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INFLUENCE OF SOLVENTS AND EFFECT OF THE PERI-METHYL GROUP IN NUCLEOPHILIC OPENING-UP OF EPOXIDES

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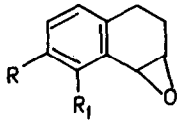
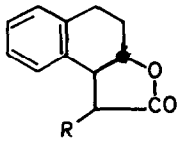
With a view to synthesising <u>trans</u> lactones of the desmotroposantonin series, van Tamelen and his associates[1] studied the interactions of the anions generated from diethyl malonate and diethyl methylmalonate with the epoxide(I) in refluxing ethanolic solution. The lactonic products thus isolated were characterised as (III). The exclusive formation of these undesired lactones was rationalised by the authors[1] by assuming that of the three contributions to the resonance hybrid of the epoxide(I), that of (A) is considerably greater than that of (B) because of the participation of the π-electrons of the benzene ring.

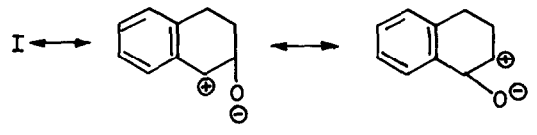


I : R = R_1 = H

II : R = OMe ; R_1 = Me



III : R = H or Me



(A) (B)

From the above findings, it is clear that electronic factors control the mode of opening-up of the epoxide of type (I). That electronic factors are at least in part overshadowed by steric factors is shown in the case of styrene oxide which gives a mixture of both possible products[2] when reacted with sodiomalonic ester. It is also well known[3] that the steric considerations of both the nucleophile and the substrate play a vital role in S_N2 displacement reactions. It was therefore of interest to investigate the direction of ring-opening of the crystalline epoxide (II)[4] with the carbanions mentioned above. We hoped that the peri-methyl group in (II) will sterically hinder the approach of the bulky nucleophiles to the 1-carbon atom and thereby the carbanions will be forced to

attack the alternative position (carbon atom - 2) to furnish the desired product (IV). Although this objective has not been realised, the results are interesting and this will be the subject matter of this communication.

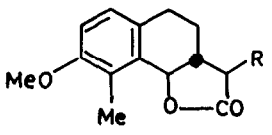
The interaction of diethyl sodiomalonate with the epoxide (II) in especially dried ethanol (4 hrs. reflux) resulted in the isolation of two γ-lactones[5]: A (48%), m.p. 109°; $\nu_{max.}$ 1775 cm^{-1}; $\lambda_{max.}$ 279 mμ (ϵ 1,998) and B (20%), m.p. 186-187°; $\nu_{max.}$ 1789 cm^{-1}; $\lambda_{max.}$ 280 mμ (ϵ 1,995). Lactone A, on heating with acetic anhydride and sulphuric acid was recovered unchanged; attempted catalytic hydrogenolysis also resulted in the quantitative recovery of the lactone. That the lactone A is a cis lactone (V)[6] was established from the ease of lactonisation of the hydroxy acid (isolation being impossible) resulting from alkaline hydrolysis of A. Lactone B, on basic hydrolysis followed by acidification furnished a stable hydroxy acid (VIII), m.p. 149°; $\nu_{max.}$ 1712 and 3550 cm^{-1}; $\lambda_{max.}$ 279 mμ (ϵ 1,995). This acid on heating above its melting point under vacuum (0.2 mm) regenerated the lactone B, and on oxidation with Jones reagent furnished a 2-keto acid (X), m.p. 161-162°; $\nu_{max.}$ 1739 (carboxy C=O intramolecularly[7] hydrogen bonded to ketone) and 1705 cm^{-1} (keto C=O); $\lambda_{max.}$ 230 and 285 mμ (ϵ 19,950 and 2,512). The above transformations suggest that the lactone B is a trans butanolide and should be represented by the expression (VI)[6].

The reaction of diethyl sodiomethylmalonate with the epoxide (II) according to the procedure of van Tamelen et al[1] (EtOH, 28 hrs. reflux) afforded a crystalline material (45%), m.p. 122° ; $\nu_{max.}$ 3584 cm^{-1}; $\lambda_{max.}$ 278 mμ(ϵ 1,950). This product was obtained in excellent yield (88%) by refluxing the epoxide(II) with ethanolic sodium ethoxide. The structure (XII) for this reaction product was supported by its oxidation to the 2-keto compound(XIII), evaporatively distilled at 100°/0.4 mm; $\nu_{max.}$ (film), 1710 cm^{-1}; $\lambda_{max.}$ 221 and 279 mμ, (ϵ 12,020 and 2,148).

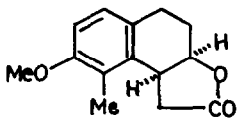
The potassium enolate prepared from diethyl methylmalonate in t-butanol was then allowed to interact (36 hrs. reflux) with the epoxide (II). The reaction mixture afforded a γ-lactone (22%), m.p. 133-134°; $\nu_{max.}$ 1785 cm^{-1}; $\lambda_{max.}$ 220 and 280 mμ (ϵ 10,000 and 1,998). This lactone on alkaline hydrolysis followed by acidification furnished a stable hydroxy acid, m.p. 153-154°;

$\nu_{max.}$ 3775 and 1705 cm^{-1}; $\lambda_{max.}$ 279 mμ (ε 2,045). This acid on heating above its melting point under vacuum (0.1 mm) was quantitatively converted to the lactone mentioned above. Oxidation of the hydroxy acid afforded a 2-keto acid (XI), m.p. 188-189°; $\nu_{max.}$ 1740 and 1704 cm^{-1}; $\lambda_{max.}$ 286 mμ (ε 2,799). The lactone and the corresponding hydroxy acid should therefore be represented by the structures(VII)[6] and (IX) respectively.

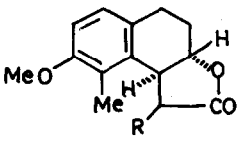
Finally the nucleophilic opening-up of the epoxide (II) with sodium salt of diethyl methylmalonate was carried out in anhydrous benzene solution (30 hrs. reflux). The reaction mixture furnished a neutral material (30%), b.p. 150°/0.3 mm; $\nu_{max.}$ (film), 1711 cm^{-1}; $\lambda_{max.}$ 280 mμ (ε 2,138). This material analysed correctly for $C_{17}H_{22}O_3$. The structure (XIV) for this compound is supported from its NMR spectrum which shows the following peaks : τ (in $CDCl_3$) 9.21 (3H, s,



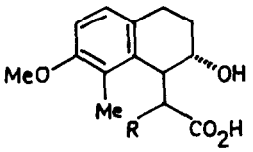
IV : R = H or Me



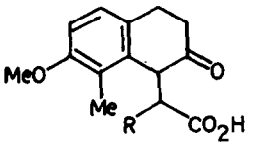
V



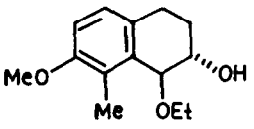
VI : R = H
VII : R = Me



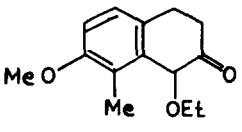
VIII : R = H
IX : R = Me



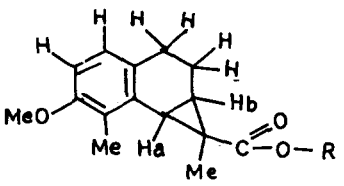
X : R = H
XI : R = Me



XII



XIII



XIV : R = CH_2CH_3 ; XV : R = H

cyclopropyl CH_3), 8.73 (3H,t, J 6.8 c/s, OCH_2CH_3), 7.96 (3H, s, aromatic CH_3), 6.22 (3H, s, OCH_3), 5.84 (2H, q, J 6.8 c/s, OCH_2CH_3), 3.35 (2H, q, aromatic protons), 7.0 - 7.85 (5H, broad multiplet, 2 CH_2 and the cyclopropyl proton H_a), the proton H_b is lost in the CH_3 signal of OCH_2CH_3. This ester on alkaline hydrolysis furnished a crystalline acid, m.p. 200-201°; $\nu_{max.}$ 1684 cm^{-1}; $\lambda_{max.}$ 280 mμ (ϵ 2,045). The NMR spectrum is consistent with the structure(XV) assigned for this acid. Catalytic hydrogenolysis of (XV) gave an oily acid, $\nu_{max.}$ 1706 cm^{-1} and this failed to give any crystalline material.

The formation of the cis lactone (V) is informative and work is in progress to account for the novel cyclopropane formation described above.

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3. E.S. Gould, Mechanism and Structure in Oirganic Chemistry, Holt,Rinehart & Winston, Inc., New York, N.Y. (1959), pp. 274-280.

4. Our unpublished work.

5. All compounds described herein gave expected elemental analyses. Ultraviolet spectra were taken in ethanol solution and IR spectra were measured in chloroform solution unless otherwise stated.

6. This structure is also supported from NMR spectrum.

7. Cf. H. O. House, H. Babad, R. B. Toothill and A. W. Noltes, J. Org. Chem., 27, 4141 (1962).