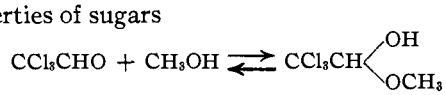
[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 196]

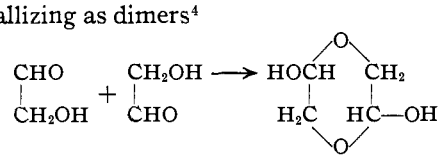
The Chemistry of the Tetrose Sugars. IV.[1] The Structure of a Methyl-*d*-erythroside.[2] The Mutarotation of *d*-Arabinose Oxime

BY ROBERT C. HOCKETT AND CARL W. MAYNARD, JR.[3]

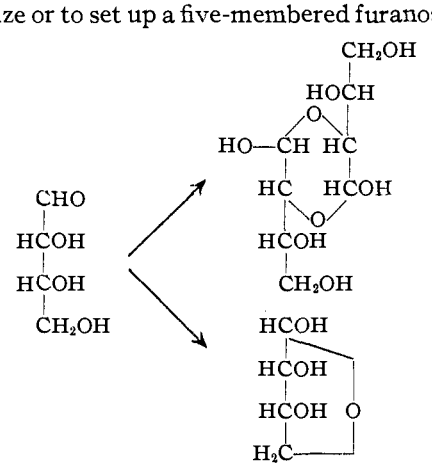
The universal affinity between carbonyl compounds and alcohols, which often impels the reversible formation of hemiacetals, underlies many of the most characteristic physical and chemical properties of sugars



Glycolaldehyde and the trioses manifest this affinity by *inter*molecular hemiacetal formation, crystallizing as dimers[4]



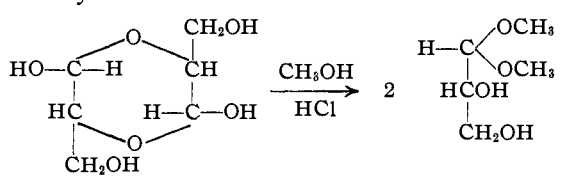
The pentoses and hexoses satisfy similar affinities by *intra*molecular addition of alcohol to aldehyde, yielding cyclic hemiacetals. The predilection in all these cases for a six-membered ring would render difficult a prediction whether the tetroses, on crystallizing, would tend rather to dimerize or to set up a five-membered furanose ring



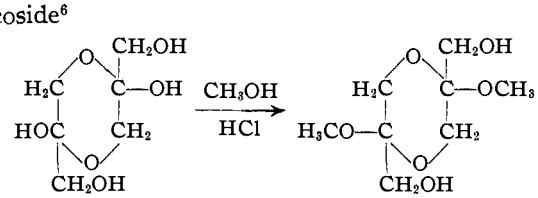
The observation that *l*-erythrose is monomeric in dilute aqueous solution[5] does not solve this question; the trioses are dissociated under like conditions.

On condensation of sugars with methanol containing hydrogen chloride, three types of behavior have been observed.

(1) The dimeric cyclic hemiacetal, glyceraldehyde, is converted into a monomeric open-chain dimethyl acetal



(2) The dimeric hemiacetal, dihydroxyacetone, is converted directly into the dimeric methyl glycoside[6]



(3) Finally, the more stable products obtained by such treatment of the monomeric inner hemiacetal, glucose, are the methyl pyranoside and the methyl furanoside.

Although isolation of a particular type of methyl derivative does not justify any conclusion regarding the preferred structure of the free sugar, it does provide *prima facie* evidence for the existence of the corresponding sugar form and provides some insight into the habits of the compound.

The first objective of the present study was to learn how *d*-erythrose would condense with meth-

(1) Number III of this series, THIS JOURNAL, **60**, 278 (1938).

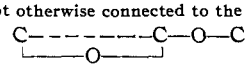
(2) This paper was read before the Division of Organic Chemistry at the Milwaukee meeting of the American Chemical Society, September, 1938. It is taken from a thesis submitted by Carl W. Maynard, Jr., to the Graduate School of the Massachusetts Institute of Technology in partial fulfilment of the requirements for the degree of Doctor of Philosophy in July, 1938.

(3) Cellulose Research Fellow during 1937–1938.

(4) Fischer and Taube, *Ber.*, **60**, 1704 (1927); *cf.* Bergmann and Miekeley, *ibid.*, **54**, 2152 (1921); *cf.* Fischer and Baer, *ibid.*, **63**, 174 (1930), for formulation as dioxane derivatives.

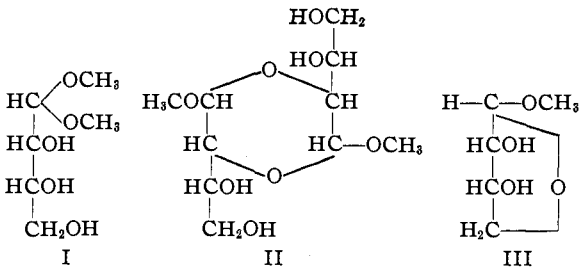
(5) Deulofeu, *J. Chem. Soc.*, 2973 (1932).

(6) We have not succeeded in finding anywhere an accurate definition of the term glycoside. The definition of Beilstein (Beil., Vol. XXXI, p. 11) is not valid since discovery of the true acetals of the higher sugars [Montgomery, Hann and Hudson, THIS JOURNAL, **59**, 1124 (1937)]. Our concept of a glycoloside provides that within such a compound a carbon atom be joined through oxygen to another carbon which is otherwise linked to the first and also through oxygen to a third carbon not otherwise connected to the first.



More concisely, a glycoside is a monocyclic mixed acetal. This definition includes the methyl glycoloside of Fischer and Baer[4] and analogous derivatives of the three-carbon sugars which are very similar in properties to the prototype, methyl glucoside. It excludes levoglucosan and arabinose dimethyl acetal, which are dicyclic and noncyclic, respectively.

anol containing 1% hydrogen chloride, the possible products being represented as follows[7]



To determine the structure of the product, both the methylation procedure and the method of cleavage oxidation[8] were employed (Fig. 2).

d-Erythrose diacetamide, obtained from *d*-arabinose by a modification of the Wohl degradation,[9] was hydrolyzed partially with sulfuric acid. The erythrose thus freed was treated with methanol containing about 1% hydrogen chloride and the methyl erythroside obtained was separated from the non-volatile nitrogenous compounds by distillation in a relatively high vacuum. On further methylation and oxidation with nitric acid, inactive dimethoxysuccinic acid was obtained, indicating that the product of condensation with methanol was a methyl-*d*-erythrofuranoside (III).

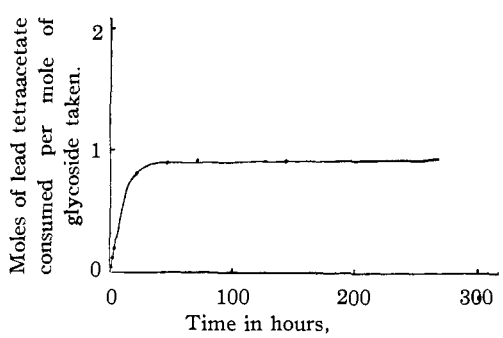


Fig. 1.—Oxidation of methyl-*d*-erythroside by lead tetraacetate.

This methyl-*d*-erythrofuranoside furnished us with a glycoside containing only two free hydroxyl groups, and those of known position and configuration, rendering possible a direct test of certain conclusions drawn by McClenahan and the senior author[8] from relatively indirect evidence, concerning the relative rates of oxidation of *cis* and *trans* glycols by lead tetraacetate. It was found that one mole of the glycoside consumes only one mole of this oxidant and that the rate of the reaction is the relatively rapid one found in the previous study to be characteristic of *cis* glycols (Fig. 1).

Moreover, after lead tetraacetate oxidation of this glycoside, the further action of strontium hypobromite yielded a crystalline salt closely resembling strontium D′-methoxydiglycolate. The latter was reported by Jackson and Hudson[8] and by McClenahan and Hockett[8] as a product of the action either of *excess* periodic acid or of lead tetraacetate (*two* moles) upon alpha-methyl-*d*-pentopyranosides, followed by treatment with strontium hypobromite. The present product showed the same composition and similar crystal habit, but differed optically, showing specific rotation $-8.94°$[13] as compared with a recorded value of $+55.0°$ for the beta and $-56.6°$[13] for the alpha isomer. This was considered evidence that our methyl-*d*-erythrofuranoside was a mixture containing about 58% of the alpha and 42% of the beta form (Fig. 2).

Data are included concerning the mutarotation of *d*-arabinose oxime and the hydrolysis of *d*-erythrose diacetamide by 0.100 *N* sulfuric acid (Table I and Fig. 3).

Experimental Part

***d*-Arabinose.**—This sugar was prepared from calcium gluconate by the procedure of Hockett and Hudson[10] modified for larger scale production.

***d*-Arabinose Oxime.**[5,11]—The method of preparation was almost the same as that described for *d*-xylose oxime.[12] The product crystallized readily from the reaction mixture, on cooling, in a yield of 86%. Recrystallized from about 70% ethanol as thin rectangular plates, washed with absolute ethanol, and dried at 50°, it showed m. p. 136–137° and rotated[13] $-13.5°$ at equilibrium (c, 2.0544; l, 2; H_2O).

The substance showed a mutarotation which was followed quantitatively. The change was found to be very nearly unimolecular.

Tetraacetyl-*d*-arabonic Nitrile.[11]—The *d*-arabinose oxime was acetylated using acetic anhydride and either fused sodium acetate or pyridine as the catalyst. In the former case, the procedure was just as described for *d*-xylose oxime,[12] dry dioxane being used as a diluent to prevent the reaction from becoming too vigorous In the second case 50 g. of pulverized oxime was suspended in 200 cc. of Eastman practical pyridine and 200 cc. of C. P. acetic anhydride

(7) *Cf.* Swan and Evans, THIS JOURNAL, **57**, 200 (1935); Felton and Freudenberg, *ibid.*, **57**, 1637 (1935).

(8) Jackson ond Hudson, THIS JOURNAL, **58**, 378 (1936); **59**, 994 (1937); Maclay and Hudson, *ibid.*, **60**, 2059 (1938); Hockett and McClenahan, *ibid.*, **60**, 2061 (1938); **61** 1667 (1939).

(9) Hockett, *ibid.*, **57**, 2265 (1935).

(10) Hockett and Hudson, THIS JOURNAL, **56**, 1632 (1934).

(11) *Cf.* Wohl, *Ber.*, **26**, 744 (1893); Ruff, *ibid.*, **31**, 1573 (1898).

(12) Hockett, THIS JOURNAL, **57**, 2265 (1935).

(13) All rotations quoted in this paper represent specific rotations of the D line of sodium at 20°; c is concentration in grams per 100 cc. of solution; and l is the tube length in decimeters.

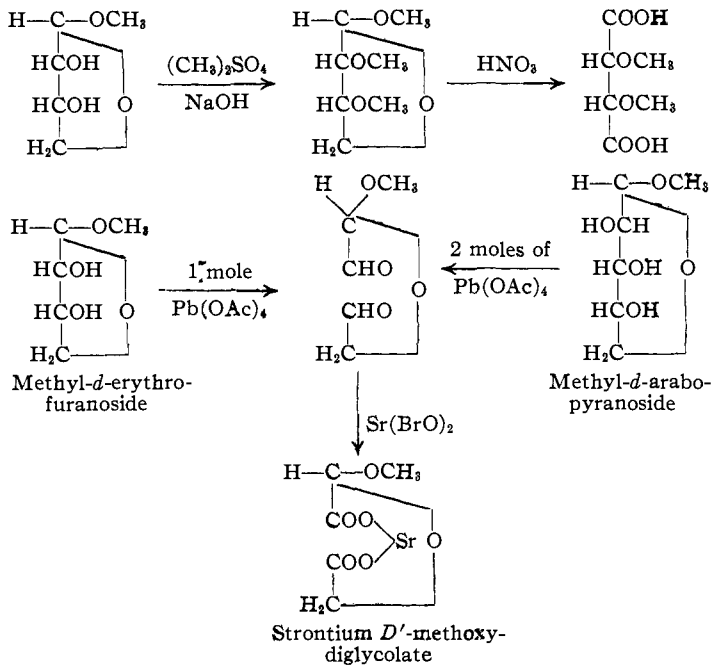


FIG. 2.

was added in three portions with cooling under the tap. The mixture was refrigerated overnight, warmed on a steam-bath for an hour, cooled, and poured upon about 500 g. of cracked ice. After refrigeration overnight, the precipitated gum had become a white solid which was washed free of pyridine with water and dried at 60° *in vacuo;* yield by either procedure, 68%. Recrystallized from absolute ethanol to constant properties, the compound melts 120–121° (corr.) and rotates −3.3° (*c*, 2.824; *l*, 2, $CHCl_3$).

Hydrolysis of *d*-Erythrose Diacetamide.—A sample of 2.0003 g. of purified *d*-erythrose diacetamide was dissolved to a volume of 50.0 cc. with 0.100 *N* sulfuric acid. This solution was poured into a 200-cc. flask submerged in a bath of rapidly boiling water and the time was noted. At noted intervals, the whole solution was cooled rapidly and its rotation read in a 4-dm. polarimeter tube. The results are represented by Fig. 3. The curve corresponds approximately to the unimolecular law; *k* (minutes and logarithms on base 10) = 0.0175. Hydrolysis was not yet complete after the last observation as demonstrated by the isolation of some unchanged *d*-erythrose diacetamide. The data could not be used to calculate a more reliable figure for the specific rotation of *d*-erythrose, owing to lack of a sample of pure sugar with which to standardize a method of estimating *d*-erythrose.[12]

d-Erythrose.—Nine grams of *d*-erythrose diacetamide was heated for seventy-five minutes with 189 cc. of approximately 0.6 *N* sulfuric acid in a boiling water-bath (see Fig. 3). After concentration to about 50 cc., the solution was extracted with ether for eight hours in a continuous extractor to remove acetic acid. The aqueous layer was then treated with barium hydroxide solution to remove sulfuric acid quantitatively, decolorized with carbon, and filtered. The colorless filtrate was concentrated in a vacuum at less than 50°, to a thick sirup which was dried by distilling dry methanol from it.

TABLE I

MUTAROTATION OF *d*-ARABINOSE OXIME IN WATER

Concentration 0.5136 g. in 25.0 cc. solution; tube length 2 dm.; temperature 20 ± 0.5°.

Time after making soln., min.	$[\alpha]^{20}D$	$k_1 + k_2$
0	−84.0[14]	
6.9	−83.4	0.0006
14.9	−82.7	.0006
20.6	−81.75	.0007
21.7	−81.05	.0009
28.1	−80.0	.0009
53.1	−77.2	.0008
72.1	−74.7	.0009
104.1	−70.8	.0009
108.7	−70.0	.0009
128.8	−67.4	.0009
177.8	−60.7	.0010
196.8	−59.00	.0010
442.0	−37.1	.0011
589.7	−29.1	.0012
777.7	−23.2	.0011
897.5	−20.65	.0011
1,072.5	−17.90	.0011
1,169.5	−16.87	.0011
1,374.5	−15.17	.0012
	−13.50	

(14) Determined by extrapolation of the nearly straight line obtained by plotting log $(r_t - r_\infty)$ against time.

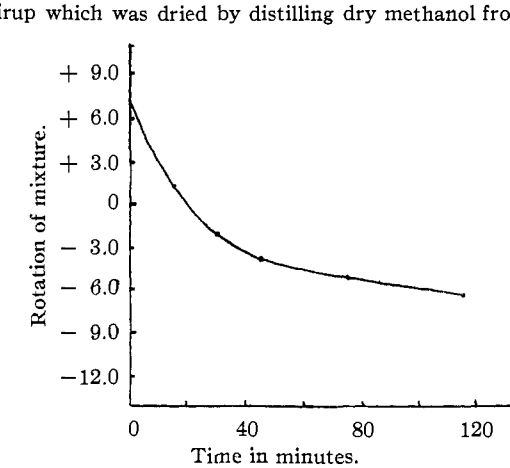


Fig. 3.—Hydrolysis of erythrose diacetamide by 0.1 *N* sulfuric acid.

Methyl-*d*-erythroside.—The erythrose described in the previous paragraph was dissolved in 100 cc. of a 1% solution of hydrogen chloride in dry methanol. The rotation in a 1-dm. tube immediately after homogenizing was −0.08°; this changed to −0.13° in about twenty minutes at room temperature and then remained constant, even though the solution was warmed on a steam-bath. The

power to reduce Fehling's solution disappeared during the same interval. The hydrogen chloride was removed with an excess of silver carbonate, and after filtration the solution was saturated with hydrogen sulfide and refiltered. The filtrate was concentrated under reduced pressure to a thick sirup. On reducing the pressure to 1–2 mm. and heating with an oil-bath, a light yellow liquid came over between 78–98° which showed a rotation[13] of −5.34° in chloroform (*c*, 3.372; *l*, 1), −5.93° in water (*c*, 3.372; *l*, 1), and $n^{20}D$ 1.5318. On another occasion, the distillate was collected in two portions, of which the first rotated −2.25° (*c*, 2.223; *l*, 2; $CHCl_3$) and the second was virtually inactive. The difference is likely due to varying proportions of the alpha and beta forms.

Dimethyl-methyl-*d*-erythroside.—An undistilled sample of methyl-*d*-erythroside weighing between 2 and 3 g. was washed with a little water into a 500-cc. three-necked flask, where, with vigorous mechanical stirring, it was treated first with 18 cc. of freshly distilled dimethyl sulfate and then with 80 cc. of 60% sodium hydroxide added very slowly drop by drop until the vigor of the reaction had slackened and then at an increased rate.[15] The mixture was warmed on a water-bath to 75° and treated with 32 cc. more of dimethyl sulfate added gradually. Finally the water-bath was maintained at boiling for half an hour. The solution was diluted with water, and extracted with 240 cc. of chloroform in four portions which were combined, dried with sodium sulfate, filtered and concentrated free from solvent. The product was distilled at 1–2 mm. with a bath temperature of 135–145°; yield, 0.194 g.

***meso*-Dimethoxysuccinic Acid.**—The 0.194 g. of dimethyl-methyl-*d*-erythroside was treated with 5 cc. of nitric acid (sp. gr. 1.2) at 85–90° for five hours. Freed from most of the nitric acid by distillation under reduced pressure, and redistillation after adding water, the resulting sirup crystallized rapidly on cooling. The large rosets, after recrystallization from a small volume of acetone and drying at 55°, weighed 0.189 g., melted from 146–152°,[16] and were inactive optically (*c*, 3.144; *l*, 2; H_2O).

Anal. Calcd. for $(COOH)_2C_2H_2(OCH_3)_2$: neut. equiv., 178; OCH_3, 34.83. Found: neut. equiv., 180; OCH_3, >31.85.

Strontium D'-Methoxy-diglycolate.—A sample of 0.83 g. (0.0062 mole) of freshly distilled methyl-*d*-erythroside was dissolved in 45 cc. of dried chloroform (calcium chloride) and stirred mechanically in a 250-cc. flask while 3.32 g. (0.0075 mole) of crystalline lead tetraacetate was added. Stirring was continued for one and one-half hours; then the nearly insoluble lead diacetate was removed by filtration and the chloroform was distilled out under reduced pressure. The residue, after solution in water, was treated with hydrogen sulfide to remove lead. After filtration and aeration, the solution was concentrated under reduced pressure to a sirup which was dried and freed from acetic acid by distilling sulfur-free toluene from the flask several times. The product was diluted to 125 cc. with water and treated with 7 g. strontium carbonate and 1 cc. of bromine in the dark at room temperature for twenty-four hours. The mixture was shaken several times during the first hour. The excess bromine was removed by aeration, the excess carbonate was filtered, soluble halides were removed with silver carbonate and, after filtration, silver was removed as the sulfide. After another filtration and aeration, and adjustment of the *p*H slightly to the alkaline side with strontium hydroxide, the solution was concentrated under reduced pressure to 5 cc. Alcohol was added to turbidity (between 2 and 3 cc.) and the solution refrigerated for an hour, whereupon a crop of fine white needles appeared, which were eventually filtered, washed with 50% alcohol and dried in air; yield 0.1085 g. These crystals showed a specific rotation[13] of −8.94° (*c*, 0.447; *l*, 2; H_2O). On addition of one molecular equivalent of 0.1 *N* hydrochloric acid, the rotation became too small to read. Since the beta form of strontium D'-methoxydiglycolate rotates +55.0° and the alpha form −56.6°, and the corresponding free acids, +11.9 and −11.5°, respectively, the particular sample of methyl erythroside employed evidently contained about 58% of the alpha isomer and 42% of the beta.

Anal. Calcd. for $C_5H_6O_6Sr \cdot 3H_2O$; H_2O, 17.8. Found: (loss in wt. at 105° *in vacuo*), 17.1. Calcd. for $C_5H_6O_6Sr$: Sr, 35.1. Found: Sr, 35.9.

Rate of Oxidation of Methyl-*d*-erythroside by Lead Tetraacetate.—A sample of 0.0923 g. (0.00069 mole) of distilled and dried methyl-*d*-erythroside was dissolved in a little less than 50 cc. of aldehyde-free glacial acetic acid in a 100-cc. glass-stoppered volumetric flask, brought to 20°, the time noted and 50.0 cc. of 0.1222 *N* lead tetraacetate solution in acetic acid was added. After making up to 100.0 cc. and mixing, the solution was placed in a 20° room. At intervals, 10-cc. samples were removed and the unconsumed lead tetraacetate estimated by the method of Hockett and McClenahan.[8] The results obtained are shown by Fig. 1. The reaction was very nearly monomolecular, the value of *k* being 0.025 (hours and logarithms on base 10).

Summary

1. *d*-Erythrose sirup has been obtained by the hydrolysis of *d*-erythrose diacetamide prepared from *d*-arabinose by a modification of the Wohl degradation.

2. *d*-Erythrose has been found to condense with methanol containing 1% hydrogen chloride in about twenty minutes at room temperature to give a mixture of α- and β-methyl-*d*-erythrofuranosides.

3. The methyl-*d*-erythrofuranoside mixture has been purified by vacuum distillation.

4. The methyl-*d*-erythrofuranoside mixture has been converted by methylation to dimethyl methyl-*d*-erythrofuranosides which are separated from other substances by high vacuum distillation.

5. Oxidation of the methyl-*d*-erythrofuranoside mixture with nitric acid yielded inactive dimethoxysuccinic acid, proving the presence and nature of the ring.

6. Oxidationof the methyl-*d*-erythrofuranoside

(15) West and Holden, THIS JOURNAL, **56**, 930 (1934).

(16) *Cf.* Purdie, *J. Chem. Soc.*, **79**, 957 (1901).

mixture with lead tetraacetate in chloroform followed by strontium hypobromite, yielded partially racemized strontium D-methoxy-diglycolate, proving independently the presence and nature of the ring and showing the proportion of alpha and beta forms in the mixture used.

7. The rate of oxidation of methyl-*d*-arabinofuranoside by lead tetraacetate, as well as the amount of oxidant consumed, have been found to be in close agreement with the predictions previously made for a substance of this structure.

8. The rate of hydrolysis of *d*-erythrose diacetamide by 0.100 *N* sulfuric acid has been measured.

9. The rate of mutarotation of *d*-arabinose oxime has been measured.

CAMBRIDGE, MASS. RECEIVED JUNE 2, 1939

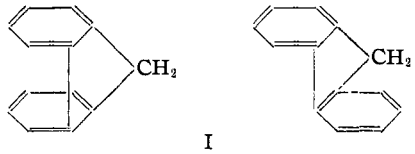
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF TRINITY COLLEGE]

The Structure of Fluorene

BY WARREN C. LOTHROP

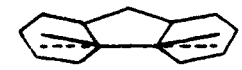
Although fluorene has been a familiar compound for many years, it has not excited the interest which has so enlarged our knowledge of the comparable tricyclic hydrocarbons anthracene and phenanthrene. Indeed a recent review of the chemistry of fluorene[1] indicates how little is known of its reactions and how much uncertainty still attaches to its structure.

Since 1925 when Kuhn and Jacob[2] proposed a space formula for fluorene (I) based on Kaufler's formula for diphenyl, in order to explain



I

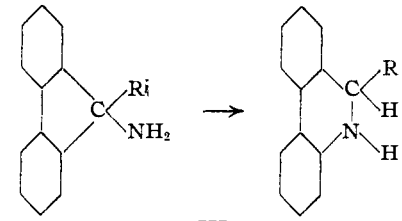
their claimed separation of two forms of 9-aminofluorene, there has been extensive investigation of the possibility of stereoisomerism of 9-substituted fluorenes. All such attempts have failed or been disproved,[3] so that the existence of such extreme forms as pictured in (I) seems unlikely if not impossible. Whether or not the two aromatic rings are inclined at a slight angle to the plane of the five-membered ring[4] cannot be stated with certainty yet, but the evidence does seem to indicate that the rings are bent away from the coaxial diphenyl bond with a distortion of the valence angles from the benzene rings by 12°,[5] to give a planar structure (II) as pictured by Pinck and Hilbert[6] where the five-membered ring is a nearly regular pentagon



II

This formula is probable from dipole measurements[5,7] and X-ray studies[8] and is further supported by the failure of fluorenone-4-carboxylic acid to close a fourth ring,[4a] the distance being too great to be bridged.

That such a planar configuration as (II) would be in a condition of some strain is to be anticipated and has been used[6] to account for the ready enlargement of the five-membered ring in the Stieglitz rearrangement of amines of the type (III) to yield phenanthridines:



III

It has been suggested further[5] that this internal strain could be relieved at least partially by a preferred arrangement of the double bonds according to the argument of Mills and Nixon[9] so that a definitely preferred bond structure (IV) should most nearly represent fluorene

(1) Rieveschl and Ray, *Chem. Rev.*, **23**, 287 (1938).

(2) Kuhn and Jacob, *Ber.*, **58**, 1432 (1925).

(3) Cook and Iball, *Chemistry & Industry*, 467 (1936), give a critical review of the stereochemistry of fluorene.

(4) (a) Mills, Palmer and Tomkinson, *J. Chem. Soc.*, **125**, 2365 (1924); (b) Iball, *Z. Krist.*, **94**, 397 (1936).

(5) Hughes, LeFèvre and LeFèvre, *J. Chem. Soc.*, 202 (1937).

(6) Pinck and Hilbert, THIS JOURNAL, **59**, 8 (1937).

(7) Bergmann, Engel and Hoffmann, *Z. physik. Chem.*, **17**, 92 (1932).

(8) Hengstenberg and Mark, *Z. Krist.*, **70**, 283 (1929).

(9) Mills and Nixon, *J. Chem. Soc.*, 2510 (1930).