the nitrogen analysis. Table II contains the data on these preparations.

Summary

Pfitzinger's method has been extended to include the utilization of alkoxyaryloxyacetones in the synthesis of ten substituted quinoline acids from isatin and 5-methylisatin, respectively.

ATLANTA, GEORGIA RECEIVED SEPTEMBER 5, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE]

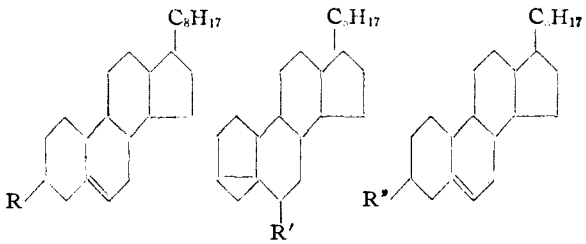
Some Reactions of Cholesteryl *p*-Toluenesulfonate[1]

BY HERBERT MCKENNIS, JR.

In a continuation of studies[2] on the relationship of the structure of cholesterol to its ability to promote growth of *Attagenus* larvae, a number of cholestene derivatives were desired. Cholesteryl *p* toluenesulfonate has been employed successfully in the preparation of 3-alkoxycholestenes,[3] 3-iodocholestene,[4] and a number of other derivatives.

The facile preparation of cholesteryl ethers by refluxing solutions of the *p*-toluenesulfonyl ester of cholesterol in an excess of various alcohols suggested the study of the possible reaction with corresponding mercaptans. This was of interest as a possible synthetic route to thioethers of cholesterol. Additional knowledge of the reactivity of cholesteryl *p*-toluenesulfonate was also desirable since we had planned to study the effect of this compound upon the growth of larvae.

Since *n*-propyl mercaptan has a boiling point quite close to that of methyl alcohol the former was selected for a preliminary study. Attempts to bring about the reaction of cholesteryl *p*-toluenesulfonate (I) with an excess of the mercaptan at reflux temperature for short periods were unsuccessful. After a three-hour period the ester was recovered in quantitative yield. Under similar conditions methanol reacts readily and cholesteryl methyl ether (IIIa) is easily obtained.



I II III

I R = $-OSO_2C_6H_4CH_3$ IIc R′ = $-CH(COOH)_2$
IIa R′ = $-OCH_3$ IIIa R″ = $-OCH_3$
IIb R′ = $-OOCCH_3$ IIIb R″ = $-CH(COOH)_2$

One suggested reason for the marked difference in reactivity was the more strongly acidic character of the thioalcohol. That this alone cannot explain the results is clearly shown in experiments in which thiophenol and benzyl mercaptan were the alcohols employed. Thiophenol, kindly supplied by Dr. E. Emmett Reid, reacted readily with the tosyl ester to yield a bis-(phenylthio)-compound which is tentatively assigned the structure of 3,5-bis-(phenylthio)-cholestane. Benzyl mercaptan also reacted. The product in this instance was not, however, obtained in pure condition.

In view of the marked differences in reactivity observed it became desirable to know whether or not *n*-propyl alcohol itself would react under conditions drastic enough for the seemingly quantitative reaction with methanol, but not sufficiently drastic or prolonged for significant reaction with *n*-propyl mercaptan. The reaction with *n*-propanol under comparable conditions proceeded readily, and cholesteryl *n*-propyl ether was obtained in good yield.

In contrast to the marked reactivity of cholesteryl *p*-toluenesulfonate with methanol, propanol, thiophenol, and benzyl mercaptan at temperatures below 70°, the ester appeared not to react at all when heated with an excess of benzylamine at 70° for two hours. At reflux temperature (185°) reaction took place with the formation of an N-benzylamino compound which is assigned the quasi-committal name, N-benzylcholesterylamine, in accordance with the precedential designation, N-phenylcholesterylamine, for the product obtained by the analogous reaction of aniline and cholesteryl *p*-toluenesulfonate.[5] Under alkaline conditions cholesteryl *p*-toluenesulfonate reacts with methanol[3a] and other alcohols[3b] to give ethers, isomeric with the compounds obtained in the absence of alkali, for which structure IIa has been proposed.[6] Wagner-Jauregg and Werner[7] have found that a comparable situation obtains when cholesteryl chloride or bromide is heated with methanol. When the reaction was carried out in the presence of potassium acetate, *i*-cho-

(1) Aided by a grant from the John and Mary R. Markle Foundation.

(2) McKennis, *J. Biol. Chem.*, **167**, 645 (1947).

(3) (a) Stoll, *Z. physiol. Chem.*, **207**, 147 (1932); (b) Beynon, Heilbron and Spring, *J. Chem. Soc.*, 907 (1936).

(4) Helferich and Gunther, *Ber.*, **72**, 338 (1939).

(5) (a) Bátyka, *Magyar Biol. Kutató Inézet Munkái*, **13**, 334 (1941); *C. A.*, **36**, 484 (1942); (b) Müller and Bátyka, *Ber.*, **74**, 705 (1941).

(6) Wallis, Fernholz and Gephart, THIS JOURNAL, **59**, 137 (1937); see also, Ford and Wallis, *ibid.*, **59**, 1415 (1937); Ford, Chakravorty and Wallis, *ibid.*, **60**, 413 (1938); and Butenandt and Suranyi, *Ber.*, **75**, 591 and 597 (1942), for additional evidence in support of this structure.

(7) Wagner-Jauregg and Werner, *Z. physiol. Chem.*, **213**, 119 (1932).

lesteryl methyl ether (IIa) was obtained, the normal ether being formed when no potassium acetate was present. The further observation that the iso compound was transformed slowly when heated with methanol and one equivalent of hydrogen chloride at 130° to the normal ether (IIIa) led to the suggestion by them that the iso compound is first formed and then, if no base is present, it is converted under the influence of liberated acid to the normal ether.

We have found that *i*-cholesteryl methyl ether in methanol containing *p*-toluenesulfonic acid is converted to IIIa in good yield at reflux temperature within three hours. Since the conditions used here were similar to those ordinarily employed for the direct preparation of the normal compound from the tosyl ester, the comparatively rapid conversion in this instance affords additional support to the conception of Wagner-Jauregg and Werner. In view of this corroboration it would be interesting to study the possible catalytic action of acids on reactions of the tosyl ester with amino and sulfhydryl compounds.

It is interesting that under certain conditions derivatives of both cholesterol and *i*-cholesterol can be obtained from cholesteryl *p*-toluenesulfonate. Beynon, Heilbron and Spring[3a] isolated cholesteryl benzyl ether and *i*-cholesteryl benzyl ether from the mixture obtained by reaction of cholesteryl *p*-toluenesulfonate with benzyl alcohol in the presence of potassium acetate. Kaiser and Svarz[8] noted that the mixture from the reaction of cholesteryl *p*-toluenesulfonate with sodiomalonic ester contained a number of cholesterol derivatives. Two compounds obtained from the saponified reaction mixture were assigned tentatively structures IIIb, 3-cholesterylmalonic acid, and IIc, *i*-cholesterylmalonic acid.[9] The latter and its methyl ester were found to give a negative Liebermann–Burchard test while the former responded positively.[9]

Wallis, Fernholz and Gephart[6] have reported the conversion of *i*-cholesteryl acetate (IIb) to cholesteryl acetate by treatment with acid, and also have described the conversion of *i*-cholesterol, which gives a positive Liebermann–Burchard reaction,[10] to a normal cholesterol derivative. *i*-Cholesteryl methyl ether which in methanolic solution can be converted to the normal ether in the presence of acid catalyst, was found in our study to give a positive Liebermann–Burchard reaction.

The positive Liebermann–Burchard reactions of *i*-cholesterol and *i*-cholesteryl methyl ether can, in view of the demonstrated conversions of iso to normal compounds, be tentatively ascribed to formation of Δ^5-3-cholestenyl derivatives which take place under the acidic conditions of the Liebermann–Burchard test and precede the development of color. In contrast, since 3-cholesterylmalonic acid gives a positive test and *i*-cholesterylmalonic acid gives a negative test, it can be assumed that the latter yields no Δ^5-3-cholestenyl derivative under the test conditions. These interpretations appear to be consistent with the known limited specificity of the Liebermann–Burchard reaction.

(8) Kaiser and Svarz, THIS JOURNAL, **67**, 1309 (1945).

(9) Svarz and Kaiser, *ibid.*, **69**, 847 (1947).

(10) Eck and Thomas, *J. Biol. Chem.*, **128**, 267 (1939).

Experimental[11]

3,5-bis-(Phenylthio)-cholestane.—A mixture of 4.50 g. of cholesteryl *p*-toluenesulfonate and 24 cc. of thiophenol was heated at 50° for two hours. The ester went into solution quickly and, in time, white crystals formed. These, presumably *p*-toluenesulfonic acid, were hygroscopic and insoluble in benzene. Excess thiophenol was removed by shaking the mixture or its ethereal solution exhaustively with 2 *N* potassium hydroxide. The oily product was dissolved in 40 cc. of hot alcohol containing enough chloroform to completely solubilize the product. The solution, on cooling to room temperature, deposited white prisms, m. p. 180–184°. A solution of the product in a minimal amount of hot chloroform was diluted to a volume of 125 cc. with 95% ethanol. The yield of glistening white product, m. p. 186–186.5°, was 2.34 g.

Anal. Calcd. for $C_{39}H_{56}S_2$: C, 79.51; H, 9.59; S, 10.89. Found: C, 79.58; H, 9.65; S, 11.30; $[\alpha]^{25}D$ −127°, *c* 1.71, carbon tetrachloride.

Benzyl mercaptan reacted with the ester under the above conditions. Crystals of alleged *p*-toluenesulfonic acid were formed. After removal of acid and excess benzyl mercaptan an oil remained. This gave strong qualitative tests for sulfur, but failed to crystallize from the usual solvents.

N-Propyl Cholesteryl Ether.—A solution of 0.500 g. of cholesteryl *p*-toluenesulfonate in 30 cc. of *n*-propyl alcohol was heated at 62–63° for three hours. The solution was cooled and 8 cc. of water was added. The crude ether, m. p. 99°, weighed 346 mg. (87% of the calculated amount). A small additional amount of ether was obtained by further dilution of the mother liquor. N-Propyl cholesteryl ether prepared by other methods has been reported to melt at 99.5–100°[12], 100°[13], and at 100–100.5°[14].

When the above components were heated at 50° for two hours, a product was obtained which melted over a wide range and contained unreacted ester.

N-Benzylcholesterylamine.—A solution of 1.00 g. of cholesteryl *p*-toluenesulfonate in 6 cc. of benzylamine, protected by a sodalime tube, was heated under reflux for three hours. The mixture was diluted with 100 cc. of ether and washed with water until no more benzylamine could be extracted. The ethereal solution was dried over anhydrous sodium sulfate and then concentrated to an oil. The oily residue was dissolved in a minimal amount of acetone and diluted with 95% ethanol until a faint turbidity was produced. The solution was cooled. The yield of crude product, m. p. 110–118°, was 0.500 g. After one recrystallization from acetone the compound melted at 118–119°. *Anal.* Calcd. for $C_{34}H_{53}N$: C, 85.82; H, 11.23; N, 2.94. Found: C, 86.06; H, 10.61; N, 3.12; $[\alpha]^{28}D$ −25.1°, *c* 2.15, chloroform.

N-Acetyl-N-benzylcholesterylamine.—A mixture of 1.00 g. of N-benzylcholesterylamine, 34 cc. of ether, and 1 cc. of acetic anhydride was heated under reflux for thirty minutes and then concentrated to a volume of 15 cc. The product, m. p. 152–153°, was obtained as clusters of needles. The yield was 0.91 g. (84% of calculated amount). An additional crop was obtained by concentrating the mother liquor. For analysis the derivative was recrystallized several times from ethyl acetate. The melting point was unchanged. *Anal.* Calcd. for $C_{36}H_{55}NO$: C, 83.50;

(11) Microanalyses by the Oakwold Laboratories, Alexandria, Virginia.

(12) Diels and Blumberg, *Ber.*, **44**, 2847 (1911).

(13) Bills and McDonald, *J. Biol. Chem.*, **72**, 1 (1927).

(14) Muller and Page, *ibid.*, **101**, 127 (1933).

H, 10.71. Found: C, 83.63; H, 10.72; $[\alpha]^{25}D$ −8.6°, *c* 0.934, carbon tetrachloride.

N-Benzylcholesterylamine Hydrochloride.—Dry hydrogen chloride was passed into a solution of 70 mg. of N-benzylcholesterylamine in 20 cc. of absolute ether until no more gelatinous precipitate formed. The salt was obtained in granular form by recrystallization from methanol containing a little hydrochloric acid. The hydrochloride melted with decomposition above 300°. *Anal.* Calcd. for $C_{34}H_{53}N \cdot HCl$: Cl, 6.92. Found: Cl, 6.59.

Cholesteryl Methyl Ether from *i*-Cholesteryl Methyl Ether.—To a solution of 100 mg. of *p*-toluenesulfonic acid monohydrate in 36 cc. of methanol was added 300 mg. of *i*-cholesteryl methyl ether. The mixture was heated under reflux for two hours and then concentrated under diminished pressure to a volume of approximately 25 cc. When the solution was chilled the product separated. It was collected and washed with a small volume of cold methanol. The yield was 279 mg. (93% of the calculated amount). The melting point, 84°, which is in agreement with reported values, was not depressed by admixture of authentic cholesteryl methyl ether.

Summary

1. The comparative reactivity of several mercaptans, alcohols, and benzylamine with cholesteryl *p*-toluenesulfonate has been studied in a qualitative manner. Under conditions favorable for the reaction of methanol and propanol with the formation of the corresponding cholesteryl ethers, *n*-propyl mercaptan, and benzylamine fail to react appreciably. Thiophenol and benzyl mercaptan react readily with cholesteryl *p*-toluenesulfonate.

2. The positive Liebermann–Burchard reaction of *i*-cholesterol and of *i*-cholesteryl methyl ether has been interpreted in the light of the known reactions of these compounds under acidic conditions, while the negative reaction of the analogous *i*-cholesterylmalonic acid has been tentatively ascribed to the inability of the latter to yield appreciable amounts of Δ^5-3-cholestenyl derivative under the Liebermann–Burchard test conditions.

3. The preparation of bis-(phenylthio)-cholestane, and of N-benzylcholesterylamine and derivatives have been described.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MARYLAND]

N,N-Dialkyl-β-hydroxyamides via the Reformatsky Reaction[1,2]

BY NATHAN L. DRAKE, CHARLES M. EAKER[3] AND WILBUR SHENK[4]

When it seemed desirable to prepare certain N,N-dialkyl-β-hydroxyamides for testing as potential insect repellents, the use of the Reformatsky reaction[9] involving N,N-dialkyl-α-haloamides suggested itself as a direct approach to the desired compounds. The present paper records the results of a study which demonstrated that N,N-dialkyl-α-haloamides can be substituted for α-bromoesters in the Reformatsky reaction with little loss in yield.

TABLE I

N,N-DISUBSTITUTED-α-HALO AMIDES

Compound	Yield, %	Formula	B. p. °C.	Mm.	Analyses,[a] % Calculated C	Calculated H	Calculated Br	Found C	Found H	Found Br
N,N-Diethylbromoacetamide[5]	74	$C_6H_{12}BrNO$	89–90	1.0						
N,N-Dipropylbromoacetamide	48	$C_8H_{16}BrNO$	98–100	2.0						
N,N-Diisopropylbromoacetamide	45	$C_8H_{16}BrNO$	70–71	0.3						
			(m. p. 65.3–66.5)		43.24	7.21		43.40	7.32	
N,N-(Mixed)-diamylbromoacetamide	71	$C_{12}H_{24}BrNO$	128–129	0.7	51.80	8.63		51.57	8.42	
N,N-Diethyl-α-bromopropionamide	77	$C_7H_{14}BrNO$	74	0.2			38.46			38.83
N,N-Diethyl-α-bromocaproamide	56	$C_{10}H_{20}BrNO$	77–78	0.1	48.00	8.00		47.93	7.97	
N-Methyl-α-bromoacetanilide[6]	75	$C_9H_{10}BrNO$	M. p. 46.8–47.3		47.37	4.39	35.07	47.40	4.67	34.98
N-Ethyl-α-bromoacetanilide	73	$C_{10}H_{12}BrNO$	125–127	0.2	49.59	4.97		49.49	5.09	
N,N-Diethylchloroacetamide[7]	80	$C_6H_{12}ClNO$	117–118	17						
N-Methyl-α-chloroacetanilide[8]	80	$C_9H_{10}ClNO$	M. p. 69–70							

[a] Microanalyses by Miss E. Werble.

Miller and Johnson[5] have reported the preparation of N,N-diethylbromoacetamide (20% yield) by allowing diethylamine to react with bromoacetyl bromide in aqueous alkali. However, it is

(1) The initial phases of this research were conducted under a contract recommended by the National Defense Research Committee between the University of Maryland and the office of Scientific Research and Development. The greater part of the work was done after the expiration of the contract.

(2) From a thesis presented by C. M. E. in partial fulfillment of the requirements for the Ph.D. degree, June 1946.

(3) Present address: Monsanto Chemical Co., St. Louis, Mo.

(4) Present address: Harshaw Chemical Co., Cleveland, Ohio.

(5) Miller and Johnson, *J. Org. Chem.*, **1**, 139 (1936).

(6) Bischoff, *Ber.*, **34**, 2125 (1901), reported a preparation of N-methyl-α-bromoacetanilide for which a melting point of 69° is given.

(7) Jacobs and Heidelberger, *J. Biol. Chem.*, **21**, 149 (1915).

(8) Jacobs and Heidelberger, *ibid.*, **21**, 105 (1915).

(9) Roger Adams, ed., "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 1.