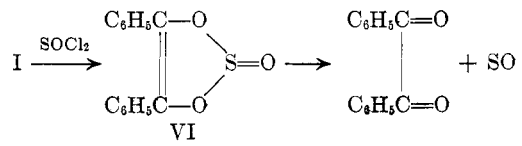
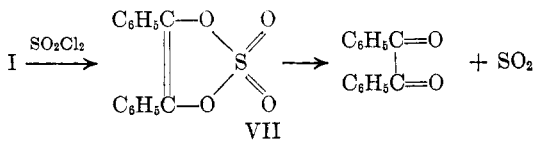
flask on the steam bath under a reflux condenser (hood). Heat the flask containing the benzoin and then pour in four milliliters of thionyl chloride through the condenser. Reflux for five minutes, then remove the condenser and heat for five minutes to drive off gases and thionyl chloride. Then connect the flask with a rubber stopper to the suction pump and heat on the steam bath to constant weight (four grams of benzoin gives four and three tenths grams of desyl chloride)."

A further study of the reaction between benzoin (one mole) and thionyl chloride (three moles) at 20° and at 0° showed that the reaction products are desyl chloride, benzil, and sulfur. We postulate that the initial product is the cyclic endiol sulfite VI, which decomposes to benzil and sulfur



VI

monoxide. This oxide is known to yield sulfur by disproportionation: $2SO \rightleftharpoons SO_2 + {}^1/_2\ S_2$.[2] Borohydride reduction of VI to desoxybenzoin is understandable. Attempts to isolate the intermediate were unsuccessful, as were attempts to isolate the sulfate ester VII from benzoin and sulfuryl chloride.



VII

However, the transient formation of VII is indicated by the observation that when a mixture of benzoin (one mole) and sulfuryl chloride (three moles) was let stand at room temperature, benzil and sulfur dioxide were formed in equivalent amounts and in high yield. That benzil is produced in higher yield in this reaction than in the reaction with thionyl chloride is perhaps due to the greater stability of the gaseous product.

Further evidence in support of the structures postulated including isolation of the crystalline 2,2′-4,4′,6,6′-hexamethyl derivative of VI from reaction of the known endiol[3] with thionyl chloride and pyridine in methylene chloride at −20°, will be presented by the junior author in candidacy for a degree in Japan.

Experimental

Reaction of Benzoin with Thionyl Chloride.—A mixture of 2 g. of benzoin and 2 ml. of thionyl chloride when let stand at 0° for 12 hr. afforded a yellow solution, and evacuation at the water pump afforded a viscous brown oil which solidified on standing. The infrared spectrum showed bands at 1718 cm.$^{-1}$ (desyl chloride) and 1686 cm.$^{-1}$ (benzil). Chromatography on alumina afforded 1.18 g. of desyl chloride, m.p. 68°, 0.71 g. (35%) of benzil, m.p. 96°, and a trace of sulfur.

For quantitative determination of both benzil and the gaseous products, 320.3 mg. of benzoin was placed in a small Claisen flask cooled in an ice bath and supplied with a gas inlet tube. The sidearm was connected through a Dry Ice–acetone trap (to catch thionyl chloride) to two absorption tubes containing 1 *N* sodium hydroxide. The system was flushed with nitrogen and then stopcocks at the ends of the system were closed and 0.45 ml. of thionyl chloride was added to the benzoin. After 12 hr., a slow stream of nitrogen was passed through the system for 3 hr. and then the system was evacuated twice to sweep gas dissolved in the reaction mixture into the absorption tubes. The residual syrup was analyzed spectrophotometrically using the benzil band at 11.52 μ and found to contain 125 mg. (39%) of the diketone. The solution in each absorption tube was neutralized with 1 *N* hydrochloric acid at 0° and titrated iodimetrically. Since the total iodine consumption was 37×10^{-4} equiv., whereas the benzil produced was only 5.9×10^{-4} equiv., considerable thionyl chloride must have been carried over into the absorption tubes. A blank run with benzil in place of benzoin showed this to be the case and afforded 22×10^{-4} equiv. of iodine. The difference, 15×10^{-4} equiv., is in the order of magnitude of the benzil formed.

In a run conducted with benzoin as before but at 20° (12 hr.), the yield of benzil was 29%.

Reaction of Benzoin with Sulfuryl Chloride.—This reaction presents a simpler case than that with thionyl chloride because the sole gaseous product is sulfur dioxide and because reagent swept into the absorption tubes is converted into sodium sulfate. In an experiment conducted like that described above, 226.5 mg. of benzoin treated at 0° with 0.4 ml. of sulfuryl chloride afforded 205 mg. (95%) of benzil, and 1.6×10^{-3} mole (94%) of sulfur dioxide.

(2) H. Zeise, *Z. Physik. Chem.*, **B51**, 120 (1942).

(3) R. C. Fuson, C. H. McKeever, and J. Corse, *J. Am. Chem. Soc.*, **62**, 600 (1940).

DL- and L-Threonine *p*-Toluenesulfonate Benzyl Ester[1]

H. R. GUTMANN AND S. F. CHANG

Veterans Administration Hospital, Minneapolis, Minn.

Received December 7, 1961

For a projected synthesis of the threonine containing chromopeptide actinomycin D, which has carcinostatic activity,[2] we required L- and/or DL-threonine benzyl ester. Since the problem of the synthesis of actinomycins has been solved in principle by the recent total synthesis of actinomycin C_3,[3] which is very closely related to actinomycin D, work on the project has been discontinued. We wish to report here the preparation and properties of DL- and L-threonine *p*-toluenesulfonate benzyl ester since these compounds might be useful for the synthesis of threonine peptides. Although DL-serine benzenesulfonate benzyl ester can be obtained readily as a crystalline solid by the

(1) Supported by a grant (C-2571) from the National Cancer Institute, U. S. Public Health Service.

(2) S. Farber, *Am. J. Path.*, **31**, 582 (1955).

(3) H. Brockmann, *Angew. Chem.*, **72**, 939 (1960).

method of Miller and Waelsch,[4] the literature contains no reference that the procedure also can be applied to the esterification of threonine.[5] The present report indicates that the esterification of threonine with benzyl alcohol by the method of Miller and Waelsch[4] proceeds very slowly and requires a reaction time which is much longer than that necessary for the esterification of other amino acids. If the reaction were carried out for the comparatively short periods of time necessary for the esterification of amino acids, such as glycine, only threonine *p*-toluenesulfonate was isolated. Even with the use of prolonged reaction times crude DL-threonine *p*-toluenesulfonate benzyl ester contained as much as 20% DL-threonine *p*-toluenesulfonate, the estimate being based on the average carbon content of different preparations. The resistance of threonine to yield the benzyl ester may be due to steric factors which are not operative in the case of serine. Molecular models show that the methyl group of threonine crowds the hydroxyl group toward the carbonyl oxygen. Because the formation of L-threonine *p*-toluenesulfonate benzyl ester necessitated heating for a prolonged period, the possibility had to be considered that the compound would racemize. However, conversion of *N*-carbobenzoxy-L-threonine benzyl ester, prepared from L-threonine *p*-toluenesulfonate benzyl ester, to L-threonine of the correct specific rotation proved that racemization did not take place under the experimental conditions. As expected of a primary aliphatic amine,[6] threonine *p*-toluenesulfonate benzyl ester and threonine benzyl ester reacted with ninhydrin. The reaction was very much slower than with threonine *p*-toluenesulfonate or threonine, the compound giving a yellow color at first which changed to the typical purple color within twenty-four hours.

Experimental

DL- and L-Threonine, $[\alpha]^{25}D$ −28.4° (*c* 3, water) were obtained from the Mann Research Laboratories, New York, N. Y. All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Amino nitrogen was determined manometrically.[7] For chromatography, Whatman #1 paper and the solvent system 95% ethanol–benzene–water (4:1:1) were used. Chromatograms were developed routinely by the descending technique. The petroleum ether used had a boiling range of 30–60°.

DL-Threonine *p*-Toluenesulfonate (I).—DL-Threonine, 0.15 g. (1.3 mmoles), and 0.27 g. of *p*-toluenesulfonic acid monohydrate (1.4 mmoles) were dissolved in 10 ml. of benzyl alcohol by warming the mixture on the steam bath to 80°. The solvent was removed slowly by vacuum distillation (80°, 1 mm.). The oily residue was washed three times with 50-ml. portions of dry ether and was then overlaid with dry ether. I, m.p. 143–145°, crystallized on standing at 4° overnight; 0.16 g., 43% yield. On paper chromatograms I migrated as a single component and gave an immediate test with ninhydrin, R_f = 0.45.

Anal. Calcd. for $C_{11}H_{17}O_6NS$: C, 45.3; H, 5.88; NH_2—N, 4.80. Found: C, 45.2; H, 5.83; NH_2—N, 4.94.

Reaction of DL-Threonine with *p*-toluenesulfonic acid in hot ethanol followed by evaporation of the solvent and crystallization of the residual oil from ether gave I in quantitative yield.

DI-Threonine *p*-Toluenesulfonate Benzyl Ester (II).—DL-Threonine, 2.0 g. (1.7 mmoles), and 3.44 g. of *p*-toluenesulfonic acid monohydrate (1.8 mmoles) were dissolved in 28 ml. of benzyl alcohol and 100 ml. of carbon tetrachloride by warming to 80°. The mixture was heated under reflux, the carbon tetrachloride being removed slowly by distillation at atmospheric pressure. After a reaction time of 15 hr. the carbon tetrachloride and approximately one half of the benzyl alcohol were removed by distillation at reduced pressure. II was precipitated as an oil by addition of dry ether. The oil crystallized on triturating the product with dry ether and cooling in an ice bath. The white solid, m.p. 98–101°, was collected, washed with petroleum ether, and dried *in vacuo* over calcium chloride; 5.48 g.; 86% yield. Further analysis of this material by paper chromatography indicated that the product, R_f = 0.86, was contaminated with I, R_f = 0.45. Attempts to separate I from II by chromatography on cellulose columns (Whatman ashless cellulose powder for chromatography) were unsuccessful. The crude material was purified by dissolving 0.38 g. (1 mmole) in 25 ml. of 5% sodium bicarbonate and extracting three times with 40 ml. of benzene. The combined benzene extracts were washed once with 40 ml. of water, and dried over anhydrous sodium sulfate. The solvent was evaporated at reduced pressure yielding the free base as a clear oil which could not be crystallized. The oil was dissolved in 10 ml. of warm ethyl acetate and 0.19 g. of *p*-toluenesulfonic acid monohydrate (1 mmole) in 3 ml. of ethyl acetate was added to this solution. The oil which was obtained on evaporation of the solvent was taken up in a minimum amount of hot benzene and the solution was filtered. Pure II crystallized upon adding dry ether, cooling in ice, and scratching; 0.10 g.; m.p. 115–117°.

Anal. Calcd. for $C_{18}H_{23}O_6NS$: C, 56.6; H, 6.08; N, 3.67. Found: C, 56.6; H, 6.09; N, 3.42.

On paper chromatograms the compound gave a delayed test with ninhydrin, R_f = 0.84. The spot which was initially yellow-brown gave the typical purple ninhydrin color only after 24 hr. Glycine *p*-toluenesulfonate benzyl ester, m.p. 132–133° (reported 132–134°),[8] when chromatographed under the same conditions, likewise gave a delayed reaction, R_f = 0.83. *N*-Carbobenzoxy-DL-threnonine benzyl ester,[9,10] m.p. 62–63°, of the correct elementary composition was prepared by treating II in dilute potassium bicarbonate solution with carbobenzoxy chloride in the usual manner.

L-Threonine *p*-Toluenesulfonate (III).—L-Threonine, 0.30 g. (2.5 mmoles) and 0.48 g. of *p*-toluenesulfonic acid monohydrate (2.5 mmoles) were dissolved in 30 ml. of ethanol with heating on the steam bath. The hot solution was filtered and the solvent removed at reduced pressure. The residual oil crystallized upon adding dry ether and cooling. The hygroscopic solid was collected and recrystallized twice from methanol–ether to yield III, m.p. 138–140°, 0.44 g., 60% yield. For analysis, the compound was recrystallized once more from methanol–ether with no change in melting point and dried *in vacuo* over phosphorus pentoxide at 56°.

(4) H. K. Miller and H. Waelsch, *J. Am. Chem. Soc.*, **74**, 1092 (1952).

(5) N. Izumija and S. Makisumi, *Nippon Kagaku Zasshi*, **78**, 662 (1957); *Chem. Abstr.*, **53**, 5148h (1959), reported that heating of DL-threonine in benzyl alcohol in the presence of one equivalent of *p*-toluenesulfonic acid failed to give a solid product.

(6) F. Feigl, "Spot Tests in Organic Analysis," 5th ed., Elsevier Publishing Co., New York, 1956, p. 283.

(7) D. D. Van Slyke, *J. Biol. Chem.*, **83**, 425 (1929).

(8) L. Zervas, M. Winitz, and J. P. Greenstein, *J. Org. Chem.*, **22**, 1515 (1957).

(9) F. Bergel and R. Wade, *J. Chem. Soc.*, 941 (1959).

(10) D. L. Ross, C. G. Skinner, and W. Shive, *J. Org. Chem.*, **24**, 1440 (1959).

Anal. Calcd. for $C_{11}H_{17}O_6NS$: C, 45.3; H, 5.88; N, 4.80. Found: C, 44.8; H, 6.04; N, 4.34.

On chromatograms III migrated as a single component, R_f = 0.42, and reacted immediately with ninhydrin.

L-Threonine *p*-Toluenesulfonate Benzyl Ester (IV).—L-Threonine, 0.30 g. (2.5 mmoles) and 0.53 g. of *p*-toluenesulfonic acid monohydrate (2.8 mmoles) were dissolved in 5 ml. of benzyl alcohol by heating on the steam bath. Carbon tetrachloride (25 ml.) was added and the mixture heated under reflux for 20 hr., the carbon tetrachloride being distilled from the mixture very slowly. Addition of dry ether precipitated an oil which was partially soluble in ethyl acetate. The material which was insoluble in ethyl acetate was identified as III, m.p. 136–137°. After 5 ml. of fresh benzyl alcohol and 25 ml. of carbon tetrachloride had been added, distillation of the carbon tetrachloride was resumed for an additional 19 hr. Addition of dry ether (100 ml.) precipitated 0.33 g. of a colorless oil after drying *in vacuo* over calcium chloride. Attempts to crystallize the oil from benzene–ether, benzene–petroleum ether, methanol–ether, and/or acetone–ether either at 0° or at −70° were unsuccessful.

Anal. Calcd. for $C_{18}H_{23}O_6NS$: NH_2—N, 3.67. Found: NH_2—N, 3.80.

Chromatography disclosed contamination of IV, R_f = 0.83, with III, R_f = 0.40. The material was dissolved in 40 ml. of benzene and purified by extraction with a dilute solution of sodium bicarbonate as described above for II. Following addition of one equivalent of *p*-toluenesulfonic acid monohydrate and evaporation of the solvent at reduced pressure, chromatographically pure IV, R_f = 0.82, was obtained as an oil, which could not be induced to crystallize. Although pure IV was obtained by this procedure in several runs, attempts to crystallize the resulting oil were unsuccessful.

***N*-Carbobenzoxy-L-threonine Benzyl Ester (V).**—L-Threonine, 0.40 g. (3.4 mmoles), and 0.71 g. of *p*-toluenesulfonic acid monohydrate (3.8 mmoles) were dissolved in 5 ml. of benzyl alcohol and 30 ml. of dry benzene. Esterification was carried out for 25 hr. as described for IV. The remaining benzene was removed by distillation at reduced pressure and IV precipitated by addition of 100 ml. of dry ether. After the ether had been decanted and the oil dried for 12 hr. *in vacuo* over calcium chloride, it was dissolved in 10 ml. of water and cooled in an ice bath. Carbobenzoxy chloride (0.60 ml.) and 1.4 g. of potassium carbonate in 25 ml. of water were added. After a few minutes of shaking, V precipitated from the reaction mixture. Following addition of a few drops of pyridine the reaction mixture was extracted with ethyl acetate. The organic phase was washed with 5% sodium bicarbonate and water in succession and dried over anhydrous sodium sulfate. After the solvent had been evaporated at reduced pressure, the oily residue solidified upon addition of petroleum ether to yield 0.80 g. of crystalline V; m.p. 79–80°, 68% yield. One recrystallization from ethyl acetate–petroleum ether afforded needles, m.p. 79–80°, $[\alpha]^{25}D$ −10.5° (*c* 2.0, 95% ethanol).

Anal. Calcd. for $C_{19}H_{21}O_5N$: C, 66.5; H, 6.17; N, 4.10. Found: C, 66.7; H, 6.23; N, 4.36.

Conversion of V to L-Threonine.—V, 0.71 g. (2.1 mmoles), was dissolved in 25 ml. of methanol. Following addition of three drops of glacial acetic acid, hydrogenolysis was carried out with palladium oxide[11] as catalyst. The product which had precipitated partially during the reaction was brought back into solution by addition of water. After the reaction mixture had been filtered, the solvent was removed at reduced pressure and the residue recrystallized from methanol–ether to yield 0.18 g. of L-threonine, $[\alpha]^{23}D$ −28.2° (*c* 1.5, water); 74% yield.

(11) R. L. Shriner and R. Adams, *J. Am. Chem. Soc.*, **46**, 1683 (1924).

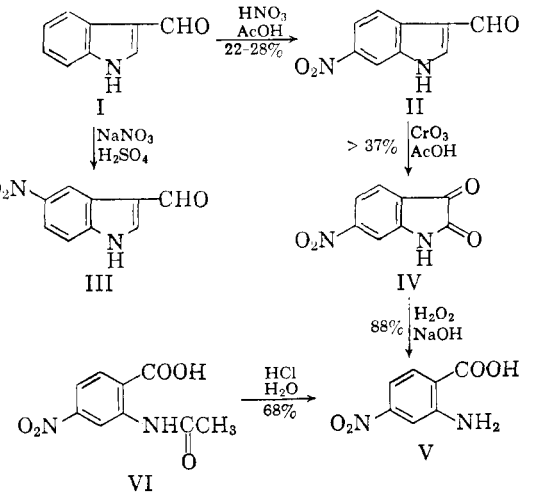
New Synthetic Route to 6-Nitroisatin *via* Nitration of 3-Indolealdehyde

WAYLAND E. NOLAND AND REUBEN D. RIEKE[1]

School of Chemistry, University of Minnesota, Minneapolis 14, Minn.

Received December 11, 1961

Nitration of 3-indolealdehyde (I) in acetic acid was first reported, by Majima and Kotake,[2] to give in unstated yield a mononitro derivative, having a melting point of 290° with decomposition, in which the position of nitration was not determined. Recently, and subsequent to the completion of our work, Berti and da Settimo[3] have reported that they have repeated the nitration of 3-indolealdehyde in acetic acid, and have obtained in 16% yield a mononitro derivative, having a melting point of 302–304° with decomposition. The mononitro derivative was proved to be 6-nitro-3-indolealdehyde (II), by oxidation to the corresponding acid and decarboxylation to authentic 6-nitroindole.[2] Berti and da Settimo[3] also reported that nitration of 3-indolealdehyde with potassium nitrate in concentrated sulfuric acid gave in 85% yield a mixture of mononitro derivatives, having a melting point of 260–270° with decomposition, shown by ultraviolet analysis to contain 66% 5-nitro-3-indolealdehyde and 34% 6-nitro-3-indolealdehyde. The structure of 5-nitro-3-indolealdehyde (III), isolated in small amount by fractional crystallization, was proved by oxidation to the corresponding acid and decarboxylation to a compound having a



melting point and ultraviolet spectrum in good agreement with those reported for 5-nitroindole.[4]

(1) From the senior thesis research of Reuben D. Rieke, 1960–1961.

(2) R. Majima and M. Kotake, *Ber.*, **63**, 2237 (1930).

(3) G. Berti and A. da Settimo, *Gazz. chim. ital.*, **91**, 728 (1961).

(4) S. M. Parmerter, A. G. Cook, and W. B. Dixon, *J. Am. Chem. Soc.*, **80**, 4621 (1958).