[CONTRIBUTION NO. 370 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Relative Stability of Aromatic and Aliphatic Monoglycerides

BY B. F. DAUBERT AND C. G. KING

Since the early investigations of Fischer[1] and associates, it has been evident that aliphatic β-monoglycerides tend to rearrange to the corresponding α-isomers, but there has been very little information available concerning the factors that accelerate the change, or concerning the relative ease of migration of the acyl group in aromatic β-mono esters.

Helferich and Sieber[2,3] prepared the β-monobenzoate of glycerol from α,α′-di-(triphenylmethyl)-β-benzoylglycerol by treatment with hydrogen bromide in glacial acetic acid, apparently with no evidence of migration. Bergmann and Carter[4] reported no shift of the β-monobenzoate, during treatment with anhydrous hydrogen chloride for drying. Hibbert and Carter,[5] however, observed a rearrangement of the β-monobenzoate, β-*p*-bromobenzoate, and β-*p*-nitrobenzoate to the α-isomers in 0.025 *N* hydrochloric acid during hydrolysis of the benzylidene compounds in 50% alcoholic solution at 80°. Jackson and King[6] observed a complete β- to α-shift of the palmityl group at temperatures as low as −30° when removing (hydrogen bromide in acetic acid) the triphenylmethyl group from the α-trityl ether of 1,2-dipalmitin. In agreement with Helferich and Sieber, however, no shift was observed when the ether group was hydrolyzed from analogous aromatic esters by the use of cold hydrogen bromide–acetic acid solution. Stimmel and King[7] found that β-monopalmitin rearranged quantitatively to the α-isomer on standing for twenty-four hours at room temperature in an alcoholic solution of 0.05 *N* hydrochloric acid or 0.1 *N* ammonium hydroxide. A number of important observations concerning changes in the molecular structure of β-glycerides have been made by Verkade and associates[8] and by Fairbourne.[9]

During the course of the present investigation, in addition to studying the β- to α-changes in molecular structure, α-monopalmitin, and glycerol α-*p*-bromobenzoate were prepared with good yields, using 1,2-benzylidene glycerol as a very satisfactory intermediate for α-ester synthesis. Since the 1,2-type compound is the dominant one obtained by direct condensation, the method is a valuable one to follow in parallel with β-glyceride syntheses.

(1) Fischer, *Ber.*, **53** 1621 (1920).
(2) Helferich and Sieber, *Z. physiol. Chem.*, **170**, 31 (1927).
(3) Helferich and Sieber, *ibid.*, **175**, 311 (1928).
(4) Bergmann and Carter, *ibid.*, **191**, 211 (1930).
(5) Hibbert and Carter, THIS JOURNAL, **51**, 1601 (1929).
(6) Jackson and King, *ibid.*, **55**, 678 (1933).
(7) Stimmel and King, *ibid.*, **56**, 1724 (1934).
(8) Verkade, Van der Lee and Meerburg, *Rec. trav. chim.*, **56**, 365, 613, 716 (1937); Verkade and Van der Lee, *Proc. Roy. Soc. Amsterdam*, **37**, 812 (1934).
(9) Fairbourne, *J. Chem. Soc.*, 369 (1930).

Experimental

Preparation of Esterified Acetals.—1,3-Benzylidene glycerol was prepared essentially by the method of Hibbert and Carter,[5] and purified by crystallization first from a mixture of benzene and heptane (1:1), and then from water.

2-Palmityl-1,3-benzylidene glycerol, m. p. 63.5°, was prepared by the method of Bergmann and Carter.[4] 2-*p*-Bromobenzoyl-1,3-benzylidene glycerol, m. p. 146°, was prepared by the method of Hibbert and Carter.[5]

The benzene–heptane solution remaining after the separation of 1,3-benzylidene glycerol was treated with an excess of silver hydroxide, shaken intermittently over a period of twelve hours, and suction filtered. After removing the benzene and heptane, the oily residue was fractionally distilled at 2 mm., the 1,2-benzylidene glycerol boiling at 139–141°.

To 5 g. of 1,2-benzylidene glycerol there was added 10 cc. of dry pyridine, followed by the slow addition of 7.6 g. of palmityl chloride. After allowing the mixture to stand for thirty minutes, 400 cc. of ice water was added to remove most of the pyridine. The acetal of the β-ester separated as a white solid. After washing with ice water until free from pyridine, and drying in a vacuum desiccator, the 1-palmityl-2,3-benzylidine glycerol was crystallized from absolute alcohol, m. p. 34.5°, yield 10 g. (86%).

Anal. Calcd. for $C_{26}H_{24}O_4$: C, 74.79; H, 10.12. Found: C, 74.57, 74.48; H, 10.06, 10.08.

Bergmann and Carter prepared the same compound by condensing α-monopalmitin with benzaldehyde (m. p. 35°).

1-*p*-Bromobenzoyl-2,3-benzylidene glycerol, m. p. 73°, was prepared from 1,2-benzylidene glycerol as described by Hibbert and Carter (m. p. 72°).

α-Monopalmitin and glycerol α-*p*-bromobenzoate were prepared from the above esterified acetals by the following method, given in detail for α-monopalmitin. Concentrated hydrochloric acid (25 cc.) was added, with cooling, to 8 g. of 1-palmityl-2,3-benzylidene glycerol dissolved in 20 cc. of ether. The α-monopalmitin separated as a white solid, upon the addition of 400 cc. of ice water. It was washed free of acid, dried in a vacuum desiccator, and crystallized from ether several times, m. p. 77°; yield, 7 g. (87%).

Preparation of β-Monoglycerides.—β-*p*-Bromobenzoate and β-monopalmitin were prepared by reduction of the corresponding esterified acetals essentially by the method of Bergmann and Carter, except that in the former case ethyl acetate was used as the solvent. It was found, as reported by Stimmel and King, that 0.5 g. of palladium black was sufficient for the reduction of approximately 10 g. of the esterified acetal.

The β-*p*-bromobenzoate (new) was crystallized twice from ethyl acetate, then from a 1:1 mixture of ether and petroleum ether, as short, colorless, prismatic crystals, m. p. 95.2°; yield, 79.2%.

Anal. Calcd. for $C_{10}H_{11}O_4Br$: Br, 29.06. Found: Br, 29.01, 29.15.

Migration of Acyl Groups.—β-Monopalmitin (0.5 g.) was dissolved in 20 cc. of alcoholic hydrochloric acid of the desired normality. After standing for twenty-four hours at room temperature (22–25°), the solution was cooled until essentially complete crystallization occurred. The crystals were suction filtered and dried in a vacuum desiccator for twenty-four hours, after which the melting points were determined. The same procedure was followed with alcoholic ammonium hydroxide. The β-*p*-bromobenzoate was recovered quantitatively from ether–petroleum ether after removal of the original alcohol under reduced pressure.

Melting Point of Recovered β-Monopalmitin (m. p. 68.5°) (m. p. of α-Monopalmitin, 77°)

Hydrochloric Acid

Normality, *N*	0.1	0.05	0.025	0.01	0.0067	0.005
M. p. of prod., °C.	77	77	66–73	51–73	50–70	68.5

Ammonium Hydroxide

Normality, *N*	0.1	0.05	0.025	0.0125	0.01
M. p. of prod., °C.	77	62–68	61–62	62–65	68.5

Melting Point of Recovered β-*p*-Bromobenzoate (m. p. 95.2°) (m. p. of α-*p*-Bromobenzoate, 74.5°)

Hydrochloric Acid

Normality, *N*	0.1	0.05	0.025	(No change with dilutions up to 0.005 *N*)
M. p. of prod., °C.	74.5	95.1	95.2	

Ammonium Hydroxide

Normality, *N*	0.1	0.05	0.025	(No change with dilutions up to 0.005 *N*)
M. p. of prod., °C.	74.5	95.2	95.2	

To check the effect of moderate heating, melting point tubes were filled partially with β-monopalmitin and β-*p*-bromobenzoate, and the tubes placed in an oven for periods of one, twelve, and twenty-four hours at approximately 7° above their melting points. After removal from the oven all of the tubes were kept at room temperature for twelve hours to permit recrystallization. Neither compound changed sufficiently to alter the melting point within one hour, but both compounds showed a marked drop in melting point after twelve hours. Neither compound changed completely to the α-isomer on prolonged heating.

Preparation of Triglycerides.—1-*p*-Bromobenzoyl-2,3-dipalmitin, m. p. 68.8°, was prepared from palmityl chloride and the above α-*p*-bromobenzoyl ester.[5]

Anal. Calcd. for $C_{42}H_{71}O_6Br$: Br, 10.63. Found: Br, 10.59, 10.51.

The symmetrical isomer, 2-*p*-bromobenzoyl-1,3-dipalmitin, m. p. 50°, was prepared both from the symmetrical dipalmitin and from the β-*p*-bromobenzoyl ester by esterification with the corresponding acyl halide. The two isomers afford another illustration of the reversal of melting point relationship between symmetrical and unsymmetrical mixed triglycerides, in comparing aromatic esters with aliphatic esters. In our experience with the latter type, the symmetrical isomers always had the higher melting point.

Anal. Calcd. for $C_{42}H_{71}O_6Br$: Br, 10.63. Found: Br, 10.54, 10.66.

Solubilities.—It is of interest to note from the data in Table I that the aromatic and aliphatic monoglycerides are reversed in their solubility ratios for α- and β-isomers. In the former case (aromatic) the β-form is less soluble, but α-monopalmitin is less soluble than β-monopalmitin. In an earlier investigation[10] it was found that the unsymmetrical mixed triglycerides of aliphatic acids were distinctly more soluble than the higher melting symmetrical isomers.

TABLE I

SOLUBILITIES OF MONOGLYCERIDES

Compound	Solvent	Temp., ±0.01° C.	Soly., g. per 100 ml.
α-*p*-Bromobenzoate	Ether	26	3.50
β-*p*-Bromobenzoate	Ether	26	3.02
α-*p*-Bromobenzoate	Alcohol	26	16.05
β-*p*-Bromobenzoate	Alcohol	26	4.41
α-Monopalmitin	Ether	25	2.75
β-Monopalmitin	Ether	25	11.15

Summary

The use of 1,2-benzylidene glycerol as an intermediate for the synthesis of α-monoglycerides was found to be satisfactory for both aliphatic and aromatic esters.

Tenth normal hydrochloric acid and ammonium hydroxide in alcoholic solution caused both aromatic and aliphatic monoglycerides to undergo a complete shift from the beta to the alpha position in a short time at room temperature. In more dilute acid or alkali, however, a marked contrast between aromatic and aliphatic β-esters was evident: $N/150$ hydrochloric acid and $N/80$ ammonium hydroxide were about as effective upon an aliphatic ester (β-monopalmitin) as $N/20$ hydrochloric acid and $N/15$ ammonium hydroxide were upon an aromatic ester (β-*p*-bromobenzoate).

Neither aromatic nor aliphatic β-esters exhibited a shift to the α-isomer when held at 7° above their melting points for one hour in the dry state.

The symmetrical and unsymmetrical *p*-bromobenzoyldipalmitins afford another example of a mixed aromatic symmetrical isomer having a

(10) Robinson, Roche and King, THIS JOURNAL, **54**, 705 (1932).

lower melting point than the unsymmetrical isomer, a reversal of the relationship for analogous aliphatic esters.

The aromatic β-monoglyceride was less soluble and had a higher m. p. than the α-isomer, in contrast to the reverse relationship for α- and β-monopalmitins.

PITTSBURGH, PENNA. RECEIVED SEPTEMBER 26, 1938

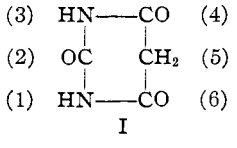
[CONTRIBUTION NO. 142 FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, THE UNIVERSITY OF TEXAS]

The Synthesis of Colored Derivatives of Nirvanol

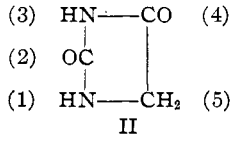
BY JAMES J. SPURLOCK[1] WITH HENRY R. HENZE

Reports are to be found in the literature of attempts to synthesize colored compounds of pronounced physiological activity. Rising[2] and collaborators have extended this type of investigation to the field of barbituric acid derivatives and have produced, from phenobarbital, mono- and dis-azo dyes in which the chromophoric grouping is attached to a phenyl radical linked to the 5-carbon atom of the barbituric acid nucleus. Buck[3] has attacked the same problem from a different angle by producing azo dyes in which the chromophore is attached to a phenyl grouping which replaces hydrogen linked to a nitrogen atom in the 1-position of the nucleus.

The definite structural similarity of barbituric acid (I) and hydantoin (II) is well known, as is

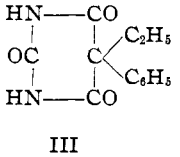


I

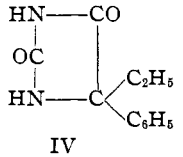


II

also the close analogy in the existence of compounds derived from substitution of identical groupings for the hydrogen atoms in the 1-, 3- and 5,5-positions of both heterocycles. Likewise, in at least one instance, substitution of ethyl and phenyl for the hydrogens attached at the 5,5-positions in both nuclei has produced useful sedatives, namely, phenobarbital (III) and nirvanol (IV), respectively. It seemed of interest, therefore, to attempt to convert nirvanol into azo dyes whose pharmacological properties might be studied subsequently.



III



IV

Nirvanol was nitrated and yielded a material whose behavior during recrystallization indicated it to be a mixture, and a pure mononitro derivative was not obtained even after ten recrystallizations. Although this mixture could be reduced catalytically, fractional crystallization proved to be unsatisfactory as a means of separating the isomeric amines formed.

Since the structure of these products, obtained from nirvanol by nitration and subsequent reduction, was uncertain, it appeared best to approach this problem from simpler compounds of established structure. Following the nitration of propiophenone, the meta derivative[4] was separated readily from its alkali-insoluble isomers and converted into 5-*m*-nitrophenyl-5-ethylhydantoin by means of the procedure of Bucherer.[5] In turn, the nitrated hydantoin was reduced in the presence of the Adams catalyst, the anticipated *m*-amine crystallizing from water as a monohydrate.

The 5-*m*-aminophenyl-5-ethylhydantoin has been diazotized and coupled with β-naphthol, β-naphthylamine, dimethylaniline and G Salt, respectively, to form azo compounds. The dyes derived from β-naphthylamine and from dimethylaniline dye wool and silk from either acid or alkaline solution; that derived from 2-naphthol-6,8-disulfonic acid dyes only from acid solution. The azo derivative of β-naphthol possesses no dyeing properties from either alkaline solution or glacial acetic acid solution.

Experimental

Nitration of Phenylethylhydantoin.—Phenylethylhydantoin was prepared according to the method of Bucherer[5]

(1) Presented before the Division of Medicinal Chemistry at the 95th meeting of the American Chemical Society, April 18 to 21, 1938, at Dallas, Texas.

(2) (a) Rising, Shroyer and Stieglitz, THIS JOURNAL, **55**, 2818 (1933); (b) Pierce and Rising, *ibid.*, **58**, 1361 (1936).

(3) Buck, *ibid.*, **59**, 1249 (1937).

(4) Comanducci and Pescitelli, *Gazz. chim. ital.*, **36**, II, 787 (1906).

(5) Bucherer and Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).