TABLE I

N.M.R. SPECTRA OF COMPOUNDS IIa, IIb, IIc

Compound	Aromatic protons	$\geqslant$C-H$_a$	-OH$_b$	-CH$_3$
IIa	Multiplet, intensities 2 and 3	Doublet, intens. 1 τ = 3.87	Doublet, intens. 1 τ = 5.62	Singlet, intens. 3 τ = 8.00
		J_{ab} 8.4 c.p.s.		
IIb	a_2b_2 pattern, intensities 2 and 2	Broad doublet, intens. 1 τ = 4.40	Broad doublet, intens. 1 τ = 5.49	Singlets, intens. 3 τ = 8.00, 6.14
		J_{ab} 6.9 c.p.s.		
IIc	a_2b_2 pattern, intensities 2 and 2	Broad doublet, intens. 1 τ = 3.69	Broad doublet, intens. 1 τ = 5.50	Singlets, intens. 3 τ = 8.05, 7.60
		J_{ab} 5.5 c.p.s.		

Anal. Calcd. for $C_{20}H_{18}N_4O$ (330.38): C, 72.70; H, 5.49; N, 16.96. Found: C, 72.60; H, 5.32; N, 16.66.

The osazone of *p*-methylphenylglyoxal was prepared in the same manner as IIa in 90% yield, m.p. 136–137°; lit.[20] α-form m.p. 145°, β-form m.p. 167–168°.

Anal. Calcd. for $C_{21}H_{20}N_4$ (328.21): C, 76.79; H, 6.14; N, 17.07. Found: C, 76.91; H, 5.95; N, 16.97.

Proton Resonance Spectra.—The structures of the new compounds described in this work have been confirmed by integrated n.m.r. spectra.[21] β-Ketosulfones[22] exhibit a singlet representing the methylene hydrogen atoms in the -CO-CH$_2$-SO$_2$- grouping. However, for the methylene group in the β-ketosulfoxides Ia–d (-CO-CH$_2$-SO-) an ab pattern is observed for the methylene protons due to the asymmetry caused by the sulfoxide group. In the spectrum of IIa there is in addition to the aromatic protons (multiplet, intensity 5, *ortho* and *meta-para* hydrogens separated), a pair of doublets (total intensity 2) for the methylene group at τ = 5.55 and 5.72 (J_{ab} 14 c.p.s.; relative intensities 0.18 and 1.82),[23] as well as a singlet at τ = 7.34 (intensity 3) for the methyl group. Similarly, Ib gives the following absorptions in addition to the aromatic protons (a_2b_2 pattern, intensity 4); a pair of doublets total (intensity 2) at τ = 5.57 and 5.77 (J_{ab} 14 c.p.s., relative intensities 0.28 and 1.72) for the methylene group, a singlet at τ = 6.12 (intensity 3) for the methoxy group and a singlet at τ = 7.27 (intensity 3) for the methyl group. Compound Ic shows an a_2b_2 pattern for the aromatic hydrogen atoms; a pair of doublets, τ = 5.50 and 5.81, J_{AB} 15.5 c.p.s. for the methylene group, and singlets at τ = 7.25 and 7.58 for the methylsulfinyl groups and *p*-methyl groups. In Id the center peaks of the ab system for the methylene group are only slightly separated.

The n.m.r. spectra of the hemimercaptals IIa, IIb, and IIc exhibit a pair of doublets for the H$_a$–C–OH$_b$ grouping. Deuterium exchange in deuterium oxide solution allowed the assignment of one doublet to the -OH$_b$ group. Further n.m.r. data are listed in Table I.

(20) E. Durio, *Gazz. chim. ital.*, **65**, 89 (1935).

(21) Spectra were taken in chloroform-*d* at 60 Mc. with tetramethylsilane as internal standard.

(22) H.-D. Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1896 (1963).

(23) Calculated; *cf.* L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

Molecular and Crystal Structure of the Di-*p*-bromobenzoate of the Methyl Ester of Gibberellic Acid

BY JEAN A. HARTSUCK AND WILLIAM N. LIPSCOMB

RECEIVED MAY 17, 1963

The complete molecular structure and stereochemistry, except for absolute configuration, have been determined by a single crystal X-ray diffraction study of the di-*p*-bromobenzoate of the methyl ester of gibberellic acid. The lactone ring is shown to be *trans* to the two-carbon bridge. The space group is C2, and there are four molecules of $C_{34}O_8Br_2$ in a unit cell having parameters a = 28.22, b = 7.69, c = 17.63 Å., and β = 125° 12′. The value of $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ is 0.13 for the 1978 observed diffraction maxima. The 30 H atoms of the molecule were not located in this study.

The gibberellins are active metabolites which have been isolated for about forty years from culture filtrates of the fungus *gibberella fujikuroi.* Plants which have been subjected to an excess of a gibberellin grow abnormally rapidly in their early stages but then wilt and die before reaching maturity. On the other hand, gibberellins have also been isolated from healthy plants.[1] Therefore, these natural products are thought to be normal plant growth hormones which cause disease when present in excess.

At least ten different, but similar, such compounds have been characterized. One of these compounds, gibberellic acid, has been most widely studied by chemists because its isolation[2] from fungal cultures is well defined, reproducible, and of high yield. The chemical evidence, reviewed by Grove,[3] for the molecular structure leaves some doubt as to the configuration of the lactone ring; but we shall show that contrary to chemical expectations the lactone bridge is in an α-orientation. Preliminary results of an independent X-ray diffraction study by McCapra, Scott, Sim, and Young[4] on methyl bromogibberellate appeared after our study was well under way. These authors[4] deduced the correct chemical structure of gibberellic acid from the stereospecificity of the bromination reaction which changes the molecular conformation.

The present X-ray diffraction study of single crystals of the di-*p*-bromobenzoate of the methyl ester of gibberellic acid confirms the chemical structure, shows that the lactone ring is indeed *trans* to the two-carbon bridge and yields for the first time detailed bond distances and angles in the essentially unaltered ring structures of the molecule.

Experimental

The di-*p*-bromobenzoate of the methyl ester of gibberellic acid was prepared by E. J. Corey and S. Barcza. Colorless, irregularly shaped single crystals were obtained from solutions in ethyl acetate. All crystals which were photographed were less than 0.08 mm. in cross section, and hence absorption and extinction corrections were not made. Reciprocal lattice symmetry of C_{2h}, the systematic extinction of reflections for

(1) P. W. Brian, J. F. Grove, and J. MacMillan, *Progr. Chem. Org. Nat. Prod.*, **18**, 350 (1960).

(2) P. J. Curtis and B. E. Cross, *Chem. Ind.* (London), 1066 (1954).

(3) J. F. Grove, *Quart. Rev.* (London), **15**, 56 (1961).

(4) F. McCapra, A. I. Scott, G. A. Sim, and D. W. Young, *Proc. Chem. Soc.*, 185 (1962).

which $h + k$ is odd, and the expectation that the derivative, like gibberellic acid itself, is optically active uniquely determined the monoclinic space group as C_2^3-C2. This space group was later confirmed as the structure determination progressed. Visual estimates were made with the use of a scale prepared from timed single crystal reflections. A total of 1978 independent reflections

TABLE I. LIST OF OBSERVED F'S

```
H=0,K,L(0)(2,13)182,160,226,208,41,11,66,32,9,24,8,8,
(2)(0,16)135,116,110,58,78,49,18,71,31,9,29,15,14,9,10,7,
6,(4)(0,12)21,62,31,36,33,20,30,11,15,6,16,10,9,(6)(0,11)
48,16,7,12,25,23,14,-,9,20,11,6,(8)(1) 11,
H=1,K,L(1)(-16,16)9,13,19,11,17,40,42,17,51,22,98,115,140,
76,183,185,226,59,296,131,64,125,18,67,20,23,37,27,32,5*,
8,4*,9,(3)(-15,12)13,18,14,29,31,-,6*,21,20,40,76,37,26,36,
18,83,99,64,109,10,120,72,34,41,20,19,27,13,(5)(-11,8)13,
16,7*,13,7*,34,26,39,6,15,46,36,24,15,16,24,20,21,29,13,
(7)(-4,5)14,-,14,-,15,18,14,-,22,16,
H=2,K,L(0)(-18,15)5,10,29,5*,21,10,25,72,58,53,64,99,83,146,
158,124,15,-,-,82,156,176,73,46,84,80,33,8,13,21,11,-,12,
13,(2)(-15,13)12,13,9,9,14,38,27,53,62,41,25,115,225,222,
274,318,214,104,72,85,128,69,55,23,27,42,8,10,12,
(4)(-12,12)12,1*,23,16,19,16,17,29,54,64,17,27,11,125,41,
17,28,53,51,27,19,17,23,8,7,(6)(-4,7)19,-,-,-,-,22,-,-,-,-,
-,22,
H=3,K,L(1)(-16,14)17,19,12,8,7,17,34,36,49,134,67,93,141,
137,38,101,204,56,234,39,61,113,95,76,50,-,18,31,26,12,9,
(3)(-14,9)16,15,13,23,26,47,43,13,68,138,99,29,8,84,148,18,
84,25,55,39,42,6*,6*,29,(5)(-11,8)18,19,18,12,6*,20,37,21,
24,5,5,10,30,32,53,49,33,27,12,22,
H=4,K,L(0)(-16,14)10,10,5*,29,26,12,39,32,109,60,76,94,189,
177,72,71,70,184,235,22,23,-,88,141,40,13,58,39,5*,5*,9,
(2)(-15,13)12,24,28,13,25,44,89,39,57,151,39,150,58,234,184,
82,149,13,67,109,73,28,70,52,27,30,22,11,11,(4)(-13,11)10,
1*,21,19,30,23,28,34,15,26,60,73,66,45,75,60,14,9,29,33,36,
25,15,12,7,
H=5,K,L(1)(-17,13)8,10,5*,12,14,24,32,58,47,131,113,57,120,
319,205,109,179,221,206,112,125,124,40,55,53,23,23,10,5*,
15,11,(3)(-10,12)42,38,42,17,40,67,10,24,7,67,42,24,25,143,
23,37,14,27,32,22,21,11,11,(5)(-10,5)11,37,44,17,31,38,62,
46,22,31,29,-,41,22,25,14,
H=6,K,L(0)(-16,15)12,15,53,21,21,19,76,109,48,75,161,41,227,
28,99,97,22,59,71,46,55,66,17,-,117,44,16,8,20,7,14,3*,
(2)(-15,13)12,9,17,22,19,34,30,87,62,86,86,126,242,41,38,
90,44,158,42,42,21,23,53,51,-,23,18,6*,9,(4)(-13,10)8,7,8,
15,12,52,58,46,14,21,81,76,60,71,53,45,29,14,23,18,23,12,
13,10,
H=7,K,L(1)(-18,13)9,4*,8,14,21,21,24,43,25,47,79,93,59,53,
111,114,109,87,127,82,34,127,63,44,20,31,15,51,37,8,6,9,
(3)(-14,10)11,7*,20,30,11,13,54,105,183,15,162,173,120,59,
27,149,115,67,40,46,29,15,18,19,14,(5)(-10,5)16,7,7,24,23,
33,5*,35,35,18,41,27,23,17,22,11,
H=8,K,L(0)(-20,14)7,4*,4*,10,10,23,7,11,12,60,19,35,35,82,
108,203,63,99,140,219,183,91,62,235,54,32,18,100,24,6,5*,
12,4*,12,7,(2)(-17,11)11,13,12,27,21,24,-,32,53,107,116,22,
11,42,99,78,35,14,25,45,41,24,30,26,23,39,10,12,8,
(4)(-13,9)15,11,12,21,18,42,49,48,45,30,68,40,41,12,24,39,
21,14,19,1*,12,14,12,

H=9,K,L(1)(-20,10)5,4*,6,12,7,10,26,27,28,53,71,76,107,155,
171,71,127,100,175,76,98,156,135,86,60,32,37,36,15,36,16,
(3)(-15,10)14,23,22,16,12,34,37,44,44,59,64,33,35,60,33,128,
20,29,35,75,37,7*,19,24,7*,11,(5)(-12,4)14,16,27,15,22,51,
32,17,15,53,35,58,-,21,32,18,29,
H=10,K,L(0)(-18,11)10,16,33,5*,10,31,78,67,-,77,36,129,36,
31,222,66,62,46,70,137,115,-,89,30,4*,48,20,5*,16,13,
(2)(-16,10)16,6*,9,9,18,49,21,35,50,42,156,151,41,68,57,98,
63,26,38,95,43,41,15,25,23,22,8,(4)(-15,9)9,1*,16,25,16,-,
31,25,38,53,37,18,15,30,39,43,34,19,28,19,17,17,9,1*,9,
H=11,K,L(1)(-21,10)4,7,4*,8,18,8,23,17,32,33,44,57,73,112,
90,128,24,15,49,86,22,116,106,13,64,21,62,22,19,12,26,20,
(3)(-15,7)20,19,13,55,64,69,39,41,103,72,97,5,42,86,123,42,
29,59,42,39*,32,7*,21,(5)(-12,5)21,8*,7*,13,34,7*,13,29,11,
13,6*,27,35,-,-,12,22,16,
H=12,K,L(0)(-21,12)5,4*,4*,4*,10,15,14,18,14,19,11,30,-,54,
98,168,69,31,24,76,185,43,43,44,-,56,41,64,34,12,10,24,9,
10,(2)(-15,10)31,28,12,40,66,58,28,47,205,115,24,81,83,62,
63,71,41,-,-,50,28,13,10,6*,6*,12,(4)(-16,8)9,8,8,1*,15,28,
43,18,30,45,58,54,28,48,42,29,40,32,1*,27,15,18,11,1*,8,
H=13,K,L(1)(-21,10)4,8,4*,8,13,14,7,21,44,-,57,62,100,48,
85,92,129,148,28,53,110,68,44,8,51,19,29,17,7,6,11,9,
(3)(-16,7)14,13,18,19,48,26,6*,38,8,43,32,52,32,21,21,-,49,
31,25,13,25,11,22,11,(5)(-11,5)18,12,20,7*,31,28,33,11,26,
35,30,20,-,-,-,-,14,
H=14,K,L(0)(-18,9)10,5*,23,53,54,22,4*,112,112,73,58,152,
239,159,51,80,93,89,73,25,20,4*,46,14,14,26,4*,7,
(2)(-16,9)12,-,-,25,29,39,28,37,63,54,67,48,85,59,22,68,72,
36,20,19,23,25,15,15,-,8,(4)(-14,6)17,14,19,16,20,35,16,23,
44,41,34,14,23,19,38,35,14,10,13,13,10,
H=15,K,L(1)(-17,6)18,27,23,27,54,40,45,41,52,67,48,43,67,
59,61,15,52,39,35,38,9,23,15,24,(3)(-15,7)14,13,17,10,14,
66,20,65,39,89,66,90,56,32,71,51,74,17,7*,7*,7*,14,12,
(5)(-11,0)19,8*,12,7*,24,29,7*,7*,25,24,-,15,
H=16,K,L(0)(-21,10)5,7,4*,8,9,17,9,46,77,74,56,13,36,21,73,
32,9,68,63,66,27,22,107,50,29,8,44,15,16,16,6,11,
(2)(-18,6)8,9,6*,20,41,23,13,31,55,71,66,19,62,97,39,40,36,
45,33,39,23,30,9,11,15,(4)(-14,5)12,11,9,14,47,38,23,20,14,
47,55,66,13,30,36,22,14,1*,8,7,
H=17,K,L(1)(-18,7)12,12,16,5*,46,34,15,50,41,43,38,36,41,
42,50,73,24,27,32,25,33,23,9,4*,24,14,(3)(-16,2)16,32,11,
28,11,60,74,34,50,49,22,6*,47,15,7*,18,24,19,29,(5)(-11,0)
12,13,16,23,11,23,22,21,27,-,-,17,
H=18,K,L(0)(-20,9)10,7,11,24,9,74,5*,62,12,22,77,44,116,29,
42,88,136,41,4*,18,29,52,37,-,5*,4*,10,11,9,6,(2)(-17,7)9,
6*,21,42,37,32,-,36,43,54,17,33,64,34,42,38,27,20,36,43,22,
6*,10,10,8,(4)(-17,2)8,1*,10,28,22,15,13,1*,36,23,1*,11,55,
1*,12,15,18,-,16,15,
H=19,K,L(1)(-21,9)5,4*,10,12,11,10,17,36,41,19,39,73,43,58,
35,30,68,31,57,24,15,25,22,-,14,14,4*,5,8,3*,2,(3)(-15,3)
15,13,13,62,36,20,26,7*,63,38,21,60,41,-,-,15,18,21,21,
(5)(-10,-2)24,25,16,8*,8*,21,17,8*,15,
H=20,K,L(0)(-21,7)8,10,4*,8,5*,28,58,5*,23,4*,28,14,4*,22,
15,38,48,4*,42,4*,64,23,-,45,25,4*,4*,7,8,(2)(-17,4)16,9,
20,22,28,32,11,39,51,84,47,9,35,67,30,16,19,11,15,14,10,10,
(4)(-16,2)11,17,17,17,20,15,11,33,31,31,24,19,14,36,21,10,-,
10,10,
H=21,K,L(1)(-19,4)11,12,8,15,13,26,33,9,49,30,10,33,40,72,
24,37,39,35,19,-,15,23,11,15,(3)(-14,0)20,23,25,26,26,66,
14,28,39,41,22,44,20,-,15,(5)(-12,-4)12,16,8*,8*,8*,18,8*,
14,17,
H=22,K,L(0)(-19,3)14,11,19,26,14,12,5*,60,77,30,22,78,66,
90,32,75,13,14,28,-,-,12,21,(2)(-18,4)8,10,16,10,15,6*,23,
29,11,18,18,42,17,23,31,26,15,20,12,-,10,8,8,(4)(-17,-2)9,
1*,13,18,1*,1*,15,12,1*,15,22,19,8,8,15,10,
H=23,K,L(1)(-21,4)7,4*,7,12,22,11,9,28,35,23,10,14,51,36,
34,43,11,37,32,32,14,12,-,13,10,9,(3)(-13,-1)12,7*,7*,28,
7*,20,13,32,36,7*,17,24,27,(5)(-13,-12)13,11,
H=24,K,L(0)(-19,5)7,8,23,5*,5*,43,22,5*,5*,5*,15,5*,84,17,
54,27,5*,15,19,-,-,-,-,-,7,(2)(-20,4)7,8,5*,10,16,21,12,-,
26,42,22,16,28,44,28,30,23,7,17,15,11,-,-,-,6,(4)(-15,-2)
9,1*,1*,12,10,1*,1*,10,1*,9,15,1*,1*,9,
H=25,K,L(1)(-20,3)7,8,4*,14,17,8,5*,8,33,38,27,14,8,15,10,
36,36,4*,13,18,15,9,3*,5,(3)(-16,-3)14,15,14,24,39,17,11,
12,43,14,20,7*,7*,13,
H=26,K,L(0)(-18,1)9,15,9,30,18,21,21,28,39,28,19,34,5*,5*,
31,9,15,15,15,8,(2)(-14,0)19,19,6*,21,16,11,30,38,19,11,10,
6*,5*,13,9,(4)(-14,-6)11,1*,1*,8,16,6,8,13,17,
H=27,K,L(1)(-20,2)8,6,4*,9,13,27,25,4*,34,37,24,13,20,13,
11,20,9,4*,7,5,4,-,4,(3)(-14,-4)15,7*,18,7*,15,13,7*,7*,
7*,14,13,
H=28,K,L(0)(-18,-1)8,17,4*,14,4*,12,9,22,8,8,5*,5*,21,11,
7,4*,4*,9,(2)(-14,-2)23,11,18,9,37,16,8,25,11,12,14,7,6,
(4)(-12,-6)12,-,9,8,10,1*,10,
H=29,K,L(1)(-19,-1)6,7,9,8,20,7,4*,21,4*,14,9,13,12,4*,15,
8,4*,4,6,(3)(-16,-5)17,6*,22,6*,14,17,17,-,-,-,10,11,
H=30,K,L(0)(-17,-3)12,4*,13,10,4*,25,7,7,28,7,17,4*,26,13,
13,(2)(-16,-4)11,11,9,5*,19,9,5*,5*,11,5*,5*,9,7,
(4)(-10,-9)8,9,
H=31,K,L(1)(-19(-2)5,6,10,7,14,17,7,7,7,15,7,13,11,11,3*,
10,3*,5,
H=32,K,L(0)(-16,-9)16,16,17,-,4*,19,18,11,(2)(-16,-8)11,7,
9,12,12,11,5*,7,12,
H=33,K,L(1)(-16,-10)5,6,6,13,3*,3*,6,
```

Absent reflections are starred; unobserved reflections are indicated by a dash. If the h even reflections are multiplied by 0.9462 and the h odd reflections are multiplied by 0.9507 these structure factors are on an absolute scale.

(Table I) were obtained from Weissenberg photographs of Hkl for $0 \leq H \leq 6$ and hKl for $0 \leq K \leq 5$, and from precession photographs of the $hk0$ level.

Unit cell parameters of $a = 28.22 \pm 0.02$, $b = 7.69 \pm 0.03$, $c = 17.63 \pm 0.09$ Å., and $\beta = 125° 12' \pm 20'$ were obtained from Weissenberg photographs upon which a powder pattern of NaCl was superimposed. Assumption of four molecules, confirmed below, in the unit cell yields a calculated density of 1.54 ± 0.02 g. cm.$^{-3}$. This value is in good agreement with a value of 1.521 $\pm$ 0.002 g. cm.$^{-3}$, measured by pyconometric methods after removal of adsorbed air from the crystal with the aid of a vacuum line.

The integrated intensities from the films were correlated by computer methods.[5] In all of the later calculations, except for the determination of the scale factors, the 172 absent reflections were included each with a value of one-half of the minimum observed intensity in the appropriate region of the film. The usual corrections were made for Lorentz and polarization factors. In addition to a single over-all scale factor for all intensities, a separate single scaling parameter was introduced, relating all reflections for which h is even to all reflections for which h is odd. However, a preliminary value of this additional scaling parameter was obtained from the $hk0$ precession photograph. We chose to introduce this additional parameter in all later refinements rather than depend upon the upper level precession photographs about the c-axis for a more complete correlation.

The standard deviations σ of the observed intensities were determined[5] during the correlation procedure. The weight $w(I_i)$ assigned to a particular measurement I_i is based upon the number of times that the reflection is observed and on the precision of reflections with the same indices. The relation of σ and $w(I_i)$ to an average intensity $\bar{I}$ is then $\sigma^2 = (\bar{I})^2/\Sigma w(I_i)$. Systematic errors, *e.g.*, neglect of anomalous dispersion, have not been included, and no decrease in weights was made in the final correlation between common reflections taken about different crystal axes. Therefore the standard deviations are perhaps small, but we feel that they establish a reasonable basis for the *relative* weights used below in the least squares refinements.

Structure Determination.—The coordinates of the two Br atoms in the molecule were located from a three-dimensional Patterson function which had been sharpened so that the average intensity is independent of sin θ. A three-dimensional electron density map based upon the 500 most intense reflections and

(5) P. G. Simpson, Ph.D. Thesis, Harvard University, 1963.

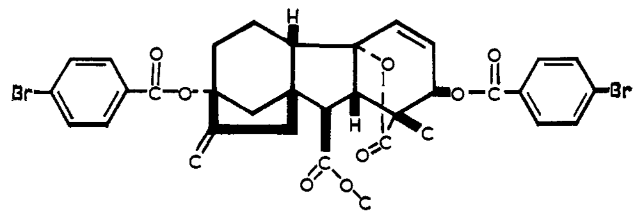


Fig. 1.—Structure of the di-*p*-bromobenzoate of gibberellic acid. The absolute configuration was not determined in this study.

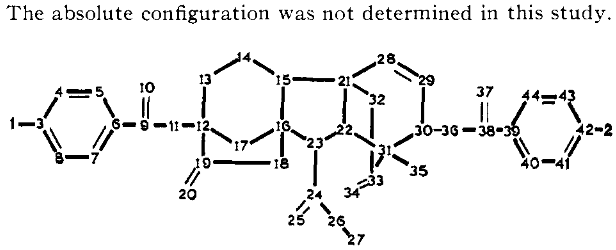


Fig. 2.—Numbering system for $C_{34}O_8Br_2$.

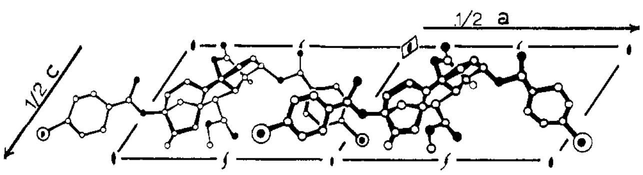


Fig. 3.—Crystal packing in $C_{34}O_8Br_2$. The origin is surrounded by a diamond.

upon the phases calculated from Br atoms failed to yield the structure. We noted that at least 400 of these most intense reflections were in common with a seperate list of 500 reflections which, at this stage, gave best agreement between observed and calculated intensities (Br only).

Concurrently, we computed a three-dimensional minimum function in which the minimum value was taken at each point from the superposition of Patterson functions[6] translated to the two Br positions in the molecule and to the two other Br positions related by the crystallographic twofold axis. From this function 32 peaks were chosen as C atoms, of which four were later shown to be incorrect, and a three-dimensional electron density map was then computed from the 500 most intense reflections, but with phases based upon the Br atoms and these 32 peaks assigned as C atoms. The contours of this function were placed on plastic sheets, from which 38 C and O atoms were located. At this stage only atoms 20, 25, 26, and 27 (Fig. 1 and 2) failed to appear. Three additional consecutive electron density maps yielded these additional atoms and also gave improved position parameters for all atoms.

The structure was refined by three-dimensional least squares methods in which off-diagonal terms were included. One cycle of refinement of all distance parameters for Br, C, and O of one individual, isotropic temperature on each of the atoms yielded a value of $R_F = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.23$. This cycle was then followed by one cycle of refinement of distance parameters and six (anisotropic) thermal parameters on each Br, C, and O. Because of the limitation of storage of the IBM 7090 this cycle had to be carried out in three separate computer runs in which different sets of atoms were refined, but in which several atoms in common between different runs were retained. Therefore, not all off-diagonal interactions have been included in this refinement, and also in a later refinement. The value of R_F reduced to 0.15. At this stage, an accurate three-dimensional model was built, and H atoms, which could not be found with certainty in difference electron density maps, were then introduced in stereochemically reasonable positions. The coordinates of these H atoms were then used to calculate fixed atom contributions in one more cycle of three-dimensional refinement of position and anisotropic thermal parameters of Br, C, and O atoms. The final parameters are shown in Table II, and the final value of $R_F = 0.13$ is compared in Table III with other criteria of agreement. The slightly higher value of R_F for the $h0l$ reflections is not surprising, because it was the first level estimated, and the data processing program also indicated that these reflections had significantly larger standard deviations than the average.

A final three-dimensional electron density map from which Br, C, and O atoms were subtracted showed only two peaks higher than 1e Å.$^{-3}$. These peaks, 3e Å.$^{-3}$ in height, were displaced from Br atoms by $(2/3)y$, and had the same x- and z-coordinates as the Br atoms. These peaks are attributed to lack of convergence of the difference Fourier series along the relatively short y-axis. No abnormalities in van der Waals contacts were found, and the molecular structure fills the unit cell so that there is no room for additional atoms. The molecular packing in the crystal is shown in Fig. 3.

(6) P. G. Simpson and W. N. Lipscomb, *J. Chem. Phys.*, **39**, 26 (1963).

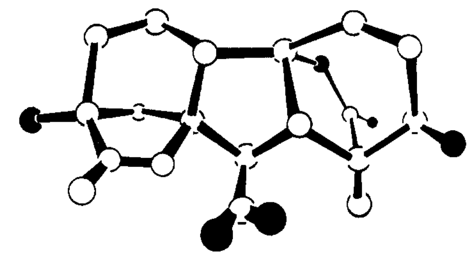


Fig. 4.—Perspective drawing of gibberellic acid. Carbons are open circles; oxygens are blacked.

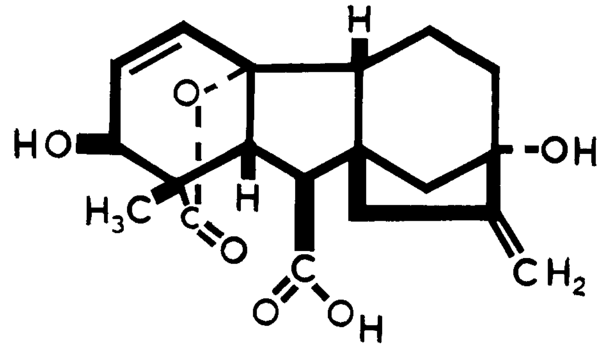


Fig. 5.—Structure of gibberellic acid ($C_{19}H_{22}O_6$) in the presumably correct absolute configuration.

Results and Discussion

The perspective drawing of the molecule in Fig. 4 is the mirror image of the known[7,8] absolute configuration. Bond distances and angles are listed in Table IV along with standard deviations computed from the variance-covariance matrix including off-diagonal terms. A reasonable limit of three times these standard deviations should, perhaps, be placed on these values, especially in the absence of any reasonable way to treat the unknown systematic errors. As sometimes occurs, the bond distances in the part of the molecule nearest the heavy atoms seem to be less reliable than those elsewhere in the structure. Half of the bond distances in the benzene rings have standard deviations of ± 0.03, while only $^1/_{18}$ of the rest of the distances have standard deviations exceeding ± 0.02 Å. Also, the Br atoms tend to produce problems of convergence of the electron density in their immediate vicinity, and the largest anisotropic thermal motions in the structure occur in the region of the *p*-Br-benzenoate groups. Hence, we feel that the larger systematic errors are probably present in the benzene rings, and that the bond distances and angles in the interesting part of the molecule can probably be considered reliable to within about twice the calculated standard deviations.

The most interesting region of the molecule is at the junction of the central five-membered ring, the lactone ring, and the cyclohexene ring. The angles at C_{21} are 15-21-22 = 105°, 22-21-32 (lactone O) = 101°, 22-21-28 = 112°, while the angle external to the rings is 15-21-28 = 123°. At C_{22} the angles are 21-22-31 = 99° and 21-22-23 = 101° in the rings, and 23-22-31 = 117° external to the rings. The angle 12-17-16 = 102° is also of interest in connection with possible small values of bond angles due to strain.

(7) G. Stork and H. Newman, *J. Am. Chem. Soc.*, **81**, 3168 (1959).
(8) J. F. Grove and T. P. C. Mulholland, *J. Chem. Soc.*, 3007 (1960).

TABLE II

FINAL STRUCTURE PARAMETERS

Atom	Atomic positions x/a	y/b	z/c
Br 1	0.300	0.673	0.376
Br 2	1.036	.999	.406
C 3	0.342	.752	.329
C 4	.319	.755	.238
C 5	.351	.813	.203
C 6	.409	.861	.269
C 7	.432	.876	.360
C 8	.398	.820	.394
C 9	.443	.895	.229
O 10	.425	.877	.147
O 11	.497	.956	.294
C 12	.539	.972	.274
C 13	.523	1.124	.202
C 14	.540	1.093	.135
C 15	.601	1.011	.185
C 16	.611	0.861	.253
C 17	.553	.808	.239
C 18	.642	.936	.354
C 19	.598	1.011	.363
C 20	.606	1.079	.439
C 21	.619	0.940	.125
C 22	.666	.806	.185
C 23	.641	.719	.237
C 24	.688	.626	.328
O 25	.738	.661	.373
O 26	.665	.507	.349
C 27	.703	.413	.439
C 28	.635	1.057	.074
C 29	.666	0.987	.045
C 30	.687	.813	.066
C 31	.662	.698	.108
O 32	.570	.821	.049
C 33	.597	.676	.039
O 34	.568	.581	−.021
C 35	.690	.521	.137
O 36	.750	.801	.133
O 37	.766	.802	.020
C 38	.784	.807	.101
C 39	.846	.838	.176
C 40	.867	.824	.269
C 41	.924	.864	.338
C 42	.962	.928	.316
C 43	.940	.940	.220
C 44	.884	.893	.150
H 45 (8)[a]	.412	.820	.470
H 46 (7)	.474	.920	.414
H 47 (5)	.338	.815	.138
H 48 (4)	.275	.725	.218
H 49 (13)	.479	1.095	.140
H 50 (13)	.515	1.250	.210
H 51 (14)	.507	1.045	.075
H 52 (14)	.540	1.230	.120
H 53 (15)	.633	1.100	.230
H 54 (17)	.505	0.765	.178
H 55 (17)	.560	0.750	.298
H 56 (18)	.663	1.055	.370
H 57 (18)	.660	0.820	.405
H 58 (20)	.640	1.050	.500
H 59 (20)	.580	1.105	.462
H 60 (22)	.711	0.845	.256
H 61 (28)	.630	1.200	.075
H 62 (29)	.679	1.120	.026
H 63 (30)	.678	0.775	.000
H 64 (44)	.864	.905	.070
H 65 (43)	.965	.990	.190
H 66 (41)	.935	.815	.405
H 67 (40)	.845	.750	.285
H 68 (23)	.602	.660	.180

Atom	Anisotropic temperature factors β_{11}[b]	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Br 1	48	630	150	−30	67	−19
Br 2	26	430	99	2	24	−2
C 3	32	320	130	1	46	24
C 4	27	190	81	41	17	12
C 5	18	520	76	−10	25	−7
C 6	27	200	75	45	31	56
C 7	26	170	93	29	32	0
C 8	31	330	87	16	41	−11
C 9	28	270	88	−2	35	−10
O 10	31	390	87	−8	34	−4
O 11	23	490	73	2	26	−16
C 12	23	240	95	11	30	18
C 13	34	340	76	40	33	33
C 14	28	420	100	52	34	66
C 15	19	260	74	17	24	21
C 16	18	300	80	−14	26	15
C 17	19	320	76	13	26	11
C 18	22	290	71	−10	25	−39
C 19	24	280	77	0	22	21
C 20	34	330	75	−24	34	−37
C 21	19	260	68	−23	16	−23
C 22	24	150	80	6	29	11
C 23	18	180	80	2	26	8
C 24	19	320	69	36	20	10
O 25	20	370	79	−29	17	29
O 26	29	270	86	7	32	19
C 27	31	450	75	58	19	45
C 28	24	240	89	−32	29	−13
C 29	25	210	98	5	34	30
C 30	20	380	64	−7	25	8
C 31	22	210	74	6	28	−15
O 32	19	380	74	−12	22	8
C 33	17	350	69	14	19	−16
O 34	25	380	78	−13	20	−15
C 35	30	280	81	−2	28	−38
O 36	24	460	79	−10	33	−15
O 37	30	640	63	−6	27	−46
C 38	26	480	92	11	34	44
C 39	18	510	81	8	26	32
C 40	24	440	70	12	25	−41
C 41	31	420	76	−7	32	−2
C 42	35	140	110	−5	42	−18
C 43	20	460	93	7	21	−1
C 44	24	340	66	−16	27	−16

[a] These hydrogen atom positions were determined from an accurate three dimensional model and were never refined. The carbon atoms to which the hydrogens are attached are indicated in parentheses. [b] Anisotropic temperature factors β_{ij} in the expression exp $-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{23}kl + 2\beta_{13}hl)$ are a six-parameter correction for thermal motion. Values for β_{ij} have been multiplied by 10^4. Each number has only two significant figures.

Atom C_{22} is 0.7 Å. out of the plane of the five-membered carbon ring, and 0.6 Å. out of the plane of the lactone ring of which it is also a member. The near-planarity of the other atoms of the lactone ring is in agreement with observations of Mathieson,[9] and we find that the bond C_{21}–O_{32} is 0.13 Å. longer than bond C_{33}–O_{32}, again in substantial agreement with his observations concerning the geometry of lactone rings.

(9) A. McL. Mathieson and J. C. Taylor, *Tetrahedron Letters*, **17**, 590 (1961).

TABLE III

SUMMARY OF AGREEMENT

$$R_F = \frac{\Sigma||F_o| - |F_c||}{\Sigma|F_o|} = 0.13 \qquad R_{F^2} = \frac{\Sigma||F_o|^2 - |F_c|^2|}{\Sigma F_o^2} = 0.23$$

$$R_{wF^2} = \left[\frac{\Sigma w||F_o|^2 - |F_c|^2|^2}{\Sigma w|F_o|^4}\right]^{1/2} = 0.28$$

hkl for	R_F	Range of sin θ (R_F as a function of sin θ)	R_F
h even	0.11	0.00–0.40	0.13
h odd	.12	.40– .50	.12
l even	.12	.50– .60	.13
l odd	.11	.60– .65	.13
h0l	.18	.65– .70	.12
		.70– .75	.17
0kl	.10	.75– .80	.16
		.80– .85	.15
		.85– .90	.16
		.90–1.00	.17

In the ester groups we find that one benzene ring is tilted about 15° about the C_6H_5–CO_2 bond relative to the plane of the CO_2 group, whereas the other benzene ring and its attached CO_2 groups are substantially planar. This molecular feature appears to us to be associated with the requirement for near-parallel stacking of the benzene rings in the crystal, and hence this deviation from coplanarity may not be a property of the molecule in solution.

For convenience to the reader we show in Fig. 5 the structure of gibberellic acid in the presumably correct absolute configuration.

We close with a comment on the strategy of the investigation. Our intuitive feeling is that superposition procedures are more powerful methods when the ratio of heavy to light atoms is as small as that present here. The ratio $\Sigma N^2/\Sigma n^2$, where N is the atomic number of the heavy atom and n is the atomic number of the light atoms, is 1.41. We were therefore led to

TABLE IV

Bond distances,[a] Å.

C–Br		C_{sp^3}–C_{sp^2}	
3–1	1.90	19–12	1.53
42–2	1.84	19–18	1.46
C–C (benzene)		24–23	1.54
4–3	1.34*	28–21	1.52
5–4	1.43*	30–29	1.42
6–5	1.41	33–31	1.51
7–6	1.34†	C_{sp^2}–$C_{benzene}$	
8–3	1.41*	9–6	1.49
8–7	1.45	39–38	1.49*
40–39	1.38	C=C	
41–40	1.40*	20–19	1.33
42–41	1.41*	29–28	1.34
43–42	1.43*	C=O	
44–39	1.43	10–9	1.25
44–43	1.39	25–24	1.20
C_{sp^3}–C_{sp^3}		34–33	1.15
13–12	1.60	38–37	1.21
14–13	1.51	C_{sp^2}–O	
15–14	1.55	11–9	1.36
16–15	1.56	26–24	1.30
17–12	1.54	33–32	1.42
17–16	1.56	38–36	1.34
18–16	1.58	C_{sp^3}–O	
21–15	1.51	12–11	1.43
22–21	1.53	27–26	1.49
23–16	1.50	32–21	1.55
23–22	1.59	36–30	1.47
31–22	1.55		
31–30	1.57		
35–31	1.51*		

Bond angles,[b] degrees

Atoms		Atoms	
1–3–4	122	22–31–30	107
1–3–8	117	31–30–29	114
3–4–5	121*	30–29–28	124
4–5–6	117	29–28–21	118
5–6–7	122	28–21–22	112
6–7–8	119	22–21–32	101
7–8–3	119	21–32–33	107
8–3–4	121*	32–33–31	108
7–6–9	124	32–33–34	118
5–6–9	114	34–33–31	134*
6–9–10	127*	33–31–22	102
6–9–11	112	22–31–35	115
10–9–11	121	30–31–35	112
9–11–12	121	16–23–24	113
11–12–13	117	22–23–24	113
11–12–19	110	23–24–25	124
11–12–17	118	23–24–26	111
12–13–14	116	25–24–26	125
13–14–15	112	24–26–27	118
14–15–16	112	29–30–36	114
15–16–17	112	31–30–36	105
16–17–12	102	30–36–38	119
17–12–13	105	36–38–37	126*
17–12–19	101	36–38–39	112
12–19–20	124*	37–38–39	121*
12–19–18	108	38–39–40	121
20–19–18	127	38–39–44	118
19–18–16	108	39–40–41	121
18–16–17	95	40–41–42	121
15–16–23	105	41–42–43	118*
16–23–22	107	42–43–44	122*
23–22–21	101	43–44–39	118
22–21–15	105	44–39–40	121
21–15–16	107	41–42–2	123
21–15–14	118	43–42–2	120
21–22–31	99		

[a] Unmarked distances have standard deviations of ±0.02 Å. Those distances indicated by an asterisk are ±0.03 Å. and by a dagger are ±0.01 Å. All standard deviations include the errors of the unit cell dimensions. [b] The central atom is the vertex of the angle. Unmarked angles have standard deviations of ±1°. Those angles indicated by an asterisk are ±2°.

Atom C_{17} is also of special interest. It is the out-of-plane member of the five-membered ring to which it belongs, and the six-membered ring of which this atom is also a member is in the boat conformation.

It would be of interest to carry out X-ray diffraction studies of other large molecules, particularly those containing five-membered rings and highly fused ring systems. There is no molecule having sufficiently well established structural parameters for comparison with the results described here.

abandon the usual heavy atom method without a fair trial based upon use of a larger number of reflections and upon weights for the Fourier coefficients which depend upon the reliability of phase determination by the heavy atoms alone. Bromine was selected as a heavy atom in order that the standard deviations for light atoms would be small. Also, two Br atoms were introduced in the molecule in order to reduce the chance that these heavy atoms would produce pseudosymmetry in the crystal, and the benzene rings were added in order to facilitate[10] the location of known molecular features in order to improve the reliability of location of the gibberellic acid part of this ester. In summary, this strategy was successful, but the disadvantages were the introduction of a relatively large number of extra atoms in the determination, and the occurrence of the strongly anisotropic thermal vibrations normal to the planes of the benzene rings.

(10) M. G. Rossmann and W. N. Lipscomb, *Tetrahedron*, **4**, 275 (1958).

Acknowledgment.—We wish to thank Professor E. J. Corey and Mr. S. Barcza for the preparation of this derivative, for helpful discussions, and for the measurement of the density of the crystal. We acknowledge use of the IBM 7090 computers at the Harvard and the MIT Computation Centers, and support of this research by the National Institutes of Health, the National Science Foundation (including a Fellowship to J. A. H.), and the Air Force Office of Scientific Research.

[CONTRIBUTION FROM THE CHANDLER LABORATORIES OF COLUMBIA UNIVERSITY, NEW YORK 27, N. Y., AND THE WEIZMANN INSTITUTE OF SCIENCE, REHOVOTH, ISRAEL]

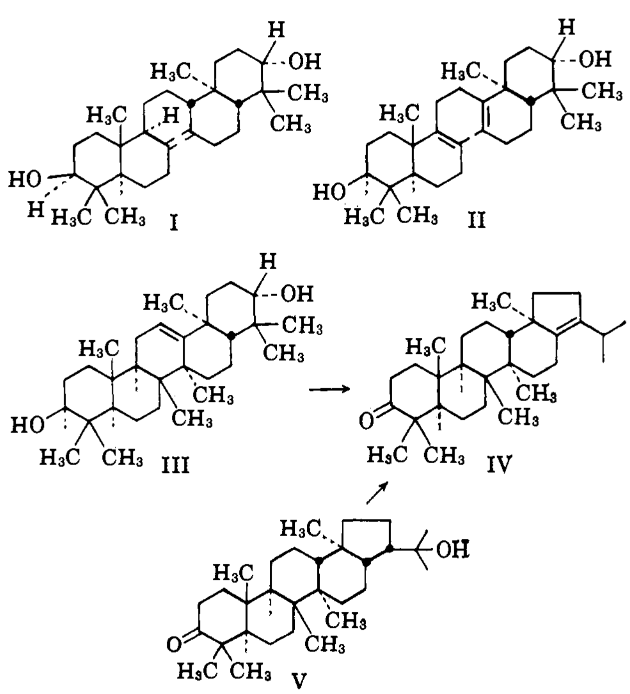
Total Synthesis of Polycyclic Triterpenes: The Total Synthesis of (+)-α-Onocerin

BY GILBERT STORK, ALEX MEISELS, AND J. E. DAVIES[1]

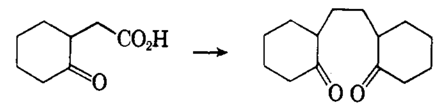
RECEIVED MAY 28, 1963

The total synthesis of the natural (+)-α-onocerin is described.

The elucidation of the structure of the triterpene α-onocerin (I) by Barton and Overton,[2] in 1955, was of considerable importance on two counts. First, this triterpene is an uncomplicated example of the squalene biogenetic hypothesis for the usual pentacyclic triterpenes and steroids, in which the assumed concerted cyclization is starting from both ends of the chain rather than proceeding unidirectionally.[3] Second, Barton and Overton[2] were able to cyclize α-onocerin, *via* the β-isomer II, to a pentacyclic triterpene system, γ-onocerin (III), which, although it has not been found in nature so far, is simply related to the natural pentacyclic triterpene hydroxyhopanone[4] (V). In fact, the dehydration product IV of hydroxyhopanone has been made from onocerin by partial synthesis by Schaffner, *et al.*[5] We now record the details of the total synthesis



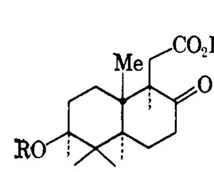
of natural α-onocerin. The starting point of the synthesis was the assumption that the Kolbe electrolytic coupling[6] of suitable γ-ketocarboxylic acids should be a simple solution to one of the problems of synthesizing this particular symmetrical molecule. Our initial experiments showed the feasibility of such a scheme: 2-oxocyclohexaneacetic acid, under the usual electrolytic coupling conditions, gave a very good yield of 1,2-di-(2-oxocyclohexyl)-ethane (VI). This result allowed the



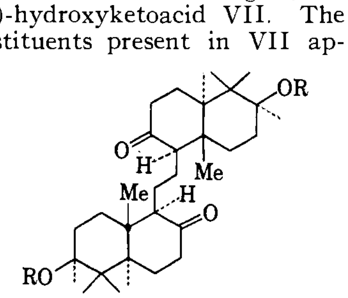
VI

dissection of the synthetic problem into three parts: (a) the construction of the proper ketoacid, *e.g.*, VII and its resolution; (b) the coupling of the substance to the symmetrical diketone VIII which should be identical with the known ozonolysis product from natural onocerin; (c) the transformation of the two carbonyl groups of the dione into the two exocyclic methylene groups of the final product.

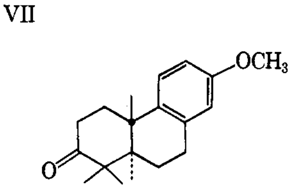
We will now turn our attention to the first goal, the construction of the (−)-hydroxyketoacid VII. The sequence of vicinal substituents present in VII ap-



VII



VIII



IX

(1) For a preliminary communication see *J. Am. Chem. Soc.*, **81**, 5516 (1959).

(2) D. H. R. Barton and K. H. Overton, *J. Chem. Soc.*, 2639 (1955).

(3) *Cf.* G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc.*, **77**, 5068 (1955); A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).

(4) H. Fazakerley, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 1877 (1959).

(5) K. Schaffner, L. Cagliotti, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **41**, 152 (1958).

(6) *Cf.* B. C. L. Weedon in "Advances in Organic Chemistry. Methods and Results," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1960, Chapter I. A related scheme has been used independently by E. J. Corey and R. R. Sauers, *J. Am. Chem. Soc.*, **79**, 3925 (1957).