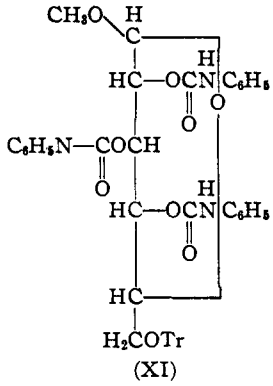
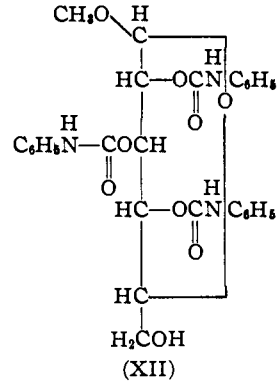


(XI)



(XII)

6-Trityl α- and β-Methyl-*d*-glucoside-2,3,4-tricarbanilates.—To 10 g. of 6-trityl-α-methyl-*d*-glucoside, dried at 100°, in 25 cc. of dry pyridine was added 15.9 g. of phenyl isocyanate. After one hour at 100°, the mixture was washed with water, then with hot ligroin, after which it solidified. Recrystallization from benzene gave 12.8 g. (83%), m. p. 229–231°, $[\alpha]^{25}D$ +52° ($CHCl_3$, C = 1).

Anal. Calcd. for $C_{47}H_{43}O_9N_3$: C, 71.2; H, 5.42; N, 5.29; trityl, 30.6. Found: C, 70.89; H, 5.35; N, 5.53; trityl, 30.1.

Prepared as the α-isomer, 10 g. of 6-trityl-β-methyl-*d*-glucoside in 15 cc. of pyridine and 15 cc. of phenyl isocyanate gave from hot benzene 7.45 g. (82%), m. p. 232–234°; $[\alpha]^{25}D$ −5° ($CHCl_3$, C = 1).

Anal. C, 71.13; H, 5.45; N, 5.35.

α- and β-Methyl-*d*-glucoside-2,3,4-tricarbanilates.—6-Trityl α-methyl-*d*-glucoside-2,3,4-tricarbanilate (4 g.) was refluxed for two hours with 20 cc. of methanol containing 1% hydrogen chloride. After cooling, the solution was seeded with trityl methyl ether. The precipitate was filtered off and the filtrate evaporated on a steam-bath to a small volume then to dryness by means of air. The residue was dissolved in acetone diluted with benzene and the solution heated until most of the acetone had boiled off. On cooling, the product was precipitated and was filtered off. This purification was repeated twice, giving 1.5 g. (54%), m. p. 192–193°; $[\alpha]^{25}D$ +84° ($CHCl_3$, C = 1). The product, when dissolved in concentrated sulfuric acid, gave no yellow color and on dilution with water produced no precipitate.

Anal. Calcd. for $C_{28}H_{29}O_9N_3$: C, 60.96; H, 5.27; N, 7.62. Found: C, 60.71; H, 5.20; N, 7.56.

Following the procedure for the α-isomer, 5 g. of 6-trityl-β-methyl-*d*-glucoside-2,3,4-tricarbanilate was refluxed for three hours in 40 cc. of methanol containing 1% hydrogen chloride. During this period of heating, β-methyl-*d*-glucoside-2,3,4-tricarbanilate precipitated. After cooling the precipitate was filtered, washed with methanol and dried; yield, 2.4 g. (68%), m. p. 230–232°. By repeated crystallization from ethyl acetate and acetone, the melting point could be raised to 234.5°; $[\alpha]^{25}D$ +6° (pyridine, C = 1).

Anal. C, 60.83; H, 5.18; N, 7.59.

Acknowledgment.—The authors wish to express their appreciation for the assistance of John T. Clarke in connection with the experimental part of this paper.

Summary

Certain mono-, di- and tricarbanilates of both α- and β-methyl-*d*-glucosides have been prepared and identified.

For preparation of glucoside derivatives these carbanilates have the advantages of being high melting, stable, readily prepared, and, in general, easily crystallized.

ROCHESTER, N. Y. RECEIVED DECEMBER 6, 1943

[CONTRIBUTION NO. 522 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Unsaturated Synthetic Glycerides. VII. Preparation and Properties of Synthetic 1-Monoglycerides and Simple Triglycerides of Linoleic and Linolenic Acids[1]

BY B. F. DAUBERT AND A. R. BALDWIN[2]

During the investigation in this Laboratory on the preparation of synthetic glycerides containing unsaturated acids, it was determined experimentally that both linoleyl and linolenyl chlorides could be prepared, in good yields, from the respective debromination acids and oxalyl chloride.[3] The total diene conjugation in each acid chloride, when examined spectrophotometrically, was less than 1%. As a result of this work these acid chlorides were considered satisfactory for the synthesis of highly purified synthetic glycerides.

Since both 1-monolinolein and trilinolein have been reportedly prepared by other methods, a comparison of the properties of the compounds prepared by independent methods would serve to establish whether the glycerides synthesized, using acid chlorides as intermediates, exhibit any significant differences in properties.

The preparation of 1-monolinolein by heating dry potassium linoleate with 1-monochlorhydrin at 160° for one hour in an atmosphere of carbon dioxide was reported by Izar.[4] This same investigator also reported the synthesis of trilinolein from trichlorhydrin and potassium linoleate. In both instances, the compounds were reported as oily liquids but were not further characterized. More recently Black and Overley[5] reported the synthesis of 1-monolinolein and trilinolein by debromination of the respective 1-(9,10,12,13-tetrabromo)-stearin and tri-(9,10,12,13-tetrabromo)-stearin; the latter compounds were synthesized using tetrabromostearyl chloride. These investigators indicated that possible configurational changes could be avoided when de-

(1) The authors are indebted to the Buhl Foundation and to Swift and Company for grants in support of this investigation.

(2) Nutrition Foundation, Inc., Fellow.

(3) Wood, Jackson, Baldwin and Longenecker, THIS JOURNAL, **66**, 287 (1944).

(4) Izar, *Biochem. Z.*, **60**, 320 (1914).

(5) Black and Overley, THIS JOURNAL, **61**, 3051 (1939).

bromination of the glycerides was delayed until the final step of the synthesis. Later, Wheeler, Riemenschneider and Sando[6] reported the preparation of trilinolein by direct esterification of glycerol with linoleic acid. While iodine values and saponification equivalents of the latter two independently prepared trilinoleins agreed well with theoretical values, the melting points and refractive indices were significantly different. To clarify the obvious discrepancies in these two physical constants we have prepared trilinolein, by an accepted method of synthesis, using linoleyl chloride and glycerol. Analytical constants of the resulting product indicated a high degree of purity. The refractive index and capillary melting point were essentially the same as those reported by Wheeler, *et al.*[6] Thermometric measurements, by a method described previously,[7] verified the existence of the two polymorphic forms reported by the latter investigators.

Experimental

Preparation of Intermediates.—Linoleic and linolenic acids were prepared from tetrabromostearic acid (m. p. 115°) and hexabromostearic acid (m. p. 186°), respectively, by debromination in ether solution according to the method of Frankel and Brown.[8]

Linoleyl and linolenyl chlorides were prepared from the respective acids by the method described previously.[3] In each case, the resulting chlorides had the same constants as those reported.

Preparation of 1-Monolinolenin.—To a cooled solution of acetone-glycerol (36 g.) and in quinoline (23 g.) and dry chloroform (40 ml.) there was added slowly linolenyl chloride (43 g.). The mixture was allowed to stand at room temperature for four hours. After the addition of dry peroxide-free ether, the solution was washed carefully and successively with cold 0.5 *N* sulfuric acid, 5% potassium carbonate solution and distilled water. The ether solution was then dried over anhydrous sodium sulfate and after filtration it was then reduced in volume to *ca.* 100 ml., *in vacuo*, at room temperature. The solution was transferred to a liter beaker and cooled to approximately 0° in an ice-bath. Hydrochloric acid (100 ml.) was poured into the solution slowly with constant stirring. After allowing the solution to stand for thirty minutes, ice water (500 ml.) was added, the separated product dissolved in peroxide-free ether, and the solution was washed with distilled water until free of mineral acid. The ether solution was dried over anhydrous sodium sulfate and after filtration it was reduced to a volume of *ca.* 75 ml. After the addition of an equal volume of petroleum ether, it was cooled to −20° for twenty-four hours. The 1-monolinolenin, which separated as a white crystalline mass, was recrystallized several times from the same mixture of solvents: melting point (capillary tube)[9] 16.0–17.0°; iodine value (Wijs) 214.8 (calcd. 216.2); molecular weight, 351.6 (calcd. 352.5); $n^{50.0}D$ 1.47589 (dn/dt = 0.00039).

1-Monolinolein was prepared in a similar manner and had the constants: m. p. (capillary tube) 14.0–15.0°; iodine value (Wijs) 142.7 (calcd. 143.3); $n^{20.0}D$ 1.47682 (dn/dt = 0.00038).

Preparation of Trilinolenin.—Glycerol (1 g.) was dissolved in a mixture of quinoline (6 g.) and dry chloroform (30 ml.) and to the solution there was added slowly linolenyl chloride (10 g.). The mixture was heated on a steam-bath for two hours, and after cooling it was dissolved in petroleum ether (300 ml.). The solution was then washed successively with cold 0.5 *N* sulfuric acid, 5% potassium carbonate solution, distilled water and dried over anhydrous sodium sulfate. The solvent was removed completely, *in vacuo*, at room temperature and the liquid residue was dissolved in 95% ethyl alcohol. Crystallization of the trilinolenin from the solution was induced at −60°. Several crystallizations from a mixture of 95% alcohol and ether (2:1) yielded a product of a high degree of purity. The trilinolenin was a colorless liquid at room temperature: melting point (capillary tube) −23.0 to −24.0°; iodine value (Wijs) 261.4 (calcd. 261.6); molecular weight, 866 (calcd. 873); $n^{40.0}D$ 1.48190 (dn/dt = 0.00040).

Trilinolein was prepared in a similar manner and had the constants: m. p. (capillary tube) −13.0°; iodine value (Wijs) 172.8 (calcd. 173.3); $n^{50.0}D$ 1.46815 (dn/dt = 0.00039).

Bromination of Monoglycerides and Triglycerides.—The bromination procedure, given in detail for trilinolenin, was essentially the same for 1-monolinolein, 1-monolinolenin and trilinolein.

Trilinolenin (2 g.) was dissolved in cold petroleum ether (50 ml.). Bromine was added dropwise to the solution, with constant stirring, until the liquid assumed a definite orange color. During the addition of the bromine a gummy mass separated. After decantation of the supernatant liquid, the gummy mass was washed repeatedly with cold petroleum ether. During this treatment practically all of the color was removed. The bromides were then dissolved in a small volume of warm dioxane and on the addition of an equal volume of petroleum ether, crystalline bromides separated. After repeated crystallizations from the same mixture of solvents, the product was dried in a vacuum desiccator; melting point 150–151°.

Anal. Calcd. for $C_{57}H_{92}O_6Br_{12}$; Br, 62.22. Found: Br, 62.18, 62.15.

Bromination of 1-monolinolenin produced a crystalline bromide melting at 172°.

Anal. Calcd. for $C_{21}H_{36}O_4Br_6$: Br, 57.63. Found: Br, 57.60, 57.55.

Melting points of the crystalline bromides obtained from 1-monolinolein and trilinolein were 101.5° and 81.0°, respectively, and were in agreement with those previously reported.[5,6]

Spectrophotometric Analyses.—Each synthetic glyceride was examined for total diene and triene conjugation using a Beckmann Quartz Spectrophotometer, Model DU. In each product, the total diene conjugation was less than 1% and the triene conjugation was negligible. The glyceride exhibiting the least conjugation, oddly enough, was trilinolenin. The absence of a greater amount of conjugation seems to indicate that the synthesis of glycerides containing linoleic and linolenic acids through the acid chlorides does not materially affect the position of the double bonds. It should be borne in mind, however, that the acids present in the synthetic glycerides, while not significantly different from the original debromination acids, may not be identical with the naturally occurring acids.[8]

Discussion

In the warming curves for trilinolein (Fig. 1) it may be observed that Form II melts at −45.6° and Form I at −12.9°. In the thermometric measurements[10] on a bulk sample (1.0 to 1.5 g.), cooling at −75° for twenty to thirty minutes was necessary for its solidification into Form II. Since the temperature of melting was so low, visual observation of the transition of Form II to Form I was possible during warming of the

(6) Wheeler, Riemenschneider and Sando, *J. Biol. Chem.*, **132**, 687 (1940).

(7) Daubert and Clarke, THIS JOURNAL, **66**, 690 (1944).

(8) Frankel and Brown, *ibid.*, **65**, 415 (1943).

(9) Liquid samples placed in capillary tubes were held at −20° for twenty-four hours prior to determination of the melting point.

(10) The assistance of Dr. T. H. Clarke in the thermometric measurements is gratefully acknowledged.

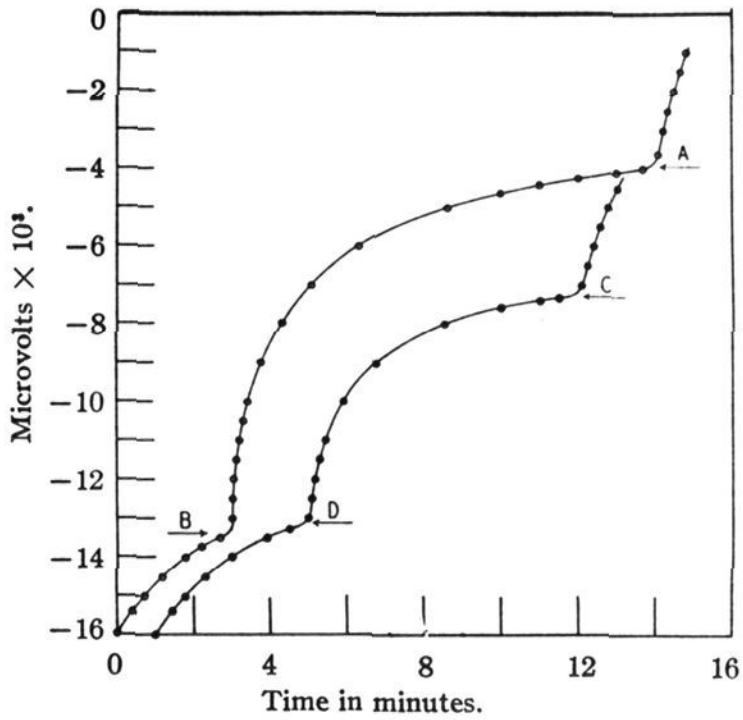


Fig. 1.—Warming curves for trilinolein and trilinolenin: trilinolein—A, 3950 microvolts = −12.9°; B, 13370 microvolts = −45.6°; trilinolenin—C, 7300 microvolts = −24.2°; D, 13100 microvolts = −44.6°.

sample at room temperature. The time required for complete melting of Form II and solidification into Form I depended on the rate of warming. To permit the change to occur sufficiently slowly for complete visual observation, the triglyceride in a small vial was cooled at −75° for thirty minutes in a dry-ice-bath; the temperature was measured with a calibrated thermel and potentiometer. At the end of thirty minutes the glyceride had completely solidified. After the vial was removed from the bath and transferred quickly to a small transparent Dewar flask cooled to −60° on the inside, it was allowed to warm spontaneously at room temperature. Complete transition of Form II into Form I, under these conditions, required approximately three minutes. In the photograph (Fig. 2) it may be seen that an actual melting of Form II occurred at the surface of the glyceride (heat leakage into the sample occurred faster through the thermel than through the sides of the vacuum flask). The progressive melting of Form II and the solidification of the liquid into Form I can be followed in the same photograph. In vials 2, 3, 4, 5 and 6, three phases are observable, solid Form II, melted Form II and solid Form I. While melting of Form II could be demonstrated in small capillary tubes on immersing them in baths of the required temperature, the evidence in Fig. 2 is much more convincing. It may be concluded, therefore, that the transition of Form II to Form I in a bulk sample of trilinolein is definitely accompanied by melting.

Transition Forms of Trilinolein

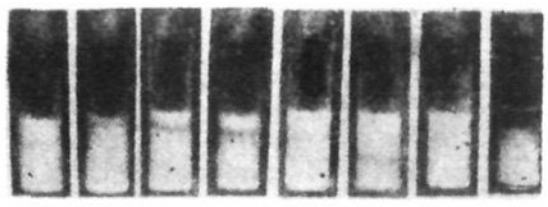


Fig. 2.—Progressive melting of the polymorphic forms of trilinolein: 1, Form II solidified at −75°; 2, Form II beginning to melt; 3, solidification of melted Form II to Form I; 4, 5, 6, progressive stages of transition; 7, completely solid Form I; 8, melting of Form I; m. p. Form II, −45.6°; m. p. Form I, −12.9°.

When the sample of trilinolein was cooled quickly to −60° in a dry-ice-bath no solidification occurred. But on removing the supercooled liquid from the bath and quickly transferring it to the small Dewar flask again cooled to −60° on the inside and allowing it to warm as before, the glyceride solidified at −45.6° in Form I which later melted normally at −12.9°.

Warming curves in Fig. 1 show that trilinolenin also may exist in at least two different forms. Cooling of a bulk sample in a similar manner to trilinolein causes solidification in Form II. Form II melts at −44.6° and Form I at −24.2°. While warming curves only are shown in Fig. 1, Form II was indicated also on cooling curves. The transition of Form II to Form I was not as sharply defined as for trilinolein and occurred much more rapidly.

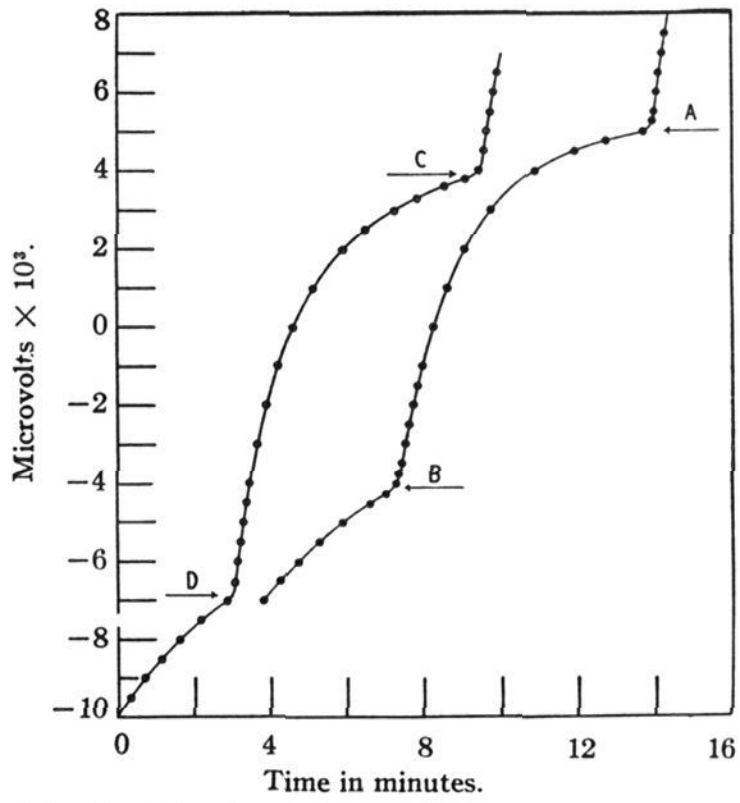


Fig. 3.—Warming curves for 1-monolinolein and 1-monolinolenin: monolinolenin—A, 5000 microvolts = 15.7°; B, 4125 microvolts = −13.5°; monolinolein—C, 3900 microvolts = 12.3°; D, 6875 microvolts = −22.8°.

Warming curves in Fig. 3 indicate the existence of two polymorphic forms for 1-monolinolenin, Form II melting at −13.5° and Form I at 15.7°. As in the case of the triglycerides, Form II was observed visually to melt in bulk sample and sub-

sequently to solidify as Form I at −13.5°. This unsaturated monoglyceride, previously prepared in this Laboratory by Dr. T. R. Wood and one of us (A. R. B.), when exposed for a short time to air at room temperature, quickly developed a film and a decrease in iodine value. The rates of oxidation of the glycerides reported in this paper are being studied and will be reported at a later date.

Two polymorphic forms (Fig. 3) were also found for 1-monolinolein, Form II melting at −22.8 and Form I at 12.3°. While other forms were anticipated for each 1-monolinolein and 1-monolinolenin on the basis of previous experience, evidence for these forms could not be found from thermometric measurements. It is interesting to note that the melting points of both Form II and Form I for 1-monolinolenin are higher than for 1-monolinolein.

Summary

Physical and chemical data are reported for two new synthetic glycerides, 1-monolinolenin and trilinolenin.

Melting point data for the polymorphic forms of 1-monolinolein, 1-monolinolenin, trilinolein and trilinolenin are also reported.

Bromination of 1-monolinolenin and trilinolenin produced two new crystalline bromides.

PITTSBURGH, PA. RECEIVED MARCH 25, 194

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Synthetic Amino Acids. Some Reactions of 3,6-*bis*-(β-Chloroethyl)-2,5-diketopiperazine

BY H. R. SNYDER AND M. E. CHIDDIX[1]

In a continuation of a study[2] of the preparation of amino acids from the easily available 3,6-*bis*-(β - chloroethyl) - 2,5 - diketopiperazine[2b] (I), this substance has been treated with a number of reagents with which it might be expected to react metathetically. In previous work the dichloro compound has been found to react normally with sodium methyl mercaptide and with thiourea. It now has been found that the substance is unexpectedly susceptible to dehydrohalogenation by alkali, a circumstance which may account for the failure of certain projected syntheses depending upon replacement of the chlorine by interaction with alkaline reagents. For example, attempts to prepare the dicyano derivative (a potential glutamic acid intermediate) by treatment of the dichloro compound with alkali cyanides were unsuccessful. Previous treatment of the dichloride with potassium iodide in acetone, to effect replacement of most of the chlorine by iodine, did not improve the reaction, nor did substitution of silver cyanide for the alkali cyanide.

Attempted syntheses of canaline intermediates from the dichlorodiketopiperazine, with or without previous treatment with potassium iodide, and the sodium salt of acetoxime, potassium benzohydroxamate or potassium hydroxylaminedisulfonate likewise were unsuccessful, despite the fact that the closely related reaction of α-benzamido-γ-iodobutyric acid and potassium benzohydroxamate is reported to occur readily.[3]

The dichlorodiketopiperazine reacted readily with sodium hydroxide in refluxing ethanol to form the divinyldiketopiperazine (II). When the chloro compound was present in slight excess the reaction mixture became neutral within twenty to thirty minutes. Although some of the experiments referred to above were carried out after the properties of the divinyl compound were known, the substance was definitely isolated as a product only from the reactions with the sodium salt of acetoxime. However, some of the impure reaction products, from which no unchanged dichlorodiketopiperazine could be recovered, did yield the hydrochloride of α-amino-γ-butyrolactone when subjected to hydrolysis with hydrochloric acid. Both the *bis*-chloroethyl- and divinyldiketopiperazines are converted to the aminolactone by this treatment. In one of the attempted reactions between the dichloro compound and potassium silver cyanide the product isolated was 3,6-*bis*-(β-hydroxyethyl)-2,5-diketopiperazine. This substance also would yield the aminolactone hydrochloride on hydrolysis with hydrochloric acid.

Certain replacements of the halogen atoms in the dichlorodiketopiperazine were effected without difficulty. Piperidine and morpholine gave the corresponding *bis*-tertiary amines (IV and V). The sodium salt of benzylmercaptan reacted to give the *bis*-benzylthioldiketopiperazine (VI). Potassium thiocyanate reacted to give the *bis*-thiocyano derivative (VII) in low yield. Attempts to alkylate acetoacetic ester were unsuccessful.

Experimental

3,6-*bis*-(β-N-Morpholinoethyl)-2,5-diketopiperazine (IV).—A mixture of 5 g. of the dichloride (I) and 15 cc. of morpholine was heated on the steam-bath to 85°. A clear dark solution resulted and the temperature rose to 125°. The mixture was allowed to cool and the crystals were separated by dilution of the liquid portion with ether

(1) Present address, General Aniline and Film Corp., Easton, Pa.

(2) (a) Snyder and Cannon, THIS JOURNAL, **66**, 511 (1944); (b) Snyder, Andreen, Cannon and Peters, *ibid.*, **64**, 2082 (1942).

(3) Kitagawa, *J. Agr. Chem. Soc. Jap.*, **12**, 871 (1936); *C. A.*, **31**, 1362 (1937).