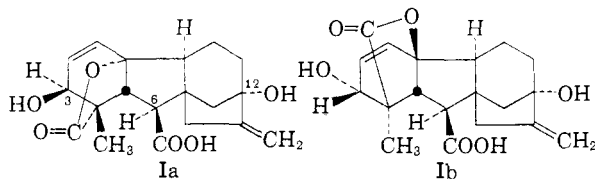


violates the Hudson-Klyne rule and they questioned the applicability of the rule to gibberellic acid. Since two stereochemical formulas (Ia and Ib) were predicted from optical rotatory dispersion curves of degradation products of I,³ Edward and co-workers preferred the alternate expression Ib.



Because of the empirical nature of the Hudson-Klyne rule, the assignment of stereochemistry to the lactone ring awaited other experimental results. We now wish to present new evidence in favor of stereochemical formula Ia for gibberellic acid.

Catalytic hydrogenation of I with 2% Pd on CaCO₃ in tetrahydrofuran afforded tetrahydrogibberellic acid (II)^{1,4} in high yield, the hydrogenolysed products amounting to less than 10%. The methyl ester (III), m.p. 245–246° (reported⁴ m.p. 233–236°) (found: C, 65.95, H, 7.80), of II was treated with one mole of phenylglyoxalyl chloride⁵ and then with isopropenyl acetate containing a trace of *p*-toluenesulfonic acid to afford methyl tetrahydrogibberellate 3-phenylglyoxalate 12-acetate (IV), m.p. 153–154°, [α]_D²⁵ +68.1° (chloroform), [α]_D²⁴ +75.5° (ethanol), infrared, 1775 cm.⁻¹, 1730 (broad), 1685, 1600 (chloroform) (found: C, 66.87, H, 6.19). Slow addition of methylmagnesium iodide (1.3–1.4 moles) to a dilute (0.01 M) solution of IV in tetrahydrofuran resulted in selective reaction of the ketonic group of IV with the Grignard reagent. Alkaline hydrolysis of the Grignard product gives optically active atrolactic acid in 71% yield,⁶ [α]_D²⁵ +3.63° (*c* 3.5 ethanol). This result establishes that the 3-hydroxyl group of III is β -oriented.

Methyl 3-epitetrahydrogibberellate (V), prepared in a manner similar to that described previously,^{1,7} was converted to its 3-phenylglyoxalate 12-acetate (VI)^{5,8} [α]_D²⁵ +39.4° (chloroform)

(3) B. E. Cross, J. F. Grove, P. McClosky, T. P. C. Mulholland and W. Klyne, *ibid.*, 1345 (1959). These authors favored Ia because of (i) the better agreement of the optical rotatory dispersion curves with formula Ia than Ib and (ii) the facile closure and stability of the lactone ring of methyl α -dihydrogibberellate. However, Ib was not positively excluded.

(4) Compare with the yields under the hydrogenation conditions reported by B. E. Cross, *J. Chem. Soc.*, 3022 (1960). II is identical with Cross' 8-epitetrahydrogibberellic acid, as judged by comparison of m.p. and optical rotation of the methyl ester. The numbering system used in reference (1) is adopted in this Communication.

(5) The 3-phenylglyoxalates of III and VI resisted crystallization and were purified by silicic acid chromatography using infrared spectra as criteria of purity.

(6) The degree of selectivity is surprising in view of the presence of the four ester carbonyls in the molecule. This modified procedure should widen the applicability of the Prelog-McKenzie method to polyfunctionalized compounds; see S. Masamune, *J. Am. Chem. Soc.*, **82**, 5253 (1960).

(7) Usually a mixture (15–25:65–40) of III and V resulted and was separated by silicic acid chromatography.

(8) VI is an amorphous solid. The homogeneity of VI was confirmed upon silicic acid chromatography by the identical infrared and ultraviolet spectra and optical rotation of every fraction.

infrared, 1775 cm.⁻¹, 1720 (broad), 1680, 1600 (chloroform) (found: C, 66.96, H, 6.51). Atrolactic acid was obtained in 68% yield from VI using conditions identical with those used for IV. This acid exhibits negative rotation, [α]_D²⁵ -2.20° (*c* 4.0 ethanol). Therefore, the 3-hydroxyl group of V must be α -oriented.

The finding that atrolactic acid of opposite rotational signs arises from IV and VI is consistent with the known epimeric relation of the 3-hydroxyl groups of III and V. Further, the assignment of absolute configuration to the 3-hydroxyl group of I has now been confirmed independently.⁹ Since a *trans* configuration of the lactone ring and the 3-hydroxyl group of I already has been established,¹ the lactone ring must be assigned an α -orientation. Optical rotatory dispersion studies definitely rule out the possibility of a *cis* juncture with an α -oriented lactone ring.^{3,10} We must conclude, therefore, that the stereochemistry of gibberellic acid is represented by Ia.¹¹

(9) All the compounds cited by Edward, *et al.*,² possess a phenanthrene skeleton, whereas the A, B and C rings of gibberellic acid constitute a fluorene system. Apparently the anomaly observed in Edward's examples does not apply to a ring system like gibberellic acid.

(10) III was treated with sodium methoxide in methanol-*d* and deuterium oxide under conditions which afforded a mixture of III and V (or the corresponding acids) in more than 50% yield, but no deuterium was incorporated at C₈. The lack of deuterium uptake means that the C₈-carbomethoxy group cannot epimerize under these conditions. Therefore, one can draw no conclusion about the stereochemistry of the A,B ring juncture from the observed failure of the C₈-carbomethoxy group to epimerize during alkaline hydrolysis.¹

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BICYCLOHEPTADIENE DIBROMIDES

Sir:

Because of the widespread interest in the behavior of bicycloheptene derivatives and related structures, we report the isolation and properties of the three dibromides and append our urgent warning regarding the possible danger of working with these compounds.

From the addition of bromine to a slight excess of bicycloheptadiene I at 0 to -20°, in carbon tetrachloride, chloroform and methylene chloride, the resulting dibromide mixture is only 17–24% unsaturated.^{1,2} The unsaturated component is clearly dibromide III, treatment of a 23% unsaturated dibromide fraction with potassium permanganate leading to a 65% yield of a dibromoglycol, m.p. 127–128°.

Anal. Calcd. for C₇H₁₀O₂Br₂: C, 29.40; H, 3.50. Found: C, 29.24; H, 3.72.

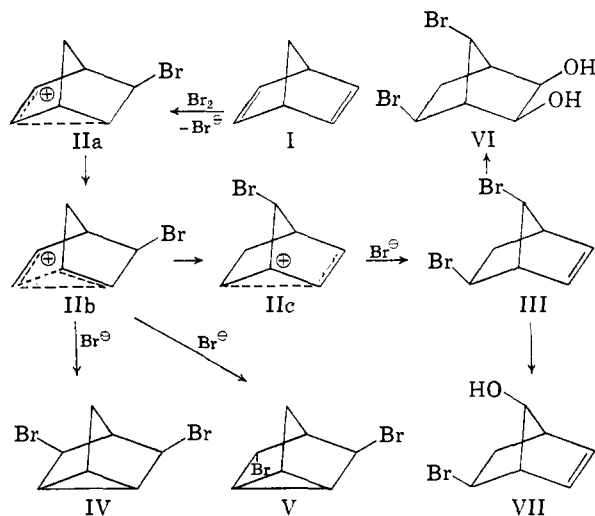
This dibromoglycol has been shown elsewhere³ to have structure VI. The unsaturated dibromide III,

(1) S. Winstein and M. Shatavsky, *Chemistry and Industry*, 56 (1956).

(2) L. Schmerling, J. P. Luvisi and R. W. Welch, *J. Am. Chem. Soc.*, **78**, 2819 (1956).

(3) S. Winstein and M. Shatavsky, *ibid.*, **78**, 592 (1956).

with its *anti*-7-bromine atom, is highly reactive in solvolysis, hydrolysis leading to bromohydrin^{3,4} VII. The latter was employed previously^{3,4} for the synthesis of *anti*-7-norbornenol and more recently for the preparation of 7-norbornadienol.⁵



Destruction of the unsaturated component of the original bicycloheptadiene dibromide mixture by treatment with potassium permanganate led to a saturated dibromide mixture, n_{D}^{25} 1.5770. Fractionation of the latter through a 40-plate center rod column at 2 mm. gave rise to fractions ranging in b.p. from 74° to 82°. Low temperature crystallizations of combined early fractions from pentane led to a saturated dibromide, m.p. 3.7–4.4°, n_{D}^{25} 1.5759, while similar treatment of a late fraction led to another saturated dibromide, m.p. 42.5–43.5°. Both dibromides gave negative permanganate tests and showed intense absorption in the infrared at 12.2–12.6 μ appropriate for 3,5-dibromonortricyclenes.

Anal. Calcd. for C₇H₈Br₂: C, 33.37; H, 3.20; Br, 63.43. Found for isomer, m.p. 3.7–4.4°: C, 33.36; H, 3.31; Br, 63.34. Found for isomer, m.p. 42.5–43.5°: C, 33.22; H, 3.40; Br, 63.31.

Dipole moments in benzene solution of 1.53 and 2.35 debye, determined by Professor Max Rogers,⁶ show that the 43° and 4° isomers have the *cis* and *trans* configurations IV and V, respectively. In solvolytic reactivity in 80% ethanol, the two isomers are nearly equal, being less reactive than nortricyclyl bromide by factors of 30–40 at 100° (Table I). The nortricyclenic dibromides are

(4) S. Winstein, M. Shatavsky, C. Norton and R. B. Woodward, *ibid.*, **77**, 4183 (1955).

(5) S. Winstein and C. Ordonneau, *ibid.*, **82**, 2084 (1960).

(6) Unpublished work of Professor Max T. Rogers of Michigan State University.

thus less reactive than the unsaturated dibromide III by a factor of *ca.* 10⁴ at 25°.

Infrared spectroscopy shows that the saturated dibromide mixture from bicycloheptadiene contains only the two nortricyclenic dibromides IV and V, the *trans*:*cis* ratio being *ca.* 2 in the various solvents. Until questions of multiplicity and behavior of homoallylic cationic species are fully settled,⁷ one cannot give a final interpretation of the mechanism of bromine addition to bicycloheptadiene. It seems possible that the unsaturated dibromide III arises from cation IIc, while the stereoisomeric mixture of nortricyclenic dibromides arises from intermediate IIb.

TABLE I
PROPERTIES OF 3,5-DIBROMONORTRICYCLENES

Nortricyclene derivative	M.p., °C.	n_{D}^{25}	Solvolytic temp., °C., 10 ⁵ h	80% EtOH (sec. ⁻¹)
<i>cis</i> -3,5-Br ₂ (IV)	43	1.5798 ^a	99.9	1.0
<i>trans</i> -3,5-Br ₂ (V)	4	1.5759	99.8	1.3
3-Br			50.1	0.204
			75.0	3.44
			99.9 ^b	40.0

^a Extrapolated value. ^b Extrapolated from the data at the other temperatures.

Despite the intrinsic interest of these unusual compounds, this laboratory has provisionally discontinued all experimental work requiring the preparation or use of the dibromides or their hydrolysis products.

There is no *a priori* reason to believe that these particular compounds are more dangerous to man than several related substances widely used as industrial chemicals; however, of the three laboratory workers who have used the dibromides and bromohydrin VII, two later developed similar pulmonary disorders which contributed to their subsequent deaths. The third has exhibited minor skin sensitivity reactions.

Although we are aware of no prior toxicological history of these compounds, one cannot ignore the possibility of an insidious long-term effect unknown to medicine. Until further information is obtained from toxicological testing, we recommend that the compounds be handled only with extreme caution, and that all persons concerned with their use be informed of their possible dangerous propensities.

We would appreciate any toxicological information on the above-mentioned or related compounds.

(7) *E.g.*, S. Winstein and E. Kosower, *J. Am. Chem. Soc.*, **81**, 4399 (1959).

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