Asymmetric Synthesis. III.[1] Experiments Toward a Total Asymmetric Synthesis of Tartaric Acid[2]

BY TENNEY L. DAVIS[3] AND JOSEPH ACKERMAN, JR.[4]

The hypothesis that the first optically active substance was produced naturally by some spontaneous photochemical reaction occurring under the influence of natural circularly polarized light is one which the evidence of experiments during the past thirty years has done much to strengthen.[5] Several total asymmetric syntheses[6] by means of circularly polarized light have been reported, but none of them has been the synthesis of a substance which occurs in nature in an optically active state—and, so far as we know, no such synthesis has been attempted.[7]

We have thought that the importance of tartaric acid in the history of optical activity gives a particular interest to the asymmetric synthesis of this substance—and have attempted to prepare it in an optically active form by a synthesis based on the photochemical addition of hydrogen peroxide to the double bond as worked out by Milas, Kurz, and Anslow[8] for the hydroxylation of diethyl maleate to diethyl mesotartrate. Diethyl fumarate was used instead in our experimentation since it yields the racemate. To determine the percentage yield which could be expected in the latter reaction and to prove that it proceeded in the same way, a non-polarized photochemical hydroxylation of diethyl fumarate with anhydrous hydrogen peroxide was carried out according to the technique developed by the above-mentioned workers, and a 6.6% yield of diethyl tartrate was obtained.

Diethyl fumarate was then hydroxylated with right circularly polarized ultraviolet radiation, 2535–7–9 Å., and in two separate experiments maximum rotations of 0.073° and 0.030° were developed. These figures are much larger than the maximum error of our experimentation (which we take to be ±0.02°) and represent the differences between the arithmetic means of the readings taken with the irradiated liquids and the

arithmetic means of the "zero" readings of the instrument, all measurements made at the same sitting. The arithmetic means of the polarimetric measurements, made at the time of maximum rotations, are based on five to eighteen readings and have probable deviations of only ±0.003°. The developed rotations are beyond the experimental error of the work and should be valid signs of developed optical activity.

All precautions were taken to prevent and account for any rotational readings due to the anisotropy shown by the end glasses of the polariscope tubes when under strain. In the first experiment, particularly, the readings showed the typical gradual increase to a maximum and the subsequent decrease to zero. In one of these experiments a 1.7% yield (40 mg.) of tartaric acid was proved. If we assume the specific rotation of dextrorotatory diethyl tartrate in hydrogen peroxide to be low, say, 14°, then the synthesis in circularly polarized light of 10% more of one diastereoisomeride than of the other would give a rotation of 0.028°. For a 5% yield of diethyl tartrate, which is easily possible, and for an analogous formation of only 2.5% more of one of the diastereoisomerides than of the other, a rotation of 0.08° would be expected.

The mechanism or manner in which the asymmetric reaction proceeds with circularly polarized ultraviolet radiation is assumed to be as follows
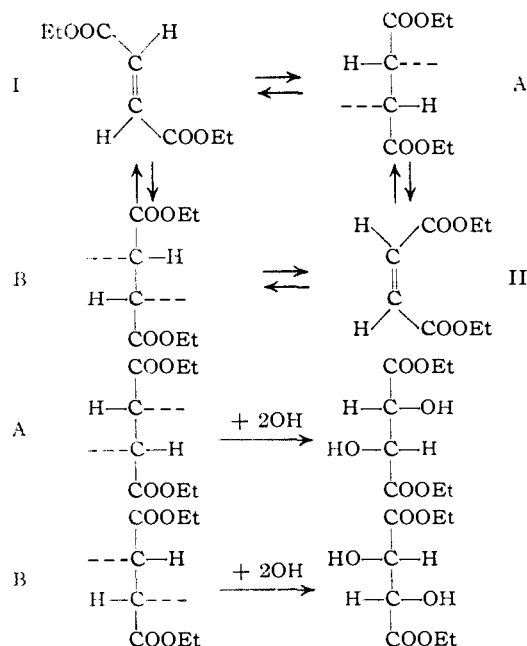
(1) Earlier papers of this series, Davis and Heggie, THIS JOURNAL, **57**, 377, 1622 (1935).

(2) An abstract of the thesis submitted by Joseph Ackerman, Jr., in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry, Massachusetts Institute of Technology, 1939.

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(5) Ritchie, "Asymmetric Synthesis and Asymmetric Induction," Oxford, 1933.

(6) Karagunis and Drikos, *Naturwissenschaften*, **21**, 607 (1933); *Nature*, **132**, 354 (1933); Davis and Heggie, *loc. cit.*; Betti and Lucchi, *Atti x° congr. internat. chim.*, **2**, 112–116 (1938), *Chem. Abstracts*, **33**, 7273 (1939).

(7) A photoasymmetric *decomposition* of a vanadium tartrate complex has been reported, Ghosh, *J. Ind. Chem. Soc.*, **16**, 51 (1939).

(8) Milas, Kurz and Anslow, THIS JOURNAL, **59**, 543 (1937).

It is believed that the diastereoisomerides, A and B, are formed in the ultraviolet irradiation of diethyl fumarate, I, for it is well known that fumaric acid is converted in part to maleic acid in the presence of non-polarized ultraviolet radiation.[9] With circularly polarized light one of the forms A or B would be present in greater amount than the other, resulting in a final preponderance of one form of the tartaric ester over the other. The formation of unequal amounts of A and B by circularly polarized ultraviolet radiation is analogous to the decomposition of unequal amounts of the diastereoisomerides in the cases where such asymmetric decomposition occurs.

Following the practice usual in photoasymmetric work, we endeavored to prove conclusively the validity of the first two experiments by hydroxylation with left circularly polarized light to obtain rotations of opposite sign. These latter experiments did not produce sufficient rotations, and a number of additional experiments were carried out before it was evident that the mirrors used to produce the circularly polarized light had become defective. The mirrors needed to be polished daily to remove the film which had formed upon them. This frequent polishing, together with the disintegration of the surface while exposed to the ultraviolet radiation,[10] finally rendered the mirrors ineffective. As there was not sufficient time available to make new ones, the experiments were stopped.

The photochemical hydroxylation of diethyl fumarate with anhydrous hydrogen peroxide had a number of advantages for photoasymmetric synthesis. The dissociation of hydrogen peroxide[11] into hydroxyl radicals occurs in the region 3000–2200 Å., which at the same time is a region of absorption for fumaric acid and its diethyl ester. Data on the absorption spectra of diethyl fumarate and diethyl tartrate in this wave length region were not available, but were expected to be nearly the same as for the acids.[12] Bielecki and Henri[13] have shown that the absorption in the ultraviolet of such esters is almost the same as that of the acids, the absorption being determined chiefly by the acid group, the alcohol radical having only a small effect. While the absorption spectrum of the ester, as compared with that of the acid, is displaced only slightly toward the longer wave lengths, the absorption spectrum in hydrogen peroxide, as compared with that in water or in alcohol solutions, would be displaced toward the shorter wave lengths (Kundt's rule) thus producing, perhaps, a final small shift toward the ultraviolet since the latter effect is greater than the

(9) Stoemer, Ber., 42, 4870 (1909).

(10) Lenard and Wolff, Ann. phys. chim., 37, 443 (1889).

(11) Urey, Dawsey and Rice, THIS JOURNAL, 51, 1371, 1958 (1929); Maass and Hatcher, ibid., 42, 2548 (1920); Maass and Hilbert, ibid., 46, 2693 (1924).

(12) Bielecki and Henri, Ber., 46, 1304, 2596 (1913); Ley and Wingchen, ibid., 67, 501 (1934).

(13) Bielecki and Henri, Compt. rend., 155, 1617 (1912); 156, 550 (1913).

former. The fact that the circularly polarized band, 2535–7–9 Å. used for the work, lies on the long wave length side of the absorption maximum for fumaric acid was considered favorable, since it has been shown that the maximum circular dichroism generally occurs at some of the wave lengths of weakest absorption.

The rotations observed must have been due to synthesis and not decomposition since the racemic or d-tartaric acid has extremely low absorption in the region 2535 to 2405 Å., and hardly any radiation below 2405 Å. came through the apparatus.

The low specific rotation of active tartaric acid and of its simple esters was a definite disadvantage, and precluded the development of any but the smallest rotations. Hydroxylation with anhydrous hydrogen peroxide rather than with an aqueous solution aided somewhat toward overcoming this disadvantage since the former reaction has a higher quantum efficiency. To offset the low specific rotations still further, a minimum quantity, 3 to 4 cc., of reacting medium was used and was arranged to cover the entire area of circularly polarized radiation, making it possible to develop the maximum rotation with the available source of energy. The small volume of reacting liquid made it necessary to take polariscope readings with a micro tube.

We are indebted to Dr. A. F. Turner, who at the time of this work was a member of the Physics Department staff, Massachusetts Institute of Technology, for devising an expedient visual method for determining the principal angles of incidence and azimuth of metallic mirrors for the 2535–7–9 Å. band.

Experiments

Source of 2535–7–9 Å. Band.—A Cooper–Hewitt lamp was used instead of a mercury resonance lamp, for although 40% of the total energy of a resonance arc is of the 2535–7–9 Å. band, the total energy is much less than that of the ordinary mercury arc. We did not attempt to use the mercury arc as a resonance lamp by inserting one end in water for fear of injuring it while using it over long periods. The wave lengths down to 3000 Å. were hardly absorbed by our reaction mixture. The 2535–7–9 Å. band was circularly polarized, and the lines in the near neighborhood were nearly circularly polarized, while those more distant were elliptically polarized. The lines below 2405 Å. were not only weak in origin but were largely eliminated by absorption through the thick calcite prisms.

Metallic Mirrors.—Nickel mirrors were chosen since they approached most nearly to our requirements of reflective capacity, size, and ease of manufacture. They reflect 50% at 3800 Å., 30.7% at 2537 Å., and 37% at 2500 Å.[14] Brass mirrors were first copper plated and then nickel plated, and each face both before and after plating was ground and polished to an optical surface. Although silicon reflects about 62.3% at 2537 Å.,[14] a large enough mirror was not available. Tests with a speculum mirror gave only 25% reflection at this wave length.

Previous to our present work, metallic mirrors have not, so far as we know, been used in photoasymmetric research for the circular polarization of ultraviolet radiation—and we are now disposed to conclude that they are probably

(14) Hulbert, Astrophys. J., 42, 235 (1915).

not as satisfactory for the purpose as the quartz rhombs which are generally used. Although mirrors of certain metals have less absorption than quartz rhombs for radiation of very low wave length, they are quickly injured by it. Moreover, they are difficult to prepare and maintain, especially in practicable sizes.

Determination of Principal Angles of ϕ and ψ.—As the exact values of the principal angle of incidence, ϕ, and the principle angle of azimuth, ψ, depend considerably on the character of the metal surface and the method of forming it, it was necessary to determine the values for these particular mirrors. Since the standard "Voigt Dot Pattern" method for ultraviolet radiation requires many optical instruments which were not available, the procedure described below for determining ϕ and ψ at the 2537 Å. line was used. The optical arrangement included in sequence a mercury resonance lamp, a quartz lens, a filter cell (solution of cobaltous and nickel sulfate for filtering out all wave lengths greater than 3300 Å.), a polarizing calcite prism, the nickel mirror, a Savart plate, a Nicol prism, a quartz lens, and finally a Willemite screen. Willemite, a natural zinc silicate, was used since it is particularly fluorescent for the 2537 Å. line. When the angle of azimuth was 45°, a very sharp series of fringes was obtained. The distance between two periodic points corresponding to a wave length, was measured with a small microscope having cross hairs, tooth scale and micrometer screw. The angle of incidence was changed from 90° until a shift of $\frac{1}{4} l$ was observed. Values found for ϕ: 62°, 63° and 62°.

ψ was determined by using a double image quartz prism in place of the Savart plate and small Nicol, and by placing a card with a small slit in front of the cell. Two images were obtained corresponding to parallel and perpendicular vibrations. ψ was noted when the images were of equal brightness. Values obtained were 29°, 29° and 30°.

We have not found in the literature any reports on ϕ and ψ for nickel mirrors at the 2535-7-9 Å. band. The nearest values of ϕ, 60°43', and ψ, 30°40', were calculated by Meier[15] for the 2573 Å. line from measurements of n, index of refraction and k, absorption index.

Apparatus.—The ultraviolet light from the Cooper-Hewitt lamp was passed through a quartz lens and calcite polarizing prism, then reflected from the nickel mirrors and into the bottom of a 50-cc. flat bottom quartz flask. Right or left circularly polarized light was produced by rotating through the angle of azimuth the same number of degrees from the perpendicular in one direction or the other. Total distance from arc to flask was 9-11 cm.

Irradiation Experiments.—The procedure used for all circularly polarized irradiations was as follows. Two to two and five-tenths grams of diethyl fumarate was added to a 5% excess of hydrogen peroxide in anhydrous ethyl ether, and the ether was then removed at room temperature by reduced pressure. The final volume of 3-4 cc. gave a thin liquid layer 0.5 cm. thick on the bottom of the flask through which the radiation was passed. It was necessary to use a fan on hot days to keep the reaction temperature below 29°, thus preventing oxidation to oxalic acid. The mercury arc was shielded except for the small portion needed for circular polarization.

A non-polarized irradiation of diethyl fumarate performed according to the technique which Milas and co-workers[3] used with diethyl maleate, gave a 6.6% yield of the diethyl tartrate after seventy-two hours of exposure. Analysis of the calcium tartrate: Ca, calcd. 29.80%, found 29.89%.

Polarimetric Measurements.—Since the rotations produced in photoasymmetric synthesis are small, it has been necessary to scrutinize carefully all sources of error in the observations and to estimate with as much precision as possible the significant and reliable magnitudes of the effects resulting from the irradiation.

No previous reports on photoasymmetric research, so far as we know, have mentioned the considerable rotations resulting from strain of the end glasses of the polariscope tubes. The too tight screwing on of the ends causes the

(15) Meier, Ann. Physik, 31, 1017 (1910).

glasses to become anisotropic. An empty 2-dcm. tube, for example, with loose end glasses gave readings of 0.02, 0.00 and 0.00°; with the end glasses tightened, the readings were 0.19, 0.22 and 0.17°; with the glasses loosened again, the readings were 0.00, 0.00°. With a 4-dcm. tube and end glasses partially tightened, the readings were 0.12, 0.13, 0.15 and 0.19°; with the end glasses partially loosened, the readings were 0.02, 0.02 and 0.00°. Screwing on of the glasses more tightly does not necessarily increase the rotation and in fact may actually decrease it. Errors from this source, however, can be eliminated by making "zero" readings with the empty polariscope tube and then filling it through the side opening without disturbing the end glasses. All polariscope tubes used for work of high precision ought to be equipped with a side opening for filling. The difference between the reading on the full tube and the reading on the empty tube will be accurate within the normal errors of reading. We have increased the precision by dealing with the difference between average readings.

We have found that the magnitude of this anisotropy with our micro tube was much less than with tubes of standard size, possibly because of the smaller size of the end glasses. Many measurements were made with the empty micro tube, the glasses being screwed to various degrees of tightness from loose to very tight and a large number of readings being made at each point. Similar measurements were also made with colored optically-inactive solutions in order to determine the precision with low brightnesses. The largest numerical value among the several arithmetical means of these series of "zero" readings was 0.008°, with an average deviation from the mean of a single observation of ±0.01°, but a probable deviation of the mean of ±0.002°.

Table I summarizes the results of two experiments with right circularly polarized light. The reported rotations are those which were actually developed and are deduced from the experimental data as the differences between the averages of from 4 to 18 readings on the full polariscope tube and of similar readings on the empty tube. The readings were taken with a 1-decimeter micro tube holding 0.2 cc. of liquid and a Schmidt and Haensch polarimeter reading directly to a hundredth of a degree. Sodium light, wave length 5890 Å., was used.

TABLE I

DEVELOPMENT OF OPTICAL ACTIVITY DURING EXPOSURE OF REACTION MIXTURE TO CIRCULARLY POLARIZED ULTRAVIOLET RADIATION

Time, hours	Rotations in degrees	Time, hours	Rotations in degrees
0	+0.002	0	−0.003
5	+ .008	43.5	− .002
21.5	+ .005	90	− .003
31	+ .010	118.5	+ .001
45	+ .010	187	+ .030
61	+ .017	236	+ .008
119	+ .073	281	+ .001
167	+ .052		
189	− .003		

The precision of all measurements was calculated and the probable deviations of the means in all cases were low, especially for the high readings. In the first experiment the mean of readings made after 119 hours was 0.073° with an average deviation of only ±0.008° and a probable deviation of the mean of ±0.003° or 5.15%.

Summary

Two experiments on the photochemical hydroxylation of diethyl fumarate with right circularly polarized light of wave length band 2535-

7–9 Å. gave a dextrorotatory product. An hydroxylation with left circularly polarized light, with the development of levorotation, remains to be carried out before the asymmetric synthesis can be considered to be proved conclusively.

The precision and accuracy of polarimetric measurements in the region of very low rotations, such as is encountered in photoasymmetric work, are discussed.

An expedient visual method, suggested by Dr. A. F. Turner, for determining the principal angles of incidence and azimuth for metallic mirrors for the 2535–7–9 Å. band is described.

A 6.6% yield of diethyl tartrate was obtained by the photochemical hydroxylation of diethyl fumarate with non-polarized ultraviolet radiation, according to the method of Milas and co-workers.


Sulfonamides of the Indole Group

BY H. J. BARBER

Although the sulfonamide derivatives of a vast number of heterocyclic systems have been described in the past few years, those of indole appear to have been overlooked, as judged from the literature which has reached this country. The derivatives now described, which were prepared in 1938, have little chemotherapeutic interest, but certain novel features in their chemistry make publication desirable. It is established beyond reasonable doubt that the common sulfonamide heterocycles, Sulfapyridine, Sulfathiazole and Sulfadiazine, are 2-substituted derivatives of the two tautomeric forms of the heterocyclic systems I and II and not substituted derivatives of the imino form III.[1]
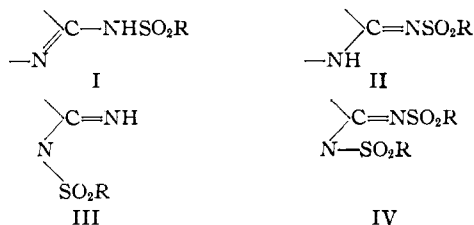
It is striking that derivatives of type III are not normally encountered in condensing sulfonyl chlorides with amino heterocycles. When two sulfonyl residues enter, as, for example, in the case of 2-aminothiazole, they give 1,2-disulfonyl derivatives IV,[2] from which the sulfonyl group in position 1 is readily removed, leaving the 2-arylsulfonamide heterocycles. 2-Amino-indole, however, with acetylsulfanilyl chloride, yielded 1-p-acetamido-benzenesulfonyl-2-imino-2,3-dihydroindole (V, R = —C₆H₄NHAc)
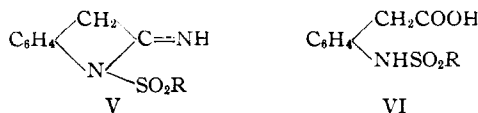

the structure being proved by hydrolysis to 2-sulfanilylaminophenylacetic acid VI (R = —C₆-

(1) Shepherd, Bratton and Blanchard, THIS JOURNAL, 64, 2532 (1942).

(2) Jensen and Thorsteinsson, Dansk Tids. Farm., 15, 41 (1941).

H₄NH₂). If the unlikely migration of the sulfanilyl group is excluded, loss of ammonia could not have occurred without loss of the sulfonyl group unless the latter was in the 1 position. Further support for this came from the fact that the same sulfonamide was readily obtained by condensation of o-aminobenzyl cyanide with acetylsulfanilyl chloride. Attempts were made to prepare the isomeric 2-sulfanilylaminoindole by methods involving the condensation of o-nitrophenylacetimino ethyl ether or o-nitrophenylacetamidine with acetylsulfanilyl chloride to give compounds of the type VII (R₁ = —OC₂H₅, —NH₂)
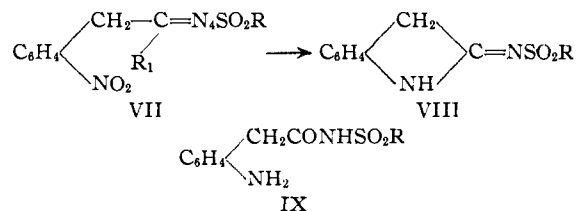
which on reduction of the —NO₂ group to NH₂ were expected to undergo intramolecular condensation with loss of alcohol or ammonia to give the required compound VIII.

Various difficulties were encountered particularly in the reduction of the nitro compounds VII (R₁ = —OC₂H₅, R = —C₆H₄NO₂, or —C₆H₄NHAc). Catalytic reduction caused fission into unidentified indole derivatives and simpler sulfanilamide derivatives. Stannous chloride reduced the nitro group but the acid conditions effected partial hydrolysis of the imino ether with the resultant formation of the amide IX. As was expected, this did not cyclise as smoothly as the iminoether might have done, and only very small quantities of the required 2-sulfanilyl indole VIII were obtained, together with various unidentified products. Though the yields were impractical, the method could probably be developed and might have application to other heterocycles where it is desired to locate the sulfonyl group on a substituent nitrogen atom with some certainty, but further investigation was not undertaken