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Participation of a Neighboring Keto Group in the Nucleophilic Displacement of Halogen. Solvolysis of a γ,δ-Dibromo Ketone

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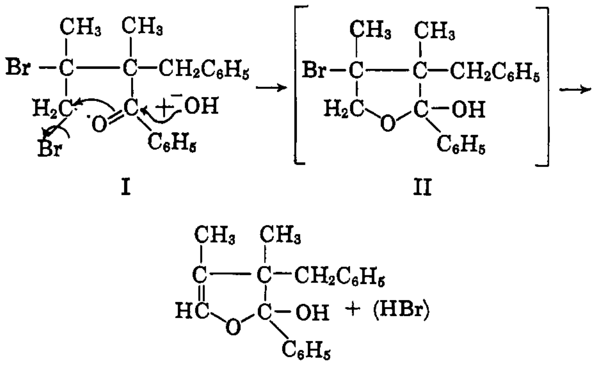
Under varying conditions, solvolysis of a γ,δ-dibromo ketone is shown to lead to a 2,7-dioxabicyclo[2.2.1]-heptane system, in addition to other products including a bromohydrin and a glycol. The latter two form as cyclic hemiketals. The dioxabicycloheptane system also forms in small yield in an unusual alkylation of a ketone with epichlorohydrin. Evidence is presented for the participation of the neighboring keto group in the nucleophilic displacement of bromide ion.

The normal reaction between an alkene dibromide and dilute, aqueous alkali is the formation of the corresponding glycol.[2,3g] If the alkali is omitted, the glycol that forms may undergo rearrangement to an aldehyde or a ketone.[3]

When a carbonyl group is located near a vicinal dibromo system, the action of aqueous alkali produces results that vary markedly with the location of the carbonyl relative to the bromines. α,β-Dibromo acids behave only partially as ordinary vicinal dibromides with respect to product types (*i.e.*, glycols). Decarboxylation is an important result and vinyl bromides are isolated. Formation of α-bromo α,β-unsaturated acids also has been reported.[4] Action of aqueous base on β,γ-dibromo acids usually produces butenolides.[5] The present brief review is concerned primarily with dihalo systems, but mention must be made of the extensive work of Zaugg and co-workers who have discovered several neighboring group reactions in monohalo-lactonic systems.[5g]

α,β-Dibromo aldehydes and ketones react rapidly with aqueous bases to give products which woldd be expected from the simple vicinal dibromo system. Both glycols and unsaturated monobromo ketones form.[6]

The first reported study of the action of aqueous base on a β,γ-dibromo ketone disclosed significant involvement of the carbonyl.[7] Action of dilute sodium hydroxide in refluxing, aqueous dioxane on 3,4-dibromo-1-phenyl-2-benzyl-2,3-dimethyl-1-butanone (I) gave 48% of 3-benzyl-3,4-dimethyl-1,2-dihydro-1-furanol (III). The mechanism proposed for this change



I II

III

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(1) (a) We are pleased to acknowledge generous support of this work by the National Science Foundation, Grant G-17559; (b) to whom inquiries should be sent.

(2) N. I. Dolgorukova-Dobryanska, *J. Russ. Phys. Chem. Soc.*, **57**, 283 (1925); *Chem. Abstr.*, **20**, 2311 (1926).

(3) (a) A. Eltekoff, *J. Russ. Phys. Chem. Soc.*, **10**, 214 (1878); *Chem. Zentr.*, 516 (1878); (b) A. Eltekoff, *Ber.*, **6**, 558 (1873); (c) W. Ipatieff, *J. prakt. Chem.*, [2]**53**, 257 (1891). (d) K. Krassuski, *J. Russ. Phys. Chem. Soc.*, **33**, 791 (1902); *Chem. Zentr.*, **I**, 628 (1902); (e) W. Froebe and A. Hochstetter, *Monatsh.*, **23**, 1075 (1902); *Chem. Zentr.*, **I**, 384 (1903); (f) W. L. Evers, H. S. Rothrock, H. M. Woodburn, E. E. Stahly, and F. C. Whitmore, *J. Am. Chem. Soc.*, **55**, 1136 (1933); (g) C. M. Suter and H. D. Zook, *ibid.*, **66**, 738 (1944). (h) These constitute a partial list of references. For a review of the literature to 1954 of the reactions of vicinal dibromides with alkaline reagents, see J. R. Holum, Ph.D. thesis, University of Minnesota, 1954; *Univ. Microfilms* (Ann Arbor, Mich.), Publ. No. 14554.

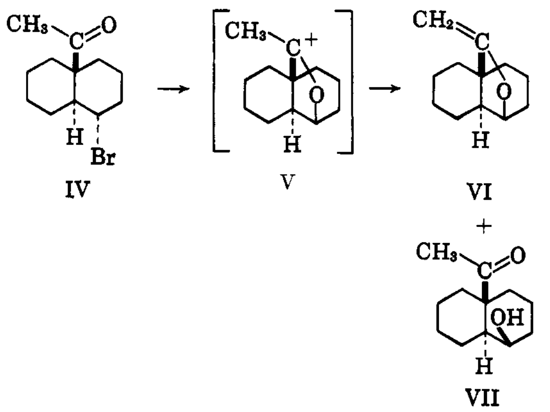
(4) (a) G. B. Bachman, *J. Am. Chem. Soc.*, **55**, 4279 (1933); (b) J. K. Farrell and G. B. Bachman, *ibid.*, **57**, 1281 (1935); (c) A. A. Alberts and G. B. Bachman, *ibid.*, **57**, 1284 (1935); (d) S. J. Cristol and W. P. Norris, *ibid.*, **75**, 632, 2645 (1953); (e) E. Grovenstein, Jr. and D. E. Lee, *ibid.*, **75**, 2639 (1953); (f) E. R. Trumbull, R. T. Finn, K. M. Ibne-Rasa, and C. K. Sauers, *J. Org. Chem.*, **27**, 2339 (1962).

(5) (a) R. Fittig and C. Geisler, *Ann.*, **208**, 45 (1881); (b) J. Thiele and W. Wedemann, *ibid.*, **347**, 137 (1906); (c) A. Courtot, *Bull. soc. chim.*, [3]**35**, 657, 969 (1906); (d) E. E. Blaise and A. Courtot, *ibid.*, [3]**35**, 989 (1906); (e) W. A. Jacobs and A. B. Scott, *J. Biol. Chem.*, **93**, 139 (1931); (f) J. C. Bardhan, *J. Chem. Soc.*, 2607 (1928); (g) H. E. Zaugg, F. E. Chadde, and R. J. Michaels, *J. Am. Chem. Soc.*, **84**, 4567 (1962), and leading references to earlier papers cited therein.

(6) (a) J. Pastureau, *Bull. soc. chim.*, [4]**5**, 226 (1909); (b) P. L. Viguier, *Ann. chim. et phys.*, [8]**28**, 454 (1913); (c) C. F. H. Allen and C. O. Edens, Jr., *Org. Syn.*, **25**, 92 (1945); (d) J. Pauly and H. Lieck, *Ber.*, **33**, 500 (1900); (e) T. Hellthaler, *Ann.*, **406**, 155 (1914); (f) C. Weygand, E. Bauer, H. Gunther, and W. Heynemann, *ibid.*, **459**, 107 (1928); (g) N. H. Cromwell, D. J. Cram, and C. E. Harris, *Org. Syn.*, **27**, 9 (1947).

(7) L. I. Smith and J. R. Holum, *J. Am. Chem. Soc.*, **78**, 3417 (1956).

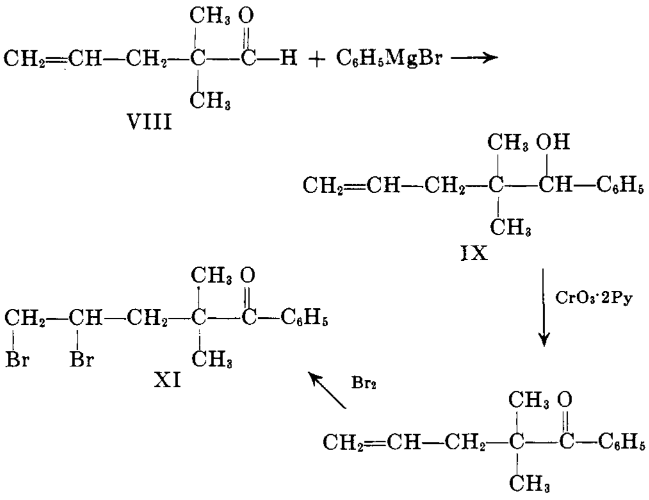
involved attack of hydroxide ion at the carbonyl carbon followed by nucleophilic attack of the carbonyl oxygen at the γ-carbon and formation of the intermediate bromohemiketal (II). This, then, according to the mechanism, lost hydrogen bromide to yield III. Operation of the *gem*-dimethyl effect[8] may have been decisive for the course of the reaction. A similar participation of the neighboring keto group in the nucleophilic displacement of bromide ion was reported by Baddeley, Baylis, Heaton, and Rasburn.[9] Unimolecular solvolysis of the γ-bromo ketone (IV) in aqueous acetone containing sodium bicarbonate gave the vinyl ether (VI) and the alcohol (VII). On the basis of kinetic data, they postulated the formation of the cation (V) as the rate-determining step.



This paper is a report of a study of the behavior of a γ,δ-dibromo ketone toward water and toward aqueous alkali.

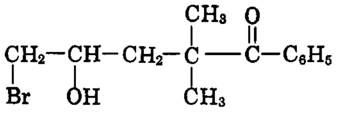
Results

Preparation and Hydrolysis of a γ,δ-Dibromo Ketone.—4,5-Dibromo-2,2-dimethyl-1-phenyl-1-pentanone (XI) was selected for study because it would give opportunity for operation of the *gem*-dimethyl effect and because it happened to be rather easily preparable. The unsaturated precursor to the dibromo ketone (X), 2,2-dimethyl-1-phenyl-4-penten-1-one, was prepared by the route VIII to X as shown.[10] 2,2-Dimethyl-4-pentenal (VIII) was available from another study during which it had been synthesized from isobutyraldehyde and allyl alcohol by the method of Brannock.[11] The oxidation of the unsaturated alcohol with the chromium trioxide–pyridine complex[12,13] was accomplished in 90% yield on a 0.2-mole scale. The reagent, therefore, is rather easily adaptable to fairly large-scale (60 g. of chromium trioxide) laboratory preparations.



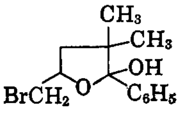
$$CH_2{=}CH{-}CH_2{-}C(CH_3)_2{-}CHO + C_6H_5MgBr \longrightarrow CH_2{=}CH{-}CH_2{-}C(CH_3)_2{-}CH(OH){-}C_6H_5 \xrightarrow{CrO_3 \cdot 2Py} CH_2{=}CH{-}CH_2{-}C(CH_3)_2{-}CO{-}C_6H_5 \xrightarrow{Br_2} CH_2Br{-}CHBr{-}CH_2{-}C(CH_3)_2{-}CO{-}C_6H_5$$

The dibromo ketone (XI) was exceptionally unstable when exposed to humid air, confirming the observations of Haller and Ramart-Lucas.[14] They reported that, when freshly prepared dibromo ketone (XI) was left exposed to (moist) air, crystals formed which analyzed for a bromohydrin, $C_{13}H_{17}BrO_2$, and for which they assigned structure XII, 5-bromo-2,2-dimethyl-1-phenyl-4-pentanol-1-one. They also reported that the same compound formed when the parent unsaturated ketone (X) was allowed to react with a solution of bromine in aqueous acetone. Their structural assignment, therefore, was consistent with Markownikoff-addition of hypobromous acid to the alkene linkage in compound X.

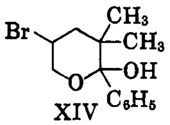


$$CH_2Br{-}CH(OH){-}CH_2{-}C(CH_3)_2{-}CO{-}C_6H_5$$

XII



XIII



XIV

We could not isolate a pure sample of the dibromo ketone (XI). The crude material was an oil that fumed strongly in even slightly humid air. The residue left after the removal of solvent (anhydrous carbon tetrachloride) following the addition of bromine to the ketone (X) gave a precipitate (presumably sodium bromide) and iodine, when it was added to sodium iodide in acetone.[15] That fact plus the well-known nature of the interaction of bromine with a double bond constituted the chief evidence that a dibromide of structure XI did in fact form. The infrared spectrum of a film of the crude dibromo ketone showed that it absorbed in the carbonyl region at 1680 cm.$^{-1}$. The relative intensity of this absorption was not so strong as expected when it was compared with the spectrum of the unsaturated ketone (X). Further, there were weak to moderate absorptions at 3500 and 3580 cm.$^{-1}$. Evidently some hydrolysis of the dibromo ketone had already occurred in spite of great effort to exclude moisture. This would explain the absorptions in the hydroxyl region *and* the weakened intensity of the carbonyl band. As shall be described shortly, hydrolysis

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[8] G. S. Hammond, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 460.

[9] G. Baddeley, E. K. Baylis, B. G. Heaton, and J. W. Rasburn, *Proc. Chem. Soc.*, 451 (1961).

[10] A reported alternative synthesis of the ketone X consisted of direct alkylation of isobutyrophenone by allyl chloride using sodium amide as the base [A. Haller and E. Bauer, *Compt. rend.*, **148**, 73 (1909)].

[11] K. C. Brannock, *J. Am. Chem. Soc.*, **81**, 3379 (1959).

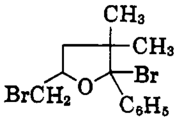
[12] G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *ibid.*, **75**, 425 (1953).

[13] J. R. Holum, *J. Org. Chem.*, **26**, 4814 (1961).

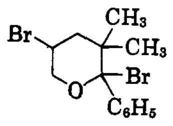
[14] A. Haller and P. Ramart-Lucas, *Compt. rend.*, **171**, 144 (1920).

[15] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, New York, N. Y., 1956, p. 158.

of the dibromo ketone leads to disappearance of the carbonyl group. (After the infrared analysis when the cell was disassembled, the film of dibromo ketone fumed strongly, and in less than a minute it had changed to crystals of what later proved to be a bromohydrin.) In view of subsequent developments and because of the work of Arnold, Campos, and Lindsay,[16,17] we could not lightly assign the open-chain structure XI to the dibromo ketone. Heterocyclic structures XV and XVI had to be considered. We were satisfied, however, that neither of these cyclic structures was correct.



XV



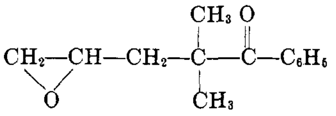
XVI

Exposure of the dibromo ketone (XI) to the moderately humid air of the laboratory produced a bromohydrin, $C_{13}H_{17}BrO_2$, melting at 101–103°. The same compound was obtained by first adding a stoichiometric amount of bromine (dissolved just before use in dioxane) to a solution of the unsaturated ketone (X) in dioxane followed by the addition of water. The bromohydrin's infrared spectrum showed no absorption between 1600 and 2850 cm.$^{-1}$. Bands at 3500 and 3650 cm.$^{-1}$ indicated the presence of a hydroxyl group. On this basis, the bromohydrin must have formed as a cyclic hemiketal, either XIII, 5-bromomethyl-3,3-dimethyl-2-phenyltetrahydro-2-furanol, or as XIV, 5-bromo-3,3-dimethyl-2-phenyltetrahydro-2-pyranol.

The action of sodium iodide in acetone[15] produced no precipitate with the bromohydrin. Alcoholic silver nitrate[18] reacted very slowly with it at 50°. These results did not permit a clear choice between the pyranol form XIV and the furanol form XIII. (However, they did rule out those isomers of XIV and XIII in which locations of bromines and hydroxyls are exchanged giving the bromine in either case a tertiary, benzylic, and α-halo ether position.)

The proton magnetic resonance spectrum of the bromohydrin will be described later in the paper together with that of the glycol related to it. Briefly, the observed chemical shifts did not permit an unambiguous choice between XIII and XIV. However, the spin-coupling pattern was inconsistent with any reasonable conformer of pyranol form XIV, but it was appropriate for furanol form XIII. Therefore, we have assigned structure XIII to the bromohydrin.

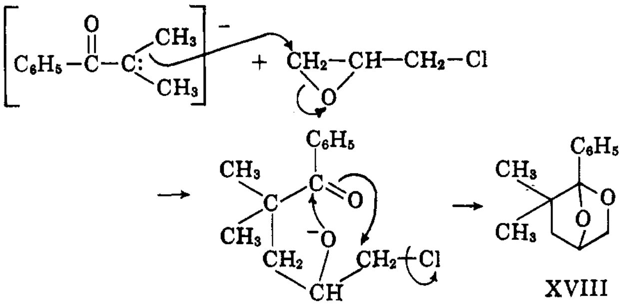
Action of Aqueous Alkali on the γ,δ-Dibromo Ketone (XI).—When freshly prepared dibromo ketone (XI) was added to a mixture of 10% aqueous sodium hydroxide in dioxane and the mixture was refluxed several hours, there was obtained in 55% yield a bromine-free solid melting at 58°, analysis $C_{13}H_{16}O_2$. Haller and Ramart-Lucas[19] obtained a 59°-melting compound, also $C_{13}H_{16}O_2$, by the action of epibromohydrin on the sodium salt of isobutyrophenone. To their product they assigned structure XVII, 4,5-epoxy-2,2-dimethyl-1-phenyl-1-pentanone. When we repeated their synthesis[20] we isolated in low yield a solid melting at 57.5–58.5°. A mixture melting point of this with our 58°-melting solid obtained from the dibromo ketone was not depressed. Further, the infrared spectra of the two were identical. The two substances, therefore, were the same, but the structure could not be represented by XVII.



XVII

The infrared spectrum of the 58°-melting compound possessed no bands characteristic of a carbonyl group, a hydroxyl group, or a carbon-to-carbon double bond. Application of the periodic acid test[21] gave positive results only after the elapse of some time. When the periodic acid test included the presence of acetic acid, conditions under which epoxides (and by inference, cyclic ketals of 1,2-glycols) are attacked,[22] the test was positive in the usual time limit.

Supported by analytical values, origin, spectrum, and chemical behavior, we have assigned to the 58°-melting compound structure XVIII, 1-phenyl-6,6-dimethyl-2,7-dioxabicyclo[2.2.1]heptane. This assignment was consistent further with the reported behavior of the 58°-melting compound toward sodiomalonic ester or sodium amide. Haller and Ramart-Lucas[19] observed that these strong nucleophiles did not react with their 59°-melting compound, a behavior inconsistent with epoxide structure XVII, for epoxides are reactive toward such reagents.[23] Such inertness, however, would be expected of a ketal system as in XVIII.



XVIII

Formation of a dioxabicycloheptane system (XVIII) *via* alkylation of a ketone with epichlorohydrin is without precedent as far as we can ascertain. The basic system itself is known. Levene and Walti[24] reported that 1,2-hexanediol-5-one, when heated at 150° for several hours, lost water. On the basis of analytical values, molar refractivity, and the parachor, they proposed for their product structure XIX, 1-methyl-

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[16] R. T. Arnold, M. Campos, and K. L. Lindsay, *J. Am. Chem. Soc.*, **75**, 1044 (1953).

[17] They reported that bromination of γ,δ-unsaturated esters gave δ-bromo-γ-lactones instead of γ,δ-dibromo esters.

[18] *Cf.* ref. 15, page 136.

[19] P. Ramart-Lucas and A. Haller, *Compt. rend.*, **158**, 1302 (1914).

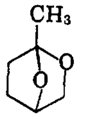
[20] We used epichlorohydrin. They used epibromohydrin, although they stated, without giving details, that epichlorohydrin did not give better results. Presumably it gave the same 59°-melting product.

[21] *Cf.* ref. 15, p. 129.

[22] R. Fuchs, R. C. Waters, and C. A. Vanderwerf, *Anal. Chem.*, **24**, 1514 (1952).

[23] *Cf.* work by W. Traube and E. Lehmann, *Ber.*, **32**, 720 (1899), or A. Haller's earlier work, *Bull. soc. chim.*, 564 (1899).

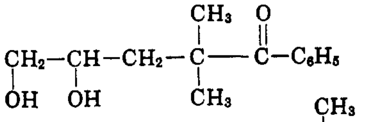
[24] P. A. Levene and A. Walti, *J. Biol. Chem.*, **88**, 771 (1930).



XIX

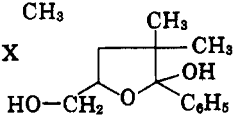
2,7-dioxabicyclo[2.2.1]heptane. The system is also quite well-known in carbohydrate chemistry.[25] The suggested mechanism shown for the formation of XVIII parallels well-known instances in which sodio derivatives of active methylene compounds attack epichlorohydrin at C-1.[26]

According to Haller and Ramart-Lucas,[19] their 59°-melting compound (now shown to have been XVIII) could be hydrolyzed to a glycol, $C_{13}H_{18}O_3$, melting at 100°, to which they assigned structure XX, 4,5-dihydroxy-2,2-dimethyl-1-phenylpentanone. The same compound was obtained when the unsaturated ketone (X) was hydroxylated by action of dilute, slightly alkaline potassium permanganate.[27] By repeating this procedure we obtained the glycol, $C_{13}H_{18}O_3$, melting at 98–100°. Since its infrared spectrum was essentially transparent in the carbonyl region between 1600 and 2000 cm.$^{-1}$, it could not have had structure XX. Cyclic, hemiketal structures XXI and XXII were considered. The glycol could be made to form, but with difficulty, by action of a boiling aqueous dioxane solution of sodium hydroxide on the bromohydrin (XIII). The yield was low and much unchanged bromohydrin was recovered. Since the bromohydrin most probably is represented by a furanol system, we have assigned the furanol form (XXI), 2-hydroxy-5-hydroxymethyl-3,3-dimethyl-2-phenyltetrahydrofuran, to the glycol.

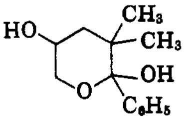


$CH_2(OH)-CH(OH)-CH_2-C(CH_3)_2-C(=O)-C_6H_5$

XX

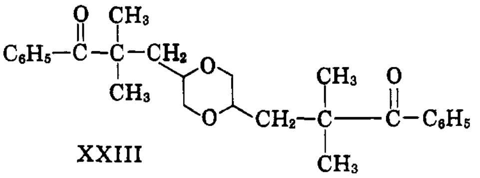


XXI

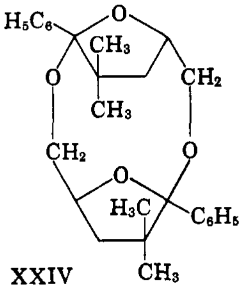


XXII

Under certain circumstances, notably acid catalysis, a dimer of the 58°-melting compound (XVIII) forms. Haller and Ramart-Lucas[19] obtained a compound, $C_{26}H_{32}O_4$, melting at 214–215°, when they added traces of acids to their 59°-melting substance. It also was obtained when attempts were made to prepare a benzoate derivative or a urethane of the glycol.[27] We did not repeat these experiments, but we did obtain the dimer, $C_{26}H_{32}O_4$, melting at 219–221°, in one experiment when chromatography onto silica gel (rather than the usual alumina) was used in an effort to isolate XVIII. The silica gel we used gave a slightly acidic reaction with water. Haller and Ramart-Lucas[19] tentatively assigned structure XXIII to the dimer. The dimer we obtained, almost certainly the same substance as theirs, did not absorb in the carbonyl region of the infrared spectrum. Bands characteristic of a hydroxyl group also were absent. In analogy with structural assignments in the carbohydrate field,[25c] we tentatively propose structure XXIV for the dimer. Our dimer gave in the presence of acetic acid (and only in its presence) a positive periodic acid test.[21,22] A compound of structure XXIII would not be expected to do this but XXIV, being a diketal of a 1,2-glycol, could.

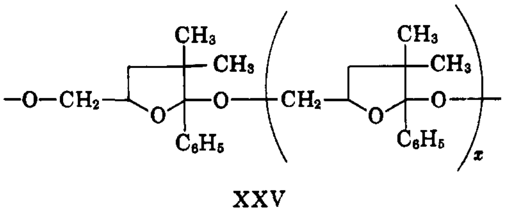


XXIII



XXIV

In addition to XVIII (or its dimer), another substance was isolated from the action of aqueous base in refluxing dioxane on the dibromo ketone (XI). This was eluted from alumina by ether and it constituted from 25–30% of the crude product's mixture. It was an amorphous solid of ill-defined melting point. Its chemical and spectral properties indicated that it might be a polymeric substance of the general type shown by XXV, in which the value of x is probably small and varied. Weak absorption at 3550 cm.$^{-1}$ in the infrared indicated the presence of hydroxyl (*e.g.*, at chain terminals). No absorption occurred corresponding to a carbonyl group. In acetic acid it gave a positive periodic acid test. XXV could form by the splitting out of hydrogen bromide from the bromohydrin (XIII) externally, while the same loss internally would produce XVIII.



XXV

N.m.r. Spectra of the Bromohydrin (XIII) and the Glycol (XXI).[28]—The proton magnetic resonance spectra of the bromohydrin and the glycol are shown in Fig. 1. In selecting reasonable candidates for the structures of the pyranol form of the bromohydrin, only chair forms were considered. It was further reasoned that the several bulky groups present on the ring would effectively inhibit interconversion of conformers at room temperature; the system would be quite rigid. Structure XXVI represents the bromine and hydroxyl *cis* to each other, and it has both the bromine and the phenyl in equatorial positions. (The alternative, both

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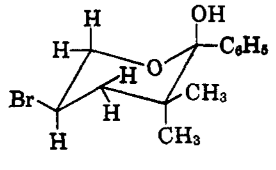
[25] (a) H. Hibbert and C. P. Burt, *J. Am. Chem. Soc.*, **50**, 1411 (1928); (b) R. J. Dimler, *Advan. Carbohydrate Chem.*, **7**, 37 (1952); (c) E. Vis and H. G. Fletcher, *J. Am. Chem. Soc.*, **79**, 1182 (1957); (d) E. Vis and H. G. Fletcher, *J. Org. Chem.*, **23**, 1393 (1958); (e) V. N. Nigam, Hsien-Gieh Sie, and W. H. Fishman, *J. Am. Chem. Soc.*, **82**, 1007 (1960).

[26] S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. 1, R. C. Elderfield, Ed., John Wiley and Sons, New York, N. Y., 1950, p. 26.

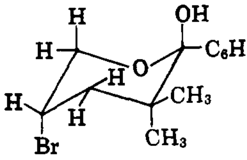
[27] J. Meyeringh and A. Haller, *Compt. rend.*, **158**, 1957 (1914).

[28] The n.m.r. spectra were obtained and interpreted for us by Dr. Donald P. Hollis of Varian Associates, Palo Alto, Calif.

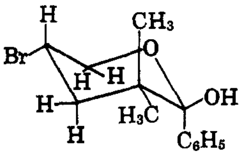
bromine and phenyl in axial positions, was regarded as a most unlikely conformer, and it was not considered.) Structures XXVII and XXVIII represent the two chair conformers of the *trans* orientation of bromine and hydroxyl. Structures XXIX and XXX show *cis* and *trans* orientations, respectively, for the bromomethyl group and the hydroxyl in the furanol form.



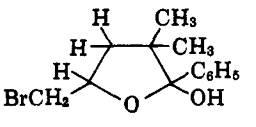
XXVI



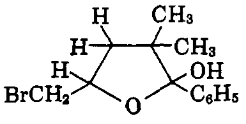
XXVII



XXVIII



XXIX



XXX

In the spectrum of the bromohydrin (Fig. 1a), the signals at 0.6 and 1.2 p.p.m., representing three protons each, correspond to the two *gem*-dimethyl groups. They have slightly different chemical shifts because of *cis–trans* relationships to the neighboring phenyl group. The patterns centered at 2.1 and 3.5 p.p.m. correspond to two protons each. The signals at 2.1 p.p.m. were assigned to the protons at position 4; those at 3.5 p.p.m., to the protons at position 6. These assignments could apply to any of the structures XXVI through XXX. The pattern at 4.5 p.p.m. corresponds to the one proton at position 5, either the tertiary proton α to the bromine and β to the ring oxygen in the pyran system (XXVI–XXVIII) or α to the ring oxygen and β to the bromine in the furan system (XXIX–XXX). α-Protons in tetrahydrofuran have $\delta = 3.75$ p.p.m. An additional 0.2–0.3-p.p.m. increase in δ could easily result from β-effects and from the fact that the C-5 proton is tertiary, not secondary. Tertiary bromine in cyclohexyl bromide has $\delta = 4.1$ p.p.m. (All δ-values are with reference to tetramethylsilane.) With the lack of chemical shift data on sufficiently similar, known systems, the observed $\delta = 4.5$ p.p.m., therefore, does not permit an unambiguous choice between the pyranol and the furanol forms.

Study of the spin-coupling pattern at $\delta = 4.5$ p.p.m., however, does appear to distinguish the two ring types. In both XXVI and XXVIII, the axial proton at C-5 has two axial and two equatorial neighbors. This arrangement is expected to produce a resonance consisting of a triplet of triplets, since the diaxial couplings are expected to be about 8–10 c.p.s., while axial–equatorial couplings are only 2–3 c.p.s. The pattern at 4.5 p.p.m., however, is either a perturbed quintet or a quartet of doublets. Hence XXVI and XXVIII are ruled out. Structure XXVII, having no diaxial neighbors for the proton at position 5, should exhibit a resonance pattern with all coupling constants in the 2–4-c.p.s. range. Hence, structure XXVII does not seem likely either.

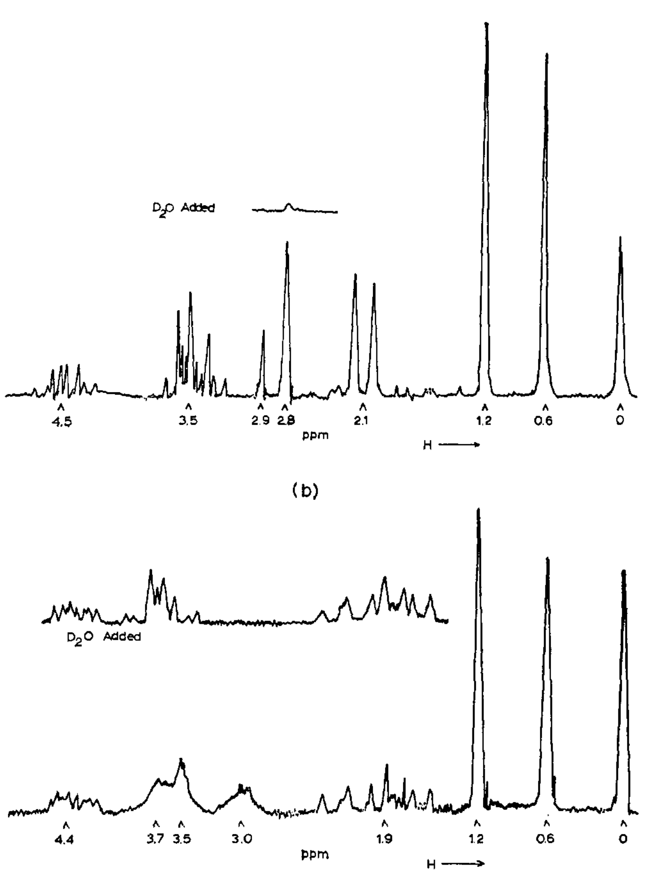


Fig. 1.—N.m.r. spectra of (a) bromohydrin XIII and (b) glycol XXI at 60 Mc. in deuteriochloroform with tetramethylsilane as the internal reference.

The furanol system (XXIX or XXX), on the other hand, could very well give the pattern observed at 4.5 p.p.m. In either form, all four protons neighboring the one at position 5 would couple to it with about the same coupling constant of about 4–7 c.p.s. There are two singlets for the hydroxyl proton of the bromohydrin, one at 2.8 p.p.m. and the other at 2.9 p.p.m. The assignment followed from the change in the spectrum when deuterium oxide was added to the solution. Two signals instead of one indicates that a mixture of XXIX and XXX are present in a ratio of roughly 3:1 (based on relative peak intensities), but which isomer is the more abundant cannot be determined from the spectrum. On other grounds it would seem that XXIX with the phenyl and bromomethyl groups *trans* to each other would be more abundant than the *cis* isomer in XXX. The *trans* isomer (XXIX) could lead to the dioxabicycloheptane system (XVIII) and the dimer (tentatively XXIV), whereas the *cis* isomer (XXX) could lead to the polymer (tentatively XXV).

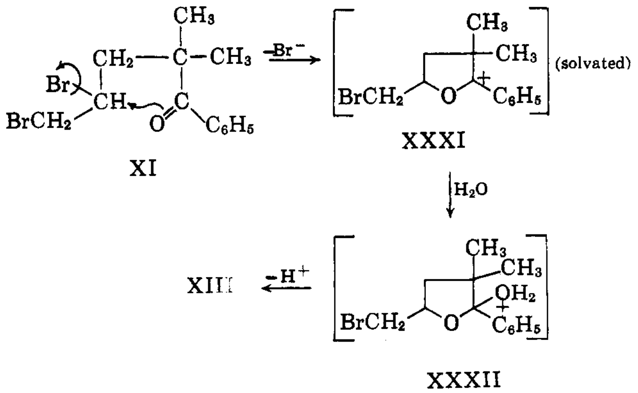
The spectrum of the glycol (Fig. 1b) is not inconsistent with the five-membered ring system, an assignment compatible with the chemical evidence that the bromohydrin can be converted into the glycol in a basic medium. Here, however, there appears to have been slight changes in some of the coupling constants for the protons at positions 4, 5, and 6, and, although the chemical shifts for these protons are virtually the same as in the spectrum of the bromohydrin, the patterns are not. We note especially the very complicated pattern centered at about 1.9 p.p.m. in the spectrum of the glycol assigned to the two C-4 protons. In the bromohydrin spectrum, these appeared as a doublet. In view of the changes in the spectrum of the glycol when deuterium oxide was added to the sample, the signals centered at 3 and 3.7 p.p.m. are assigned to the two hydroxyl groups. In summary, then, the n.m.r. spectra and chemical evidence support tetrahydrofuran systems for both the bromohydrin and the glycol, represented respectively without regard to *cis–trans* isomerism by XIII and XXI.

Discussion of Results

The formation of the bromohydrin (XIII) from the dibromo ketone (XI) conceivably could have occurred in such a way that the keto group did not significantly affect the rate-determining step. Thus, simple solvolysis of the dibromo ketone to the open-chain bromohydrin (XII) might have occurred. Ring closure would then be unsurprising, for it is well-known that γ- and δ-hydroxy aldehydes and ketones often exist largely in cyclic, hemiacetal, or hemiketal forms.[29]

What was unusual, however, about the dibromo ketone was its extreme reactivity toward even the moisture in humid air. This behavior was not consistent with a simple 1,2-dibromo system, even if one of the bromines were secondary. Suter and Zook,[3g] for example, reported that first-order hydrolysis of 2,3-dibromo-2-methylbutane occurred at a convenient rate at 45°, at which temperature they conducted kinetic studies. The initial product was the bromohydrin, 3-bromo-2-methyl-2-butanol. Thus, even the tertiary bromine in their vicinal dibromide was not unusually reactive in the way our dibromo ketone (XI) was.

The kinetic studies made by Baddeley, Baylis, Heaton, and Rasburn,[9] described earlier (*cf.* IV to VII), provided a way of rationalizing both the reactivity of our dibromo ketone toward water as well as the bromohydrin it formed. We suggest the following mechanism.



The solvated carbonium ion (XXXI) would receive stabilization through delocalization of the charge both into the phenyl ring and to the oxygen. Such stabilization of a similar carbonium ion was postulated by Oae[30] to explain the reactivity of 4-bromo-1-phenyl-1-butanone toward mercuric nitrate. Depending upon how a water molecule became attached to position-2 of the ring, isomers XXIX or XXX would form.

Experimental[31]

2,2-Dimethyl-1-phenyl-4-penten-1-ol (IX).—2,2-Dimethyl-4-pentenal (VIII) was prepared by Brannock's procedure B[11] in 74% yield from isobutyraldehyde and allyl alcohol and had b.p 124–126.5°, $n^{27}\mathrm{D}$ 1.4176; lit.[11] b.p. 124–126°, $n^{20}\mathrm{D}$ 1.4200. The infrared spectrum of this compound showed absorptions at 1725 (m–s) and 2700 cm.$^{-1}$ (w) for an aldehyde. Bands at 920 (s), 988 (m–s), and 1640 cm.$^{-1}$ (w) correlated with a terminal double bond. The strongest band in the spectrum was at 1160 cm.$^{-1}$.

A solution of 2,2-dimethyl-4-pentenal (67 g., 0.6 mole) in anhydrous ether (120 ml.) was added over a period of 30 min. to a stirred, chilled, freshly prepared solution of phenylmagnesium bromide (from 104 g., 0.66 mole of bromobenzene and 16.1 g., 0.66 g.-atom of magnesium turnings) in ether (270 ml.). The mixture remained at room temperature, protected by a drying tube, over a weekend. It was hydrolyzed with 10% sulfuric acid and the layers were separated. The ether layer was washed with saturated sodium chloride and dried (potassium carbonate). Removal of the ether left an oil which was distilled. Material boiling between 116–133° (1 mm.), $n^{27}\mathrm{D}$ 1.5227, was used in the subsequent oxidation with chromium trioxide–pyridine. An analytical sample was prepared and had b.p. 90° (0.75 mm.), $n^{26}\mathrm{D}$ 1.5225.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.81; H, 9.53.

The infrared spectrum of this compound (10% in carbon tetrachloride/carbon disulfide) had its strongest band at 703 cm.$^{-1}$. A sharp band at 3670 cm.$^{-1}$ (m–w) together with a broader band at 3540 cm.$^{-1}$ (m–w) indicated hydroxyl. Bands at 915 (s), 1000 (m), and 1640 cm.$^{-1}$ (m–w) supported the inclusion of a vinyl group in the structure.

2,2-Dimethyl-1-phenyl-4-penten-1-one (X).—The chromium trioxide–pyridine complex was made by adding chromium trioxide (63.5 g., 0.64 mole) *in small portions* during a 45-min. period *to well-stirred*, chilled (ice bath) anhydrous pyridine (720 ml.). A Hershberg stirrer rather than a blade or a magnetic capsule must be used. (See also ref. 12 and 13.) 2,2-Dimethyl-1-phenyl-4-penten-1-ol (39 g., 0.21 mole) was added using small portions of pyridine (total, 15 ml.) for rinsing. The mixture was stirred for 15 min. as it slowly darkened, and then it was left in a stoppered flask undisturbed at room temperature for 22 days. The mixture was poured into water (1 l.) and extracted with three 300-ml. portions of ether. The ether layers were combined and washed with four 200-ml. portions of 10% hydrochloric acid, seven 50-ml. portions of water, and two 50-ml. portions of 10% sodium carbonate. The solution was dried (sodium sulfate), the ether was removed at the aspirator, and the residue was fractionated. Oil (31 g., 0.18 mole, 90%), boiling at 74–85° (0.45–0.7 mm.), was shown to be homogeneous by refractive indices on three portions, taken at the beginning ($n^{25}\mathrm{D}$ 1.5200), in the middle ($n^{25}\mathrm{D}$ 1.5196), and near the end ($n^{25}\mathrm{D}$ 1.5195) of the temperature range. In another experiment on a smaller scale (0.1 mole) and a shorter reaction time (4 days), the yield was 92%. For an analytical sample, a small portion was fractionated with a small spinning-band column (Nester and Faust) and had b.p. 61–61.5° (0.2 mm.), $n^{21}\mathrm{D}$ 1.5215.

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 83.19; H, 8.57.

The infrared spectrum of this compound (as a film) showed that it absorbed intensely at 1680 (aromatic ketone[32]) and at 917 (s),

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(29) *Cf.*, for example, C. D. Hurd and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **74**, 5324 (1952).

(30) S. Oae, *ibid.*, **78**, 4031 (1956).

(31) Infrared spectra were determined with a Perkin-Elmer Infracord Model 137. "Carbon tetrachloride/carbon disulfide" means that carbon tetrachloride was the solvent between 4000 and 1300 cm.$^{-1}$ and carbon disulfide was the solvent between 1300 and 665 cm.$^{-1}$. In all spectra taken of solutions, sodium chloride cells of 0.1-mm. thickness were used. Unless otherwise specified, a 0.025-mm. spacer was used for spectra of liquid films. Structure spectra correlations were based usually on data found in L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, New York, N. Y., 1958.

All melting points were uncorrected and were determined on a Fisher–Johns melting point apparatus.

Carbon–hydrogen analyses were obtained at the Microanalytical Laboratory, University of Minnesota.

(32) J. L. Adelfang, P. H. Hess, and N. H. Cromwell, *J. Org. Chem.*, **26**, 1402 (1961).

996 (m), and 1640 cm.$^{-1}$ (m-w), bands characteristic of a vinyl group. (These bands disappeared when bromine was added to this compound.)

4,5-Dibromo-2,2-dimethyl-1-phenyl-1-pentanone (XI).—2,2-Dimethyl-1-phenyl-4-penten-1-one (2.0 g., 0.011 mole) was dissolved in anhydrous carbon tetrachloride (10 ml., Baker analyzed), and the solution was cooled to ice-bath temperature. A solution of bromine (1.7 g., 0.011 mole) in anhydrous carbon tetrachloride (40 ml.) was added slowly. The reaction was very rapid, yet the solution was allowed to remain undisturbed for 30 min. Removal of the solvent in a rotating evaporator left a pale yellow oil. Attempts to purify it further were unsuccessful. A drop of this oil added to freshly prepared sodium iodide in acetone reacted to produce a precipitate (presumably sodium bromide) and an iodine coloration.

An infrared spectrum of this oil (as a film) showed that it absorbed in the infrared at 1680 cm.$^{-1}$ (m). There was a slightly weaker band near this at 1710 cm.$^{-1}$ which we cannot explain. Weak bands at 3580 and 3500 cm.$^{-1}$ indicated that absorption by hydroxyl had occurred. The oil film on the sodium chloride windows changed to crystals within a minute after the windows were separated. This was accompanied by very obvious fuming of hydrogen bromide. A spectrum of a Kel-F mull of the crystals had no bands between 1510 and 2800 cm.$^{-1}$. A sharp band occurred at 3490 cm.$^{-1}$ (m). Broad, strong, unresolved absorption occurred between 1100 and 1250 with other strong bands centered at 900 to 1060 cm.$^{-1}$.

The dibromo ketone (XI) was prepared in dioxane just before use and not isolated in all experiments in which it was allowed to react with aqueous sodium hydroxide in dioxane.

5-Bromomethyl-3,3-dimethyl-2-phenyltetrahydro-2-furanol. (XIII, "Bromohydrin").—A solution of bromine (3.84 g., 0.024 mole) in dioxane (30 ml.) was added dropwise (15 min.) to 2,2-dimethyl-1-phenyl-4-penten-1-one (X) (4.52 g., 0.024 mole). Water (5 ml.) was added, and the mixture was stirred 15 min. It was neutralized with 10% sodium bicarbonate and the solution was concentrated *in vacuo* at room temperature. The residue, largely solid, was taken up in ether–ligroin, washed with water, and dried. Removal of the solvent left tan crystals (5.94 g., 0.019 mole, 80%) melting at 94–99°. An analytical sample was prepared by crystallization of this crude material five times from ether–ligroin. It melted at 101–103°. (Haller and Ramart-Lucas[14] reported a melting point of 106° for their bromohydrin to which they, not having infrared spectrophotometers, quite reasonably assigned structure XII, the open-chain form of XIII. We were certain that our bromohydrin was the same substance as theirs.)

Anal. Calcd. for $C_{13}H_{17}BrO_2$: C, 54.75; H, 6.01. Found: C, 54.57; H, 5.99.

The infrared spectrum of this material (10% in carbon tetrachloride/carbon disulfide) showed no absorption between 1600 and 2850 cm.$^{-1}$. Bands at 3500 (m-w) and 3650 cm.$^{-1}$ (m-w) indicated a hydroxyl group. The strongest absorption occurred at 1030 with side bands at 1010, 1040, and 1055 cm.$^{-1}$.

This compound gave no precipitate with sodium iodide in acetone at 50°. In alcoholic silver nitrate, it produced a cloudiness; boiling the solution did not materially affect this result.

2-Hydroxy-5-hydroxymethyl-3,3-dimethyl-2-phenyltetrahydrofuran. (XXI, "Glycol").—A solution of 3% potassium permanganate in 1% potassium hydroxide was added slowly to a stirred suspension of 2,2-dimethyl-1-phenyl-4-penten-1-one (5.0 g., 0.027 mole) in water (50 ml.). The permanganate color gave way to a sludge of manganese dioxide very quickly. The solids were collected on a filter and washed with ether. Removal of the ether left a solid (3.8 g.) which was recrystallized five times from petroleum ether (b.p. 30–60°) containing a trace of ether and had m.p. 98–100°. (By the same procedure, Haller and Meyeringh[27] prepared a glycol, m.p. 100°, to which they assigned structure XX.)

The solid was insoluble in 10% sodium hydroxide, and no precipitate was obtained by acidification of the aqueous filtrate obtained from this operation. In water, the solid gave a negative periodic acid test, but in the presence of acetic acid, the test was positive.[21,22] It did not decolorize bromine in carbon tetrachloride.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.15. Found: C, 69.99; H, 8.21.

The infrared spectrum (5% in carbon tetrachloride/carbon disulfide) showed that it absorbed at 3450 cm.$^{-1}$ with an intensity equal to the intensity of absorption at 2960 cm.$^{-1}$, the most intense band in the C–H stretching region. The relative intensity of absorption by hydroxyl in the glycol was considerably greater than in the bromohydrin. In a Kel-F mull, the hydroxyl peak was at 3370 cm.$^{-1}$ with a slightly larger relative intensity. The strongest absorption (as with the bromohydrin) occurred at 1030 cm.$^{-1}$. Strong to moderate side bands were at 1000 (m), 1055 (s), 1075 (m), and 1105 cm.$^{-1}$ (m).

1-Phenyl-6,6-dimethyl-2,7-dioxabicyclo[2.2.1]heptane (XVIII). A. From 4,5-Dibromo-2,2-dimethyl-1-phenyl-1-pentanone (XI).—A solution of bromine (4.25 g., 0.027 mole) in dioxane (25 ml. m.p. 10–11°) was added to a solution of 2,2-dimethyl-1-phenyl-4-penten-1-one (X) (5 g., 0.027 mole) in dioxane (10 ml.) to form a dioxane solution of the dibromo ketone (XI). This solution was added in one portion to a mixture of 10% sodium hydroxide (25 ml., approx. 0.062 mole of sodium hydroxide) in dioxane (125 ml.). The mixture was stirred and refluxed for 4 hr. A brown aqueous layer was separated from the dioxane layer, and the latter was poured into water (1 l.) and extracted with four 200-ml. portions of ether. The ether layers were combined and washed with two 100-ml. portions of water and three 40-ml. portions of saturated sodium chloride. Removal of the ether left an oil (5.62 g.) which was chromatographed from petroleum ether onto alumina (120 g., Fisher A-540, 80–200 mesh). Elution with petroleum ether and with 10:1 petroleum ether–ether gave a white, crystalline solid (2.98 g., 55%) which proved to be 1-phenyl-6,6-dimethyl-2,7-dioxabicyclo[2.2.1]heptane (XVIII). Elution with ether gave an amorphous solid (1.73 g.). Elution with ethyl acetate yielded a thick viscous material (0.37 g.).

The crystalline solid eluted largely by petroleum ether was crystallized several times from petroleum ether to a constant melting point of 58°.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.67; H, 8.01.

The infrared spectrum of this solid (10% in carbon tetrachloride/carbon disulfide) showed no absorption between 1600 and 2850 and between 3100 and 4000 cm.$^{-1}$. Hence, both hydroxyl and carbonyl groups were absent. Several needle-sharp absorptions occurred between 850 and 1140 cm.$^{-1}$, the strongest in the entire spectrum being at 975 cm.$^{-1}$. Others were at 1130 (m), 1065 (s), 1035 (m-s), 1025 (m), 1005 (m-w), 996 (s), 985 (m), 963 (m-s), 955 (m), 915 (m-w), and 860 cm.$^{-1}$ (w, broad). These bands were undoubtedly associated with the C–O and C–C of the ketal system. (Steroidal sapanogens, wherein the ketal group is part of a spiro- rather than a dioxabicyclo system, also show several sharp absorptions in this region.[33]) In addition to these bands, three sharp, strong bands appeared at 700, 734, and 770 cm.$^{-1}$.

This compound did not react with either aqueous potassium permanganate or with bromine in carbon tetrachloride. In acetic acid, the periodic acid test was positive.[21,22]

The amorphous solid eluted with ether could not be purified to a sharp melting point. The best melting point, 84–87°, was of slightly cream-colored material obtained directly from the chromatographic column. It was not analyzed for carbon and hydrogen. It was very soluble in petroleum ether, ether, alcohol, and acetone. Cooling of these solutions or evaporating the solvents in each attempt gave a sticky material that hardened to a very viscous glass. Its infrared spectrum (in both 10 and 20% solutions in carbon tetrachloride/carbon disulfide) showed that it absorbed at 3550 cm.$^{-1}$, indicating hydroxyl. Strongest absorptions occurred between 980 and 1110 cm.$^{-1}$, and though resolution was poor, specific bands could be discerned at 980 (shoulder), 1010, 1050, 1080, and 1095 cm.$^{-1}$. No absorption for carbonyl was found between 1600 and 2800 cm.$^{-1}$. A sharp, moderate band occurred at 910 cm.$^{-1}$.

In acetic acid, the amorphous solid gave a positive periodic acid test.[21,22]

B. From Isobutyrophenone and Epichlorohydrin.—All reagents were used as commercially available without further purification. Sodium amide was obtained from City Chemical Corporation, New York.

A suspension of sodium amide (7.8 g., 0.2 mole) in anhydrous ether (100 ml.) was stirred, as isobutyrophenone (29.6 g., 0.2 mole) in anhydrous ether (30 ml.) was added in one portion. The mixture was refluxed and stirred for 5.5 hr. and allowed to remain at room temperature overnight, protected by a soda-lime tube. Epichlorohydrin (18.4 g., 0.2 mole) in ether (30 ml.) was

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[33] C. R. Eddy, M. E. Wall, and M. K. Scott, *Anal. Chem.*, **25**, 266 (1953).

added, and the mixture was stirred and refluxed for 7 hr. and allowed to remain at room temperature overnight. The mixture was poured into an equal volume of water and the layers were separated. The ether layer was washed free of alkaline substances with eight 20-ml. portions of water and dried (sodium sulfate). Removal of the ether *in vacuo* at room temperature left an oil (30.8 g.) which was fractionated. Isobutyrophenone (15.9 g., 54%) was recovered at 51° (0.5 mm.). A fraction boiling at 93–98° (0.4 mm.), 6.1 g., possessed an infrared spectrum that indicated it was a mixture of isobutyrophenone and 1-phenyl-6,6-dimethyl-2,7-dioxabicyclo[2.2.1]heptane (XVIII). Accordingly, a portion (5.0 g.) of this fraction was chromatographed from petroleum ether onto alumina (120 g., Alcoa F-20). Elution with petroleum ether gave 1.4 g. of isobutyrophenone (identified by comparing its infrared spectrum with the spectrum of an authentic sample), followed by 0.40 g. of XVIII. Additional XVIII, 1.34 g. (total, 1.74 g.), was obtained by elution with 9:1 petroleum ether–ether. A center fraction melted without further purification at 57.5–58.5°; mixture melting point with the 58°-melting solid obtained in procedure A was 57–57.5°. The infrared spectra of the two were identical. The total yield of pure XVIII by this method was 4% based on original isobutyrophenone taken. Attempts to isolate and to characterize any other products from this reaction were not made.

Action of Aqueous Base on the Bromohydrin (XIII).—A mixture of the bromohydrin (XIII, 1.5 g., 5.3×10^{-3} mole), 10% sodium hydroxide (2.5 ml., estimated 6.3×10^{-3} mole of sodium hydroxide), and dioxane (50 ml.) was stirred and refluxed for 4 hr. It was poured into water (1 l.), and this mixture was extracted with four 200-ml. portions of ether. The ether extracts were combined and washed with five 100-ml. portions of water and three 40-ml. portions of saturated sodium chloride. Removal of the ether at room temperature left an orange oil (1.22 g.) which was chromatographed from petroleum ether onto alumina (37 g., Alcoa F-20). Elution with petroleum ether and with 10:1 petroleum ether–ether gave 0.75 g. (50%) of a white solid, m.p. 99–100°, which proved to be starting material (bromohydrin) by comparing its infrared spectrum with that of an authentic sample. Elution with ether gave a white solid (0.36 g., 30%), melting at 97–98°, which was glycol XXI, according to its infrared spectrum. Material with analysis agreeing with XVIII was not isolated.

In another experiment in which the crude oil obtained from the reaction was heated on the steam bath before it was chromatographed, only the amorphous solid, identified by its infrared spectrum, also obtained in procedure A in the previous synthesis, was isolated.

Dimer of XVIII (XXIV).—In one experiment designed to prepare XVIII, silica gel (Baker, 80–200 mesh) was used instead of alumina as the adsorbant for chromatography. The silica gel, when mixed with water, liberated enough acid to test with indicator paper. The principal product (4 g. from an initial 5 g., 0.027 mole of unsaturated ketone X) was a white solid, m.p. 219–221°, after recrystallization from ligroin.

Anal. Calcd. for $C_{26}H_{32}O_4$: C, 76.44; H, 7.90. Found: C, 75.83, 75.96; H, 7.96, 8.03.

Our molecular weight determinations (cryoscopic in benzene), while giving reasonable results with naphthalene (Calcd. for $C_{10}H_8$: 128. Found: 125, 125, 118, 118.) and with *p*-dibromobenzene (Calcd. for $C_6H_4Br_2$: 236. Found: 223, 221, 224, 220.), gave low results for the dimer, $C_{26}H_{32}O_4$ (Calcd., 408. Found: 371, 342, 335.). That our product was indeed the dimer seemed evident from the work of Haller and Ramart-Lucas[19] who obtained a compound, $C_{26}H_{32}O_4$ (m.p. 214–215°; mol. wt. found, 396). Although they assigned structure XXIII to their compound, the origin was such that their 214–215°-melting material and our 219–221° substance were almost surely the same.

The compound did not react with bromine in carbon tetrachloride. In acetic acid it gave a positive periodic acid test.[21,22]

The infrared spectrum of the product (as a 5% solution in carbon tetrachloride/carbon disulfide) showed that it did not absorb between 1600 and 2800 or between 3100 and 4000 cm.$^{-1}$. Several sharp bands occurred between 970 and 1110 cm.$^{-1}$, the two strongest at 1050 and 1065 with others at 1115 (s), 1085 (m–s), 1035 (w), 1015 (m–s), 995 (w) and 980 cm.$^{-1}$ (w). Three sharp bands appeared at 705 (s), 748 (w), and 777 cm.$^{-1}$ (m). The spectrum was significantly different from either that of the "monomer" (XVIII) or of the amorphous material, both described earlier.

Acknowledgment.—We wish to express our gratitude to Dr. Donald P. Hollis and Varian Associates of Palo Alto, California, for the n.m.r. analyses.

The Structure of Isomaltol[1]

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Isomaltol is shown to be 3-hydroxy-2-furyl methyl ketone. Isomaltol *O*-methyl ether was ammonolyzed to produce both a pyrrole (3-methoxy-2-pyrrolyl methyl ketone) and a pyridine derivative (4-methoxy-2-methyl-3-pyridinol). Removal of the *O*-methyl group of the pyridinol gave the same 3-hydroxy-2-methyl-4-(1*H*)-pyridone that was obtained by ammonolysis of maltol *O*-methyl ether (3-methoxy-2-methyl-4*H*-pyran-4-one) to 3-methoxy-2-methyl-4-(1*H*)-pyridone, followed by removal of the *O*-methyl group. Oxidative degradation of the acetyl side chain of isomaltol *O*-methyl ether gave 3-methoxy-2-furoic acid, which was decarboxylated to the known 3-methoxyfuran. The acidity of isomaltol is attributed to a carboxylic acid-like resonance that extends from the carbonyl group to the enolic hydroxyl group and that diminishes the aromaticity of the furan nucleus. The infrared spectra indicate isomaltol to be strongly hydrogen bonded as a dimer in the crystalline state, and possibly also as a dimer, or intramolecularly, in organic solvents.

Isomaltol first was isolated from bread as a crystalline enol by Backe.[3] He obtained it in trace amounts from the steam distillate of a bread baked from a special flour that contained dried milk. He named the compound isomaltol because some of its properties were similar to those of isomeric maltol (3-hydroxy-2-methyl-4*H*-pyran-4-one). Backe suggested a 4-pyrone structure for isomaltol.

Hodge and Nelson[4] produced isomaltol β-D-galactopyranoside from lactose by the same reaction with secondary amine salts that gave the amino-hexose-reductones from hexoses.[5] The *O*-galactoside was easily hydrolyzed to yield Backe's isomaltol. How-

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(2) A laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture; article is not copyrighted.

(3) A. Backe, *Compt. rend.*, **150**, 540 (1910); **151**, 78 (1910).

(4) J. E. Hodge and E. C. Nelson, *Cereal Chem.*, **38**, 207 (1961).

(5) (a) J. E. Hodge, U. S. Patent 2,936,308 (May 10, 1960); (b) J. E. Hodge, E. C. Nelson, and B. E. Fisher, unpublished results; (c) F. Weygand, H. Simon, and W. Bitterlich, and also J. E. Hodge and B. E. Fisher, *Tetrahedron*, **6**, 123 (1959).