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OXIDATIVE RING-CONTRACTION IN THE *sym*-DICYCLOHEXYLETHANE SERIES

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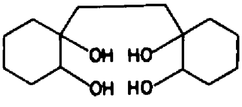
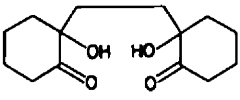
Abstract—The oxidation with CrO_3 of the two isomeric tetrols (I) containing *cis*-1,2-diol groupings has been investigated. This reaction leads to the hydroxy-ketal III (two isomers), as well as to the hemi-ketals XI and XIV containing a five-membered ring. The mode of formation of these substances is discussed, and our results are related to previous work with α-methylenecyclohexanone dimer (V) carried out by Mannich and by Böhme *et al.*

In the course of work with *sym*-dicyclohexylethane derivatives,[1] the oxidation of the two isomeric tetrols (I) containing *cis*-1,2-diol groupings (isomers A and B)[2] was investigated. As mentioned previously,[1] this oxidation proved to be more complex than anticipated.

Of the various conditions studied, those involving oxidation with chromium trioxide in acetate and dilute sulphuric acid[3] gave the most clear-cut results, and the products described below were obtained from I by this method. The expected dihydroxy-dione (II) was not formed, but a number of new substances could be isolated instead, some of which resulted from rearrangement of the carbon skeleton. The compounds were separated by chromatography on alumina, and will be described in order of their elution.



I



II

The first crystalline substance (m.p. 114–115°) to be eluted from the oxidation of the tetrol (I), isomer A, was not structurally identified. The elemental analysis indicated that this product was formally derived from I by the addition of one molecule of acetone and loss of two molecules of water. The IR spectrum revealed the presence of hydroxyl, but no carbonyl groups. No analogous compound was obtained by oxidation of I, isomer B.

The next substance (m.p. 65–66°) obtained from I, isomer A, proved to be the hydroxy-ketal (III). This compound is derived from I by oxidation of one of the secondary hydroxyl groupings to a ketone, and subsequent intramolecular ketal formation of the resulting trihydroxy-ketone (VI). An analogous hydroxy-ketal (m.p. 107–108°) was obtained by oxidation of I, isomer B. The structures assigned to both isomers of III are based on their elemental compositions, the fact that the IR spectra

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[1] E. Ghera, M. Gibson and F. Sondheimer, *J. Amer. Chem. Soc.* **84**, 2953 (1962).

[2] These isomers represent the meso and racemic forms, although no specific assignment can be made.

[3] *Inter al.*, K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946); P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch and G. W. Wood, *Ibid.* 2402 (1951); R. G. Curtis, I. M. Heilbron, E. R. H. Jones and G. F. Woods, *Ibid.* 457 (1953).

indicated the presence of hydroxyl (but no ketone) groupings, while acetylation with acetic anhydride and *p*-toluenesulphonic acid led to the corresponding tertiary acetates. Treatment of either isomer of III with acetic anhydride and pyridine resulted in the recovery of starting material, showing the hydroxyl group to be tertiary.

The hydroxy-ketal structure III has been assigned by Böhme *et al.*[4] to two stereoisomeric substances, obtained from α-methylenecyclohexanone dimer (V) by reduction to the corresponding two stereoisomeric alcohols (IV) and subsequent peracid oxidation. One of Böhme's hydroxy-ketals (III) was reported[4] to show m.p. 107–108°, and is therefore presumably identical to our isomer B.[5] Consequently, its precursor IV[4,6] must be the isomer possessing the two oxygen groupings in the *cis*-relationship. The second of Böhme's hydroxy-ketals (III; m.p. 163°) must be derived from the precursor (IV) having a *trans*-relationship of the oxygen groupings, and, as expected, this isomer is not identical to our isomer A.

It has been shown that both of Böhme's hydroxy-ketals (III) on treatment with conc. sulphuric acid are converted to the hemi-ketal (VIII)[4] previously obtained from α-methylenecyclohexanone dimer (V) by means of dilute hydrochloric acid.[6,7] The change from III to VIII presumably involves opening to the trihydroxy-ketone (VI) followed by dehydration to the hydroxy-dione (VII) and hemi-ketal formation. In agreement with the assigned structures, both our isomers of III on treatment with conc. sulphuric acid were transformed to the hemi-ketal (VIII). The last-mentioned compound was found to be identical with an authentic sample[4,6] through direct comparison.

The next substance to be eluted (m.p. 134–135°) was obtained from both isomers of the tetrol (I). The IR spectrum showed a hydroxyl band, as well as carbonyl absorption at 5·75 and 5·84 μ. The first of these carbonyl bands indicated the presence of a cyclopentanone grouping, suggesting that a rearrangement had occurred. Treatment with hydroxylamine led to a dioxime, the IR spectrum of which showed that the cyclopentanone grouping was still present. The substance therefore appeared to be a triketone. After further experimentation, it was found (by direct comparison) that the compound was identical with a substance (m.p. 136°), assigned the hydroxy-triketone structure (XIII), first obtained by Mannich[6] by the oxidation of α-methylenecyclohexanone dimer (V) with chromium trioxide in acetic acid.

The mechanism involved in the oxidative rearrangement leading from V to XIII was not elucidated by Mannich,[6] but certain experiments bearing on this transformation were carried out subsequently by Böhme *et al.*[4] The latter group reported that oxidation of V with monoperphthalic acid led to the dihydroxy-dione (XVI) containing a cyclopentanone grouping, which was shown to exist as the bishemiketal (XVII; "β-DDK") as well as another cyclic form ("α-DDK"). Oxidation of these cyclic forms of XVI with various oxidising agents had given Mannich's triketone (XIII), while reduction of the latter with magnesium regenerated XVII.[4]

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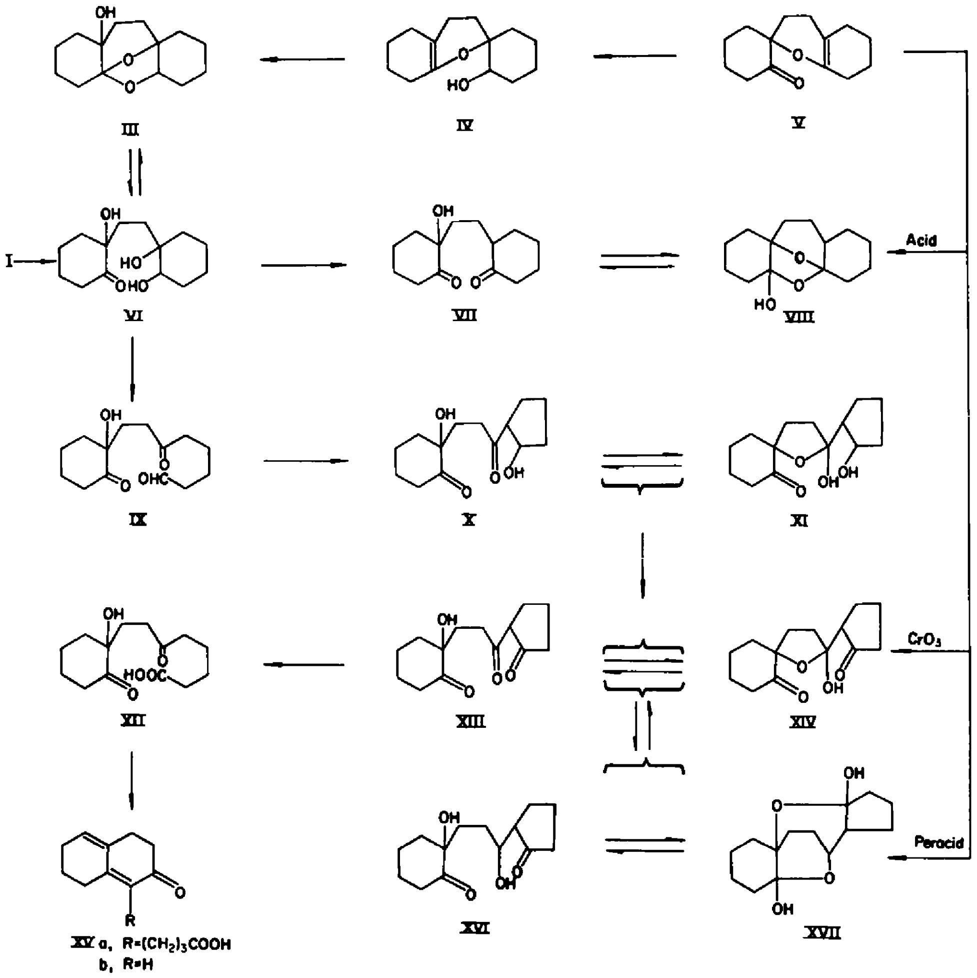
[4] H. Böhme, H. J. Bohn, I. Henning and A. Scharf, *Liebigs Ann.* **642**, 49 (1961).

[5] Unfortunately, it was not possible to carry out a direct comparison, since a sample of Böhme's compound was no longer available.

[6] C. Mannich, *Ber. Dtsch. Chem. Ges.* **74**, 557 (1941).

[7] Substance VIII was originally assumed to exist in the open hydroxy-dione form VII[6], but subsequently the crystalline compound was shown to be present as the hemi-ketal [E. W. Warnhoff and W. S. Johnson, *J. Amer. Chem. Soc.* **75**, 496 (1953)].



The gross structure of XIII is undoubtedly correct, in view of the evidence given by Böhme *et al.* for the structure of the precursor (XVI; cyclic forms),[4] and certain transformations carried out by Mannich.[6] One of these involves treatment of XIII with hot aqueous potassium hydroxide, whereby the dienone-acid (XVa) is obtained through cleavage of the β-diketone grouping to give the hydroxydiketo-acid (XII), followed by intramolecular aldol condensation and dehydration. We repeated the preparation of the dienone-acid (XVa) in this way from our hydroxy-triketone (XIII), and confirmed its structure by comparison of the UV spectrum [λ_{max}^{EtOH} 235 and 297 mμ (ε 3,600 and 13,500, respectively)] with that of the dienone (XVb) bearing one less substituent [λ_{max}^{EtOH} 233 and 289·5 mμ (ε 4,700 and 16,000, respectively)][8,9] However, the hydroxy-triketone cannot exist as the open structure (XIII) neither in the enolic

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[8] K. Takeda, H. Minato, K. Hamamoto, I. Horibe, T. Nagasaki and M. Ikuta, *J. Chem. Soc.* 3577 (1964).

[9] The additional α-substituent in XVa compared with XVb would be expected to result in a bathochromic shift of the main maximum of ca. 10 mμ [R. B. Woodward, *J. Amer. Chem. Soc.* **63**, 1123 (1941); **64**, 76 (1942); L. F. Fieser and M. Fieser, *Steroids* p. 19. Reinhold, New York, N.Y. (1959)].

form (no high-intensity UV absorption, no colour with ferric chloride), nor in the non-enolic form (no band below τ 7·25 in the NMR spectrum). By comparison, 2-acetylcyclopentanone exists partly as the enol [λ_{max}^{EtOH} 286 mμ (ε 6,600)][10] and partly as the diketone (NMR multiplet at ca. τ 6·6, due to the proton between the carbonyl groups).[10] The hydroxy-triketone presumably exists as the hemi-ketal (XIV), which can react in the open form, e.g. in the preparation of the bisoxime, base cleavage, etc.

The last compound to be eluted (m.p. 107°) was again obtained from both isomers of the tetrol (I). It appeared to be closely related to the previously eluted substance (XIV) since the latter was formed in almost quantitative yield on oxidation with chromium trioxide in pyridine, or in acetone–dilute sulphuric acid. The elemental analysis indicated the substance to contain two more hydrogen atoms than XIV. The IR spectrum revealed a hydroxyl band of considerably higher intensity than that of XIV, as well as a carbonyl band at 5·84 μ, but the cyclopentanone band at 5·75 μ was absent. Acetylation with acetic anhydride in pyridine yielded a monoacetate, pointing to the existence of a secondary hydroxyl group. These observations show the compound under investigation to be the dihydroxydione (X). It presumably also exists as a hemi-ketal (XI), since the intensity of the IR carbonyl peak at 5·84 μ suggested the presence of one rather than two keto groups, and the very detailed IR spectrum in the 7–12 μ region corresponded closely to that of XIV.

It is of interest to note that the dihydroxy–dione structure (X) had been considered (but rejected) by Böhme *et al.* for the substances obtained from the monoperphthalic acid oxidation of the dimer (V) and for which cyclic structures derived from the isomeric dihydroxy-dione (XVI) were then established.[4]

Substance XI was found to be rather unstable, and was converted to a crystalline isomer (m.p. 94–95°) on treatment with dilute acid, on heating, and even on standing in the solid state. The new substance no longer contained a secondary hydroxyl group, since it was recovered unchanged after treatment with acetic anhydride in pyridine, or with chromium trioxide in pyridine. The structure of this isomer is still under investigation.

The formation of the oxidation products (III, XI and XIV) by treatment of the tetrols (I) with chromium trioxide can be explained readily. A secondary hydroxyl group in I is first oxidized to a ketone to give the trihydroxy-ketone (VI), of which III is the internal ketal. The *cis*-1,2-diol grouping in VI is then cleaved[11] to the keto-aldehyde (IX), which by intramolecular aldol condensation is converted to X, the open form of XI. Finally, oxidation of the secondary hydroxyl group to a ketone leads to XIV. The fact that the trihydroxy-ketone (VI) is an intermediate in the formation of XIV is confirmed by Böhme's observation that the latter substance is obtained by the chromium trioxide oxidation of both isomers of the hydroxy-ketal (III; prepared from V via IV).[4]

EXPERIMENTAL

M.ps are uncorrected. UV spectra were measured in 95% EtOH solution on a Cary model 14 recording spectrophotometer. IR spectra were determined in $CHCl_3$ solution (except those marked

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[10] Observation made in our laboratory. 2-Acetylcyclopentanone was prepared by the method of R. M. Manyik, F. C. Frostick, J. J. Sanderson and C. R. Hauser, *J. Amer. Chem. Soc.* **75**, 5030 (1953).

[11] For the ready cleavage of *cis*-1,2-diols with chromium trioxide, see J. Roček and F. H. Westheimer, *J. Amer. Chem. Soc.* **84**, 2241 (1962).

"KBr", which were measured as KBr pellets) on a Perkin-Elmer Infracord recording spectrophotometer. NMR spectra were determined in $CDCl_3$ solution on a Varian A-60 instrument, tetramethylsilane being used as an internal standard. Analyses were carried out in our microanalytical laboratory under the direction of Mr. Erich Meier.

Oxidation of tetrol (I; *isomer* A) *with chromium trioxide*

A standard 8N CrO_3 solution in H_2SO_4aq (0·8 ml)[3] was added dropwise during 1 min to a stirred solution of 440 mg I (isomer A)[1] in 400 ml acetone (freshly distilled from $KMnO_4$) at room temp, and stirring was continued for a further 5 min. A sat. NaCl solution was then added, and the mixture was extracted repeatedly with ether. The combined ether extracts were washed with $NaHCO_3$aq and water, and were then dried and evaporated, finally under red. press. The residue (220 mg) was chromatographed on 10 g alumina (Merck, acid-washed).

The first fractions, eluted with pentane, yielded an unidentified oil. The next fractions, eluted with pentane–ether (9:1), after evaporation and crystallization from pentane furnished 25 mg substance, m.p. 114–115°; IR bands at 2·78 μ (hydroxyl) and doublet at 7·27 and 7·33 μ (gem-dimethyl?), no carbonyl bands. (Found: C, 73·12; H, 9·95. $C_{17}H_{28}O_3$ requires: C, 72·82; H, 10·06%). Treatment with acetic anhydride and pyridine at room temp or with LAH in boiling ether (4 hr) resulted in recovery of starting material.

The next fractions, eluted with pentane–ether (4:1), on evaporation and crystallization from pentane produced 34 mg III (isomer A), m.p. 60–64°. Further crystallization led to the analytical sample, m.p. 65–66°; IR bands at 2·72 and 2·81 μ (hydroxyl), no carbonyl bands. (Found: C, 70·42; H, 9·12. $C_{14}H_{22}O_3$ requires: C, 70·55; H, 9·31%). Treatment with acetic anhydride and pyridine at room temp effected no change. Treatment with acetic anhydride and a few crystals of *p*-toluenesulphonic acid monohydrate at room temp for 16 hr resulted in a mixture of starting material and the tertiary acetate. The latter after separation by chromatography on alumina showed m.p. 107°; IR bands at 5·78 and 7·98 μ (acetate), no hydroxyl band. Treatment of III (isomer A) with conc H_2SO_4 under the conditions of Böhme *et al.*[4] led to VIII, m.p. 153–154°. This substance was identified with an authentic sample (m.p. 154–155°)[4,5] through non-depression of the m.p. on admixture, and IR comparison.

The next crystalline substance was eluted with pentane–ether (7:3). Crystallization from ethyl acetate led to 25 mg substance XIV, m.p. 134–135°; IR bands at 2·78 μ (hydroxyl), 5·75 μ (cyclopentanone) and 5·84 μ (ketone); UV λ_{max} 284 mμ (ε 50); NMR, see Theoretical; no colour with $FeCl_3$. The substance gave no m.p. depression on admixture with an authentic sample (m.p. 135–136°)[4,5] and the IR spectra were identical. The dioxime (prepared with hydroxylamine in pyridine at room temp for 16 hr) after crystallization from pentane–benzene showed m.p. 169–170°; IR (KBr) band at 5·74 μ (cyclopentanone). (Found: C, 59·12; H, 7·91; N, 9·63. $C_{14}H_{22}O_4N_2$ requires: C, 59·55; H, 7·85; N, 9·92%).

Repetition of the conversion of XIV to XV by means of hot KOHaq (see Mannich[6]) gave the latter substance, m.p. 110–111°; UV λ_{max} 235 and 297 mμ (ε 3,600 and 13,500).

The last crystalline compound to be eluted [with pentane–ether (3:2)] proved to be XI (32 mg). On crystallization from pentane–ether, it showed m.p. 107°; IR bands at 2·85 μ (strong, 2 hydroxyls) and 5·84 μ (intensity suggestive of 1 carbonyl group), no band at ca. 5·75 μ. Practically every one of the more than 20 IR bands in the 7–12 μ region corresponded to those of XIV. (Found: C, 66·39; H, 8·98. $C_{14}H_{22}O_4$ requires: C, 66·11; H, 8·72%). Acetylation with acetic anhydride in pyridine (room temp, 16 hr) led to the corresponding monoacetate, which on crystallization from pentane showed m.p. 124–125°; IR bands at 2·85 μ (hydroxyl), 5·79 and 8·00 μ (acetate), and 5·84 μ (ketone). (Found: C, 64·84; H, 8·00. $C_{16}H_{24}O_5$ requires: C, 64·84; H, 8·16%).

Oxidation of 25 mg XI in 1 ml pyridine with 60 mg CrO_3 (room temp, 16 hr) yielded 22 mg XIV. Similarly, XI could be oxidized to XIV in high yield with CrO_3 in acetone and dil H_2SO_4.[3]

A solution of 30 mg XI in 5 ml dioxane containing 0·5 ml 20% (v/v) H_2SO_4aq was allowed to stand at room temp for 48 hr. Isolation with ether and crystallization from pentane–ether gave 15 mg substance, m.p. 89–93°, which on further crystallization showed m.p. 94–95°; IR bands at 2·86 μ (hydroxyl, weaker than in XI) and 5·82 μ (ketone); general pattern of IR spectrum considerably different from that of XI. (Found: C, 65·85; H, 8·80. $C_{14}H_{22}O_4$ requires: C, 66·11; H, 8·72%). This substance was also obtained from XI through heating at 180° under N_2 for 10 min, or merely by standing in the solid state for several weeks. The same compound was also isolated occasionally in trace amounts directly from the chromatogram, elution occurring between XIV and XI. Attempted acetylation with acetic anhydride in pyridine at room temp resulted in recovery of starting material, as did attempted oxidation with chromium trioxide in pyridine.

Oxidation of tetrol (I; *isomer* B) *with chromium trioxide*

A solution of 525 mg I (isomer B) in 220 ml acetone was oxidized with 1·0 ml CrO_3 solution,[3] as described above for isomer A (less acetone could be used with isomer B than with isomer A, in view of its greater solubility in this solvent). The resulting product (270 mg) was chromatographed on 10 g alumina (Merck, acid-washed).

The first crystalline compound was eluted with pentane–ether (4:1). Crystallization from pentane yielded 60 mg III (isomer B), m.p. 102–106°, which after further crystallization showed m.p. 107–108°; IR bands at 2·70 and 2·79 μ (hydroxyl), no carbonyl bands, spectrum similar to that of isomer A. (Found: C, 70·58; H, 9·07. Calc. for $C_{14}H_{22}O_3$: C, 70·55; H, 9·31%). Treatment with acetic anhydride and a few crystals *p*-toluenesulphonic acid monohydrate at room temp for 16 hr yielded the tertiary acetate (this reaction proceeded much more smoothly than with isomer A, and no unchanged starting material remained). The acetate after crystallization from pentane showed m.p. 67–68°; IR bands at 5·78 and 7·99 μ (acetate), no hydroxyl band. (Found: C, 68·32; H, 8·35. $C_{16}H_{24}O_4$ requires: C, 68·55; H, 8·63%). Treatment of III (isomer B) with conc H_2SO_4 under the conditions of Böhme *et al.*[4] yielded VIII, m.p. 154–155°, identified with an authentic sample (m.p. 154–155°)[4,6] by mixture m.p. determination and IR comparison.

Further elution of the column yielded 28 mg XIV and 49 mg XI. Each of these substances was identified by direct comparison (mixture m.p., IR) with the respective one obtained by oxidation of I (isomer A).

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