Acknowledgment.—The authors are grateful to the Petroleum Research Fund of the American Chemical Society (Grant 1467-B5) and to the National Science Foundation for support of this work. We are indebted to the Eastman Kodak Company for a generous sample of I, and to Mr. D. Ketchum of that company for performing the elementary analyses reported in this paper.

(8) National Science Foundation Postdoctoral Fellow, Harvard University, 1963–1964.

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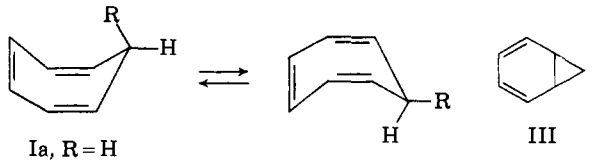
RECEIVED DECEMBER 5, 1963

The Structure and Interconversion of Cycloheptatriene

Sir:

Recent interest[1-4] in the structure of cycloheptatriene (Ia) has concerned the contribution of the norcaradiene structure (III) to a resonance hybrid or as a discrete molecule in equilibrium with Ia. We now report that the low temperature proton magnetic resonance spectra show that I is a mixture



Ia, R = H
b, R = D

IIa
b

III

of rapidly equilibrating, nonplanar conformers Ia and IIa, and report the energy barrier for this interconversion. The equilibrium I ⇄ II has been shown previously for 2-*t*-butyl-3,7,7-trimethylcycloheptatriene[1] and suggested from spectroscopic evidence for 7-deuteriocycloheptatriene (Ib ⇄ IIb).[5] The spectra of Ib and IIb, in addition to supporting a nonplanar conformation, show that the equilibrium constant for the Ib ⇄ IIb interconversion is not one, but the conformer with hydrogen *syn* to the ring (IIb) is present in greater concentration. This difference in stability is attributed to greater eclipsing effects of the *anti*-1-hydrogen with the 2- and 7-hydrogens for protium than for deuterium.

Using new apparatus[6] developed in this laboratory, it was possible to obtain good high resolution n.m.r. spectra at very low temperatures. The spectrum of cycloheptatriene in trifluorobromomethane does not change between room temperature and about −120°, but below this temperature, the methylene triplet begins to broaden. Between −130° and −140° there is only a single broad peak in the aliphatic region. At −141°, two peaks begin to appear at the sides of the main peak, and as the temperature is lowered, the side peaks grow at the expense of the main peak and move away from it. At −170°, the two signals are separated by 86 c.p.s. From the theory of rate processes and assuming an AX spin system,[7] ΔF^* for interchange of the two protons at $^3/_4$ separation is calculated as 5.7 ± 0.1 kcal./mole ($T_{3/4}$ = 120.6 ± 1°K., δ_{max} = 87.5 ± 3 c.p.s.).

Since the spectra are broadened by coupling and do not allow more accurate calculations, 7-deuteriocycloheptatriene (Ib) was synthesized by reduction of tropilium bromide with lithium aluminum deuteride ($LiAlD_4$, 95%; 7-deuterium in product was 94 ± 1% by n.m.r. spectroscopy). The spectra of Ib and IIb in trifluorobromomethane are similar to those of Ia and IIa, and a triplet structure in the methylene peaks can be discerned at −168°. However, the chemical shift of the methylene peak above the transition temperature changes with temperature and the areas of the methylene peaks below the transition are not equal (Table I). From a consideration of the dihedral angles between the methylene and vinyl hydrogens (124 ± 3° and 4 ± 3° from Dreiding models), and the coupling constants calculated from the Karplus curve ($J_{124°}$ = 3.4 and $J_{4°}$ = 8),[8] the high-field hydrogen is assigned ($J_{H-vinyl}$ = 4.0 ± 0.3) to IIb and the low-field one ($J_{H-vinyl}$ = 7.2 ± 0.3) to Ib. These data allow the calculation of thermodynamic parameters for the equilibrium Ib ⇄ IIb. From the variation of the areas with temperature and the formula $\Delta H - T\Delta S = RT \ln K$ (K = IIb/Ib), ΔH = −142 ± 30 cal./mole and ΔS = −0.7 ± 0.3 e.u. Thus, the structure with hydrogen *syn* to the ring is favored.

TABLE I

CHEMICAL SHIFTS OF THE METHYLENE PROTONS OF CYCLOHEPTATRIENE AND 7-DEUTERIOCYCLOHEPTATRIENE AT VARIOUS TEMPERATURES AND THE ENERGY DIFFERENCES FOR THE EQUILIBRIUM OF Ib AND IIb

Cycloheptatriene

Temp., °C.	δ_A[d]	δ_B[d]	$\delta_A + \frac{\delta_B - \delta_A}{2}$	K_{areas}[a]
+25	132 + 1[b]			
−86 ± 5	130.8 ± 0.1[b]			
−158 ± 1	94.4 ± 0.2	166.8 ± 0.3	130.6 ± 0.3	
−166 ± 1	91.3 ± 1	169.7 ± 0.3	130.5 ± 1	0.97 ± 0.02
−168 ± 1	91.2 ± 0.6	170.4 ± 1	130.8 ± 1	
−170.7 ± 1	86.1 ± 1	172.9 ± 0.6	129.5 ± 1	

7-Deuteriocycloheptatriene

Temp., °C.	δ_A[d]	δ_B[d]	$\delta_A + \frac{\delta_B - \delta_A}{2}$	K[a]	ΔF, cal./mole
+25	128 ± 1[s]				
−114 ± 1	125.8 ± 0.4[b]			1.10[c]	−30
−127 ± 1	125.0 ± .4[b]			1.14[c]	−38
−141 ± 1	123.2 ± .3[b]			1.24[c]	−56
−158 ± 1	87.3 ± 0.1	168.6 ± 0.3	127.9 ± 0.3	133 ± 0.02	−65
−166 ± 1				1.37 ± 0.02	−67
−168 ± 1	86.2 ± 0.8	169.3 ± 0.1	127 ± 0.3	1.41 ± 02	−72

[a] II/I. All data taken at 60 Mc.; solvent is CF_3Br. [b] Spectra show only a single average peak. [c] From average chemical shift. [d] From TMS internal standard c.p.s. downfield.

Preferential methylene protium– over deuterium–hydrogen bond formation with the 4,5-double bond cannot account for the observed conformational preference, since deuterium hydrogen bonds are stronger than protium hydrogen bonds.[9] Similarly, the effect cannot arise from a steric effect with the opposite double bond, since deuterium is smaller than protium.[10] However, the correct explanation appears to be steric in origin and to arise from eclipsing of the *anti*-1-hydrogen by the 2- and 7-hydrogens. The interactions with eclipsed deuterium are expected to be smaller than with protium leading to a greater stability for structure IIb. From these results, it is estimated that in ethane and derivatives, each deuterium–protium eclipsed pair

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should have an energy barrier above 70 cal./mole less than the corresponding protium–protium barrier. In cyclohexane, the 1,3–1,5-hydrogen axial interactions should be at least as large as the observed effect in cycloheptatriene and therefore relative to protium, deuterium should be more stable in the axial position (enthalpy contribution) by 140 ± 30 cal./mole.

The data support the equilibria of Ia and IIa and of Ib and IIb. No evidence was found indicating the presence of norcaradiene (III). If III were in equilibrium with Ia, the hydrogens at C-1 and C-6 would appear further upfield, the equilibrium constant would not be unity, and there would be a change in the vinyl region with temperature. (The vinyl hydrogens show no change in chemical shifts from room temperature to −165°.)

Acknowledgment.—This work was supported by a grant (P-14311) from the National Science Foundation.

(11) Sloan Foundation Fellow, 1961–1965.

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RECEIVED DECEMBER 11, 1963

Phytolaccagenin: A Light Atom X-Ray Structure Proof Using Chemical Information

Sir:

In 1949, Ahmed, Zufall, and Jenkins[1] reported the isolation, by a long and tedious process, of the toxic principle of pokeroot, *Phytolacca americana* L. They followed their enrichment by biological testing and proposed for their final product the formula $C_{55}H_{90}O_{22}\cdot 2H_2O$, suggesting that it was a steroidal glycoside. We have repeated the isolation by a simplified, but still tedious, route and obtained the same material, for which we propose the name phytolaccatoxin.

Hydrolysis of phytolaccatoxin in either methanol–hydrochloric acid or dioxane–hydrochloric acid gives glucose and xylose, identified paper chromatographically, and a crystalline aglycone, m.p. 317–318° dec., $C_{31}H_{48}O_7$, which we have named phytolaccagenin. Chemical studies on phytolaccagenin indicated that it was not a steroid, but rather the monomethyl ester of a trihydroxytriterpene diacid of the β-amyrin series. Because of the large number of functional groups to be located and because of the difficulties involved in the preparation of enough aglycone for extensive chemical investigations, we turned to X-ray methods for the solution of our structural problems.

Attempts to prepare heavy atom derivatives of suitable crystal habit were unsuccessful, all of the products appearing as extremely fine needles. When the amorphous phytolaccagenin triacetate was converted by thionyl chloride to its acid chloride, this treated with β-bromoethylamine, and the acetate groups removed by hydrolysis with potassium carbonate in aqueous dioxane, a product was obtained which crystallized as well-formed prisms of considerable size. Combustion analyses showed, however, that the material was not the β-bromoethylamide, but rather the 2-oxazoline resulting from cyclization and loss of HBr. Despite the absence of a phase-determining heavy atom the favorable crystalline form impelled us to carry out the structure analysis on this derivative.

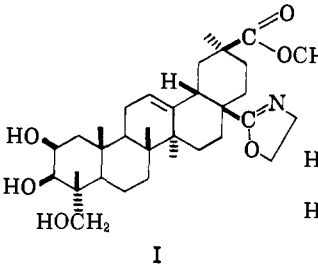
The crystals proved to be orthorhombic, space group $P2_12_12_1$, with axes a = 12.13 Å., b = 13.62 Å., and c = 18.28 Å. and four molecules in the unit cell (mol. wt. calcd., 558; found, 554). Integrated intensities for 3199 reflections were obtained photometrically from Weissenberg films, with 2648 (82.8%) being considered to be "observed." The intensities were reduced to $|F_{rel}|$ in the usual manner and a three-dimensional sharpened, origin removed Patterson function was calculated.

Twenty-nine carbon atoms (C-29 omitted) of the observed structure of ursolic acid[2] were taken as a model of the triterpene skeleton. An extensively modified version of the rotation program of Nordman[3] was then used to fit this model to the Patterson. Because of the approximations which were made to accommodate our larger model and slower (IBM 709) computer, as well as the imperfections in the model, the rotation fitting did not lead to a single, clear-cut orientation but rather to a number of possible ones. Each of these was investigated by taking advantage of the rapidity with which structure factors may be calculated for a model translated as a whole through the unit cell.[4]

The model was extended by adding C-30 (β-amyrin numbering) and by fitting the oxazoline ring about C-28 on the basis of chemical evidence that the free carboxyl group of phytolaccagenin was located at this position. The resulting model, oriented in one of the possible ways, was translated by steps of $^1/_8$ of a cell edge while structure factors were calculated after each step for the seventeen reflections with no index higher than 2. A three parameter least-squares refinement of the molecular location provided for a search of the volume bounded by the stepping points. A complete search in this fashion required less than 2 min.

Only those orientations and positions which appeared promising ($R < 35\%$) at this stage were carried further. For these, the translational search was repeated on smaller blocks about the suggested locations using data with indices to 3 (48 reflections) and 4 (103 reflections). The number of possibilities thinned rapidly and a final check on 195 reflections with a maximum index of 5 showed one set of parameters to be markedly superior.

These parameters gave R = 49% on all of the reflections (620) to sin θ/λ = 0.35. A number of cycles of structure factor, Fourier, and weighted difference map[2] calculations using data with sin $\theta/\lambda \leq 0.40$ permitted the correction of sizable errors in atomic positions and gradually revealed all of the missing atoms. The final structure appeared as that shown in I, proving phytolaccagenin to be II.



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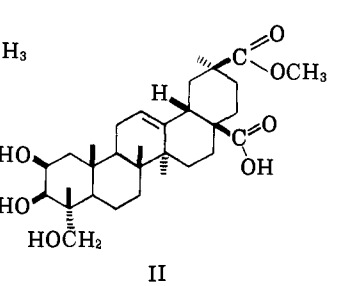

II

Refinement after the location of all of the atoms was by full matrix least squares on 479 observed reflections selected approximately at random, then by block diagonal least squares using all the data. The residual index R is currently 14.5% over all the observed reflections. Refinement is continuing.

It is important to note in connection with the structural approach outlined above that the correct solu-

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