β-Bromo Acids. II. Solvolysis of Cyclic β-Bromo Acids[1-3]

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A series of cyclic β-bromo acids has been subjected to solvolysis, in order to examine the effect of the β-carboxylate anion on the solvolytic rate. Comparison with several identical systems lacking the β-carboxylate indicates that appreciable acceleration, not attributable to direct participation by the carboxylate function, occurs. There is reason to believe that in most cases this acceleration is the result of differences in solvation between ground and transition states. Four of the acids (2-exo-bromobicyclo[2.2.1]heptane-1-carboxylic acid (I), 2-bromobicyclo[2.2.2]octane-1-carboxylic acid (III), 2-(equatorial)-bromobicyclo[3.2.1]octane-1-carboxylic acid (IV), and 2-(axial)-bromobicyclo[3.2.1]octane-1-carboxylic acid (V)) possess a bridgehead carboxyl group incapable of β-lactonization. One of the acids (2-exo-bromobicyclo[2.2.1]heptane-2-carboxylic acid (II)), is an α-bromo acid intimately related to I, and one of the acids (3-(equatorial)-bromobicyclo[3.2.1]octane-2-(equatorial)-carboxylic acid (VI)) is a conformationally rigid analog of trans-2-bromocyclohexanecarboxylic acid (VII). The remaining two acids (cis-2-bromocyclohexanecarboxylic acid (VIII) and cis-2-bromocyclopentanecarboxylic acid (IX)) represent relatively rigid systems, which cannot experience concerted β-lactonization. Whereas I and II are interconvertible and solvolyzed via a common intermediate, as observed elsewhere for 2-bicyclo[2.2.2]octyl derivatives, no such equilibration is observed for III and indeed the isomer corresponding to II (2-(axial)-bromobicyclo[3.2.1]octane-2-carboxylic acid (XVI)) has proved to be elusive. It is noteworthy that I and II afford identical mixtures of solvolysis products and that III, V, and VI afford the same solvolysis products with the mixture proving identical in the cases of III and V.

The problem of the behavior of β-bromo acids on solvolysis has previously been studied in this laboratory[6] and elsewhere,[7] but apart from considerations of *cis vs. trans* dehalogenative decarboxylation (fragmentation), no attempt has been made to determine kinetically the extent to which more precisely defined conformational effects may govern the competition between fragmentation and lactonization (or other solvolytic processes). Unlike the β-halo amine systems studied by Grob,[8] there is present in the β-halo acylates an anionic center which potentially may exert a substantial field or inductive effect on the solvolytic rate. Consequently, before any definitive study of the fragmentation of β-halo acids can be undertaken, it is necessary to know to what extent the β-carboxylate may influence the rate of halide solvolysis *without* mechanistic participation in the process.

To this end the present study was undertaken, and a series of β-bromo acids was prepared, the configurations of which are such as to preclude direct interaction between carboxylate and the bromine-bearing carbon atom. The choice of the several acids investigated was dictated by the various environments in which the bromine normally might be found in cyclic systems: essentially axial, essentially equatorial, subject to great or little anchimeric assistance by neighboring carbon, or wholly independent of such assistance. And in a number of instances, the corresponding simple bromide was also prepared and solvolyzed under identical conditions in order to obtain data relative to the acceleration provided by the proximate carboxylate group. Since the simple bromides are not water soluble, "80%" ethanol was used for such comparisons, and then the bromo acids were also solvolyzed in pure water to examine the effects of a substantial change in reaction medium. The present paper describes the preparation of the bromo acids, with pertinent structure and configuration proof and identification of the solvolysis products in most cases; and an attempt is made to explain the observed behavior of the bromo acids on solvolysis.

Synthesis

Four of the bromo acids employed were previously known: 2-*exo*-bromobicyclo[2.2.1]heptane-1-carboxylic acid (I),[9] 2-*exo*-bromobicyclo[2.2.1]heptane-2-carboxylic acid (II),[10] *trans*-2-bromocyclohexanecarboxylic acid (VII),[11] and its epimer VIII.[11]

Treatment of cyclopentenecarboxylic acid with hydrogen bromide in toluene (satisfactory kinetic control of hydrobromination[1]) afforded essentially pure *cis*-2-bromocyclopentanecarboxylic acid (IX), whereas in hydrogen bromide–glacial acetic acid a mixture of IX and its epimer X, in which X predominated (subsequent epimerization[1]), was obtained. Conversion of IX to X was also achieved in 30% hydrogen bromide–acetic acid, in consonance with previous work.[1]

The synthesis of 3-(equatorial)-bromobicyclo[3.2.1]-octane-2-(equatorial)-carboxylic acid (VI) was developed[1] while the present work was in progress.

(1) Previous paper in this series: W. R. Vaughan and R. Caple, *J. Am. Chem. Soc.*, **86**, 4928 (1964).

(2) Abstracted in part from the Ph.D. dissertation of Peter Scheiner, The University of Michigan, 1961.

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(4) National Science Foundation Cooperative Fellow, 1962–1964.

(5) National Institutes of Health Predoctoral Fellow, 1960–1961.

(6) W. R. Vaughan and R. L. Craven, *J. Am. Chem. Soc.*, 77, 4629 (1955).

(7) (a) S. J. Cristol and W. J. Norris, *ibid.*, **75**, 632 (1953); (b) E. Grovenstein and D. E. Lee, *ibid.*, **75**, 2639 (1953); (c) E. R. Trumbull, R. T. Finn, K. M. Ibne-Rasa, and C. K. Sauers, *J. Org. Chem.*, 27, 2339 (1962).

(8) (a) C. A. Grob and W. Baumann, *Helv. Chim. Acta*, **38**, 594 (1955); (b) C. A. Grob, *Experientia*, **13**, 126 (1957); (c) C. A. Grob, "Kekulé Symposium on Theoretical Organic Chemistry," Butterworth and Co. (Publishers) Ltd., London, 1959, p. 114 ff.

(9) W. E. Boehme, *J. Am. Chem Soc.*, 80, 4740 (1958); **81**, 2762 (1959).

(10) K. Alder, R. Hartmann, and W. Roth, *Ann.*, **613**, 6 (1958).

(11) W. R. Vaughan, R. L. Craven, R. Q. Little, Jr., and A. C. Schoenthaler, *J. Am. Chem. Soc.*, 77, 1594 (1955).

Several unsuccessful approaches to the synthesis of 2-bromobicyclo[2.2.2]octane-1-carboxylic acid (III) were undertaken[2] before the present one was adopted: conversion of 1-carbomethoxybicyclo[2.2.2]octane-2-carboxylic acid[12] to the methyl ester of III (III′) *via* brominative decarboxylation using either the Hunsdiecker silver salt (silver bromide removed prior to decomposition of the acyl hypobromite) procedure or the more recent mercury salt procedure,[13] which proved more convenient. Conversion of III′ to III was accomplished by treatment with hydrogen bromide–glacial acetic acid, a procedure which appears quite satisfactory for the cleavage of even highly hindered esters, since isopropyl mesitoate affords a quantitative yield of mesitoic acid under similar conditions. Hydrogenolysis of III afforded the known bicyclo[2.2.2]octane-1-carboxylic acid (XI), thereby assuring the integrity of the bicyclooctane system. The nonidentity of III with 4-bromobicyclo[2.2.2]-octane-1-carboxylic acid[14] and with 3-bromobicyclo-[2.2.2]octane-1-carboxylic acid (XII) along with the method of synthesis, places the bromine in III in the 2-position.

The preparation of XII was the result of an unsuccessful approach to III: hydrobromination of the methyl ester (XIII′) of bicyclo[2.2.2]octene-1-carboxylic acid (XIII) resulted in both addition and cleavage of XII′ (as for III′); and hydrogenolysis of XII afforded XI. The solvolysis (no kinetic information) of XII afforded 3-hydroxybicyclo[2.2.2]octane-1-carboxylic acid (XIV) which was readily oxidized to the corresponding keto acid XV, whose methyl ester XV′ could not be cleaved with methoxide, thereby precluding existence of a β-keto ester structure for XV′. The character of the solvolysis of III, described in the sequel, confirm its own structure as well as that of XII, as does the relationship between III, IV, and V.

The suggestion[9] that I and II might be readily interconvertible was confirmed by heating pure II at its melting point for a prolonged time, whereupon more than 90% conversion to I was effected. However, no analogous conversion was achieved with III; but refluxing a solution of III′ in 48% hydrobromic acid afforded an isomer IV, which proved to be 2-(equatorial)-bromobicyclo[3.2.1]octane-1-carboxylic acid, rather than the expected 2-(axial)-bromobicyclo-[3.2.1]octane-2-carboxylic acid (XVI).

In another attempt to prepare XVI, 2-(equatorial)-hydroxybicyclo[3.2.1]octane[15] was converted to 2-(equatorial)-bromobicyclo[3.2.1]octane,[16] from which the Grignard reagent was prepared and carbonated to give an acid XVII which could be neither crystallized nor sublimed, some of the original alcohol and a dimeric hydrocarbon, presumably the coupling product of the bromide. Solvolysis in acetic acid of the bromide, followed by hydrolysis of the acetate regenerated the original alcohol, further identified by oxidation to bicyclo[3.2.1]octan-2-one.[15]

The crude XVII was subjected to the Hell–Volhard–Zelinsky reaction whereupon a bromo acid V rather than XVI (or its epimer XVIII) was obtained.

Structure and Configurations of IV and V

Hydrogenolysis of IV and V gives a common product XIX, which is not XI. The n.m.r. spectra[17] of IV, V, and XIX lack any signal attributable to a proton α to carboxyl, and XIX′ is not epimerizable by base. Thus, since XIX and XI are not identical, XIX must possess the bicyclo[3.2.1]octane skeleton; and the bridgehead position for the carboxyl group was confirmed by failure of XIX to experience deuterium exchange in alkaline D_2O (n.m.r.).

The striking similarity of both infrared and n.m.r. spectra of IV and V to each other strongly suggests that they are epimers, and the nature of their solvolysis products (below) supports this hypothesis. Partial conversion of V′ to IV′ was observed in the course of v.p.c. analyses at various temperatures, and treatment of V′ with 48% hydrobromic acid at reflux temperature afforded a mixture of IV and V, the former predominating (n.m.r.).

In the n.m.r. spectra of IV and V there appears a single proton signal downfield from the main envelope of signals in a position characteristic of a proton α to bromine. In the spectrum of IV′ (methyl ester) this signal is a poorly resolved multiplet centered at ~246 c.p.s., while in that of V′ it is a poorly resolved quartet centered at ~267 c.p.s. Previous work in this laboratory[1] permits the inference that the bromine in IV is equatorial and in V is axial. In addition the spin–spin multiplet (apparent J values ~6 and 10 c.p.s.) in the latter is consistent only for an equatorial proton in the 2-position. Consequently IV is the 2-(equatorial)-bromo- and V the 2-(axial)-bromo- derivative of XIX.

The relationships between III, IV, and V are best understood by reference to Figure 1. It must be assumed that the extensive interconversions, A ⇌ B and B ⇌ C, which are not normally observed[18] are the consequence of the carboxylate substituent at or adjacent to the critical reaction sites. It is possible that classical carbonium ion intermediates intervene between A, B, C, and products, but there is no evidence for the formation of more than one epimer for any given structure, either for the bromo acids or their solvolysis products.

The axial position for the carboxyl group is assigned in XVII, since the epimeric XX is known[1] and nonidentical; and beginning with XVII, the Hell–Volhard–Zelinsky reaction is expected to lead to XVI *via* electrophilic bromination[18b] at C-2 (axial attack). In view of the ready reaction II → I (above), one might expect XVII → XVI → A → III; but instead one apparently observes XVII → XVI → A → B → C → V. Furthermore, under more drastic conditions the apparent sequence III → A → B → IV is observed. We suggest that V is kinetically favored over III and IV, and that IV is thermodynamically favored over III and V (V → IV in 48% hydrobromic acid). The elusive character of

(12) P. Scheiner, K. K. Schmiegel, G. Smith, and W. R. Vaughan, *J. Org. Chem.*, **28**, 2960 (1963).
(13) S. J. Cristol and W. C. Firth, Jr., *ibid.*, **26**, 280 (1961).
(14) J. D. Roberts, W. T. Moreland, Jr., and W. Frazer, *J. Am. Chem. Soc.*, **75**, 637 (1953).
(15) K. Alder, K. Heimbach, and R. Reubke, *Chem. Ber.*, **91**, 1515 (1958); K. Alder and R. Reubke, *ibid.*, **91**, 1525 (1958).
(16) *Cf.* J. A. Berson and P. Reynolds, *J. Am. Chem. Soc.*, **84**, 682 (1962), for evidence in support of equatorial configuration.
(17) Obtained using a Varian A-60 instrument (60 Mc.) using internal tetramethylsilane reference.
(18) (a) H. L. Goering, R. W. Greiner, and M. F. Sloan, *J. Am. Chem. Soc.*, **83**, 1992 (1961); (b) H. Kwart and F. V. Scalzi, *ibid.*, **86**, 5496 (1964).

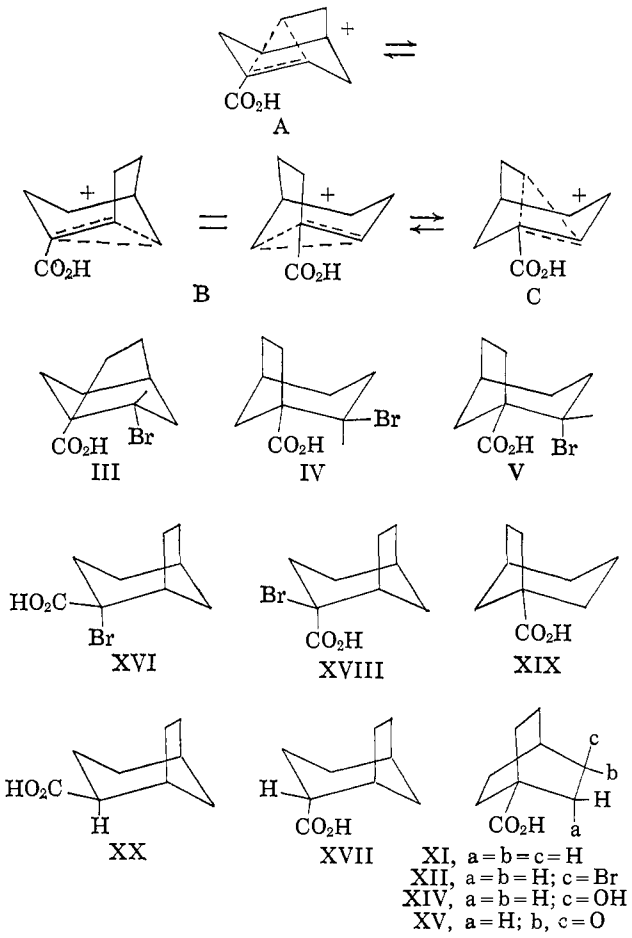

Figure 1.

XVI (and XVIII) suggests that β-bromo acids, for reasons not immediately apparent, are favored over α-bromo acids, in bicyclic bridgehead acids, precedent for which is seen in the II → I conversion.

Solvolytic Products

Monocyclic Systems. No attempts were made to identify products from the solvolyses of the cyclopentane or cyclohexane bromo acids beyond noting that cyclopentene was obtained in approximately 35% yield from IX (*cis* fragmentation) and in 26% yield (*trans* fragmentation) from X in aqueous bicarbonate. The corresponding cyclohexane acids afforded, respectively, 7.5% cyclohexene (*cis* fragmentation) and 49.7% cyclohexene (*trans* fragmentation), under similar conditions.[6]

Bicycloheptane System. When a dilute solution of either I or II in sodium bicarbonate (1:4) in water was heated for about 20 min. at 60–70° the products were the same and in the same ratio (v.p.c. of methyl esters (LAC at 170°) and identical infrared spectra for crude solvolysis products). The product ratio for the acids XXI, XXII, and XXIII is 1:4:11.5. Oxidation of the crude solvolysate affords crude norcamphor (bicyclo[2.2.1]heptan-2-one) in appreciably lower yield (~37%) than obtained for a keto acid (~55%). Thus the most abundant product (XXIII) must be 2-*exo*-hydroxybicyclo[2.2.1]heptane-1-carboxylic acid (m.p. 76–77°, 79–80°; from neutral hydrolysis, 63–70% yield). The norcamphor is the product of oxidative decarboxylation of XXII, 2-*exo*-hydroxy[2.2.1]-heptane-2-carboxylic acid (m.p. 113–114°)[19]; and XXI proved to be the elimination product, nortricyclene-1-carboxylic acid (m.p. 115.5–117.5°).[20] The identical ratios of solvolysis products from I and II indicate a common intermediate ion in the reaction, and only one such ion is realizable.

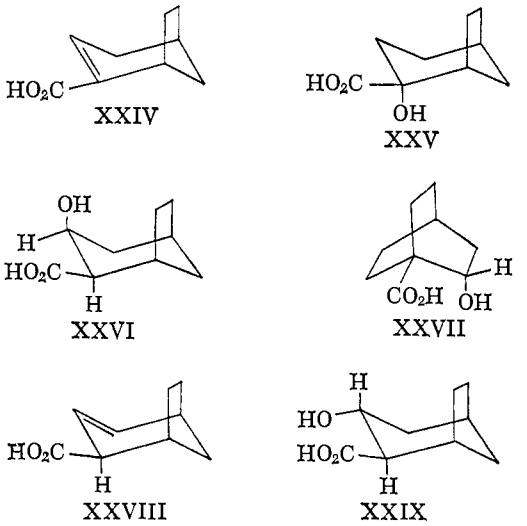

Figure 2. Hydrolysis products from III, V, and VI.

Bicyclooctane Systems. The solvolyses of the related acids, III, IV, and V and the apparently unrelated VI were studied, and, except for IV, all of them afford the same products, III and V producing them in identical amounts. These products (XXIV–XXIX) are illustrated in Figure 2, structural evidence being presented below. In water (1:4 bromo acid–sodium bicarbonate) at ~80° for 2 hr. compounds XXIV–XXVII are produced from III and V in 53, 13, 13, and 20 mole %, respectively, while XXVIII and XXIX are produced in <1% each (v.p.c. of methyl esters).

The solvolysis of IV, which appears to be the most stable of the β-bromo acids in this group (formed under equilibrium conditions, highest melting point, lowest solvolysis rate) affords only XXX (no XXXI). In view of the conversion of 2-(equatorial)-bromobicyclo-[3.2.1]octane to the equatorial alcohol (above) on solvolysis, it would seem reasonable that **B** (Figure 1) should afford XXXI as the major product. Consequently it appears unlikely that **B** is involved in the solvolysis of IV, especially since an analogous bridged ion (from I and II) leads to more of the β-hydroxy bridgehead acid XXIII. The appreciably slower rate of solvolysis as compared with VI which also has its bromine rigidly equatorial suggests a more highly specialized steric requirement (effective entropywise) in solvolysis, *e.g.*, solvent attack at the bridgehead concerted with migration of the methylene bridge. This better counts for the observed stereospecificity than invoking **B** or classical carbonium ions as intermediate(s). The choice of XXX (instead of XXXI) (Figure 3) for the product is made on the basis of its complete inertness to Jones' reagent oxidation, the

(19) H. Kwart and G. Null, *J. Am. Chem. Soc.*, 82, 2348 (1960).
(20) (a) K. Alder, R. Hartmann, and W. Roth, *Chem. Ber.*, 93, 2271 (1960); note that this paper wrongly assigns the structure XXII to the acid melting at 79–80° (*cf.* ref. 19); (b) H. Hart and R. A. Martin, *J. Org. Chem.*, 24, 1267 (1959).

fact that the band for its methyl ester XXX′ appears later in the v.p.c. spectrum than that of its epimer (XXV′, below), and the absence of a signal for a proton α to hydroxyl in the n.m.r. spectrum.

The structure of XXIV was shown by isolation and comparison with an authentic sample,[1] and a mixture of XXV and XXVII was available for comparative v.p.c. and behavior on oxidation, during which (warm acidic permanganate on methyl esters) only one member of the pair was affected (XXVII). The identity of XXVI with one of the two principal solvolysis products from VI was established by comparative v.p.c. (methyl esters and methyl esters of Jones' oxidation products); only XXVI′ is oxidized while XXIX has the longer retention time. The structure of XXVIII is speculative, but the v.p.c. band for its methyl ester merged with that of XXIV′ on treatment with base (prior to methylation). The equatorial orientation for the carboxyl group of XXVIII follows from the character of hydride migration necessarily involved in the production of XXVI, XXVIII, and XXIX from A and from the solvolysis of VI.

The solvolysis of VI, as noted above, provided the same products as from III and V, but in different amounts. The predominant products were XXVI and XXIX, of which only XXVI admitted of isolation in sufficient purity for analysis. The production of the other solvolytic products is presumed to be the consequence of a certain amount of vicinal hydride shift leading from an initial classical carbonium ion to A, *i.e.*, the reverse of what happens with III and V. Evidently there is a high energy barrier to such rearrangement from either direction.

One curious feature of the solvolysis of VI is noteworthy: a lower relative yield of the unsaturated acids XXIV and XXVIII is obtained at higher pH, while the relative yield of XXVI is increased at the expense of XXIX, these latter epimers being produced in about equal amounts at lower pH values. This observation resulted from employing excess sodium carbonate for higher pH and sodium bicarbonate for lower pH. That it is not to be attributed to a salt effect follows from the fact that increase or decrease in bicarbonate concentration does not affect the product distribution. The orientations for the alcohol functions are assigned on the basis of the fact that only XXVI is readily affected by Jones' reagent. Thus inversion of configuration is promoted by increasing pH, as observed for α-bromo acids[21] as well as for β-bromo acids.[6,22]

Kinetics of Solvolysis

A concise review of the nature of bromo acid solvolysis involving participation of the carboxylate group[23] attributes observed rate differences to the size of an intermediate lactone ring (up to a six-membered ring), since there is a virtually constant entropy of activation[22,24,25] (~11.5 e.u.). The constant entropy factor has been attributed to a loss of solvating molecules in passing from ground to activated states; and when coupled with facile ring formation, this is enough to mask any contribution from a simpler field effect attributable to the carboxylate group.[26]

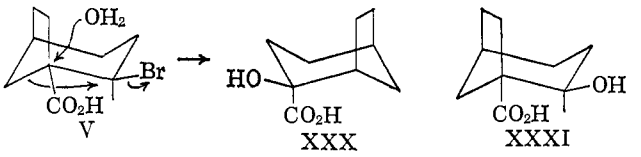

Figure 3.

If configuration of a β-bromo acid inhibits anchimeric assistance in solvolysis, two electrostatic effects remain in opposition to each other: facilitation of ionization by a field or inductive effect[26] and resistance to formation of a higher energy species (dipolar ion). An examination of the data displayed in Table I reveals invariable rate enhancement for the β-bromo acids over the simple bromides (8–42-fold) in 80% ethanol, and still further rate enhancement (Table II) for such β-bromo acids (III, VIII, and IX) in water.

Although activation parameters have been calculated using but two temperatures (*cf.* ref. 21, 22, and 25), it is noteworthy that for III and IX ΔE_a is appreciably *larger* in water than in 80% ethanol whereas ΔS^* is >30 e.u. more positive in water. Furthermore an increase toward more positive values of 21 ± 5 e.u. is to be noted between the simple bromides and the β-bromo acids (I, III, VIII, and IX) in 80% ethanol, whereas ΔE_a for the acids is 4 ± 1 kcal. larger than for the simple corresponding bromides.

The increase in ΔE_a is in line with the anticipated effect of a more energetic transition state for the bromo acids compared to the simple bromides, but one would also anticipate attainment of this condition with less expenditure of energy in water than in 80% ethanol, unless "shedding" of solvent molecules is required. It would appear that intrusion of a positive pole at C^β induces a decrease in electrophilic solvation at the carboxylate group and is itself better compensated by the latter than by nucleophilic solvation as the transition state is approached (*cf.* the real though small effect on pK_a of a β-bromine in I and III, Table III). The consequence is extreme in III. The internal return phenomenon further complicates the picture in the cases of the bridgehead bicyclic acids, though it appears to be less significant in the present media (dielectric constants: 80% ethanol, 34; water, 80) than in the acetolysis (acetic acid dielectric constant 7.14) of the related bicyclo[3.2.1]oct-2-yl tosylate,[18] since kinetic plots of ln [RBr] *vs.* time for III in both 80% ethanol and water are straight lines from less than 10% reaction out to more than 80% reaction. Such medium effects have been noted elsewhere.[18,27] The phenomenon is most pronounced, however, in the case of I and II, for on solvolysis of II the rate of bromide release falls dramatically from an initially very rapid specific rate to that obtained for I after a very short reaction time. Furthermore, the change

(21) W. A. Cowdrey, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1208, 1243 (1937).
(22) A. R. Olson and R. T. Miller, *J. Am. Chem. Soc.*, 60, 2687 (1938).
(23) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., pp. 116–119.
(24) J. F. Lane and H. W. Heine, *J. Am. Chem. Soc.*, 73, 1348 (1951).
(25) H. W. Heine, E. Becker, and J. F. Lane, *ibid.*, 75, 4514 (1953).
(26) *Cf.*, however, C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., pp. 327–329, wherein the inductive effect of a proximate carboxylate group is likened to that of a methyl group.
(27) S. Winstein and K. C. Schreiber, *J. Am. Chem. Soc.*, 74, 2165 (1952).

Table I. Kinetics in 80% (Vol.) EtOH–HCO_3^-

Compd.	Temp., °C.	$k \times 10^5$, sec.$^{-1}$ [a]	E_a, kcal.	ΔS^*, e.u.	$k \times 10^5$, sec.$^{-1}$, 62°	k relative to parent compd. at 60°
Cyclopentyl bromide[b]	72.7	4.09				
	61.5	1.70	18.3	−28	1.70	1
IX[b]	61.5	9.73				
	50.4	2.84	23.8	−8.0	9.73	8
Cyclohexyl bromide[c]	99.8	2.31				
	80.0	0.354	25.0	−15	0.046	1
VII	45.3	128				
	40.1	56.0				
	32.3	23.4	25.3	+5.5	1040	21,600
VIII[b]	71.1	6.12				
	60.0	1.66	26.8	−2.0	1.93	42
exo-Norbornyl bromide[d]	65.0	9.14				
	60.0	5.72	21.9	−17	6.55	1
I[d]	45.0	7.78 (i)				
		8.53 (f)[e]				
	40.0	4.16 (i)				
		4.14 (f)	28.6	+11	72.5	11
II[d]	45.0	69.9 (i)				
		8.72 (f)[f]				
Bicyclo[2.2.2]oct-2-yl bromide[d]	85.0	8.62 (i)				
		4.50 (f)				
	65.0	2.22 (i)				
		0.945 (f)				
	50.0	1.05 (i)				
		0.222 (f)	19.9	−25	0.665	1
III[d]	65.0	6.4 (i)				
		18.9 (f)				
	60.0	5.0 (i)				
		10.2 (f)[g]				
	55.0	3.9 (i)				
		5.78 (f)	26.1	0	11.2	17

[a] The letters i and f refer to initial and final rates. The former are derived from plots of integrated rate constants *vs.* time extrapolated back to zero time (*cf.* ref. 18). [b] Automatic titrator method. [c] H. L. Goering and H. H. Espy, *J. Am. Chem. Soc.*, **78,** 1454 (1956). [d] Volhard titration method. [e] Using the automatic titrator method a value of 10.5×10^{-5} was obtained. Extrapolation to zero time showed no deviation from a straight line. [f] Using the automatic titrator method a value of 10.3×10^{-5} was obtained. The kinetic plot did not become linear until ~34% reaction. [g] Using the automatic titrator method a value of 15.4×10^{-5} was obtained at 61.8°. Extrapolation back to zero time showed no deviation from a straight line. This is to be compared with a value of 11.7×10^{-5} obtained from the Arrhenius equation at the same temperature.

from the initial to final specific rates diminishes with falling temperature; *i.e.*, there is more of the less stable α-bromo acid present in equilibrium with the more stable β-isomer at higher temperatures. Unfortunately the α-bromo isomer corresponding to III has proven elusive, further rearrangement intervening to produce IV or V, which solvolyze at slower rates than III.

Table II. Solvolysis in H_2O–HCO_3^-

Compd.	Temp., °C.	$k \times 10^5$, sec.$^{-1}$	E_a, kcal.	ΔS^*, e.u.
III	62[a,b]	2120		
	40.3	69.5		
	35.1	29.9	31.1	+20
IV	61.8	4.76		
V	61.8	55.6		
VI	61.8	10.4		
VII	61.8[a]	790		
	45.3	77.0		
	32.3	11.8	27.9	+13
VIII	61.8	52.7		
IX	62[a]	164		
	45.3	18.2		
	35.1	4.24	27.9	+10

[a] Calculated from an Arrhenius plot. [b] Solubility in pure water containing bicarbonate too slow for satisfactory study. Acid dissolved in acetone and then diluted with bicarbonate solution. Final solution >95% H_2O.

Table III. Apparent pK_a Values in 80% Ethanol at 25°

Acid	pK_a[a]
I	6.93
Bicyclo[2.2.1]heptane-1-carboxylic acid	7.59
III	7.15
XI	7.91

[a] Determined by half-neutralization in 80% ethanol (by volume). Titration followed with a Beckman pH meter, and plots of apparent pH *vs.* milliliters of standard sodium hydroxide afforded smooth curves from which the apparent pH at half-neutralization was easily obtained. The apparent pK was obtained from the apparent pH at half-neutralization using the Henderson–Hasselbach equation (*cf.* J. S. Fruton and S. Simmonds, "General Biochemistry," John Wiley and Sons, Inc., New York, N. Y., 1959, p. 87).

No attempt was made to look for the internal return phenomenon in pure water, but it seems safe to assume (in view of its minor importance in 80% ethanol) that no ion-pair intermediate survives long enough in

water to permit isomer equilibration, *i.e.*, it dissociates at once.

The order of solvolytic reactivity for the bridgehead acids (III, IV, and V; Table II) is the same as observed for the corresponding tosylates,[18] and the suggestion that the tosylate corresponding to IV experiences little if any anchimeric assistance[18] in acetolysis is confirmed by comparison of the rates of hydrolysis for IV and VI, which are conformationally similar while VI does not admit of anchimeric assistance by neighboring carbon. At the same time the conformationally similar VIII (axial bromine[1]) and V hydrolyze at nearly comparable rates, suggesting that anchimeric assistance by neighboring carbon has minimal *absolute* significance, though its *relative* importance (*cf.* III, IV, and V and corresponding tosylates[18]) is probably the same as in acetolysis of the corresponding tosylates.

The data obtained for the various β-bromo acids provide norms for solvolysis of such systems with a variety of stereochemical environments for the bromine, such that any effect of the proximate carboxylate must be nonanchimeric. Thus IV and VI represent the least favorable equatorial situation for bromine, or a minimum hydrolysis rate, while V and VIII represent a more favorable situation (axial bromine). Finally IX represents a situation wherein bromine and carboxylate are essentially eclipsed and no anchimeric assistance is available while III represents a situation wherein the dihedral angle between bromine and carboxylate is nearly the same as in IV (and V or VIII), but with the possible intervention of assistance to solvolysis by neighboring carbon (as in I, for which such assistance is clearly expected). That some anchimeric assistance for bicyclo[2.2.2]oct-2-yl bromide and III obtains may be inferred from the behavior of the corresponding tosylate.[18] But since the principal acceleration in III over the simple bromide appears to derive from the entropy of activation, it seems reasonable to attribute this to solvation differences in ground and transition states for the related systems. In comparing the solvolyses of the bromo acid in 80% ethanol and in water, the general effect appears to be in line with better ground-state solvation in water coupled with a necessity to lose the solvating molecules at the transition state. The special case of VII shows the striking difference encountered when anchimeric assistance by carboxylate is involved (*cf.* VII and VIII, Tables I and II).

Conclusions

When steric considerations inhibit anchimeric assistance by a carboxylate group β to bromine, there is appreciable rate acceleration on solvolysis. This may be attributed to a field effect which is the consequence of mutually opposed electrostatic effects in the transition state resulting in a decrease in solvation as the transition state is achieved.

The presence of the carboxylate group appears to facilitate the interconversion of the hitherto rather discrete[18] nonclassical carbonium ions of the bicyclooctane system,[28] possibly because any polar group associated with the positively charged centers of the ions introduces energy differences which appear to reduce the energy barriers between the ethylene-bridged ions, A and C, and the methylene-bridged ion, B. The previously suggested minimal anchimeric assistance in the solvolysis of an equatorially substituted bicyclo[3.2.1]oct-2-yl derivative[18] may arise from the fact that the solvent is required in a specific manner to effect heterolysis of the carbon-leaving group bond (*e.g.*, concerted solvent attack, heterolysis, and rearrangement), as in the hydrolysis of IV.

Unless a special steric situation permits neighboring carbon participation (*e.g.*, in I and probably III), any distinctive rate increases above that of a simple halide larger than those herein reported may be attributed to participation by the carboxylate in achieving a transition state (*cf.* VII with VIII and cyclohexyl bromide, Table I). Conversely, any reactions, such as fragmentation or lactonization, of β-bromo acids which exhibit specific rates comparable with those of the models reported in Tables I and II cannot involve anchimeric participation by the carboxylate group.

Experimental[29,30]

Methyl 2-Bromobicyclo[2.2.2]octane-1-carboxylate (III'). *A.* A solution of 22.1 g. (0.104 mole) of 1-carbomethoxybicyclo[2.2.2]octane-2-carboxylic acid[10] in 55 ml. of absolute methanol was titrated with methanolic potassium hydroxide (phenolphthalein), and the resulting solution was treated with stirring with 17.7 g. (0.104 mole) of silver nitrate in 35 ml. of methanol and 45 ml. of water. The white precipitate was filtered, washed with absolute methanol, and dried in the dark at 70° (5 mm.) for 40 hr. yielding 37.8 g. (86.5%). The product comprises the silver salt and potassium nitrate (about 1:1). Next 36.0 g. of this dried and powdered salt mixture was added in small portions to a chilled (−28 ± 5°) solution of 16.0 g. (0.100 mole) of bromine (dried over phosphorus pentoxide) in 250 ml. of dried carbon tetrachloride with good stirring, which was continued for 15 min. after complete addition. The resulting mixture was then filtered rapidly through coarse filter paper in a vacuum-jacketed funnel. The filtrate was kept cool and refiltered, allowed to warm slowly to room temperature, and then was refluxed for 5 hr., washed with 100 ml. of 10% sodium bisulfite, and dried over magnesium sulfate. Removal of solvent and vacuum distillation afforded 9.1 g. (43%) of III', b.p. 75–77° (0.15 mm.), $n^{22}D$ 1.5151, $n^{17}D$ 1.5162.

B. A mixture containing 126 g. of 1-carbomethoxybicyclo[2.2.2]octane-2-carboxylic acid,[10] 100 g. of bromine, and 80 g. of mercuric oxide[11] in 500 ml. of carbon tetrachloride at 0° was allowed to warm slowly, with stirring, until carbon dioxide evolution commenced, whereupon occasional cooling (ice bath) was used to moderate the vigorous reaction. After carbon dioxide evolution subsided, the mixture was refluxed for 2 hr., during which time the bromine color disappeared. The mixture was then cooled and filtered with the aid of Celite, and removal of solvent afforded 140 g. (94%) of III', identical with that pre-

(28) *Cf.* J. A. Berson and P. Reynolds-Warnoff, *J. Am. Chem. Soc.*, **86**, 959 (1964); J. A. Berson and D. Willner, *ibid.*, **86**, 609 (1964).

(29) Boiling and melting points uncorrected unless otherwise noted.

(30) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra obtained from Nujol mulls (solids) or liquid films, Perkin-Elmer Model 21 infrared spectrometer. N.m.r. spectra obtained using a 60-Mc. Varian Model A-60 instrument. All spectra prepared by Mr. B. E. Wenzel and Mr. Frank Parker, of this laboratory.

pared above (infrared, refractive index). Distillation in either case failed to afford a good analytical sample owing to facile dehydrobromination. Consequently crude material was used in subsequent reactions.

Hydrogenolysis and Hydrolysis of III′ to XI. Hydrogenation (1 g. of 5% palladium–carbon) of an initially cooled solution of III′ (0.5 g.) and 0.3 g. of potassium hydroxide in 25 ml. of 60% aqueous ethanol was carried out at atmospheric pressure. After removal of catalyst the solution was refluxed overnight and then was concentrated and acidified with concentrated hydrochloric acid to give 0.4 g. of crude XI. One recrystallization from water afforded pure XI, m.p. 140–141°, which did not depress the melting point of an authentic sample of bicyclo[2.2.2]octane-1-carboxylic acid (XI)[31,32] and which provided an identical infrared spectrum.

2-Bromobicyclo[2.2.2]octane-1-carboxylic Acid (III). The methyl ester III′ was cleaved by heating in 30% hydrogen bromide–acetic acid in a sealed tube at 100° for 30 hr. Cooling afforded a nearly quantitative yield of III. Alternatively 13.3 g. of III′ (0.054 mole) was refluxed with 90 ml. of 50% hydrogen bromide–acetic acid for 2 hr. after which 3 hr. of gentle evaporation in an air stream afforded 13.3 g. (100%) of crude III, m.p. 161–165°.[33] Repeated recrystallization from hexane afforded the analytically pure material used for kinetic studies, m.p. 169.5–170.0°.

Anal. Calcd. for $C_9H_{13}BrO_2$: C, 46.37; H, 5.67; Br, 34.28. Found: C, 46.47; H, 5.71; Br, 34.18.

Hydrogenolysis of III to XI. A solution of 0.3 g. (1.3 mmoles) of III and 0.2 g. (3.6 mmoles) of potassium hydroxide in 10 ml. of 70% aqueous ethanol was hydrogenated at atmospheric pressure over 0.5 g. of 5% palladium on carbon. After filtration the solution was diluted with water and then concentrated to *ca.* 5 ml. by boiling. Acidification with concentrated hydrochloric acid afforded pure XI, m.p. 140–141°, providing an identical infrared spectrum and mixture melting point with authentic XI.[31,32]

Bicyclo[2.2.2]octene-1-carboxylic Acid (XIII). A suspension of 18.8 g. (0.079 mole) of 1-carbomethoxybicyclo[2.2.2]octane-*cis*-2,3-dicarboxylic anhydride[34] in 56 ml. of 20% aqueous potassium hydroxide was warmed on the steam bath for 10 min. after dissolution, and then 15 ml. of concentrated hydrochloric acid was added cautiously whereupon a precipitate appeared and was filtered off and washed thoroughly with water. After drying at 100° (0.35 mm.) for 1 hr., the dibasic acid weighed 16.7 g. (82.5%), m.p. 162–163° dec. Of this substance 16.6 g. (0.065 mole) was added to 64 ml. of acetonitrile (anhydrous), 10 ml. of anhydrous pyridine, and freshly recrystallized (glacial acetic acid) lead tetraacetate (3.14 g., 0.071 mole). The mixture was stirred at room temperature until a clear, deep yellow solution was obtained, and then the flask was warmed to 60° and maintained at this temperature for 1 hr., by which time the moderate gas evolution had abated and a white precipitate was present. After discontinuing the heat, the mixture was diluted with 100 ml. of water (complete resolution) and then twice extracted with 70-ml. portions of 40–60° petroleum ether. The organic extracts were washed with 60-ml. portions of dilute hydrochloric acid, water, and then dried over magnesium sulfate. Evaporation of the solvent afforded 6.4 g. (59%) of XIII′, the methyl ester of XIII, b.p. 62° (1.3 mm.), $n^{22}D$ 1.4820.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.37; H, 8.51.

A 6.0-g. (0.036 mole) sample of this ester was refluxed with 3.5 g. of potassium hydroxide in 7 ml. of water and 20 ml. of methanol for 2 hr., and the clear solution was then concentrated by evaporation under reduced pressure until solid material began to appear when it was diluted with 20 ml. of water and acidified with 10% hydrochloric acid. The resulting precipitate was collected, washed well with water, and dried at 55° (35 mm.) for 2 hr. yielding 5.3 g. (97%), m.p. 117.5–118.5°, from 10% ethanol–water.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.13; H, 8.02.

Hydrogenation of XIII afforded XI, indistinguishable from an authentic sample.[31,32]

3-Bromobicyclo[2.2.2]octane-1-carboxylic Acid (XII). A solution of 7.7 g. (0.046 mole) of the methyl ester of XIII (XIII′) in 50% hydrogen bromide–acetic acid was magnetically stirred in a pressure bottle for 43 hr. at room temperature, after which the mixture was evaporated to a thick paste in an air stream and transferred to a porous plate. The dried residue (9.8 g., 91.5%) of white powder melted at 110–120°, and five recrystallizations from hexane afforded pure XII, m.p. 144.0–144.5°. The infrared spectrum is different from that of III.

Anal. Calcd. for $C_9H_{13}BrO_2$: C, 46.37; H, 5.62; Br, 34.28. Found: C, 46.56; H, 5.69; Br, 34.15.

Hydrogenolysis of XII to XI. This was carried out as reported above for III with the same results. The product was indistinguishable from authentic XI.[31,32]

2-(Equatorial)-bromobicyclo[3.2.1]octane-1-carboxylic Acid (IV). A mixture of 1.0 g. of III′ or III (4.05 mmoles) and 10 ml. of 48% aqueous hydrobromic acid was refluxed for 1.5 hr. On cooling 0.7 g. of gummy white solid was deposited (~70%). Four recrystallizations from hexane (or benzene–petroleum ether) afforded analytically pure IV, m.p. 218.5–219.5°.

Anal. Calcd. for $C_9H_{13}BrO_2$: C, 46.37; H, 5.62; Br, 34.28. Found: C, 46.31; H, 5.72; Br, 34.16.

The n.m.r. spectrum of the methyl ester of IV (IV′, diazomethane) shows a poorly resolved multiplet centered at 246 c.p.s. corresponding to a single proton, and no other signals outside the methyl ester signal and the complex envelope of signals due to the rest of the structure.

Hydrogenolysis of IV to XIX. This was carried out as for previous bromo acid hydrogenolyses. The product was purified by sublimation, m.p. 73.5–74.5°.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.08; H, 9.16. Found: C, 70.28; H, 8.99.

The n.m.r. spectrum of XIX′ (methyl bicyclo[3.2.1]octane-1-carboxylate) shows no signal outside the complex methylene–methine envelope but the methyl ester signal. The v.p.c. retention time and infrared spectrum of XIX′ remained unaltered after prolonged

(31) C. A. Grob, M. Ohta, E. Renck, and A. Weiss, *Helv. Chim. Acta*, 41, 1191 (1958).
(32) J. D. Roberts and W. T. Moreland, Jr., *J. Am. Chem. Soc.*, 75, 2167 (1953).
(33) Similar treatment of isopropyl mesitoate afforded a quantitative yield of mesitoic acid, identified by mixture melting point.
(34) A. Sayigh, Dissertation, Columbia University, 1952, p. 86.

refluxing with methanolic sodium methoxide. Furthermore, no change in the n.m.r. spectrum of XIX itself (as potassium salt) in deuterium oxide was observed over a 1-week period, indicating no deuterium exchange, *i.e.*, no hydrogen α to carboxyl.

2-(Axial)-bromobicyclo[3.2.1]octane-1-carboxylic Acid (V). A. 2-(Equatorial)-bromobicyclo[3.2.1]octane. The corresponding alcohol[15] (50 g.) was refluxed with 250 ml. of 48% hydrobromic acid for 4 hr. Then 50 ml. of concentrated sulfuric acid was added and the refluxing was continued for 1 additional hr., after which it was diluted with water and extracted with methylene chloride. Distillation at 10 mm. afforded 63 g. (84%), b.p. 75–80°.

Anal. Calcd. for $C_8H_{13}Br$: C, 50.8; H, 6.93; Br, 42.3. Found: C, 50.9; H, 7.06; Br, 41.9.

Acetolysis followed by alkaline hydrolysis and oxidation of the resultant alcohol afforded bicyclo[3.2.1]-octan-2-one, identified by comparison with an authentic sample (*cf.* ref. 1). V.p.c. analysis of the bromide (10% silicone oil) shows >99% purity. The equatorial configuration is assigned in line with other work on this system.[16]

B. 2-(Axial)-bicyclo[3.2.1]octanecarboxylic Acid (XVII). The preceding bromide was converted to the Grignard reagent by the procedure in which the magnesium is retained in a column above refluxing ether while the ethereal halide solution is slowly allowed to pass through the magnesium column. Two products were obtained; one was a neutral hydrocarbon, m.p. 75–76° (*Anal.* Calcd. for $C_{16}H_{26}$: C, 88.9; H, 11.1. Found: C, 88.9; H, 11.2); the other was acidic, (5.3 g., 48%) and without a well-defined melting point. Thin layer chromatography (30% ether–10% acetone–60% benzene) showed but one component, and this could neither be crystallized nor sublimed. Since the 2-equatorial acid[1] as well as the bridgehead acid (XIX, above) in this system differ markedly in properties, the 2-*axial* position is assigned to the carboxyl in this compound (XVII).

C. V. A 5.3-g. sample of the preceding acid was treated with 6.6 g. (20% excess) of bromine and a few drops of phosphorus tribromide on the steam bath (24 hr.) and then was poured into water. Ether extraction followed by isolation of the acidic component (2.5 g., 32%) afforded V, m.p. 188°, from benzene.

Anal. Calcd. for $C_9H_{13}BrO_2$: C, 46.37; H, 5.62; Br, 34.30. Found: C, 46.17; H, 5.68; Br, 34.50.

The n.m.r. spectrum of V′ (methyl ester of V, diazomethane) shows a signal at 267 c.p.s. for one proton, and except for the methyl ester signal, no other signals apart from the main envelope. A sample of V′ was isomerized to IV by heating with 48% hydrobromic acid as for the preparation of IV from III′, and by using a relatively high temperature on v.p.c. this isomerization could be observed (V′ → IV′) on the column.

Hydrogenolysis of V to XIX. This was accomplished as for IV with identical results. The product XIX was treated as above with no deviation from the reported observations.

2-cis-Bromocyclopentanecarboxylic Acid (IX). A nearly quantitative yield of IX may be obtained by allowing cyclopentene-1-carboxylic acid[35] to stand at room temperature for 8 days in 30% hydrogen bromide–acetic acid, m.p. 100.0–100.5°. The same product is obtained from hydrogen bromide in toluene.

Anal. Calcd. for $C_6H_9BrO_2$: C, 37.33; H, 4.69; Br, 41.40. Found: C, 37.22; H, 4.62; Br, 41.60.

Treatment of IX with diazomethane afforded the methyl ester.

Anal. Calcd. for $C_7H_{11}BrO_2$: C, 40.60; H, 5.36; Br, 38.59. Found: C, 40.52; H, 5.24; Br, 38.50.

2-trans-Bromocyclopentanecarboxylic Acid (X). A 1.0-g. sample of cyclopentene-1-carboxyli cacid[35] (8.9 mmoles) in 10 ml. of 30% hydrogen bromide–acetic acid was heated in a sealed tube for 12 hr., after which the excess reagent was removed *in vacuo* with gentle heating. The dark residue was taken up in ether, dried over magnesium sulfate, and decolorized with Norit. Removal of the solvent afforded an oil which solidified on being cooled by Dry Ice, and addition of a few drops of 60–70° petroleum ether induced crystallization. Four recrystallizations from this solvent afforded pure X, m.p. 42–43°.

Anal. Calcd. for $C_6H_9BrO_2$: C, 37.33; H, 4.69; Br, 41.40. Found: C, 37.21; H, 4.54; Br, 41.40.

Treatment of X with diazomethane afforded the methyl ester, which was shown by v.p.c. to be free of the *cis* isomer.

Anal. Calcd. for $C_7H_{11}BrO_2$: C, 40.60; H, 5.36; Br, 38.59. Found: C, 40.80; H, 5.43; Br, 38.39.

It is possible to prepare X from IX by epimerization, presumably *via* the acid enol.[1] Thus heating IX in 30% hydrogen bromide–acetic acid at 100° for 10 min. affords 60% X to 40% IX (v.p.c. of methyl esters, LAC 446). This is faster isomerization than observed for the corresponding cyclohexane system, but a competition experiment involving cyclohexene-1-carboxylic acid and cyclopentene-1-carboxylic acid in the hydrogen bromide–acetic acid reagent (*cf.* ref. 1) shows that the latter also reacts from 1.5 to 2.0 times as fast as the former.

Thermal Isomerization of I and II. In a closed flask 6.1 g. of carefully purified II[9] was heated to 150 ± 5° for 11.5 hr. On cooling, a gray product, m.p. 128–142°, was obtained. The infrared spectrum of this substance showed it to be I, slightly contaminated with II. Two recrystallizations from 90–100° petroleum ether afforded I, m.p. 149.5–150.5°. Authentic I[9] melts at 150.0–150.5°, and a mixture melting point showed no depression.

Hydrolysis of I and II. Both compounds gave exactly similar results under the following conditions. A solution of 5.5 g. of bromo acid (0.025 mole) in 40 ml. of 5% aqueous sodium hydroxide was refluxed for 7 hr. Following extraction with four 40-ml. portions of ether of the acidified mixture, the extracts were combined and dried over magnesium sulfate. Removal of the solvent afforded 3.8 g. (~97%) of a viscous oil whose infrared spectrum showed absorption for hydroxyl at 3350 and carbonyl at 1700 $cm.^{-1}$, the entire spectrum being identical with either I or II.

Oxidation of the Hydrolysate of I or II. A 4.00-g. sample of crude hydrolysate from I (or II) suspended in 50 ml. of dilute sulfuric acid was treated with 3.08 g. (0.0195 mole) of solid potassium permanganate with stirring, and then the mixture was heated on the steam

(35) W. Dieckmann, *Ann.*, **317**, 66 (1901).

bath for 20 min., after which the dark brown suspension was cooled and treated with 3.0 g. of solid sodium bisulfite in small portions. After warming to expel sulfur dioxide, the pale yellow solution was extracted with four 40-ml. portions of ether which in turn were combined and extracted with two 30-ml. portions of 3% aqueous sodium hydroxide.

The residual ether solution was evaporated, leaving 1.0 g. (37% of the crude hydrolysate) of a fragrant white solid, m.p. 69–85°. This was identified as norcamphor from its infrared spectrum (carbonyl absorption, 1745 $cm.^{-1}$), its physical properties, and its semicarbazone, m.p. 198°, previously reported, 196–197°.[36]

The basic extracts were combined and concentrated by boiling and then acidified with concentrated hydrochloric acid. On cooling there separated a small amount of white solid, which after recrystallization from pentane melted at 115.5–117.5° (XXI). The infrared spectrum showed only carboxyl function, and nortricyclene-1-carboxylic acid has been reported to melt at 116[19] and 117–118°.[20]

After filtration from the nortricyclene-1-carboxylic acid the filtrate was extracted with four 25-ml. portions of ether. After drying evaporation afforded 2.0 g. (51–57%) of a viscous oil, which upon seven recrystallizations from 90–100° petroleum ether melted at 128.0–128.5°. The infrared spectrum was that of a keto acid with no contamination with XXI. This compound is presumed to be 2-ketobicyclo[2.2.1]-heptane-1-carboxylic acid.

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.37; H, 6.54. Found: C, 62.47; H, 6.52.

Repetition of the hydrolysis and esterification of the acidic product with diazomethane afforded a mixture which upon v.p.c. analysis (LAC at 170°) could be shown to consist of three components in the ratios, 1:4:11.5. The source of the keto acid thus is 2-*exo*-hydroxybicyclo[2.2.1]heptane-1-carboxylic acid (XXIII), the most abundant product. This was isolated after neutral hydrolysis of 2.0 g. of I by refluxing in water for 55 hr. followed by extraction with four 50-ml. portions of ether, which, after drying over magnesium sulfate, afforded 0.9 g. (63%) of viscous oil. Repeated recrystallization from hexane gave a product, XXIII, m.p. 79–80°, previously reported 76–77°.[28]

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.64; H, 7.78.

Solvolysis of II under similar conditions afforded the same product.

Hydrolysis of IX and X. These compounds were treated identically. Bromo acid (100 mg.) and 100 mg. of potassium bicarbonate were added to a mixture of 10 ml. of water and 10 ml. of chloroform in a test tube which was sealed and heated on the steam bath for 30 min. with occasional shaking. The tube was then opened, the contents was transferred to a separatory funnel, and the tube was rinsed with 10 ml. of additional chloroform which was added to the original extract. After separation, the chloroform layer was treated with a 5% bromine–chloroform solution until a faint color persisted. The solution was then dried and the solvent was removed, after which a known quantity of toluene was added (*ca.* 0.4 mmole), and the ratio of toluene to 1,2-dibromocyclopentane was determined by programmed v.p.c. analysis, using a known mixture to establish reliability (LAC at 446). The average amount of cyclopentene from the *cis* acid IX was 35 ± 5% and from the *trans* acid X was 26 ± 4% (four determinations each).

Hydrolysis of XII to XIV. A solution of 1.6 g. (6.9 mmoles) of XII in 30 ml. of water was refluxed for 46 hr. The solution was then extracted with three 30-ml. portions of ether, and the extracts were dried over magnesium sulfate and evaporated to yield 0.9 g. (77%) of white crystalline product, m.p. 145–148°. Four recrystallizations from benzene–ethyl acetate (3:1) afforded pure 3-hydroxybicyclo[2.2.2]octane-1-carboxylic acid (XIV), m.p. 153–154°.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.41; H, 8.29. Found: C, 63.62; H, 8.18.

Oxidation of XIV to XV. A solution of 0.32 g. (1.88 mmoles) of XIV in 10 ml. of reagent grade acetone was chilled in an ice–salt bath and treated dropwise with 0.50 ml. (1.25 mmoles) of 2.67 *M* Jones' reagent.[37] After 5 min. of stirring the green mixture was filtered and the solvent was removed by boiling. An oil (0.31 g., essentially quantitative) which crystallized on standing was obtained, m.p. 85–93°. The infrared spectrum showed carbonyl bands at 1720 and 1690 $cm.^{-1}$ and no hydroxyl absorption. Conversion to the methyl ester (diazomethane) followed successively by refluxing in methanolic sodium methoxide for 11 hr. and dilution with water followed by an additional 5 hr. refluxing permitted essentially quantitative recovery of XV (3-ketobicyclo[2.2.2]octane-1-carboxylic acid; infrared).

Solvolysis Procedure for III–VI. For purposes of isolation of solvolytic products and/or identification by v.p.c. analysis, each of the bromo acids was dissolved in excess (1:4) 5% sodium bicarbonate solution and heated at 80–100° from 2 to 24 hr., the former time appearing to suffice. Cooling followed by acidification and extraction with ether effected isolation of all organic material. Individual products were isolated by evaporation of the ether and appropriate recrystallization. Usually a portion of the ethereal extract was treated with diazomethane to provide methyl esters for v.p.c. The individual v.p.c. bands were then identified insofar as possible by adding specific methyl esters in small amounts to the ethereal solution of mixed esters and noting either new bands or distinct increase in one of the bands already present.

In a number of cases it was necessary to investigate the effect of oxidizing agents (*e.g.*, permanganate, Jones' reagent), on an ester mixture. Under these circumstances the ether was removed and the residue was treated with the desired reagent. Then the organic material was redissolved in ether and again subjected to v.p.c., the disappearance of one or more bands with the appearance of new bands being noted.

Solvolysis of III and V. V.p.c. (LAC at 180°) analysis showed four major components (molar ratios, 53:13:20:13) and two minor components each in less than 1 mole %. The principal product was isolated and characterized as bicyclo[3.2.1]oct-2-ene-2-carbox-

(36) O. Diels and K. Alder, *Ann.*, 470, 62 (1929).

(37) C. Djerassi, R. R. Engel, and A. Bowen, *J. Org. Chem.*, 21, 1547 (1956).

ylic acid by comparison with an authentic sample (XXIV)[1] (by infrared and mixture melting point).

The next two components were identified by comparison with a previously independently prepared binary mixture of XXV and XXVII.[1] Oxidation with dilute acidic potassium permanganate at 60–80° affects but one of the methyl esters (XXVII′). The band for XXV′ appears at shorter retention time than does that for XXIX′.

The remaining major component, 3-(axial)-hydroxybicyclo[3.2.1]octane-2-(equatorial)-carboxylic acid (XXVI), is the only one which is affected by Jones' reagent[37] at 0°. Isolation yielded a product with an unsharp melting point (155–160°) which corresponded in properties and behavior on oxidation (of methyl ester) followed by v.p.c. with one of the major components of solvolysis of VI.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.60; H, 8.26.

The band due to the methyl ester of XXVIII disappears after permanganate oxidation, or upon bromination. Upon longer treatment with base, the band due to XXVIII′ merges with that due to XXIV′.

The band with the longest retention time (XXIX′) corresponds to one of the two major bands in the v.p.c. of the solvolysis products of VI (mixed samples).

Solvolysis of VI. Under the same conditions the bands which appear in the v.p.c. of the methyl esters are the same as observed for III or V, but the relative amounts of products differ, XXVI and XXIX being produced in approximately equal quantities and being the major products. Solvolysis using relatively more concentrated bicarbonate does not affect the product distribution, but solvolysis at higher pH (sodium carbonate) reduces the relative amounts of the unsaturated acids XXIV and XXVIII and at the same time the distribution in the epimeric pair XXVI and XXIX is altered in favor of XXVI (the only component affected by Jones' reagent).

Solvolysis of IV. Upon evaporation of the ethereal extract the product crystallized readily, and methylation with diazomethane followed by v.p.c. showed but one component. The product, 2-(equatorial)-hydroxybicyclo[3.2.1]octane-2-(axial)-carboxylic acid (XXX), melts at 212–213° (215°, hexane–ethyl acetate, 2:1).

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.64; H, 8.28.

The product XXX and its methyl ester are inert to Jones' reagent, and no absorption in the n.m.r. spectrum attributable to a proton on an hydroxyl-bearing carbon is detectable. It should also be noted that the band for the methyl ester of XXX has a longer retention time than that for the epimer, XXV.

Kinetics of Solvolysis. Most of the data reported in Tables I and II were obtained with the assistance of an Aminco-Cotlove chloride automatic titrator, using the "low" setting for titration rate. Bromide ion concentration (including blank) was obtained in seconds, and the recorded seconds were subtracted from the infinity titer. The natural logarithm of this value was plotted *vs.* time.

The reactions were carried out in a 10-ml. volumetric flask immersed in the constant temperature bath, and at appropriate times duplicate samples were removed (100 in all) and added to the quenching agent (nitric acid–acetic acid) in a titration cell and stored at 0° until all samples were ready for titration (save for the infinity sample). Quantities of bromo acid such that the infinity titer fell at about 150 sec. (*ca.* 0.22 mmole) were used with the appropriate excess of *ca.* $6–8 \times 10^{-2}$ *M* potassium carbonate.

Except for the cases of I and II, no deviation from straight-line plots were detectable, even when points were taken within seconds of the start of the reaction.

In the cases of I, II, and III, as well as for *exo*-norbornyl bromide and 2-bromobicyclo[2.2.2]octane (Table III), the Volhard procedure was also used. In these determinations the initial concentration of bromo compound was $4.4–4.9 \times 10^{-2}$ *M*, and 1.00 g. of sodium carbonate was employed. The 80% ethanol solution of the bromo compound was transferred to a round-bottom reaction flask, fitted with stirrer, and at exactly 2 min. before each appropriate time interval, a sample (*ca.* 12 ml.) of the reaction mixture was withdrawn and allowed to stand at ambient temperature for 1.5 min., and at correct time (±2 sec.), 10.0 ml. of the reaction mixture was pipetted into 10 ml. of 6 *N* nitric acid, previously chilled to 0°. All organic material was then extracted into chloroform, using a standardized procedure, and the aqueous solution containing bromide was supplied with 5.00 ml. of standardized 0.1 *N* silver nitrate and back titrated with standardized sodium thiocyanate with ferric ion indicator. The infinity titer was obtained by adding excess silver nitrate to an acidified aliquot of the reaction mixture, allowing 20 hr. for complete reaction, and then titrating. Values obtained in this way agreed within[2] 2% of the theoretical values.