Notes

Dewar Benzene Oxide Isomerization. A Forbidden Reaction

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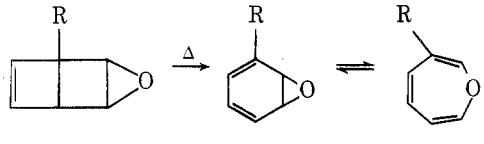
In 1967 Carty and von Tamelen reported[1] that thermolysis of Dewar benzene oxide (**1a**) afforded benzene oxide

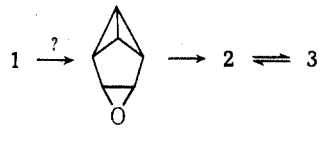


(1)

1 **2** **3**

a, R = H
b, R = D

(**2a**)–oxepin (**3a**).[2] Since a concerted least-motion mechanism for this reaction would involve a process predicted to be "forbidden" by orbital symmetry criteria,[3] we decided to determine whether such a process is, indeed, responsible for this transformation. Our idea was that a "forbidden" process should have a relatively high activation energy[3d] and, thus, the actual mechanism might be more complex[4] in order to minimize energy requirements. For example, the conversion of **1** to **2** ⇌ **3** might proceed by way of an initial isomerization to benzvalene oxide (**4**) which then



(2)

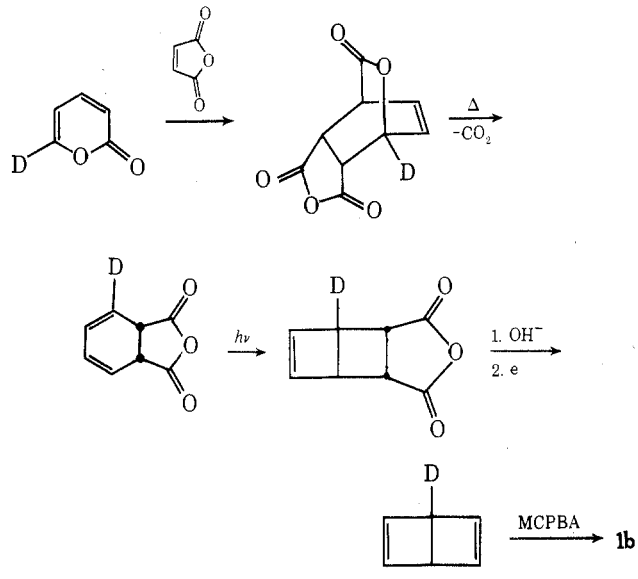
4

would undergo rearrangement to the observed products. The first step in this process is analogous to the reaction of bicyclo[2.2.0]pyran-2-one reported by Corey and Pirkle[5] and the ready thermal conversion of benzvalenes to benzene derivatives is known.[6] For the first part of this study, we selected the bridgehead labeled deuterio-Dewar benzene oxide **1b**. Such a labeling pattern would allow us to detect skeletal rearrangement occurring during the reaction.

The synthesis of **1b** was accomplished as shown in Scheme I. All of the methods used have been previously published[1,7] and the labeled materials were compared spectroscopically and, where possible, by mixture melting point with authentic unlabeled materials at each stage. The 6-*d*-pyrone was prepared by the method of Corey and Pirkle.[5] Integration of the ^1H NMR spectrum of **1b** indicated 102 ± 5%[8] bridgehead monodeuteration.

A sample of **1b** (0.1 M) in CCl_4 was heated at 120 ± 10 °C (sealed tube) and the reaction monitored by NMR spectroscopy. As reported for **1a**,[1] the characteristic absorptions due to the α, β, and γ protons of **2b** ⇌ **3b** (δ 5.4, 5.7, and 6.2, respectively)[2] appeared replacing in a continuous fashion those due to **1b**. **1b** exhibits a half-life under these conditions of ca. 1 h.[9] Integration of these signals afforded an α:β:γ proton ratio of 1.95 ± 0.10:1.00 ± 0.10:1.98 ± 0.10.[8]

Scheme I



This result demonstrates that **1** rearranges to **2** ⇌ **3** in the straightforward manner.

The second part of this study involved a determination of the activation energy for the isomerization. Sealed samples of **1a** (0.05 M) in tetrachloroethene were heated at 97.8 and 109.5 (±0.2) °C and the progress of the reaction monitored by NMR spectroscopy. Each reaction was followed for at least 2 half-lives and a plot of log [**1a**] vs. time afforded a straight line in each case. The rate constant for the rearrangement was 3.4×10^{-5} s^{-1} at 97.8 °C and 1.2×10^{-4} s^{-1} at 109.5 °C.

The derived free energy of activation at 97.8 °C is 29 ± 3 kcal/mol.[10] The limited nature of these data does not allow a reliable calculation of the activation enthalpy and entropy.

These results suggest that the thermal isomerization of **1a** resembles that of Dewar benzene itself ($\Delta G^{\ddagger}$ = 25 kcal/mol[11]). They are consistent with both fully concerted[12] (symmetrical) and biradical mechanisms. Dewar has reported calculations[3d] which indicate that the favored pathway for a thermal disrotatory cyclobutene opening involves an unsymmetrical transition state. Further mechanistic discussion should await a determination of whether **2** or **3** is the initial reaction product.

Experimental Section

General. Proton magnetic resonance spectra were determined on a Varian Associates T-60 instrument. The labeled and unlabeled Dewar benzene oxides were prepared by the method of van Tamelen and Carty.[1] The labeled dihydrophthalic anhydride was prepared by the cycloaddition of maleic anhydride and 6-*d*-pyrone[5] followed by decarboxylation in boiling xylene by the method of Goldstein and Thayer.[7b]

Pyrolysis of 3-Oxatricyclo[3.2.0.0^{2,4}]hept-6-ene-*1-d* (1b). A sample of **1b** (5.0 mg, 0.053 mmol) in 0.5 ml of carbon tetrachloride was sealed in an NMR tube.[13] This tube was then inserted in an oil bath kept at 120 ± 10 °C on a hot plate. The reaction progress was monitored by periodically removing the NMR tube from the oil bath and determining the spectrum. Careful integration of the starting material and product[2] proton absorptions showed that 52 ± 3% of **1b** had been converted to **2b** ⇌ **3b** in 60.0 min. The heat-

ing was continued for a total of 240 min before the final NMR analyses were done.

Pyrolysis of 3-Oxatricyclo[3.2.0.0^{2,4}]hept-6-ene (1a). Sealed tubes[13] of **1a** in tetrachloroethene were inserted in the condensing vapors of toluene (109.5 °C) and *p*-dioxane (97.8 °C) and the reaction progress monitored by NMR spectroscopy.

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Registry No.—**1a**, 16622-65-4.

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(4) For some examples see (a) H. H. Westberg, E. N. Cain, and S. Masamune, *J. Am. Chem. Soc.*, **91**, 7512–7514 (1969); (b) E. L. Allred and B. R. Beck, *ibid.*, **95**, 2393–2394 (1973); (c) J. E. Baldwin and M. S. Kaplan, *ibid.*, **93**, 3969–3977 (1971); (d) J. E. Baldwin and M. S. Kaplan, *ibid.*, **94**, 668–669 (1972); (e) E. Vedejs, *Chem. Commun.*, 536–537 (1971).
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(7) The α-pyrone–maleic anhydride cycloaddition and decarboxylation sequence has been described: (a) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **490**, 257 (1931); (b) M. J. Goldstein and G. L. Thayer, Jr., *J. Am. Chem. Soc.*, **87**, 1925–1933 (1965).
(8) The error limits given are the average deviation found in eight or more separate integrations.
(9) Reference 1 indicates a half-life of 18 min in cyclohexane-d_{12} or *n*-dodecane at 118 °C.
(10) The error limits arise from an estimate of an error of ±10% in each rate constant.
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(13) All glassware used for **1** was washed with potassium hydroxide solution and rinsed with water.

2-Acyloxymethylbenzoic Acids. Novel Amine Protective Functions Providing Amides with the Lability of Esters

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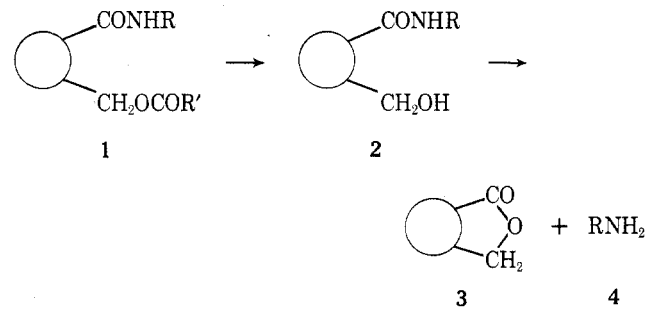
To confer more desirable pharmacokinetic properties on certain antitumor agents a novel drug latentiation scheme was earlier proposed.[2] To release agent from the latentiated derivatives a trigger mechanism utilizing a hydroxy acid component was suggested; elimination of the hydroxy acid unit as the corresponding lactone would release the core antitumor agent. In the example provided (Scheme I) the carbonyl group of the hydroxy acid component is linked to drug –NH– in an amide bond. Such hydroxy amides (**2**) are relatively unstable, the products of intramolecular hydroxyl group attack on amide carbonyl being the lactone **3** and amine **4**. Masking of hydroxyl function in **2** by acylation provides stable derivatives **1** which can be readily manipulated and purified. It was envisaged that in vivo serum esterase action on such acyl derivatives (**1**), by providing the unstable hydroxylic compound **2**, could trigger the release of the core species **4**.

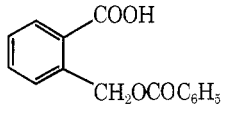
Scheme I



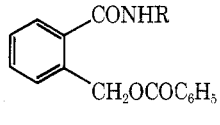
1 2 3 4

Similarly in vitro, any chemical treatment resulting in ester cleavage or exchange in the acyloxy amides (**1**) could result in liberation of the amine component **4**. Such amides might then also be useful for the protection of amino groups during synthesis with the ultimate ease of demasking approaching the ease of cleavage of an ester.

For the preparation of acyloxy amides of type **1** the most readily available precursors are the lactones but no directly useful example of a reaction for conveniently modifying a lactone could be found. Possibly the simplest method of obtaining useful intermediates from lactone precursors, Schotten–Baumann acylation of alkaline hydrolysates of a lactone, appears not to have been successfully applied. Employing phthalide as a model compound it was found that addition of benzoyl chloride to alkaline solutions of this lactone provided 2-benzoyloxymethylbenzoic acid (**5**) in 62% yield. Attempted acid chloride preparation from this acid with thionyl chloride alone returned phthalide and benzoyl chloride. However, by inclusion of 1 mol of pyridine in such reactions crystalline 2-benzoyloxymethylbenzoyl chloride could be isolated in 89% yield. From this acid chloride amide derivatives and the 4-nitrophenyl ester could be readily prepared. The latter 4-nitrophenyl ester also resulted from the action of tri(4-nitrophenyl) phosphite on the acid **5** in pyridine solution. The 4-nitrophenyl ester with suitable amines also furnished amide derivatives and phosphorazo[3,4] coupling of amines and **5** provided a further route to the amides.



5



6a, R = CH_2CONH_2
b, R = 4-$CH_3C_6H_4$

An aliphatic (**6a**) and an aromatic amide (**6b**) of 2-benzoyloxymethylbenzoic acid were prepared and subjected to usually employed reagents and conditions for protective group removal in peptide synthesis;[5] details are tabulated in Table I. The first reagent listed (NaOMe–MeOH) is not normally applied in peptide chemistry but is commonly employed to catalyze ester exchange. It can be noted that those reagents which are normally considered to promote ester hydrolysis or exchange are those which produced amide cleavage in **6a** and **6b** (Table I).

For drug latentiation purposes 2-acyloxymethyl functions other than that containing the lipophilic benzoyl residue were desired. Use of acetic anhydride in the initial Schotten–Baumann conditions provided mixtures and TLC of these showed that the desired 2-acetoxymethylbenzoic acid was being produced but the marked lability of this, providing acetic acid and phthalide, prevented com-