lized from methylene chloride–hexane to afford estrone (5 mg.), m.p. 242–252°, showing an ultraviolet absorption maximum at 280–282 mμ (log ϵ 3.30) and an infrared spectrum essentially identical with that of authentic estrone.

4-Bromoestra-1,3,5(10)-triene-3,17β-diol Diacetate (XIIa).—Oily fractions totaling 1.2 g. containing the bromohydrin XIa were obtained from the column chromatography of this bromohydrin (*vide supra*) and from recrystallization of the mother liquors. Treatment with methanolic sodium methoxide (50 ml. of 1 *N*) during 15 min. at 10°, followed by work-up as described above, then acetylation in the normal manner (Ac_2O–pyridine) yielded an oily product (700 mg.), where solid 5α,10α-epoxide Vb had been obtained earlier. The oil was placed on a column of silica (100 g.) and elution with benzene–hexane (40:60) gave a new product (310 mg.), less polar than epoxy diacetate Vb which was eluted in later fractions. Recrystallization of this new product from methylene chloride–hexane gave 4-bromoestra-1,3,5(10)-triene-3,17β-diol diacetate (XIIa), the analytical specimen of which showed m.p. 171–173°; $[\alpha]_D$ +24°; ν_{max} 1770 and 1200 (phenolic acetate), 1735, and 1255 cm.$^{-1}$ (acetate); λ_{max} 268–270 (log ϵ 2.59) and 277 mμ (log ϵ 2.56); λ_{max} (for alkaline ethanol solution) 244 (log ϵ 3.86) and 304 mμ (log ϵ 3.87).

Anal. Calcd. for $C_{22}H_{27}BrO_4$: C, 60.68; H, 6.39; Br, 18.36; O, 14.70. Found: C, 60.31; H, 6.41; Br, 18.68; O, 14.60.

4-Bromoestra-1,3,5(10)-triene-3,17β-diol (XIIb).—Potassium carbonate (400 mg.) was added to a mixture of the above diacetate XIIa (160 mg.) and methanol (20 ml.), and the whole was maintained at reflux during 0.75 hr. before being neutralized with acetic acid. Concentration *in vacuo* to 3–4-ml. volume was followed by dilution with water (50 ml.). The resultant precipitate was collected and washed with water, giving 110 mg. of the diol XIIb, m.p. 160–190°. Chromatographic purification over alumina followed by one crystallization from methylene chloride–hexane afforded a crystalline solid (40 mg.), m.p. 203–215°, further purified by recrystallization to m.p. 209–212°; $[\alpha]_D$ +41° (in ethanol); ν_{max} 3580, 3300, 1615, 1565, and 1495 cm.$^{-1}$; λ_{max} 284 mμ (log ϵ 3.26); λ_{max} (for alkaline ethanol solution) 244 (log ϵ 3.88) and 314 mμ (log ϵ 3.51).

Anal. Calcd. for $C_{18}H_{23}BrO_2$: C, 61.53; H, 6.59; Br, 22.75; O, 9.10. Found: C, 61.52; H, 6.96; Br, 23.16; O, 9.36.

10β-Bromo-5α-fluoroestrane-3α,17β-diol (XIII).—A precooled (*ca.* −80°) suspension of estr-5(10)-ene-3α,17β-diol (IVa, 500 mg.) and N-bromoacetamide (270 mg.) in dry methylene dichloride (20 ml.) was added with stirring to a solution of anhydrous hydrogen fluoride (3.41 g.) in tetrahydrofuran (5.98 g.) at *ca.* −80° (acetone–Dry Ice). After stirring at −80° for 1 hr. and then at 0° for a further 16 hr., the reaction mixture was added to an excess of ice-cold sodium bicarbonate solution. Isolation with methylene dichloride and crystallization of the product from methanol afforded 10β-bromo-5α-fluoroestrane-3α,17β-diol (XIII, 330 mg.), m.p. 157–161° raised by several crystallizations from methanol to 169–171° dec., $[\alpha]_D$ 0°.

Anal. Calcd. for $C_{18}H_{28}BrFO_2$: C, 57.62; H, 7.55; Br, 21.29; F, 5.06. Found: C, 57.48; H, 7.48; Br, 22.28; F, 4.88.

Estra-4,9-diene-3,17-dione (XIV).—An excess of 8 *N* chromic acid (permanent orange coloration) was added to a solution of 10β-bromo-5α-fluoroestrane-3α,17β-diol (XIII, 500 mg.) in acetone (80-ml.) at 0°. After a further 2 min. at 0°, addition of water and isolation with methylene chloride afforded the crude oxidation product which was immediately heated under reflux for 3 hr. in methanol solution (150 ml.) containing sodium acetate (1.5 g.). Addition of ice–water and filtration gave a solid product which was adsorbed from hexane-benzene (1:1) onto alumina (25 g.). Elution with hexane–benzene (30:70, 500 ml.) and crystallization from acetone–hexane afforded estra-4,9-diene-3,17-dione (XIV, 120 mg.), m.p. 139–141° raised by crystallizations from the same solvent mixture to 141–143°, $[\alpha]_D$ −152°, λ_{max} 300–302 mμ (log ϵ 4.34), lit.[4] m.p. 130–131°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20; O, 11.84. Found: C, 80.24; H, 8.29; O, 11.61.

5α-Fluoro-10β-iodoestrane-3α,17β-diol (XV).—A precooled (*ca.* −80°) suspension of estr-5(10)-ene-3α,17β-diol (IVa, 500 mg.) and N-iodosuccinimide (384 mg.) in methylene chloride (50 ml.) was added to a solution of anhydrous hydrogen fluoride (10.0 g.) in tetrahydrofuran (17.6 g.) at *ca.* −80° (acetone–Dry Ice). After stirring at −80 for 1.5 hr. and then at 0° for a further 16 hr., the reaction mixture was added to an excess of ice-cold sodium bicarbonate solution. Isolation with methylene chloride and crystallization from methylene chloride–hexane afforded 5α-fluoro-10β-iodoestrane-3α,17β-diol (XV), m.p. 128–130° dec., unchanged after several crystallizations from the same solvent mixture.

Anal. Calcd. for $C_{18}H_{28}FIO_2$: C, 51.2; H, 6.68; F, 4.50; I, 30.05. Found: C, 51.23; H, 6.84; F, 4.78; I, 30.23.

The Photochemical Reaction of Nitrobenzene and Tolane

MONTE L. SCHEINBAUM[1]

The Converse Laboratories, Harvard University, Cambridge, Massachusetts

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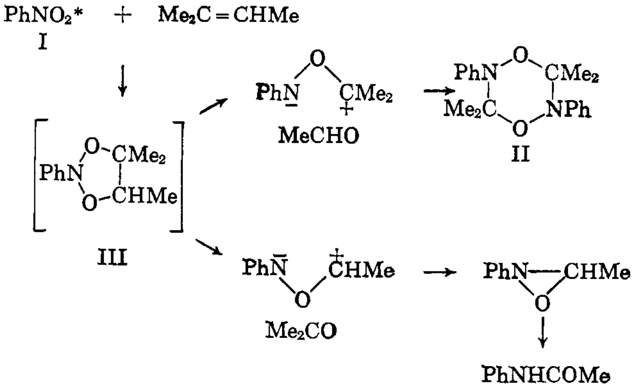
Products arising from the photochemical reaction of nitrobenzene and diphenylacetylene have been identified. Diphenylketene is postulated as an intermediate in the formation of benzophenone anil (V), carbon dioxide, and the β-lactam of β-anilinotetraphenylpropionic acid (VIII). Mechanistic pathways are discussed to account for the formation of dibenzanilide (VI) and other products. The photochemical rearrangements of N-phenylphenylbenzoyl nitrone (XVII) to dibenzanilide and of triphenyl nitrone to N,N-diphenylbenzamide are reported.

Büchi and Ayer[2] found that photochemically excited nitrobenzene (I) can effect cleavage of an olefinic double bond in a manner analogous to that of ozone. On irradiation of nitrobenzene with 2-methyl-2-butene, they obtained acetaldehyde, acetone, acetanilide, and a dimer (II). They postulated a 1,3,2-dioxazolidine intermediate (III), which is an analog of a primary ozonide.

The present paper is concerned with the action of photochemically excited nitrobenzene on tolane (IV). A petroleum ether (b.p. 38.7–57.9°) solution of tolane and nitrobenzene was irradiated for 3 days under an atmosphere of nitrogen with a mercury arc lamp (Hanovia Type A). A Pyrex filter was employed to remove the lower wave lengths capable of exciting to-



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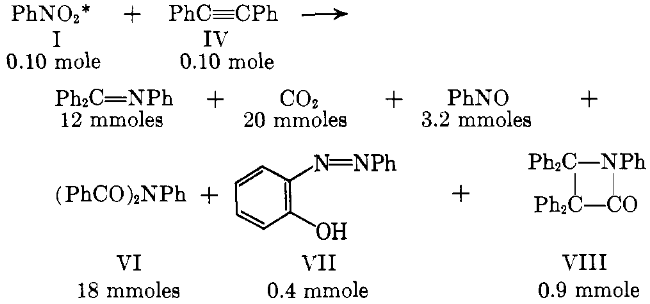
[1] Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, Zurich, Switzerland.

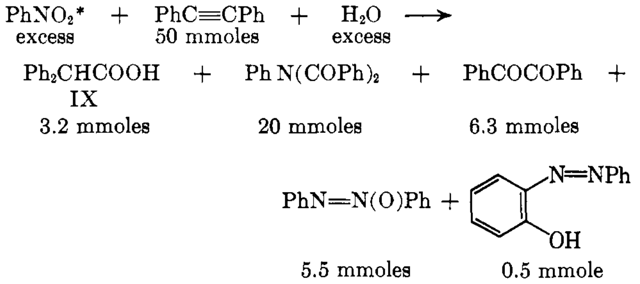
[2] G. Büchi and D. E. Ayer, *J. Am. Chem. Soc.*, **78**, 689 (1956).

lane.[3] Tolane, itself, is known to undergo photochemical transformations.[4]

The products of the photochemical reaction of nitrobenzene and tolane are benzophenone–anil (V), carbon dioxide, nitrosobenzene, dibenzanilide (VI), 2-hydroxyazobenzene (VII), and the β-lactam of N-phenyl-β-aminotetraphenylpropionic acid (VIII). Recovered starting materials and tars were also obtained.



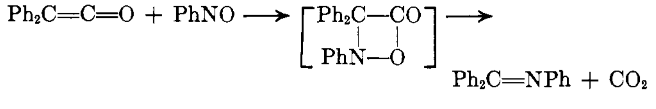
When the photolysis is carried out in aqueous dioxane, the products are diphenylacetic acid (IX), dibenzanilide, benzil, azoxybenzene, and 2-hydroxyazobenzene. Recovered tolane (16 mmoles) and some intractable material were also isolated.



Diphenylketene as an Intermediate.—The reaction probably proceeds through the intermediacy of diphenylketene (X). Diphenylketene can be formed by transfer of an oxygen atom from nitrogen to acetylenic carbon, followed by cleavage of nitrosobenzene and migration of a phenyl group.

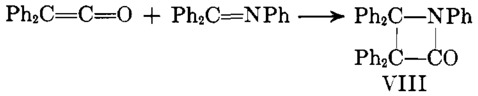
$$PhNO_2^* + PhC{\equiv}CPh \longrightarrow PhNO + \underset{X}{Ph_2C{=}C{=}O}$$

The formation of benzophenone anil and carbon dioxide can be explained by the reaction of diphenylketene with nitrosobenzene, first observed by Staudinger and Jelagin.[5]



$$Ph_2C{=}C{=}O + PhNO \longrightarrow \left[\begin{array}{l} Ph_2C{-}CO \\ PhN{-}O \end{array}\right] \longrightarrow Ph_2C{=}NPh + CO_2$$

The β-lactam (VIII) can form by condensation of diphenylketene and benzophenone anil. This condensation is, in fact, a method for preparing the β-lactam (VIII).[5]



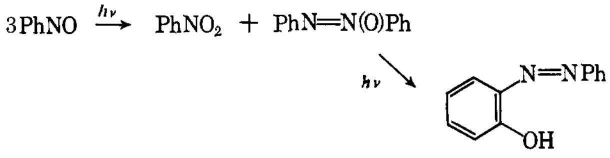
$$Ph_2C{=}C{=}O + Ph_2C{=}NPh \longrightarrow \begin{array}{l} Ph_2C{-}NPh \\ Ph_2C{-}CO \end{array}$$

VIII

When the irradiation of tolane and nitrobenzene is carried out in aqueous dioxane, then benzophenone anil, carbon dioxide, and the β-lactam (VIII) are absent in the products, since diphenylketene is rapidly hydrolyzed to diphenylacetic acid.

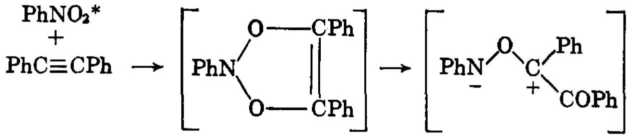
$$Ph_2C{=}C{=}O + H_2O \longrightarrow Ph_2CHCOOH$$

2-Hydroxyazobenzene.—The isolation of 2-hydroxyazobenzene (VII) is not surprising since this compound is a known product of the photochemical disproportionation of nitrosobenzene.[6] It can be prepared by the photochemical rearrangement of azoxybenzene.[7]



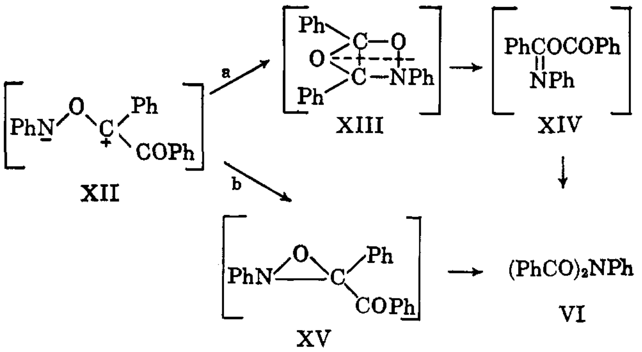
VII

Dibenzanilide.—As in the photochemical reaction of nitrobenzene and olefins, an analogy to ozonolysis can be postulated for the reaction with diphenylacetylene. Nitrobenzene and tolane can form an unstable 1,3,2-dioxazole (XI), analogous to an acetylenic primary ozonide.[8] This intermediate can cleave at one of the weak O–N bonds to form the zwitterion XII. The



XI XII

zwitterion is then capable of rearranging to dibenzanilide (VI). One possible pathway (a) involves the strained intermediate XIII, which would be expected to cleave at its weakest bonds to form XIV, the mixed anhydride of benzoic acid and benzanilide. The intermediate XIV would not be isolated because it can rearrange to the more stable dibenzanilide VI. Attempts to prepare XIV have led to the formation of dibenzanilide.[9] The questionable intermediate XIII casts some doubt on this mechanism. A more likely pathway (b) would proceed through the oxazirane intermediate XV, which could undergo benzoyl migration to dibenzanilide.



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(3) For ultraviolet spectra of tolane and nitrobenzene, respectively, see (a) H. H. Schlubach and V. Franzen, *Ann.*, **573**, 110 (1951); and (b) D. W. Sherwood and M. Calvin, *J. Am. Chem. Soc.*, **64**, 1351 (1942).

(4) G. Büchi, C. W. Perry, and E. W. Roff, *J. Org. Chem.*, **27**, 4106 (1962).

(5) H. Staudinger and S. Jelagin, *Ber.*, **44**, 373 (1911).

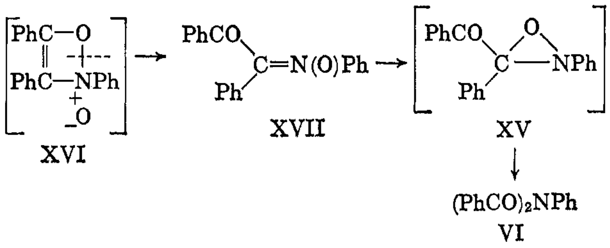
(6) E. Bamberger, *ibid.*, **35**, 1610 (1902).

(7) W. M. Cumming and G. S. Ferrier, *J. Chem. Soc.*, **127**, 2374 (1925).

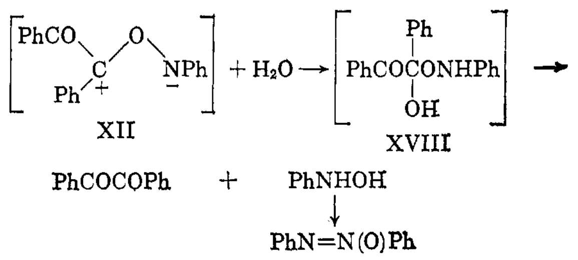
(8) R. Criegee and M. Lederer, *Ann.*, **583**, 29 (1953).

(9) (a) O. Mumm, *Ber.*, **43**, 889 (1910); (b) H. C. Wheeler and T. B. Johnson, *Am. Chem. J.*, **30**, 34 (1903).

Another mechanistic possibility is the participation of a four-membered ring intermediate (XVI), rather than the 1,3,2-dioxazole. This intermediate could cleave to N-phenylphenylbenzoylnitrone (XVII), which is indeed photochemically rearranged to dibenzanilide, probably through the intermediacy of the oxazirane (XV).[10]



Benzil and Azoxybenzene.—In aqueous dioxane, the zwitterionic intermediate XII may be converted to the hydrated intermediate XVIII, which could subsequently cleave to benzil and N-phenylhydroxylamine. N-Phenylhydroxylamine would not be isolated as such under the conditions of the work-up, but rather as the more stable azoxybenzene. Azoxybenzene is a common degradation product of N-phenylhydroxylamine.[11]



The formation of benzil and azoxybenzene in aqueous dioxane calls into question the participation of N-phenylphenylbenzoylnitrone (XVII) in the photochemical reaction of nitrobenzene and tolane, since the nitrone is not at all hydrolyzed to benzil under these conditions, but converted completely to dibenzanilide.

Experimental

Materials.—Tolane (diphenylacetylene) was purchased from Pilot, m.p. 63°. Nitrobenzene (Eastman) was redistilled before use. Airco Prepurified nitrogen was employed. Petroleum ether refers to Fischer Certified Reagent petroleum ether, b.p. 38.7-57.9°.

Photochemical Apparatus.—Irradiations were carried out employing a 550-w., high pressure mercury arc lamp (Hanovia, Type A), with a water-cooled, quartz immersion well (Hanovia, Cat. No. 19434) and a Pyrex filter sleeve. Photochemical reactions were run under nitrogen with magnetic stirring.

Photochemical Reaction of Nitrobenzene and Tolane.—A mixture of 17.8 g. (0.1 mole) of tolane and 12.3 g. (0.1 mole) of nitrobenzene dissolved in petroleum ether was irradiated for 3 days. During the course of the irradiation the exhaust nitrogen was passed through a known volume of 1 *N* carbonate-free sodium hydroxide solution. At the completion of the irradiation the alkaline solution was treated with excess barium chloride. Carbon dioxide could be estimated by standard volumetric or gravimetric procedures. The yield of carbon dioxide was about 20 mmoles.

A. **Steam Distillation of the Reaction Mixture.**—The early fractions of the steam distillate exhibited a green color. The green fractions were combined, dried over sodium sulfate, and chromatographed on a Perkin-Elmer vapor fractometer Model 154, employing a C-column. The components of the mixture were identified as nitrosobenzene and nitrobenzene. Nitrosobenzene was assayed colorimetrically by virtue of its absorption peak at 770 mμ (ϵ 45). The yield was 3.2 mmoles.

After removal of the unchanged nitrobenzene, the residue from the steam distillation was extracted with ether, dried over sodium sulfate, and evaporated to dryness. The residue was extracted with cold petroleum ether.

B. **Chromatography of the Petroleum Ether Extract.**—The petroelum ether extract was chromatographed on a column of Florisil. The first fractions obtained with petroleum ether elution contained recovered tolane (9.0 g.), a 51% recovery. On further elution with petroleum ether, 80 mg. (0.4 mmole) of 2-hydroxyazobenzene (red-orange needles, m.p. 83°) was obtained. The compound was identical with a known sample of 2-hydroxyazobenzene[7] by mixture melting point and ultraviolet, infrared, and n.m.r. spectral comparisons.[12] Immediately following the 2-hydroxyazobenzene band, another orange band was obtained. Rechromatography of the material on Florisil with petroleum ether elution afforded 3.08 g. of yellow needles, m.p. 110°. The material was identified by comparison with a known sample of benzophenone anil.[13] The yield of benzophenone anil was 12%.

C. **Chromatography of the Petroleum Ether Insoluble Residue.**—The residue from petroleum ether extraction was dissolved in a few milliliters of benzene and charged to a column of Florisil packed in carbon tetrachloride. Elution with benzene afforded 0.41 g. (1.8% yield) of the β-lactam (VIII). The compound was identified by its elementary analysis, infrared spectrum (5.76 μ in chloroform), and comparison with a known sample prepared according to Staudinger and Jelagin.[5]

With ether as the eluent, 5.41 g. (18% yield) of dibenzanilide was obtained. The material was identical in spectral and melting point properties with dibenzanilide prepared by the method of Freundler.[14] Further elution afforded intractable material.

Irradiation of Tolane and Nitrobenzene in Aqueous Dioxane.—A solution of 8.90 g. (50 mmoles) of tolane, 25 ml. of nitrobenzene, 150 ml. of dioxane, and 10 ml. of distilled water was irradiated for 27 hr. No carbon dioxide was observed. The dioxane and nitrobenzene were removed by steam distillation. No nitrosobenzene was detected. The residue was extracted with 10% aqueous potassium bicarbonate solution. Acidification of the bicarbonate extract afforded 0.69 g. (6.4% yield based on tolane) of diphenylacetic acid, identical with an authentic sample.

The residue was chromatographed on Florisil with petroleum ether elution A total of 2.83 g. (32%) of tolane was recovered, and 0.10 g. (0.5 mmole) of 2-hydroxyazobenzene was isolated. A white solid (1.01 g., m.p. 33°) was obtained with spectra identical with that of azoxybenzene. A mixture melting point with authentic azoxybenzene was undepressed. Further elution provided 0.90 g. of a yellow solid, m.p. 92–94°. The material was identified as benzil by spectral and melting point studies; the yield was 12.5%. Elution with benzene afforded 6.19 g. (40% yield) of dibenzanilide. With more polar solvents, only intractable material was obtained.

Irradiation of N-Phenylphenylbenzoylnitrone.—N-Phenylphenylbenzoylnitrone (XVII), m.p. 156°, was prepared by the procedure of Kröhnke.[15] A solution of 1.0 g. of the nitrone (XVII) in 50 ml. of dioxane was irradiated for 24 hr. The dioxane was evaporated leaving a solid, m.p. 157–160°. The compound was indentified as dibenzanilide by its infrared spectrum and undepressed mixture melting point. Similar results were obtained when the irradiation was carried out in aqueous dioxane.

Irradiation of Triphenylnitrone.[10]— A solution of 0.55 g. of

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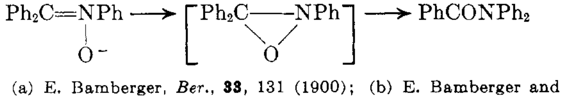
[10] It was also observed that triphenylnitrone is quantitatively converted to N,N-diphenylbenzamide by irradiation.



[11] (a) E. Bamberger, *Ber.*, **33**, 131 (1900); (b) E. Bamberger and F. Tschirner, *ibid.*, **32**, 342 (1899); (c) R. Willstätter and S. Dorogi, *ibid.*, **42**, 2167 (1909).

[12] The n.m.r. spectrum of 2-hydroxyazobenzene exhibits a sharp singlet of area 1 at τ −2.7.

[13] G. Reddelien, *Ber.*, **42**, 4760 (1909).

[14] P. Freundler, *Compt. rend.*, **137**, 712 (1903).

[15] F. Kröhnke, *Ber.*, **72B**, 534 (1939).

triphenylnitrone[16] in 5 ml. of dioxane was irradiated for 2 days. Removal of the solvent afforded a white solid, m.p. 178–180°, identical with N,N-diphenylbenzamide, in essentially quantitative yield.

Acknowledgment.—The author thanks the National Science Foundation and the National Institutes of Health for research fellowships and expresses gratitude to Professor Robert Burns Woodward for supervision of the work.

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[16] H. Rupe and R. Wittwer, *Helv. Chim. Acta*, **5**, 220 (1922).

The Synthesis of L-1,4-Thiazane-3-carboxylic Acid 1-Oxide[1]

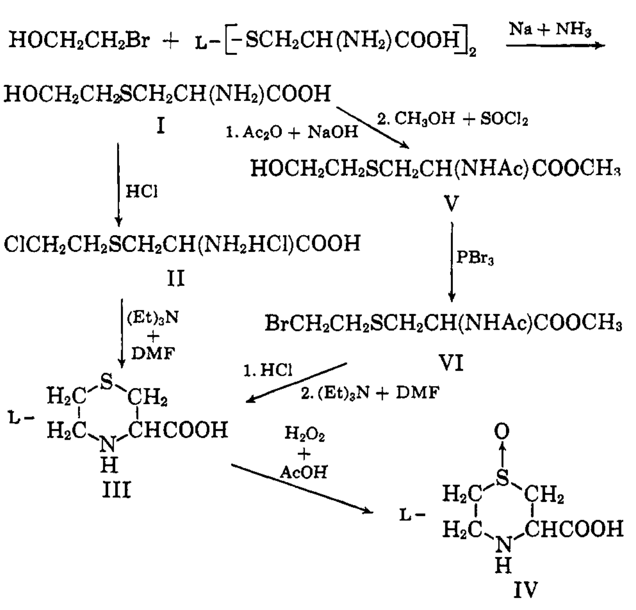
J. F. Carson and Francis F. Wong

Western Regional Research Laboratory,[2] Albany, California

Received February 13, 1964

S-(2-Hydroxyethyl)-L-cysteine (I) has been converted to S-(2-chloroethyl)-L-cysteine hydrochloride (II). Cyclization of this compound in dimethylformamide containing triethylamine yielded L-1,4-thiazane-3-carboxylic acid (III, reduced "chondrine"). Oxidation yielded a mixture of diastereoisomeric sulfoxides from which (+)-L-1,4-thiazane-3-carboxylic acid 1-oxide (IV, "chondrine") was obtained.

Kuriyama, *et al.*,[3] isolated the sulfoxide amino acid "chondrine" (L-1,4-thiazane-3-carboxylic acid 1-oxide, IV) from the red alga *Chondria crassicaulis*. More recently, this compound has been isolated from a brown alga *Undaria pinnatifida*.[4] This compound was of interest to us because of its relation to the other known cyclic sulfoxide amino acid "cycloalliin" (L-5-methyl-1,4-thiazane-3-carboxylic acid 1-oxide) obtained from onions.[5] We have synthesized L-1,4-thiazane-3-carboxylic acid (III), which Kuriyama[3] obtained by hydriodic acid reduction of "chondrine." The DL-amino acid was also synthesized. Oxidation of III with hydrogen peroxide in acetic acid yielded a mixture of diastereoisomeric sulfoxides from which the dextrorotatory isomer was obtained by fractional crystallization, $[\alpha]^{26}D$ +19.0.



The identity of the intermediate (III) with the reduced "chondrine" obtained by Kuriyama was established by analysis and specific rotation; the structure was confirmed for the DL-compound by Raney nickel desulfurization which yielded the expected N-ethyl-DL-alanine. Reduced "chondrine" (III) was also characterized by the preparation of a crystalline hydrochloride and a cyclohexylamine salt of the N-2,4-dinitrophenyl derivative.

Bromoethanol and L-cystine were condensed with sodium in liquid ammonia to give S-(2-hydroxyethyl)-L-cysteine (I, 94%). This compound on heating in reagent hydrochloric acid (38%) gave S-(2-chloroethyl)-L-cysteine hydrochloride (II, 70–90%). Finally, the chloride was cyclized in dimethylformamide–triethylamine to give III in an 80% yield. The corresponding DL-compound was also prepared in a similar manner from S-(2-chloroethyl)-D,L-cysteine hydrochloride. This intermediate was prepared by addition of β-mercaptoethanol to α-acetamidoacrylic acid[6] to give S-(2-hydroxyethyl)-N-acetyl-DL-cysteine as an oil which, on heating with 38% hydrochloric acid, yielded the DL-chloride (II).

In a modification of this general procedure, I was acetylated and methylated to yield the crystalline S-(2-hydroxyethyl)-N-acetyl-L-cysteine methyl ester (V) which was converted to the bromide (VI). When VI was hydrolyzed with 38% hydrochloric acid at 90–95° and cyclized as before, III was obtained in good yield. However, when VI was hydrolyzed by refluxing in 2.5–3.0 *N* hydrochloric acid for 18 hr., extensive decomposition occurred and further reaction with triethylamine–dimethylformamide produced a complex mixture of products. The thiazane carboxylic acid could then be obtained in maximum yields of only 7% by ion-exchange chromatography. These results are similar to the findings of Welti and Whittaker[7] who observed that refluxing β-hydroxyethyl sulfides in dilute hydrochloric acid yielded a mixture of decomposition products in contrast with heating in concentrated acid, in which case high yields of β-chloroethyl sulfides were obtained.

When cyclization was attempted in aqueous base (barium hydroxide or sodium carbonate at pH 8–10), no

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[1] Presented before the Division of Biological Chemistry at the 135th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

[2] A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

[3] M. Kuriyama, M. Takagi, and K. Murata, *Hokkaido Daigaku Suisan Gakubu Kenkyu Iho* (*Faculty of Fisheries Bulletin, Hokkaido University*), **11**, 58 (1960).

[4] F. Tominaga and K. Oka, *J. Biochem.* (Tokyo), **54**, 222 (1963).

[5] A. I. Virtanen and E. J. Matikkala, *Acta Chem. Scand.*, **13**, 623 (1959).

[6] A. Schöberl and A. Wagner, *Chem. Ber.*, **80**, 379 (1947); D. McHale, P. Mamalis, and J. Green, *J. Chem. Soc.*, 2847 (1960).

[7] D. Welti and D. Whittaker, *ibid.*, 3955 (1962).