and analyzed for consumed periodate, formic acid and acetaldehyde. The results showed that the oxidations were represented within close limits by the equation $C_{12}H_{15}N_3O_3 + 2NaIO_4 \rightarrow C_9H_7N_3O + HCOOH + CH_3CHO + 2NaIO_3 + H_2O$, which proves that the structures of the L-rhamnose and L-fucose phenylosotriazoles are as represented by formulas I and II.

Summary

The phenylosotriazoles of L-rhamnose, L-fucose and melibiose and some of their acetyl and benzoyl derivatives are described.

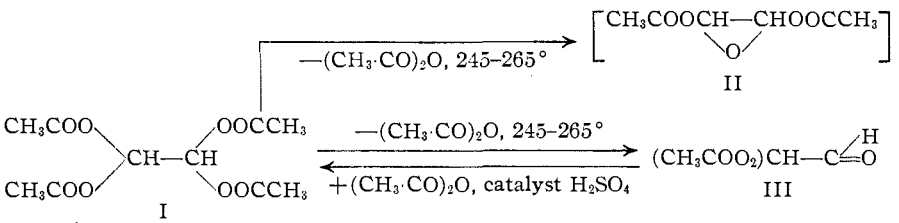
BETHESDA, MARYLAND RECEIVED MARCH 6, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BANTING INSTITUTE, UNIVERSITY OF TORONTO]

Glyoxal Semiacetate

BY ERICH BAER AND HERMANN O. L. FISCHER

In the course of a study of the pyrolysis of glyoxal tetraacetate (I) in the temperature range of 245–265° (normal pressure) it was observed that the *pure* compound decomposes smoothly, giving rise to volatile liquid reaction products and a small residue of carbonized matter. Fractional vacuum distillation of the slightly colored distillate led to its separation into two major fractions with greatly differing boiling ranges. The main compound (A) of the lower boiling fraction [b. p. (6 mm.) 37–41°] was easily identified as acetic anhydride by its odor, boiling point and its ability to form acetanilide (m. p. 114.5–115.5°). The higher boiling fraction, on repeated fractional distillation *in vacuo* yielded an as yet unknown substance [compound B, b. p. (6 mm.) 92–93°] to which, on the basis of its elementary composition (C, 44.93; H, 4.98) and molecular weight (161.8, cryoscopic in benzene) the empirical formula of $C_6H_8O_5$ was assigned. The presence of two acetyl groups in the molecule and the quantitative formation of glyoxal osazone, together with the fact that the other main product of the pyrolysis is acetic anhydride, made it probable that compound B was either the 1,2-diacetyl 1,2-anhydroglyoxal dihydrate (II) or the 1,1-diacetylglyoxal monohydrate (III).



(IV) $(CH_3COO)_2CH—CH=N—NHC_6H_3(NO_2)_2$-2,4

(V) $(CH_3COO)_2CH—CH=C_{16}H_{22}O_4$

The presence of a free carbonyl group in compound B seemed to be established when a 2,4-dinitrophenylhydrazone IV (m. p. 143–144°) and a dimedone compound V (m. p. 169.5–170.0°) were obtained. It was recognized, however, that the formation of these two unsymmetrically substituted glyoxal derivatives did not prove unequivocally the aldehyde structure of compound B; the possibility of a structural rearrangement (II→III) during the preparation of the hydrazone and the dimedone compound could not be overlooked. It was therefore desirable to obtain an independent proof of the aldehyde structure under conditions which would not occasion rearrangement. Dr. R. N. Jones of Queen's University, Kingston, Ontario,[1] kindly consented to determine the ultraviolet absorption spectrum of compound B and summarized his results as follows: "The substance has a well defined absorption maximum at 2960 Å. (see Fig. 1) with a molecular extinction coefficient of about 10. This is in the correct position and of the correct order of intensity for a saturated aliphatic aldehyde with heavy substituents on the β-carbon atom. The results are reconcilable with the aldehyde structure (III) but not with the alternative oxide ring structure (II)." Thus the absorption spectrum of the compound and the chemical evidence previously cited led to the assignment of structure III to compound B.

With regard to the formation of glyoxal semiacetate we are unable at present to say by which mechanism (I→III or I→II→III) the reaction takes place. The fact that at higher temperatures and in the presence of catalysts the acetates of aldehydes are known[2] to break down with the formation of the aldehyde and acetic anhydride would seem to speak in favor of the direct formation of glyoxal semiacetate (I→III) from glyoxal tetraacetate.

In its structure the glyoxal semiacetate resembles glyoxal semiacetal[3] but is less stable and apparently more inclined to undergo polymerization. In spite of these limitations the glyoxal semiacetate should prove itself a valuable material for synthetic purposes.

(1) Present address: National Research Council, Ottawa, Canada.

(2) J. Houben, "Die Methoden der organischen Chemie," vol. II, 3rd ed., 1925, p. 547.

(3) H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **18**, 514 (1935).

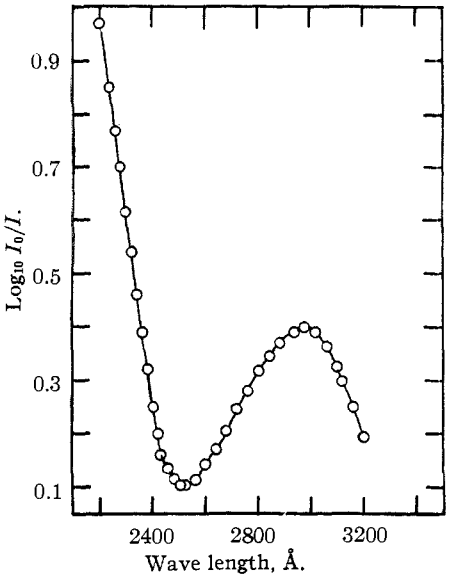


Fig. 1.—Ultraviolet absorption spectrum of glyoxal semiacetate (compound B) in dioxane solution. Because the hygroscopic nature of the substance made exact weighing on the micro balance difficult and the intensity of absorption decreased fairly rapidly with time the intensity is not expressed in terms of molecular extinction coefficient, but left as optical density ($\log_{10} I_0/I$). An approximate calculation of the extinction coefficient at the maximum showed it to be about 10.

Experimental

Glyoxal Tetraacetate[4]

A solution of 150 g. of thoroughly dried glyoxal sulfate[5] in a mixture of 375 g. of acetic anhydride and 750 g. of glacial acetic acid contained in a 2-liter round flask provided with reflux condenser was heated to incipient boiling in the course of fifteen to twenty minutes. At this point the flame was extinguished immediately and the exothermic reaction, which caused a vigorous reflux lasting for several minutes, was permitted to proceed without further heating. Five minutes after the reflux had subsided the almost colorless reaction mixture was cooled rapidly with running water to room temperature and poured with stirring into 3.6 liters of ice water. The colorless crystals were filtered with suction, washed on the filter with water and dried *in vacuo* over calcium chloride. The recrystallization of the crude material (m. p. 97–100°, 151.5 g., 84%) from *i*-propyl ether by means of a Soxhlet extractor yielded 132.0 g. (73.3%) of analytically pure glyoxal tetraacetate; m. p. 104.5–105.5°.

Anal. Calcd. for $C_{10}H_{14}O_8$ (262:1): CH_3CO-, 65.65. Found: CH_3CO-, 65.63.

Glyoxal Semiacetate

The pyrolysis of the glyoxal tetraacetate[6] (50 g.) was carried out at atmospheric pressure, under anhydrous conditions, in a short-necked distilling flask (100-ml. capacity) with sealed-on receiver.[7] The heat was so regulated that within fifteen minutes the temperature of the glyoxal tetraacetate melt had risen to 248° and from there on increased 5° per thirty minutes[8] until the final temperature of 272° had been reached. The slightly yellowish-green colored product of pyrolysis, weighing 46 g., was separated immediately into its components by fractional distillation *in vacuo*. Two volatile fractions were collected: fraction A (19 g.) distilling from 37–41° (6 mm.), which consisted mainly of acetic anhydride (acetanilide, m. p. 114.5–115.5°) containing small amounts of acetic acid and free glyoxal, and fraction B (17 g.) distilling from 85–105° (6 mm.), bath 100–150°, which was already fairly pure glyoxal semiacetate. The residue (9.3 g.), a viscous oil, solidified slowly on standing and yielded on recrystallization from 45 ml. of warm, dilute ethanol (50%), 4.0 g. of glyoxal tetraacetate (m. p. 102–104°, phenylosazone, m. p. 171–172°). The fractional distillation of fraction B *in vacuo* yielded 15.6 g. (55.6% after deduction of the recovered glyoxal tetraacetate) of pure glyoxal semiacetate, b. p. (6 mm.) 92–93°, $n^{22}D$ 1.4230 (determined ten minutes after the completion of the distillation).

Anal. Calcd. for $C_6H_8O_5$ (160): C, 45.00; H, 5.00; CH_3CO-, 53.7; mol. wt., 160. Found: C, 44.93; H, 4.98; CH_3CO-, 53.7; mol. wt. (cryoscopic in benzene), 161.8.

Glyoxal Determination: A. Gravimetric.—The solution of 0.6522 g. of glyoxal semiacetate in 15 ml. of 0.1 *N* sulfuric acid was refluxed for twenty minutes. After the addition of sodium acetate the phenylosazone was precipitated in the customary manner, sucked off, washed and dried. There was obtained 0.9452 g. of glyoxal phenylosazone.

B. Volumetric.—The titration of the glyoxal semiacetate with hypoiodite solution was carried out in a carbonate–bicarbonate solution according to Auerbach and Bodländer.[9] After standing for two hours at room temperature, 183.6 mg. of glyoxal semiacetate had used up 44.12 ml. of 0.100 *N* iodine solution.[10]

Anal. Calcd. for $C_6H_8O_5$: glyoxal, 36.2. Found: glyoxal, 35.35 (gravimetric), 34.8 (volumetric).

The glyoxal semiacetate gives immediately a strong positive test both with Schiff reagent and with a specially prepared ammoniacal silver nitrate solution,[11] but does not reduce Fehling's solution. In a moist atmosphere the glyoxal semiacetate takes up water and decomposes. In the course of several months, even in a sealed-off glass container, the substance changes gradually[12] from a mobile liquid to a transparent and glass-like mass. Concurrently, the amount of glyoxal semiacetate recoverable by vacuum distillation decreases with time. Triethylamine accelerates the polymerization of glyoxal semiacetate greatly. This polymerization is exothermic and takes place almost instantaneously. The reaction products are fairly hard and glass-like masses. The use of zinc chloride as catalyst requires higher temperatures (*e. g.*, boiling water-bath) in order to effect the polymerization

(4) A method for the preparation of glyoxal tetraacetate has been reported previously by one of the authors (H. F.) and C. Taube. *Ber.*, **59**, 851 (1926). The procedure as described, however, was not only of a rather violent nature yielding a strongly colored product which was difficult to purify but the size of the batch which could be safely handled in the laboratory was restricted to about 25 g. of glyoxal sulfate. These difficulties have now been overcome by working in greater dilution. The modified procedure is described.

(5) An excellent procedure for the preparation of glyoxal sulfate is described by Melvin A. Perkins, U. S. Patent 1,999,995 (1935).

(6) It is essential that only pure glyoxal tetraacetate be used. The pyrolysis of impure glyoxal tetraacetate takes place at a much lower temperature and follows a different course, yielding mostly free glyoxal and acetic anhydride.

(7) E. Baer, *Ind. Eng. Chem., Anal. Ed.*, **16**, 399 (1944).

(8) If the temperature of the melt is raised too quickly a considerable amount of glyoxal tetraacetate escapes pyrolysis by distillation.

(9) F. Auerbach and E. Bodländer, *Angew. Chem.*, **36**, 603 (1923).

(10) The product of oxidation was identified as oxalic acid.

(11) Tollens silver nitrate solution cannot be used here in its original form, since the test fails to work in the presence of sodium hydroxide or excess of ammonia because of the prompt rearrangement (Cannizarro) of glyoxal to glycolic acid. A suitable ammoniacal silver nitrate solution is prepared by adding just so much of dilute ammonia that a small part of the silver oxide remains undissolved. It is removed by centrifugation and the clear solution is used.

(12) All physical measurements, analytical determinations and reactions were carried out with freshly prepared glyoxal semiacetate.

in a reasonable length of time. These condensation products are also fairly hard, transparent masses, which on heating soften between 70–80° and form mobile liquids in the neighborhood of 90°.

Glyoxal Semiacetate 2,4-Dinitrophenylhydrazone.—To a lukewarm and clear solution of 2.34 g. of 2,4-dinitrophenylhydrazine in 72 ml. of concentrated acetic acid were added 1.8 g. of freshly prepared semiacetate. After standing for ten minutes at room temperature 150 ml. of distilled water were added in small portions, the hydrazone sucked off, washed with water and dried *in vacuo* over sodium hydroxide. Yield 2.75 g. (72%) of already analytically pure glyoxal semiacetate 2,4-dinitrophenylhydrazone: m. p. 143–144°.

Anal. Calcd. for $C_{12}H_{12}O_8N_4$ (340): N, 16.48; CH_3CO-, 25.3. Found: N, 16.33, 16.38; CH_3CO-, 25.3, 25.6, 25.3.

At room temperature the hydrazone is readily soluble in benzene, dioxane and chloroform, slightly soluble in methanol, ethanol and ether, and insoluble in petroleum ether and water.

Glyoxal Semiacetate Dimedone Compound.—To a solution of 6.3 g. of dimedone in 75 ml. of concentrated acetic acid was added 3.6 g. of freshly prepared glyoxal semiacetate and the mixture was set aside at room temperature. After twenty-four hours the solution was diluted with 400 ml. of distilled water, the dimedone compound sucked off, washed with water and dried *in vacuo* over sodium hydroxide. The crude product, which weighed 2.3 g. (24.2% yield) and melted at 168–169°, was dissolved in 25 ml. of acetone and reprecipitated by the addition of 75 ml. of water; yield 2.1 g. of fairly pure glyoxal semiacetate dimedone compound, m. p. 169.5–170°.

Anal. Calcd. for $C_{22}H_{30}O_8$ (422.2): C, 62.52; H, 7.10; CH_3CO-, 20.36. Found: C, 62.12; H, 7.20; CH_3CO-, 19.80, 19.75.

Glyoxal Tetraacetate from Glyoxal Semiacetate (III → I).—To a mixture of 0.58 g. of freshly prepared glyoxal semiacetate and 0.40 g. of acetic anhydride was added a small drop of concentrated sulfuric acid. The mixture became immediately very warm and crystals formed. After the reaction had subsided, the almost solid product was drowned in ice water, the crystals collected at the pump, washed with water and dried *in vacuo* over sodium hydroxide. The yield of fairly pure glyoxal tetraacetate (m. p. 96–100°) was 0.78 g. or 82.2%. It was obtained in analytically pure form by recrystallization from ethyl acetate, m. p. 103–104°. A mixed melting point with an authentic sample of glyoxal tetraacetate showed no depression.

Acknowledgment.—The authors wish to express their sincerest thanks to Dr. R. N. Jones, for his investigation of the ultraviolet absorption spectrum of the glyoxal semiacetate.

Summary

The pyrolysis of pure glyoxal tetraacetate in the temperature range of 245 to 265° (normal pressure) yields two main reaction products, namely, glyoxal semiacetate and acetic anhydride. The glyoxal derivative has been isolated in a yield of 55%.

An improved method for the preparation of glyoxal tetraacetate is described.

TORONTO, CANADA RECEIVED FEBRUARY 19, 1947

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, COLUMBIA UNIVERSITY AND THE UNIVERSITY OF NOTRE DAME]

Some Derivatives of 6-Methoxy-8-aminolepidine[1,2]

BY KENNETH N. CAMPBELL, ROBERT C. ELDERFIELD, WALTER J. GENSLER, ARMIGER H. SOMMERS, CHESTER B. KREMER, S. MORRIS KUPCHAN, JOHN F. TINKER, JANE A. DRESSNER, B. NOEL ROMANEK AND BARBARA K. CAMPBELL

In the latter part of the antimalarial program carried out under the Committee on Medical Research, it was found that 8-(6′-diethylaminohexylamino)-6-methoxylepidine (SN-14,011)[3] had an extremely high antimalarial activity in avian tests; the introduction of the 4-methyl group had increased the quinine equivalent by about tenfold when tested against lophurae malaria in the duck. In view of this remarkable effect of the 4-methyl group, it became desirable to synthesize other 8-aminolepidines for testing as antimalarials. Several such compounds have been prepared at Columbia University and the University of Notre Dame, and are reported jointly in this paper.

In general, the synthesis followed the one described earlier[4] but certain modifications were made which improved the yields. In particular, it was found that 6-methoxy-8-nitrolepidine could be reduced to the amino compound more readily by iron and acetic acid than by catalytic hydrogenation. Reduction by stannous chloride in hydrochloric acid led to a product contaminated by a chloro compound (presumably the 5-chloro derivative); this is in agreement with the results obtained by others[5] in the reduction of 8-nitroquinolines by stannous chloride.

Experimental[6]

4-Methyl-6-methoxy-8-nitroquinoline.—The reaction was carried out as described previously[4] using either 1,3,3-trimethoxybutane or methyl vinyl ketone (du Pont 80–85% azeotrope), but the reaction mixture was worked

(1) This work was carried out on contracts, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Notre Dame and Coumbia University.

(2) A part of this material was presented before the Medicinal Chemistry Division of the American Chemical Society, Chicago, September, 1946.

(3) The Survey Number of a drug identifies it in the files of the Antimalarial Survey Office; the antimalarial activities of these drugs are tabulated in a monograph, "Antimalarial Drugs, 1941–1945," Edwards Brothers, Ann Arbor, Michigan, 1946.

(4) Campbell, Sommers, Kerwin and Campbell, THIS JOURNAL, **68**, 1556 (1946).

(5) Dikshoorn, *Rec. trav. chim.*, **48**, 147 (1929); Elderfield, *et al.*, THIS JOURNAL, **68**, 1589 (1946).

(6) The microanalyses were carried out by Miss Lois May, Columbia University, and by Mr. Charles Beazley, Microtech. Laboratory, Skokie, Illinois.