated to dryness *in vacuo*, giving a white, crystalline solid which showed only very slight absorption at 2.95 μ. Recrystallization from methanol–ethanol gave white crystals which when placed on a melting stage preheated to 180° darkened above 210° and melted with severe decomposition at 237–238°.

Anal. Calcd. for $C_{12}H_{20}O_3NBr$: C, 47.10; H, 6.54; N, 4.58; Br, 26.20. Found: C, 46.88; H, 6.40; N, 4.65; Br, 26.41.

6β-Hydroxy-7β-methoxytropinone Methobromide (IX).—A solution of 175 mg. of analytically pure 6β-hydroxy-7β-methoxytropinone[8] in 2 ml. of methanol was treated with excess methyl bromide. After standing overnight in the refrigerator, the solution was evaporated to dryness *in vacuo*, giving 252 mg. of white, crystalline product, m.p. 183–185°.

6β,7β-Dimethoxytropinone Methobromide (X).—The 6β,7β-dimethoxytropinone methobromide used in these experiments was made available to us through the courtesy of Dr. A. Heusner. It was prepared from 6β,7β-dimethoxytropinone, the synthesis of which has already been reported.[8] The following data for 6β,7β-dimethoxytropinone methobromide were supplied by its donor. Recrystallization of X from methanol–isopropyl alcohol (2:1) gives colorless plates, m.p. 207–208° dec. The melting point is to some extent dependent on the rate of heating.

Anal. Calcd. for $C_{11}H_{20}O_3NBr$: C, 44.91; H, 6.85; N, 4.76; Br, 27.16; CH_3O, 21.10. Found: C, 44.69; H, 6.95; N, 4.76; Br, 27.52; CH_3O, 20.77.

Degradation of Teloidinone Acetonide Methobromide (VIII).—A solution of teloidinone acetonide methobromide (7.7 mg., 0.025 mmole) and sodium bicarbonate (4.2 mg., 0.05 mmole) in 50 ml. of distilled water was heated on a steam-bath. Aliquot samples were withdrawn every 30 minutes, diluted to a suitable concentration with 0.1 *N* sodium hydroxide, and the intensity of absorption at 360 mμ determined. After 120 minutes, the intensity of the 360 mμ absorption maximum did not increase. The analysis indicated a 41% yield of γ-tropolone. Five ml. of 48% hydrobromic acid was added, and the solution was heated on a steam-bath for several hours. This did not increase the yield of IV.

Degradation of 6β-Hydroxy-7β-methoxytropinone Methobromide (IX).—A solution of 6β-hydroxy-7β-methoxytropinone methobromide (7.0 mg., 0.025 mmole) and sodium bicarbonate (4.2 mg., 0.05 mmole) in 50 ml. of distilled water was heated on a steam-bath. After 90 minutes, no increase in 360 mμ absorption intensity of an aliquot portion could be detected. The analysis indicated a 48% yield of γ-tropolone. One ml. of 48% hydrobromic acid was added, and the solution was heated on a steam-bath for 105 minutes. After neutralizing the acid, analysis as above indicated a 66% yield of IV.

Degradation of 6β,7β-Dimethoxytropinone Methobromide (X).—A solution of 6β,7β-dimethoxytropinone methobromide was treated as described above. After 60 minutes, the absorption spectrum, $\lambda_{\max}^{0.1\,N\ \mathrm{NaOH}}$ 226 mμ (4.30) and 332 mμ (4.13), did not change. One ml. 48% hydrobromic acid was added, and the solution was heated on a steam-bath for 90 minutes to bring about hydrolysis of the methyl ether. After neutralizing the acid, analysis of this solution indicated a 91% yield of IV.

γ-Tropolone Methyl Ether (XI).—A solution of 6β,7β-dimethoxytropinone methobromide (26.24 g., 0.0893 mole) and sodium bicarbonate (7.50 g., 0.0893 mole) in 358 ml. of distilled water was heated on a steam-bath for 1.5 hours. The solution, which was red in color, was continuously extracted with ether for two days. Drying over anhydrous magnesium sulfate and careful evaporation of the ether gave a brown oil (11.47 g., 94%) which solidified on standing in the refrigerator. Distillation of this material gave pure γ-tropolone methyl ether (8.90 g., 73%), b.p. 103–104° (0.58 mm.). Some decomposition occurred during the distillation. The distilled product melted at 28–29° (lit.[4] 29–30°) and showed $\lambda_{\max}^{\mathrm{CH_3OH}}$ 223 mμ (4.19) and 325 mμ (4.04) (lit.[4] 223 mμ (4.23) and 325 mμ (4.04)). On standing in the refrigerator for several days the γ-tropolone methyl ether turned pale yellow.

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[8] R. Zeile and A. Heusner, *Ber.*, **87**, 439 (1954). See also the Experimental section.

[9] The hydrolysis of XI under vigorous conditions has been described by A. W. Johnson and co-workers, ref. 4. This hydrolysis has also been found to proceed under considerably milder conditions (see Experimental section).

[10] J. C. Sheehan and B. R. Bissell, *J. Org. Chem.*, **19**, 270 (1954); A. Heusner, *Ber.*, **87**, 1032 (1954).