

## Thermal Rearrangement of Enol Ester Epoxides. II. The Intramolecularity of the Rearrangement<sup>1</sup>

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Received February 6, 1962

The thermal rearrangements of mixtures of 1-acetoxy-1,2-epoxy-4-methylcyclohexane (I) and 1-propionoxy-1,2-epoxycyclohexane (II) have been carried out. Identification of the products as their 2,4-dinitrophenylhydrazones shows that I and II rearrange intramolecularly. N.m.r. spectra of the two 2,4-dinitrophenylhydrazones, m.p. 165.5–166° and 185.5–186°, of 2-acetoxy-4-methylcyclohexanone, indicate that they are the derivatives of the *cis* and *trans* isomers.

The thermal rearrangement of enol ester epoxides has been reported for the steroid system by Gallagher<sup>2</sup> and, recently, by Johnson,<sup>3</sup> while the case of 1,2-epoxy-1-acetoxycyclohexane has been reported from this laboratory.<sup>1b</sup> Attempts to prepare epoxides of enol esters have led in other cases<sup>4,5</sup> to the isolation of products corresponding with rearrangement; it is an open question whether or not in these cases the products arose from an intermediate epoxide or from direct attack on the ester.

We have been interested in the scope of this reaction in single ring compounds and have investigated the rearrangement of 1-acetoxy-1,2-epoxy-4-methylcyclohexane (I) and 1-propionoxy-1,2-epoxycyclohexane (II). Thermal rearrangement of I and II separately and in mixture has shown that these rearrangements are intramolecular. The products expected from rearrangement by 1,2-migration of the acyloxy group were synthesized and converted to the 2,4-dinitrophenylhydrazones. The synthetic 2-propionoxycyclohexanone (III) gave a derivative (C) with melting point 163–163.5°. Synthetic 2-acetoxy-4-methylcyclohexanone (IV) gave two derivatives: A, m.p. 165.5–166° and B, m.p. 185.5–186°. Samples of liquid IV deposited on long standing in the refrigerator the solid isomer, m.p. 58–58.5°, which gave the derivative B.

Thermal rearrangement of I gave IV. Treatment of the IV with 2,4-dinitrophenylhydrazine gave A. Rearrangement of II gave III and this was characterized as the derivative C. Rearrangement of mixtures of I and II were carried out after ascertaining that the rates of rearrangement were not markedly different. Products of rearrangement were converted quantitatively to 2,4-dinitrophenylhydrazones and identified by X-ray powder pattern technique. The results showed that all derivatives

originated from intramolecular rearrangement products. The derivatives obtained from mixtures of I and II were A, B, and C. In no case was the powder pattern of the derivative (E) of 2-acetoxycyclohexanone (V) observed. X-Ray patterns of the residues of 2,4-dinitrophenylhydrazones of both synthetic IV and IV obtained by rearrangement showed the presence of small quantities of a third solid (D), which we were unable to isolate. The pattern attributable to D was not similar to that of E.

The n.m.r. spectra of A, B, and E were recorded and indicate that A and B are derivatives of the *cis* and *trans* isomers of IV. The spectra are given in Fig. 1.

The spectrum of E shows a poorly resolved triplet at low field, corresponding with coupling of a C-2 proton with the C-3 protons and indicates equivalence of the C-3 protons by inversion. The spectrum of A in the same region shows two doublets with over-all spacing of 17 c.p.s. indicative of an equatorial C-2 acetate leading to an a-a plus an a-e coupling between the C-2 and C-3 protons. The spectrum of B is somewhat similar but the pair of doublets shows signs of collapsing to a pattern with an over-all width of 14 c.p.s. suggesting an equilibrium between two conformations in which the C-2 proton is more axial than equatorial.

In the region of  $\delta = 2.5$  to 3.5, A shows a doublet with spacing of 15 c.p.s. characteristic of a-e coupling between the two protons on C-6 in which each component is further split by coupling with the C-5 protons. By contrast, rapid inversion in E averages the C-6 protons and coupling is no longer observable. The 11 c.p.s. doublet of B in this region has its center at  $\delta = 2.75$  compared with 2.9 for A and 2.56 for E, suggesting again that B is an equilibrium of the two chair forms but predominantly one configuration.

The remaining ring proton signals are distributed between the acetate methyl and the C-4 methyl. The change from general merging of these signals in E to wide dispersal in A is also consistent with the interpretation of changing from a rapidly inverting pair in E to a one configuration system in A.

These data suggest that in A the C-4 methyl and C-2 acetate are *cis*-(e-e), while in B they are *trans*.

(1)(a) Part of this paper was delivered at the 137th Meeting of the American Chemical Society, Cleveland, April, 1960; (b) For Part I see H. J. Shine and G. E. Hunt, *J. Am. Chem. Soc.*, **80**, 2434 (1958).

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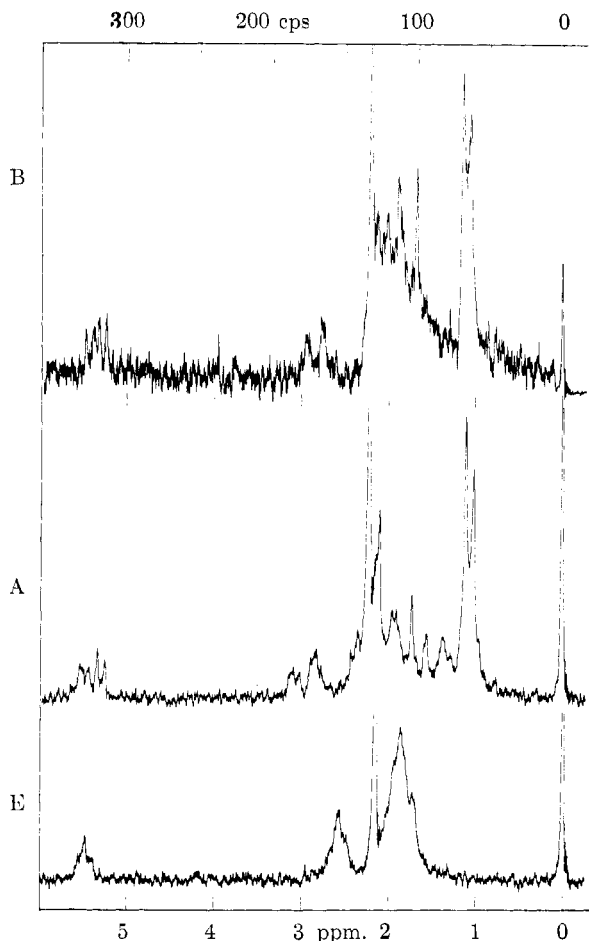


Fig. 1.—N.m.r. spectra of 2,4-dinitrophenylhydrazones A, B, and E.

### Experimental

Analyses by Schwarzkopf Laboratories, Woodside, Long Island, N.Y.

**Materials.**—Cyclohexanone (Matheson, Coleman and Bell) and 4-methylcyclohexanone (Distillation Products) were fractionally distilled giving, respectively, b.p. 145–148°,  $n_D^{25}$  1.4476, and b.p. 165°,  $n_D^{25}$  1.4434,  $\lambda_{\max}$  for carbonyl 1718  $\text{cm}^{-1}$ . Acetic anhydride (Fisher Scientific) and propionic acid and propionic anhydride (Distillation Products) were re-distilled without fractionation. N-Bromosuccinimide (Arapahoe Chemicals) was used without further treatment. Monoperphthalic acid was prepared<sup>6</sup> and used in ether solution. Its concentration was determined iodometrically.

**1-Acetoxy-4-methylcyclohexene.**—The procedure of Mannich and Hancu<sup>7</sup> was followed in part. The product, 37.4 g. (13.6% yield) was collected over the range of b.p. 99–100° (38 mm.),  $n_D^{25}$  1.4503.

*Anal.* Calcd. for  $\text{C}_9\text{H}_{14}\text{O}_2$ : C, 70.10; H, 9.15. Found: C, 70.49; H, 9.23.

**1-Propionoxycyclohexene.**—The method of Machinskaya<sup>8</sup> for the corresponding acetate was followed. Fractional distillation gave 87.5 g. of product (22.3% yield), b.p. 30–31° (0.07 mm.),  $n_D^{25}$  1.4532.

**1-Acetoxy-1,2-epoxy-4-methylcyclohexane (I).**—To an ice-cold ether solution containing an equimolar quantity of

monoperphthalic acid standing over anhydrous magnesium sulfate was added 37.4 g. (0.243 mole) of 1-acetoxy-4-methylcyclohexene. The solution was stirred at 0° for 24 hr. and then placed in the refrigerator and stirred occasionally. Aliquots were removed periodically and analyzed for monoperphthalic acid iodometrically. After 7 days the rate of disappearance of the acid had become slow enough to warrant working up the product. The filtered solution was washed with saturated sodium bicarbonate solution, dried and fractionally distilled through a 6-in. Vigreux column to avoid prolonged heating, giving 8.6 g. of product (21% yield), b.p. 32–33° (0.2 mm.),  $n_D^{25}$  1.4436.

*Anal.* Calcd. for  $\text{C}_9\text{H}_{14}\text{O}_3$ : C, 63.51; H, 8.29. Found: C, 63.79; H, 8.32.

**1-Propionoxy-1,2-epoxycyclohexane (II).**—The method above was used with 87.0 g. of 1-propionoxycyclohexene, giving 18.5 g. of product (19.3% yield), b.p. 40–40.5° (0.1 mm.),  $n_D^{25}$  1.4460.

*Anal.* Calcd. for  $\text{C}_9\text{H}_{14}\text{O}_3$ : C, 63.51; H, 8.29. Found: C, 63.65; H, 8.41.

**2-Bromo-4-methylcyclohexanone.**—(a). To a refluxing solution of 50.0 g. (0.446 mole) of 4-methylcyclohexanone in 100 ml. of freshly distilled carbon tetrachloride was slowly added 73.0 g. (0.410 mole) of N-bromosuccinimide. External heating was stopped during this addition, the solution being kept at reflux by heat of reaction. This procedure was found advisable in order to avoid the very vigorous reaction that resulted if all of the NBS were added at once.<sup>9</sup> The mixture was next refluxed for 40 min., allowed to cool, filtered, and fractionally distilled giving 9.2 g. (11% yield), b.p. 40–43° (0.2–0.3 mm.),  $n_D^{25}$  1.4950,  $\lambda_{\max}$  for carbonyl 1727  $\text{cm}^{-1}$ .

(b). To a stirred mixture of 100 g. (0.892 mole) of 4-methylcyclohexanone and 300 ml. of water was added dropwise 47.7 ml. (0.825 mole) of bromine. The temperature was kept at 30° with an ice bath. Addition of the bromine took 30 min. and the liquids were then colorless. The aqueous layer was extracted with ether after separation and the combined organic phases were dried over magnesium sulfate. Fractional distillation gave 74.0 g. (41.3% yield), b.p. 53° (0.25 mm.)  $n_D^{25}$  1.4961,  $\lambda_{\max}$  for carbonyl 1727  $\text{cm}^{-1}$ .

**2-Bromocyclohexanone.**—This was prepared by the bromine method giving a product with b.p. 49–52° (0.7 mm.),  $n_D^{25}$  1.5101 (lit.,<sup>10</sup>  $n_D^{25}$  1.5101).

**2-Acetoxy-4-methylcyclohexanone (IV).**—An excess of a saturated solution of anhydrous sodium acetate in acetic acid was boiled for 24 hr. with 74.0 g. (0.413 mole) of 2-bromo-4-methylcyclohexanone. The precipitated sodium bromide was filtered off, the acid solution taken up in ether, washed with saturated sodium bicarbonate until effervescence ceased, dried, and fractionally distilled, giving 16.4 g. (23.3% yield) of IV, b.p. 53–55° (0.25 mm.),  $n_D^{25}$  1.4541.

*Anal.* Calcd. for  $\text{C}_9\text{H}_{14}\text{O}_3$ : C, 63.51; H, 8.29. Found: C, 63.31; H, 8.35.

The keto acetate *via* the NBS route gave a semicarbazone, m.p. 192–193°.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{17}\text{N}_3\text{O}_3$ : C, 52.85; H, 7.54; N, 18.49. Found: C, 53.30; H, 7.69; N, 18.27.

A 2,4-dinitrophenylhydrazone was prepared from the same sample of keto acetate by the diglyme-acetic acid method.<sup>11</sup> The crude derivative had the X-ray pattern of A plus some B. Several recrystallizations from ethanol gave golden yellow needles of A, m.p. 165.5–166°.

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{19}\text{O}_5\text{N}_4$ : C, 51.42; H, 5.18; N, 15.99. Found: C, 51.61; H, 5.45; N, 16.05.

The residues of these recrystallizations were contaminated with a small amount of a pale yellow derivative (D) and a bright red solid which was isolated and shown to be 2,4-dinitrophenylhydrazine. It was not found possible to ob-

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tain enough of the D for identification or melting point determination. However, in X-ray patterns it showed a characteristic long spacing of 15 Å.

A 2,4-dinitrophenylhydrazone was prepared in a similar manner from the keto acetate obtained *via* the bromine route. The crude derivative was pale yellow. Fractional crystallization from ethanol gave six crops. X-Ray patterns showed that the first two of these contained only A and B; the third and fourth contained A, B, and the bright red 2,4-dinitrophenylhydrazine; the fifth was D and the 2,4-dinitrophenylhydrazine, while the last was 2,4-dinitrophenylhydrazine only.

**Solid Ketone from 2-Acetoxy-4-methylcyclohexanone.**—Samples of the liquid keto acetate IV prepared *via* the bromine route slowly deposited a solid when stored in the refrigerator. Filtration and crystallization from ligroin gave blunt prisms, m.p. 58–58.5°.

*Anal.* Calcd. for  $C_9H_{14}O_3$ : C, 63.51; H, 8.29. Found: C, 63.73; H, 8.54.

The 2,4-dinitrophenylhydrazone (B) from ethanol had m.p. 185.5–186° (ethanol).

*Anal.* Calcd. for  $C_{15}H_{18}O_6N_4$ : C, 51.42; H, 5.18; N, 15.99. Found: C, 51.25; H, 5.09; N, 16.15.

**2-Propionoxycyclohexanone.**—Using 124 g. (0.700 mole) of 2-bromocyclohexanone and an excess of a saturated solution of sodium propionate in propionic acid there was obtained 67.4 g. of product (56.5% yield), b.p. 79–80° (0.6 mm.),  $n_D^{25}$  1.4560.

*Anal.* Calcd. for  $C_9H_{14}O_3$ : C, 63.51; H, 8.29. Found: C, 63.70; H, 8.26.

The 2,4-dinitrophenylhydrazone (C) had m.p. 163.5–164°.

*Anal.* Calcd. for  $C_{15}H_{18}O_6N_4$ : C, 51.42; H, 5.18; N, 15.99. Found: C, 51.74; H, 5.45; N, 16.15.

Attempts to prepare a semicarbazone were unsuccessful.

**Rearrangement Products.**—The epoxides were sealed in glass tubes and placed in a bath at 90°. The keto esters formed were converted to their 2,4-dinitrophenylhydrazones by emptying a cooled tube into an ice-cold solution of excess 2,4-dinitrophenylhydrazine in diglyme and adding a few drops of either acetic acid or concentrated hydrochloric acid. Water was added periodically to the refrigerated solution to precipitate fractionally the products and the precipitates obtained were collected separately. The water dilution was continued until no further precipitation occurred on standing in the refrigerator several days. Each precipitate was dried in a vacuum desiccator and its X-ray diffraction pattern was recorded. The precipitates were combined and fractionally crystallized from ethanol and aqueous ethanol. Each crop and the final residue was again subjected to X-ray analysis. The derivatives A, B, and C were similarly treated and their X-ray patterns were used as standards. Also, 2,4-dinitrophenylhydrazine itself

was treated similarly and was used to provide X-ray standards.

Rearrangement of mixtures of I and II was carried out three times for product analyses. The results were similar in all cases. In the first 0.085 g. of I plus 0.088 g. of II was kept at 90° for 45 hr. The derivatives were obtained by the diglyme method using hydrochloric acid. Four precipitations gave a total of 0.412 g. of dry product (theoretical 0.358 g.). In the second, using ethanol and hydrochloric acid 0.127 g. of I and 0.123 g. of II (90° for 19 hr.) gave 0.502 g. of product (theoretical 0.515 g.). In the third, using diglyme and acetic acid 0.083 g. of I and 0.080 g. of II (90° for 27 hr.) gave 0.403 g. of product (theoretical 0.335 g.). Thus, in each case we were confident that very little, if any, of the carbonyl derivatives remained in solution.

X-Ray powder patterns of the separate precipitates and of the crops obtained from ethanol crystallizations gave the same results in each case. That is, the first precipitates (and crops) consisted of A, B, and C. Subsequent precipitates and crops contained small amounts of D and the red 2,4-dinitrophenylhydrazine. We were never able to obtain the D free of the other materials, but it was possible to isolate the fine, soluble, red form of 2,4-dinitrophenylhydrazine.

The X-ray work was carried out using a General Electric camera and a North American Phillips X-ray diffraction unit.

**Kinetic Measurements.**—The epoxides in a stoppered tube were placed in a bath thermostatted to  $\pm 0.1^\circ$ . Samples were removed periodically. Refractive index was recorded and the samples were stored at  $-20^\circ$  for later infrared analysis. Infrared spectra were determined using a Perkin-Elmer Model 112 spectrometer with a 0.025-mm. fixed path cell and sodium chloride optics. Standard spectra of pure epoxide and keto ester were used for calibration. The rates of disappearance of prominent bands in an epoxide spectrum were measured from standard first order plots of optical density against time. Rates of rearrangement from refractive index data were obtained by standard plots. Both methods showed that the rates of rearrangement of I and II were close enough (a ratio of approximately 1:2.5) to permit the study of mixtures.

**N.m.r. Spectra.**—A Varian Associates Model A-60 spectrometer was used. The solvent was deuteriochloroform and tetramethylsilane was used as an internal standard shown at 0 p.p.m. in Fig. 1.

**Acknowledgment.**—We are grateful for support of this work from the Petroleum Research Fund of the American Chemical Society. W.E.S. was supported by a fellowship from the Robert A. Welch Foundation.