solution of ethanolic sodium ethoxide, and 7.5 ml. of absolute ethanol. The resulting solution was refluxed for 20 hr. under nitrogen. At the end of this period 5.6 mg. (0.093 mmole) of glacial acetic acid was added to neutralize the base. Evaporation of the solvent under reduced pressure left a small quantity of liquid which was extracted with two 10-ml. portions of ether. Drying of the ethereal solution over magnesium sulfate and evaporation of the solvent gave 10 mg. (43%) of a colorless oil. Gas–liquid chromatography of the oil on a column containing 20% XF-1150[16] on 80–100-mesh Chromosorb P showed two peaks in the ratio of 5 to 1. The lesser component was eluted first and had the same retention time as **15A**. The larger peak had the same retention time as **15B**.

Diethyl Bicyclo[2.2.2]octane-1,3-dicarboxylate (16B) from Diethyl Bicyclo[2.2.2]oct-5-ene-1,*endo*-3-dicarboxylate (15D).—A 12.5-mg. sample of **15D** (containing 4.2% of **15B**) was hydrogenated by platinum oxide in ethanol (1 ml.). Removal of the catalyst and evaporation of the solvent under reduced pressure gave 12.3 mg. (98%) of a colorless liquid giving two peaks on a g.l.p.c. column containing 25% 710 silicone oil on Chromosorb P. The two peaks were in the ratio of 23 to 1. The major component had the same infrared spectrum and retention time as **16B**-

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[16] A nitrile–silicon polymer obtained from General Electric.

The Lactones of *cis*- and *trans*-2-Hydroxycycloheptaneacetic Acid[1]

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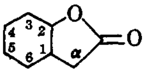
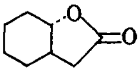
The *cis*- and *trans*-lactones of 2-hydroxycycloheptaneacetic acid have been prepared and equilibrated at various temperatures. The *cis* isomer predominates slightly in the temperature range 384–423°K. The thermodynamic quantities have been calculated and the conformations are discussed and contrasted with those of the cyclohexane analogs. Two examples of what appears to be partial *cis*-electrophilic addition to the cycloheptene double bond have been observed.

The lactone of *cis*-2-hydroxycyclohexaneacetic acid[3–6] (I) is more stable than the *trans* isomer (II),[7] the *trans* compound being convertible to the *cis* under the influence of sulfuric acid–acetic acid.[3,5] An analogous acid-catalyzed rearrangement is well known in the santonin series where the allylic position of the lactone ether oxygen renders the isomerization more facile,[8] but many other instances of this stability relationship among lactones of substituted 2-hydroxycyclohexaneacetic acid could be cited.[9]

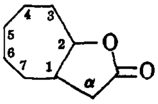
In the last decade, a group of new sesquiterpene lactones has been discovered in which the γ-lactone ring is fused onto the seven-membered ring portion of perhydroazulene skeleton.[10] In discussions dealing with the stereochemistry of the new lactones, it has been tacitly assumed[11] that commonly accepted generalizations about γ-lactones fused onto six-membered rings can be extended to γ-lactones fused onto seven-membered rings. Because of our interest in naturally occurring perhydroazulenic lactones, we decided to examine this supposition by the synthesis and study of the previously unreported title compounds III and IV.



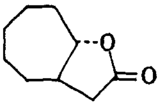
I



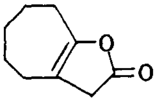
II



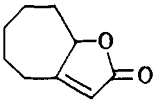
III



IV



V



VI

The energetics of *cis*- and *trans*-ring fusion to cycloheptanes have, in the meantime, been considered by Hendrickson,[12] with particular reference to the *cis*- and *trans*-bicyclo[5.3.0]decanes (perhydroazulenes). The conclusion was reached that the energy difference between *cis*- and *trans*-perhydroazulene was likely to be virtually negligible, experimental support for this having been provided by Allinger and Zalkow.[13] When a lactone is substituted for a five-membered ring, inspection of Dreiding models suggests that in the *cis* isomer III the favored twist-chair conformation[12] of the cycloheptane ring may be destabilized somewhat because of angle strain. Of the two *trans*-forms of IV, the 2e-3e isomer appears to be affected only slightly, the 3e-4e isomer more so. The over-all effect is difficult to assess but would not be expected to alter the stability relationships significantly.

Lactone III was prepared from VI, or more conveniently from the mixture of V and VI prepared by cyclization of 2-oxocycloheptaneacetic acid.

Lactone IV was synthesized in a manner similar to that adopted by Newman and Vander Werf[3] for the preparation of II. However, the first step, the reaction of cycloheptene oxide with malonate ion, was exceedingly slow as compared with the analogous reaction of cyclohexene oxide which reacts at least 10 times as rapidly.

The reasons for this difference in reactivity are not quite clear. It has been shown that cyclohexene oxide reacts with methoxide ion about 1.5 times as fast as

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[1] Supported in part by a grant from the National Science Foundation (NSF-G 14396).

[2] Abstracted from a thesis submitted in partial fulfillment of the requirements for the degree Doctor of Philosophy, 1963.

[3] M. S. Newman and C. A. Vander Werf, *J. Am. Chem. Soc.*, **67**, 233 (1945).

[4] J. Klein, *J. Org. Chem.*, **23**, 1209 (1958).

[5] J. Klein, *J. Am. Chem. Soc.*, **81**, 3611 (1959).

[6] E. H. Charlesworth, H. J. Campbell, and D. L. Stachiw, *Can. J. Chem.*, **37**, 877 (1959).

[7] S. Coffey, *Rec. trav. chim.*, **42**, 387 (1923).

[8] Y. Abe, T. Miki, M. Sumi, and T. Toga, *Chem. Ind.* (London), 953 (1956); H. Ishikawa, *J. Pharm. Soc. Japan*, **76**, 504 (1956); M. Sumi, *J. Am. Chem. Soc.*, **80**, 4869 (1958); D. H. R. Barton, J. E. D. Levisalles, and J. T. Pinhey, *J. Chem. Soc.*, 3472 (1962); W. Cocker, B. Donnelly, H. Gobinsingh, T. B. H. McMurray, and M. A. Nisbet, *ibid.*, 1262 (1963).

[9] See, for example, M. Hinder and M. Stoll, *Helv. Chim. Acta*, **36**, 1995 (1953); W. Klyne, *J. Chem. Soc.* 3072 (1953).

[10] The most recent review of this rapidly moving field is already very much out of date, T. Nozoe and S. Ito, *Fortschr. Chem. Org. Naturstoffe*, **19**, 32 (1961).

[11] See, for example, J. W. Huffman, *Experientia*, **16**, 120 (1960). The complications have been recognized by J. B. Hendrickson and R. Rees, *Chem. Ind.* (London), 1424 (1962).

[12] J. B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 4537 (1961).

[13] N. L. Allinger and V. B. Zalkow, *ibid.*, **83**, 1144 (1961).

cyclopentene oxide,[14] but no data are available on the reaction of cycloheptene oxide. However, a number of reactions are known in which cyclopentane and cycloheptane derivatives react at comparable rates which may be greater or less than the rate of the corresponding cyclohexane derivative.[15–17] The greater susceptibility of cyclohexane oxide to ring opening compared with that of cyclopentene oxide may be attributed to greater relief of eclipsed hydrogen interactions in the cyclohexane oxide system. A further effect is probably operative in cycloheptene oxide where Dreiding models indicate that there may be considerable steric hindrance to nucleophilic displacement of epoxide oxygen by the bulky malonate ion which would result in rate retardation.

Nuclear Magnetic Resonance Spectra.—Since the main objective of this work was the determination of the relative thermodynamic stabilities of lactones III and IV, a method for the analysis of mixtures of III and IV was necessary. In spite of prolonged and tedious efforts, artificial mixtures of III and IV could not be separated satisfactorily by gas liquid chromatography. Also, while the infrared spectra of III and IV were different, the distinguishing bands overlapped and the analysis by this method would have been difficult indeed.

A more than adequate solution to this problem was offered by n.m.r. spectroscopy. Table I lists important n.m.r. peaks of lactones I–IV, whose implications will now be discussed.

TABLE I[a]

Lactone	C_2-H[b]	Hα[c]	CH_2[d]
I	4.60 q (4)	2.45 m	1.2–2.0 e, 1.55 s
II	3.97 h (10,4)	2.45 n,e	1.33–2.04 e
III	4.75 o	2.66 m	1.2–2.0 e
IV	4.25 n	2.42 m	1.62 s

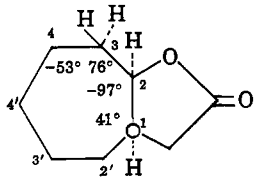
[a] Spectra were determined in CCl_4 solution on Varian HR-60 or A-60 spectrometers. Values in p.p.m. relative to tetramethylsilane as internal standard. Signals are described as follows: e, envelope; h, sextet; m, multiplet of uncertain multiplicity; n, unresolved multiplet; o, octet; s, relative sharp signal corresponding to several protons. Numbers in parentheses denote coupling constants in c.p.s. [b] Intensity one proton. [c] Intensity two protons. [d] Ring protons other than H_2.

C_2-H of I gives rise to a quadruplet at 4.60 p.p.m. characteristic of the A portion of an AX_3 system. The multiplicity indicates that the three adjacent protons have approximately the same dihedral angle, a situation which would prevail in a chair conformation in which C_1-H is axial and C_2-H is equatorial. The dihedral angles are then near 60°. This is in reasonable agreement with experimental values observed elsewhere.[18] However, the observed multiplicity of C_2-H could arise equally well from the time-averaged values of dihedral angles in a system which changes conformations rapidly compared with the spin frequency. Since the methylene region indicates a fair degree of flexibility (*vide infra*), it is not possible to decide between the two alternatives.

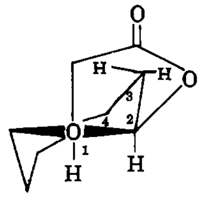
The two α-protons give rise to a complex system of bands centered at 2.45 p.p.m. which appears to contain two triplets at 2.51 (J = 3.5) and 2.38 p.p.m. (J = 2.2). The methylene region contains an envelope from which there projects a relatively sharp high-intensity band at 1.55 p.p.m. This suggests a certain amount of methylene proton equivalence and a reasonable degree of ring flexibility as would be expected from a *cis* isomer.

By contrast, the n.m.r. spectrum of II exhibits only a broad envelope extending from 1.33 to 2.04 p.p.m., but no strong projecting peak. This is consistent with the assumption of a more rigid ring system. The situation is reminiscent of that prevailing in *cis*- and *trans*-hydrindane,[19] with the lactone ring of I and II replacing the alicyclic five-membered ring. The α-protons of II are unresolved, but C_2-H gives rise to a sextet centered at 3.97 p.p.m. which corresponds to X of an A_2BX system (J_{AX} = 10). This indicates that II is a chair in which C_1-H and C_2-H are axial, in accordance with the required *trans*-diequatorial fusion of five- and six-membered rings. The shielding of C_2-H in II, as compared with C_2-H of I, is as expected; the coupling constants are in agreement with the assumption that the dihedral angles between C_2-H and the three adjacent protons are approximately 180, 180, and 60°.

Comparison of the n.m.r. spectra of I and II with those of III and IV reveals highly significant differences which point out the danger of drawing analogies between bicyclo[5.3.0] and bicyclo[4.3.0] ring systems. C_2-H of the *cis*-fused lactone III gives rise to a complex multiplet centered at 4.75 p.p.m. which can be analyzed as an octet closely approximating X of an ABCX system where J_{AX} = 10, J_{BX} = 7, and J_{CX} = 4 c.p.s. Dreiding models suggest that the most likely conformation is a chair in which C_1-H and C_2-H are quasi-axial and the five-membered ring is quasi-diequatorially oriented. This should give rise to dihedral angles of about 0, 82, and 158°.[12] A better fit is obtained by the twist-chair conformation advocated by Hendrickson[12]; this is shown in the appended formulae where the dihedral angles are marked.[20] III is quite rigid as shown by the envelope in the 1.2–2-p.p.m. region. The α-protons give rise to a multiplet which could not be analyzed satisfactorily.



H-H	angle	J_{H-H}
1α–2α	41°	7
2α–3α	97°	4
2α–3β	143°	10



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[14] G. Gee, W. C. E. Higginson, P. Levesley, and K. J. Taylor, *J. Chem. Soc.*, 1338 (1959).

[15] N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5727 (1959).

[16] H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *ibid.*, **73**, 212 (1951).

[17] E. L. Eliel in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 121; E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 265–269.

[18] M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

[19] W. B. Moniz and J. A. Dixon, *J. Am. Chem. Soc.*, **83**, 1671 (1961).

[20] We wish to thank one of the referees for drawing our attention to this point.

The *trans*-lactone IV on the other hand is very flexible as shown by the strong relatively sharp band at 1.67 p.p.m. The flexibility of the seven-membered ring portion affects the dihedral angles and, hence, coupling of C_2-H. This proton which remains quasi-axial in all easily formed conformations gives rise to an unresolved multiplet at 4.25 p.p.m. The α-hydrogens are signaled by a multiplet centered at about 2.4 p.p.m. C_2-H of III and IV are apparently both axial, but Dreiding models of III indicated that C_2-H of III is less shielded by the C_3–C_4 and C_7–C_1 bonds than the corresponding proton of IV. This may account for the observed chemical shift.

The n.m.r. spectra of III and IV are in harmony with the suggestion[12] that there are two equal conformations for cycloheptane with a *trans*-fused ring while there is only one energetically preferred conformation of cycloheptane with a *cis*-fused ring.

Models[12] of *cis*- and *trans*-bicyclo[5.3.0]decane suggest that, just as in the case of lactones III and IV, the *trans* isomer may be more flexible also. If this were so, the explanation of the small entropy change in the equilibrium *cis*- ⇄ *trans*-bicyclo[5.3.0]decane given by Allinger and Zalkow[13] would be in error. These workers assumed that the *cis* isomer was more flexible and that this was responsible for lowering the calculated entropy difference (1.4 e.u. greater for the *trans* isomer) to the observed small value of 0.3 ± 0.4 e.u.

Equilibration of III and IV.—Lactones III and IV were equilibrated under the influence of acid. The pronounced difference in the n.m.r. spectra of III and IV permitted the analysis of mixtures with an accuracy of ± 0.5% and a standard deviation of ± 0.24% using the H_2 signal. Heating III or IV with acetic acid at temperatures up to 473°K. resulted only in recovery of starting material. Equilibration with 5% sulfuric acid in acetic acid was quite incomplete, but use of 50% aqueous sulfuric acid in the temperature range 384–423°K. resulted in smooth equilibration. This suggests that the reaction involves hydronium ion catalysis. At lower temperatures the reaction was too slow to be useful; at more elevated temperatures extensive decomposition occurred.

Results for the equilibration at 384°K. for various times are tabulated in the Experimental section (Table II).

Equilibrium was approached from both sides but was reached only slowly at 384°K. After 48 hours, III yielded a mixture containing 41.8 ± 0.8% of IV. Similar treatment of IV yielded a mixture containing 44.7 ± 1% of IV. The average, 43 ± 1%, approximates the experimental errors and was used to calculate K_e 1.32 (384°K.) and ΔF -0.215 kcal./mole.

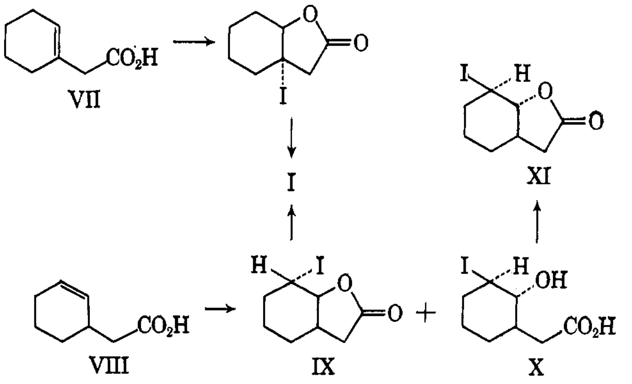
Measurements were also carried out at 401 and at 420°K. and ln K *vs.* $1/T$ was plotted. Intercept and slope of the line drawn through the experimental points by the least squares method gave, for the liquid phase isomerization of III ⇄ IV, $K_{\epsilon\,401°}$ 1.17 ± 0.05, ΔF -0.13 ± 0.03 kcal./mole, $\Delta H_{401°}$ -0.17 ± 0.06 kcal./mole, and $\Delta S_{401°}$ -0.13 ± 0.3 e.u.

The smallness of these quantities is surprising and is comparable to the values found by Allinger and Zalkow[13] for the isomerization *cis*- ⇄ *trans*-bicyclo[5.3.0]decane under conditions which were vastly different. At the higher temperatures at which their equilibrations were carried out, the *trans* isomer was more stable than the *cis*, but enthalpy and entropy differences were small. At the lower temperatures used in this study, *cis*-lactone III is slightly more stable than *trans*-lactone IV, but extrapolation indicates that the situation should be reversed at temperatures above 437°K.

The assumption that *cis*-lactones fused to seven-membered rings will necessarily be more stable than *trans*-lactones is, therefore, not supported by evidence. Minor changes in structure may easily change the relationship deduced for III and IV, particularly in complex systems like the guaianolides. The results offer a sharp contrast to the experiments reported by Klein[5] for the acid-catalyzed equilibration of I and II. His results indicated that less than 5% of the *trans*-lactone II was present at equilibrium. Recovery of only 50% of starting material was attributed to selective destruction of the more reactive II. If equilibrium was indeed attained, K_e for *cis*-I ⇄ *trans*-II would be greater than 19 and $\Delta F < -2.2$ kcal./mole.[21]

Cyclizations of Cyclohepteneacetic Acids.—Overwhelming predominance of I in the equilibrium mixture of I and II suggested[10] that the sole formation of the more stable isomer I on acid treatment of 1-cyclohexeneacetic acid (VII), originally[4] attributed to stereospecific protonation of the double bond, followed by cyclization, might conceivably involve an equilibration step. The existence of an equilibrium, however, does not necessarily eliminate stereospecific *trans*-addition as a possible mode of formation of the stable *cis* isomer as long as the *trans*-lactone equilibrates *via* the olefin acid VII which then undergoes stereospecific *trans*-addition to I,[23] and not by way of the carbonium ion.[23 24]

Stereospecific syntheses of I were achieved *via* the iodolactonization reactions of VII and VIII. Exclusive formation of I by the second sequence was explained in terms of *trans*-diaxial attack from the less hindered side of the molecule. Later work, however, has shown[25] that iodine also attacks VIII from the



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[21] Professor E. L. Eliel has pointed out (private communication) that the claimed preponderance of I over II is somewhat surprising, since the results of Allinger and Coke on the relative stabilities of *cis*- and *trans*-hydrindane[22] do not differ materially from those on the bicyclo[5.3.0]-decanes.[13]

[22] N. L. Allinger and J. L. Coke, *J. Am. Chem. Soc.*, **82**, 2553 (1960).

[23] D. H. R. Barton, *J. Org. Chem.*, **15**, 466 (1950).

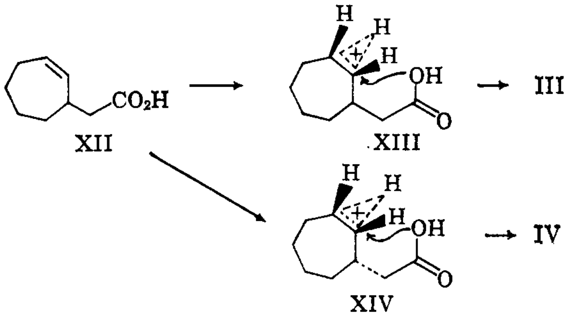
[24] C. H. Collins and G. S. Hammond, *ibid.*, **25**, 911 (1960).

[25] M. M. Shemyakin, Yu. A. Arbuzov, M. N. Kolosov, and Yu A. Ovchinnikov, *Dokl. Akad. Nauk SSSR*, 133, 1121 (1960); Yu. A. Arbuzov, M. N. Kolosov, Yu. A. Ovchinnikov, and M. M. Shemyakin, *ibid.*, 377 (1961).

more hindered side. The resulting iodo acid X was converted to the *trans*-lactone XI.

Since the composition of the equilibrium mixture of III and IV had been determined, it was now possible to study analogous cyclizations of the corresponding cycloheptenacetic acids and to determine whether this results in a greater degree of selectivity than could be expected on the basis of the equilibrium studies. The results were also expected to have a bearing on the mode of addition to double bonds in seven-membered rings.

2-Cycloheptene-1-acetic acid (XII), prepared from 3-bromo-1-cycloheptene by condensation with diethyl malonate, hydrolysis to 2-cycloheptene-1-malonic acid, and decarboxylation, was refluxed with 50% aqueous sulfuric acid in acetic acid for 4 hours. The neutral product contained 53% ± 4% *cis*-lactone III and 47 ± 4% *trans*-lactone IV, a composition which closely resembles that of the equilibrium mixture. This suggests that equilibration is involved in the acid-catalyzed cyclization and that the unsaturated acid or the corresponding carbonium ion may be an intermediate in the acid-catalyzed equilibration of III and IV. If bridged ions are involved, little preference must be shown for the formation from XII to XIII or XIV, since rearward attack by the carboxyl group in XIII leads to III, and in XIV to IV.

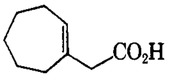


The mixture of 1-cycloheptene-1-acetic acid (XV) and $\Delta^{1,\alpha}$-cycloheptaneacetic acid (XVI) usually obtained by the literature method[26] was refluxed with acid for 11 hours in the usual way. The neutral product contained 26.3 ± 1.6% of the *trans*-lactone IV, a result which could not have arisen through prior formation of the *cis*-lactone III followed by partial equilibration, since (see Table II, Experimental) after 12 hours under these conditions, pure III yields only 17.5 ± 1% of IV. We, therefore, conclude that the acid-catalyzed cyclization of XV does probably not proceed stereospecifically toward the *cis*-lactone by *trans*-quasi-diaxial electrophilic addition, but does produce stereoselectively a preponderance of the *cis* isomer. The formation of 26% of the *trans* isomer requires an appreciable amount of *cis*-addition.[27]

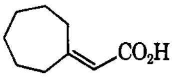
The iodolactonization of acids XII and XV led to analogous results. Addition of the sodium salt of XII to iodine and potassium iodide furnished a noncrystallizable, easily decomposed mixture of iodolactones (82%) whose hydrogenolysis resulted in a fraction containing 54 ± 2% III and 46 ± 2% IV. Thus, iodination occurs from both sides of the cycloheptene ring system; the greater flexibility and more facile formation of a *trans*-lactone, compared with the situation prevailing in the iodolactonization of VIII, results in the formation of both III and IV, whereas in the cyclohexene system, one of the intermediate bridged iodonium ions (iodine *cis* to the side chain) undergoes hydroxylation rather than lactone ring closure to XI.

Iodolactonization of the mixture of acids XV and XVI led, in relatively low yield, to a mixture of iodolactones whose hydrogenolysis resulted in 66 ± 1% of III and 34 ± 1% of IV. Again, the formation of IV in appreciable amounts indicates that in the cycloheptene series *trans*-addition to the double bond is not the exclusive process demonstrated in the cyclohexene series.

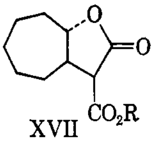
The apparent nonstereospecificity of electrophilic additions to the cycloheptene ring system which has been observed in this study should be a source of caution to workers in this area. It appears that nucleophilic addition to activated double bonds, for example to 1-cyanocycloheptene, leads to *trans*-disubstituted compounds, but this is apparently due to the rapid base-catalyzed isomerization of the initially formed *cis*-1,2-disubstituted cycloheptane to the more stable *trans*-1,2-diequatorially substituted cycloheptane.[28,29] Thus both electrophilic and nucleophilic additions to cycloheptenes may lead to mixed products.



XV



XVI



XVII

Experimental[30]

2-Oxocycloheptaneacetic Acid.—Ethyl 1-carbethoxy-2-oxocycloheptane-1-acetate[31], b.p. 133–140° (1 mm.), was hydrolyzed and decarboxylated by the literature method[31] to give 23.8 g. (71%) of acid, b.p. 125–130° (0.5 mm.), n^{25}_{D} 1.4873. In order to obtain this yield it was necessary to rehydrolyze the distillation foreruns.

Lactones of 2-Hydroxy-1-cycloheptene-1-acetic Acid (V) and 2-Hydroxycycloheptane-$\Delta^{1,\alpha}$-acetic Acid (VI).[31].—Treatment of 29.8 g. of the previous compound with acetic anhydride and a drop of acetyl chloride furnished, after removal of acetic anhydride 25 g. of crude lactone mixture. Distillation furnished three fractions: b.p. 93–105° (0.6 mm.), 4.6 g.; b.p. 105–113° (0.8 mm.), 11.2 g.; b.p. 113–121° (0.8 mm.), 5.1 g.; total yield, 22.7 g. (85%). Fraction 3 crystallized and fraction 2 crystallized on seeding. The solid material was taken up in ether, washed with dilute bicarbonate solution, water, dried, and the residue, 10.5 g. (39%), crystallized from hot pentane; yield,

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[26] G. G. Ayerst and K. Schofield, *J. Chem. Soc.*, 3445 (1960). Since XVI should not cyclize unless prior rearrangement to XV occurs, its presence was not considered disturbing.

[27] A referee has commented that the results could be explained by assuming that XV (approximately 60% of the mixture) undergoes stereospecific *trans*-addition to *cis*-lactone which in the course of 11 hr. equilibrates to approximately 85% *cis*-lactone, while XVI (40% of mixture) is converted to A and then to B which immediately furnishes the equilibrium mixture of III and IV (41–45%) of *cis*-lactone.

[28] D. C. Ayres and R. A. Raphael, *J. Chem. Soc.*, 1779 (1958).

[29] J. Sicher, F. Šipos, and J. Jonáš, *Collection Czech. Chem. Commun.*, **26**, 262 (1961).

[30] Melting points and boiling points are uncorrected. Analyses were by Drs. Franz Pascher, Bonn, Germany, and Weiler and Strauss, Oxford, England. N.m.r. spectra were run by Mr. Fred Boerwinkle and Mr. Gerald Caple on a Varian HR-60 or A-60 spectrometer. The A-60 instrument was purchased with the aid of a grant from the National Science Foundation. Infrared spectra were run in carbon tetrachloride solution unless otherwise specified. Ultraviolet spectra were determined in 95% ethanol solution on a Cary Model 14 recording spectrophotometer. Gas–liquid chromatograms were run on an F & M Model 500 instrument using 0.25 ft. × 2 ft. copper tubing programmed from 85–220° at 11°/min. and held at the higher temperature, carrier gas helium at 60 ml./min.

[31] Pl. A. Plattner, A. Fürst, and K. Jirasek, *Helv. Chim. Acta*, **29**, 730 (1946).

8.3 g. of VI; m.p. 52–55° (lit. m.p. 55–56°); infrared bands at 1760 and 1630 cm.$^{-1}$ The liquid fractions were redistilled; b.p. 83–93° (0.4 mm.); yield, 6.5 g. (24%). The infrared spectrum indicated that this material was a 3:2 mixture of V–VI, bands at 1800 and 1680 cm.$^{-1}$ corresponding to V and bands at 1760 and 1630 cm.$^{-1}$ corresponding to VI.

Lactone of *cis*-2-Hydroxycycloheptaneacetic Acid (III).—Small-scale hydrogenation of 0.47 g. (0.00312 mole) of VI in 30 ml. of ethanol with platinum oxide required 70 ml. (0.00312 moles) of hydrogen. The catalyst was filtered; titration of the filtrate with sodium hydroxide solution revealed the presence of 0.00018 equivalents (5–7%) of acid. Work-up in the usual manner furnished 0.3 g. of III, b.p. 94–96° (0.4 mm.); infrared band at 1780 cm.$^{-1}$ (γ-lactone); n^{25}_{D} 1.4857.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.98; H, 9 07.

The hydrazide, feathery needles from benzene, melted at 129–130.5°.

Anal. Calcd. for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 57.78; H, 9.74; N, 15.10.

In a subsequent run, reduction of 2.97 g. of lactone mixture with W-2 Raney nickel in a Parr hydrogenator furnished 2.03 g. (68%) of III.

Lactone of *trans*-2-Hydroxycycloheptaneacetic Acid.—To a solution of sodium ethoxide (2.18 g. of sodium) in 70 ml. of ethanol was added with stirring 15.2 g. of malonic ester and then, after 15 min. and cooling to 17°, dropwise 9.8 g. of cycloheptene oxide[32] The mixture was stirred at 70° for 32 hr., decomposed with water, and made alkaline with 8.1 g. of potassium hydroxide. Solvent was partially evaporated, the remainder refluxed for one hour, cooled, and acidified to pH 4. The acid solution was continuously extracted with ether for 1 day and the ether extract concentrated. The residue, 6.8 g., was decarboxylated by heating at 185° for 2 hr., distilled, and the fractions, b.p. 92.5–98° (0.4 mm.), collected (3.05 g. 23%). The analytical sample boiled at 91–92° (0.3 mm.), n^{25}_{D} 1.4826, infrared band at 1785 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.25; H, 9.56.

The hydrazide was recrystallized from benzene, m.p. 131–132°, melting point depressed to 115–125° on admixture of the hydrazide of III.

Anal. Calcd. for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 57.89; H, 9.64; N, 14.69.

In an attempt to increase the yield, the condensation of 16 g. of cycloheptene oxide with sodium malonic ester was carried out in refluxing amyl alcohol. The work-up was modified by cooling and acidifying with dilute acetic acid. Distillation furnished 1.51 g. of cycloheptene oxide, 3.3 g. of diethyl malonate, 1.09 g. of a mixture of diethyl malonate, and lactone IV (1:1), 1.3 g. of a mixture of lactone IV,[33] and lactone ester XVII, and 3.0 g. of lactone ester XVII (mixture of ethyl and amyl esters), b.p. 128° (0.1 mm.).

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 66.30; H, 9.29, 9.07.

The base-soluble fraction and water washings from this reaction were hydrolyzed with sodium hydroxide. The usual work-up, followed by distillation, furnished 3.71 g. of IV (25%).

Lactones of *cis*- and *trans*-2-Hydroxycyclohexaneacetic Acid (I and II).—These compounds were prepared by the method of Newman and Vander Werf[3]: lactone I, 57% yield, b.p. 105–108° (3.5 mm.); lactone II, 50% yield, b.p. 87–88° (0.3 mm.). Heating of 0.500 g. of I with 50% aqueous sulfuric acid in acetic acid as described by Klein[5] gave 0.282 g. of pure I in the neutral fraction. II furnished 0.240 g. of a 7:3 mixture of I and II, but more prolonged heating might possibly have caused complete conversion of II to I.[5] Analyses were carried out by n.m.r. spectroscopy which would have detected less than 5% of either isomer.

Equilibration of III and IV.—Artificial mixtures of III and IV were analyzed by n.m.r. spectroscopy, using neat samples in the Varian HR-60 n.m.r. spectrometer. There was a small overlap of the H_2 bands, but it was possible to cut out each band and weigh the pieces. Five to ten integrations of this type for each artificial mixture gave an accuracy of ± 1% with a standard deviation of 0.55–1.0%. For example, five spectra of a mixture containing 41.2% of IV gave a value of 41.3 ± 0.5% of IV. Machine integration of the same mixture in deuteriochloroform on a Varian A-60 spectrometer, which became available later, yielded the composition 41.6 ± 0.5% of IV with a standard deviation of the mean of ±0.24%.

Equilibrations were carried out by refluxing 0.500 g. of the lactone with 5 ml. of glacial acetic acid and 3 ml. of 50% aqueous sulfuric acid for the desired period. The mixture was cooled and extracted with three 10-ml. portions of benzene. The benzene was washed with 10- and 5-ml. portions of 5% sodium bicarbonate solution and dried. Removal of benzene typically yielded 0.40–0.45 g. of residue which, on distillation, furnished 0.25–0.3 g. of mixed lactones, b.p. 72–75° (0.2 mm.), which were analyzed neat by n.m.r. spectroscopy. Results are tabulated in Table II.

For equilibrations carried out at temperatures above the boiling point, the solutions were placed in Carius tubes (1 × 6 in. heavy wall), sealed under nitrogen, and heated in a sealed tube furnace for the desired period. The tubes were cooled, opened, and the contents worked up in the usual manner. By-product undistillable material was somewhat greater and total recovery smaller.

TABLE II

EQUILIBRATION OF THE LACTONES OF *cis*- AND *trans*-2-HYDROXYCYCLOHEPTANEACETIC ACID

Starting Material	Temp., °C.	Time, hr.	% *cis*	% *trans*	Intersection[a]
III	111	6	89.8 ± 0.8	10.2 ± 0.8	41% IV
IV	111	6	13.5 ± 2.0	87.5 ± 2.0	
III	111	12	82.5 ± 1.0	17.5 ± 1.0	41% IV
IV	111	12	25.8 ± 0.7	74.2 ± 0.7	
III	111	18	74.7 ± 1.7	25.3 ± 1.7	41% IV
IV	111	18	37.0 ± 1.3	63.0 ± 1.3	
III	111	48	58.2 ± 1.0	41.8 ± 0.8	43% IV
IV	111	48	55.3 ± 1.0	44.7 ± 1.0	
III	128	12	54 ± 1	46 ± 1	46% IV
IV	128	12	54 ± 1	46 ± 1	
III	147	3	52.3 ± 0.8	47.7 ± 0.8	47.6% IV
IV	147	3	52.5 ± 1.0	47.5 ± 1.0	

[a] Intersection of plot of composition *vs.* time at the indicated temperature.

2-Cycloheptene-1-acetic acid (XII).—To 100 ml. of sodium ethoxide solution (from 1.77 g. of sodium) was added 12.4 g. of diethylmalonate with stirring. After 15 min. the solution was cooled with ice and 13.5 g. of 3-bromo-1-cycloheptene[35] in 15 ml. of ethanol was added dropwise. Stirring was continued at room temperature for 16 hr., the solution filtered, diluted with water, and extracted with ether. The combined organic layers were dried and distilled; yield, 13.8 g. (71%); b.p. 105–106° (0.2 mm.).

The malonate, 12.0 g., was refluxed for 12 hr. with 8.05 g. of potassium hydroxide in 50 ml. of ethanol and 30 ml. of water. The base was neutralized with dilute hydrochloric acid and the solution evaporated at room temperature. The residue was thoroughly extracted with hot ethyl acetate and the extract concentrated; yield, 5.4 g. (58%) of 2-cycloheptene-1-malonic acid; m.p. 144–145° dec. Recrystallization from ethyl acetate furnished needles, m.p. 151–152 dec.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.52; H, 7.12.

2-Cycloheptene-1-acetic acid was prepared in 70% yield by heating the malonic acid at 180° for 1 hr. and distilling the product at 80–90° (0.2 mm.). Redistillation furnished the analytical sample, b.p. 85° (0.2 mm.).

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.95; H, 9.17.

Cyclizations of XII. (**A**).—A mixture of 0.7 g. of XII, 6 ml. of acetic acid and 4 ml. of 50% sulfuric acid was refluxed for 11 hr. and worked up as usual to yield 0.35 g. of neutral material (50%).

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[32] P. B. Talukdar and P. E. Fanta, *J. Org. Chem.*, **24**, 555 (1959).

[33] The direct decarbethoxylation of the condensation product to IV on refluxing with alkoxide finds it parallel in a recently reported reaction of diethyl malonate with 1-cyclohexenecyanide.[34]

[34] R. A. Abramovitch, L. X. Mallavarapu, and D. L. Struble, Report No. 6, Petroleum Research Fund, American Chemical Society, 1961, p. 146.

[35] E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 607 (1954).

The distillate, b.p. 75–80° (0.3 mm.), 0.19 g., was analyzed by n.m.r. spectroscopy, which indicated 46.7 ± 4.1% of IV and 53.3 ± 4.1 % of III.

(B).—To 3.5 g. of iodine and 6.8 g. of potassium iodide in 60 ml. of water was added the sodium salt of XII (from 1.0 g. of XII and 1.73 g. of sodium bicarbonate) in 30 ml. of water. A heavy oil which separated was extracted with ether. The extracts were washed with sodium bisulfite solution until colorless, sodium bicarbonate solution, and water and dried. Removal of ether furnished 1.5 g. (82%) of an undistillable (dec.) noncrystallizable oil which represented the iodolactone (infrared spectrum). Hydrogenolysis with W-2 Raney nickel in ethanol and triethylamine was only partially successful, whereas hydrogenolysis with nickel and sodium bicarbonate completed removal of iodine. Infrared and n.m.r. spectra of the product indicated that it was composed of III and IV; n.m.r. analysis indicated the presence of 54.2 ± 2% III and 45.8 ± 2% IV.

1-Cycloheptene-1-acetic Acid (XV) and Cycloheptane-$\Delta^{1,\alpha}$-acetic Acid (XVI).—Dehydration of the hydroxy ester, obtained in 67% yield by the Reformatsky reaction of cycloheptanone and ethyl bromoacetate, with thionyl chloride furnished a mixture of α,β- and β,γ-unsaturated ester; b.p. 71–82° (1.5 mm.); yield, 51%; infrared bands at 1740 (ester), 1715 (conjugated ester), and 1635 cm.$^{-1}$ (conjugated double bond) which contained 60% of the β,γ-unsaturated compound (v.p.c.). Hydrolysis gave a mixture of the title compounds, b.p. 110–114 (18 mm.), 74% yield, which was used directly for the following reactions.

(A).—Cyclization of the mixture with dilute sulfuric acid–acetic acid for 11 hr. and work-up in the usual manner gave 57% of a neutral fraction, b.p. 68–73° (0.15 mm.), whose n.m.r. analysis indicated that it was composed of 73.7 ± 1.6% *cis*-lactone III and 26 ± 1.6% *trans*-lactone IV.

(B).—Iodolactonization of the mixed acids yielded 26% of a noncrystallizable oil which decomposed on attempted distillation but was a mixture of iodolactones (infrared spectrum). W-2 Raney nickel hydrogenolysis in ethanol with sodium bicarbonate gave a mixture of lactones III and IV, b.p. 88–92° (0.6 mm.), 44% yield, which contained 66 1% of III ± and 34 ± 1% of IV.

The Reactions of Phosphonic Acid Esters with Acid Chlorides. A Very Mild Hydrolytic Route

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The reaction of trimethylchlorosilane with a number of dialkyl esters of phosphonic acids and the hydrolysis of the resultant silyl phosphonates was studied as a means of preparing the phosphonic acids under very mild conditions. 2-Vinyloxyethylphosphonic acid, β-cyanovinylphosphonic acid, and vinylphosphonic acid were successfully prepared and characterized as their dicyclohexylamine salts. The reaction of primary, secondary, and tertiary alcohols with bis(trimethylsilyl) methylphosphonate results in an equilibrium mixture containing starting materials, acidic products, and mixed ethers [$ROSi(CH_3)_3$]. Mercaptans do not react. The reaction of excess acetyl chloride with dimethyl methylphosphonate yields methyl chloride, acetic anhydride, and dimethyl dimethylpyrophosphonate. The stability of the latter in excess acetyl chloride is discussed. Mechanistic interpretations of all reactions are presented.

The conventional means of converting a phosphonic acid ester into the corresponding phosphonic acid is by refluxing in concentrated aqueous acid.[1] However, this method is not applicable to phosphonates containing acid or water sensitive groups like nitriles, vinyl ethers, acetals, etc. During an investigation of the preparation and reactions of bis(trimethylsilyl) benzylphosphonate it was noted that this compound was hydrolyzed in high yield to benzylphosphonic acid when shaken in water at room temperature. Furthermore, the liquid bis(trimethylsilyl) ethylphosphonate slowly dissolved in water to give a strongly acidic solution. This suggested that conversion of phosphonates of the general formula $RP(O)(O\text{-alkyl})_2$ where R contains an acid labile group, to the corresponding bistrimethylsilyl phosphonates and subsequent hydrolysis should result in the preparation of phosphonic acids which ordinarily would be difficult to obtain.

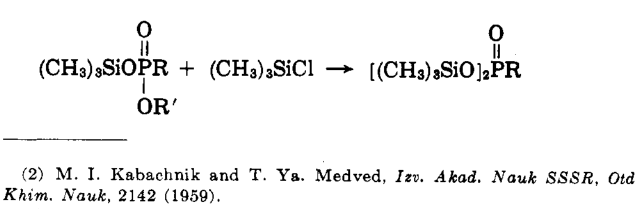
Diethyl β-cyanovinylphosphonate was converted in high yield to bis(trimethylsilyl) β-cyanovinylphosphonate. This was hydrolyzed in water, and a 30% yield of the β-cyanovinylphosphonic acid was isolated and characterized as the crystalline dicyclohexylamine salt. When the bis(trimethylsilyl) compound reacted with methanol, a quantitative yield of the phosphonic acid was obtained. Diethyl 2-vinyloxyethylphosphonate was converted in good yield into the corresponding bistrimethylsilyl compound which, upon reaction with methanol, gave the phosphonic acid as an oil. It was characterized as the crystalline dicyclohexylamine salt. Finally bis(β-chloroethyl) vinylphosphonate and diethyl vinylphosphonate were converted, using this procedure, to vinyl phosphonic acid. Vinyl phosphonic acid has been a rather elusive compound and was reported only recently.[2]

$$2ClSi(CH_3)_3 + NCCH{=}CHP(O)(OC_2H_5)_2 \longrightarrow 2C_2H_5Cl + NCCH{=}CHP(O)[OSi(CH_3)_3]_2$$

$$NCCH{=}CHP(O)[OSi(CH_3)_3]_2 \xrightarrow[\text{or } CH_3OH]{H_2O} NCCH{=}CHP(O)(OH)_2$$

Discussion

The reaction of trimethylchlorosilane with phosphonates as well as phosphates to yield the corresponding trimethylsilyl derivatives has been described.[3] Although no mechanism is proposed it appears likely



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[2] M. I. Kabachnik and T. Ya. Medved, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2142 (1959).

[3] H. W. Kohlschutter and H. Simoleit, *Kunststoffe—Plastics*, **6**, 9 (1959).