that of the optically active ethers from which it was prepared.

Partial racemization always accompanied this change. This fact is significant in view of the absence of racemization observed in this Laboratory in rearrangements of the Curtius, Hofmann and Lossen types.

A discussion of these facts is given in the light of certain mechanisms for the reaction.

PRINCETON, N. J. RECEIVED FEBRUARY 16, 1934

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Some Thiomorpholine Derivatives[1]

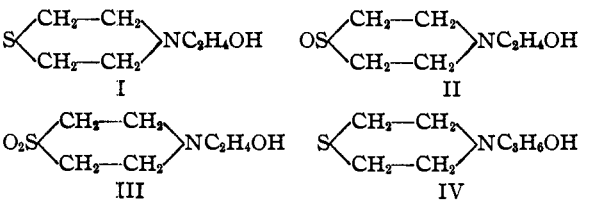
BY LAWTON A. BURROWS[2] AND E. EMMET REID

Introduction

In view of the local anesthetic activity and low toxicity of the esters of β-4-morpholine-ethanol and γ-4-morpholine-propanol,[3] it was thought that a study of the preparation and properties of analogous compounds in which the oxygen of the morpholine ring is replaced by sulfur should be of interest. Several investigators[4] have prepared derivatives of thiomorpholine but little attention has been paid to their pharmacological properties. Derivatives from amino alcohols have not been described.

Preparation

Thiomorpholine-4-ethanol, I; its oxide, II and its dioxide, III; Thiomorpholine γ-4-propanol, IV.



I II III IV

I.—A solution of one mole of β,β′-dibromodiethyl sulfide in 1500 cc. of benzene was placed in a three-necked flask fitted with a reflux condenser and mechanical stirrer. Three moles of monoethanolamine[5] was added slowly. The reaction mixture was warmed on the steam-bath for six hours with constant stirring. After cooling, it was filtered through dry cotton and the residue was extracted three times with 200-cc. portions of benzene. The combined extracts were added to the original filtrate and dry hydrogen chloride was bubbled through the solution until precipitation was complete. The hydrochloride was recrystallized from 95% alcohol; yield 43.5% of theoretical.

II.—The procedure was exactly the same as in the preparation of I except that the solution of β,β′-dibromodiethyl sulfoxide was cooled to 20° during the addition of the amino alcohol and then warmed on the steam-bath for three hours; yield 45% of theoretical.

III.—The general procedure was the same as for I but chloroform was used as a solvent due to the insolubility of III in benzene. The solution of β,β′-dibromodiethyl sulfone was cooled in ice water during the entire addition of the monoethanolamine. The reaction was then allowed to run for one hour at room temperature and two hours on the steam-bath; yield 58% of theoretical.

IV.—A mixture of 32.5 g. of γ-propanolamine in 150 cc. of chloroform and 35.8 g. of β,β′-dibromodiethyl sulfide was heated on the steam-bath four hours. The hydrobromide of the amino alcohol which was formed in the reaction was filtered off and 15.5 g. of γ-propanolamine was recovered from it. The hydrochloride of IV was precipitated from the filtrate by dry hydrogen chloride and recrystallized from 95% alcohol: yield 42% of theoretical.

In the preparation of I, II, III and IV, it was found that much better yields were obtained and the products were more easily isolated when three moles of the amine were used to one of the dibromo compound instead of using only one mole of amine and sodium acetate or sodium carbonate to take up the hydrogen bromide liberated in the reaction. It was also found essential to use a non-polar solvent and isolate the products as their hydrochlorides instead of as the free bases. The use of alcohol as a solvent led to very poor yields. The above condensations were also tried using β,β′-dichlorodiethyl sulfide, sulfoxide and sulfone, but the corresponding β,β′-dibromo compounds gave much better yields.

Aliphatic Esters of I, II and III

I.—The aliphatic esters of I from the acetate to the heptoate inclusive were prepared by warming 10 g. of the hydrochloride of I with an excess of the proper acid chloride or anhydride until solution took place. The reaction mixture was then heated to 125° for ten minutes and poured with stirring into cold ether. The crystals were filtered, washed several times with ether and recrystallized from 95% alcohol. Yields in all cases were 90 to 95% of the theoretical.

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(1) Abstract of dissertation submitted by Lawton A. Burrows in partial fulfilment of requirements for the degree of Doctor of Philosophy in Chemistry at The Johns Hopkins University, Baltimore, Maryland. Read in preliminary form at the Chicago meeting of the American Chemical Society, September, 1933.

(2) William R. Warner & Co., Inc., Fellow 1931–34.

(3) J. H. Gardner and E. O. Haenni, THIS JOURNAL, **53**, 2767 (1931); J. H. Gardner, D. V. Clarke and Joseph Semb, *ibid.*, **55**, 2999–30 (1933).

(4) Clarke, *J. Chem. Soc.*, **101**, 1538 (1912); Davies, *ibid.*, **117**, 297 (1920); Helfrich and Reid, THIS JOURNAL, **42**, 1208 (1920); Cashmore and McCombie, *J. Chem. Soc.*, **123**, 2884 (1923); Lawson and Reid, THIS JOURNAL, **47**, 2821–2836 (1925); Alexander and McCombie, *J. Chem. Soc.*, 1913–1918 (1931).

(5) The monoethanolamine used in this investigation was generously furnished by the Carbide and Carbon Chemicals Corp.

I is a white crystalline solid but all of its aliphatic esters are colorless viscous oils. I and its acetate are water soluble, the propionate slightly soluble but the higher esters are insoluble in water. They are readily soluble in alcohol, chloroform, ether and benzene. These compounds are sufficiently stable to be distilled at 15 mm. pressure. On cooling they form glassy solids which are difficult to crystallize. The hydrochlorides of this series are white crystalline solids with sharp melting points. They are quite stable when protected from moisture and have been kept for a year without decomposition. All of these hydrochlorides are soluble in cold water and hot alcohol.

II.—The aliphatic esters of II from the acetate to the heptoate inclusive were prepared by warming 10 g. of II with a 10% excess of the acid anhydride for ten minutes at 120°. The reaction mixture was dissolved in ether and dry hydrogen chloride was passed through the solution until precipitation was complete. The hydrochlorides of the esters usually came down as oils and sometimes required several hours for crystallization. They were washed thoroughly with ether and recrystallized from absolute alcohol. Yields ran from 50% for the lower members of the series up to 60% in case of the heptoate. Attempts to prepare esters of II using acid chlorides failed. Purple residues were obtained from which none of the esters could be isolated.

The aliphatic esters of II are viscous oils while II is a white crystalline solid. The members of series II are slightly more soluble in water and slightly less soluble in alcohol than those of series I. The hydrochlorides are all white crystalline solids. Unlike those of series I, however, they do not melt sharply, decomposing as they melt. They are all water soluble and very soluble in alcohol, making them difficult to recrystallize and purify.

The compounds of series II are comparatively unstable, the hydrochlorides becoming gummy after two or three months. The free bases gradually darken on standing and decompose if heated.

III.—These from the acetate to the heptoate, inclusive, were best prepared exactly as the esters of II, but were also prepared by the method used for the esters of I. The hydrochlorides crystallized readily and were recrystallized from 95% alcohol. Yields were 90 to 95% of theoretical in all cases.

The bases and hydrochlorides of series III are quite similar to those of series I. In general their melting points are higher, they are more soluble in water and less soluble in alcohol and benzene than the compounds of series I. They are more stable toward heat than those of series II but less stable than those of series I. Boiling points cannot be determined due to decomposition.

All the esters and the four alcohols were separated as free bases, by suspending the purified hydrochlorides in chloroform, bubbling dry ammonia gas through the suspension, filtering free of ammonium chloride and evaporating the solvent under reduced pressure over solid potassium hydroxide.

Aromatic Esters

Benzoate of I.—The Schotten–Baumann reaction was used and gave 60% yield. The hydrochloride of the ester was also prepared by refluxing the hydrochloride of I with excess benzoyl chloride until all of the hydrochloride dissolved. The reaction mixture was poured into ether and filtered. The hydrochloride of the ester was washed several times with ether and recrystallized from 95% alcohol: yield 80% of theoretical.

***p*-Nitrobenzoate of I.**—A mixture of 10 g. of the hydrochloride of I and 12 g. of *p*-nitrobenzoyl chloride was melted and heated on the hot-plate until no more gas was evolved. After cooling the resulting mass was washed with chloroform to remove unreacted acid chloride, dried, and then washed with water to remove unreacted I. The hydrochloride was dissolved in 200 cc. of boiling water and ammonium hydroxide added until the solution was slightly alkaline. The ester was filtered, washed with hot water and recrystallized from 95% alcohol: yield 84% of theoretical.

***p*-Aminobenzoate of I.**—An excess of granulated zinc was added to a solution of 3 g. of the *p*-nitrobenzoate in 30 cc. of 30% acetic acid. The mixture was boiled gently for forty minutes, filtered and diluted with 150 cc. of water. The solution was cooled to 0° and ammonium hydroxide added until zinc hydroxide just started precipitating. The ester precipitated as a light yellow gummy mass and was recrystallized from 60% alcohol: yield 50% of the theoretical. The dihydrochloride was prepared by dissolving the ester in concentrated hydrochloric acid and adding 95% alcohol to precipitate the dihydrochloride.

Benzoates of III and IV.—Prepared exactly as benzoate of I. The Schotten–Baumann method gave 50% yield. The other method gave 80% yield for III and 85% for IV.

***p*-Nitrobenzoates of III and IV.**—Prepared as corresponding ester of I: yield 82% of theoretical for III and 86% for IV.

***p*-Aminobenzoate of III.**—An excess of granulated zinc was added to a solution of 3.3 g. of the *p*-nitrobenzoate of III in 30 cc. of 30% acetic acid. The solution was gently boiled until practically all of the acetic acid had reacted (about forty minutes) and then filtered. On cooling to 0° the ester separated and was recrystallized from 95% alcohol: yield 74% of theoretical. The dihydrochloride of the ester was prepared exactly as that of the corresponding ester of I.

***p*-Aminobenzoate of IV.**—Water was added to a solution of 2 g. of the *p*-nitrobenzoate in 50 cc. of alcohol until it became cloudy. Sodium hydrosulfite was added slowly with shaking and the reaction mixture was kept slightly alkaline by adding sodium carbonate. A bright reddish-purple color was noticed as the reduction passed through the azo stage. When all color disappeared, the solution was made strongly alkaline with sodium carbonate and extracted three times with 50-cc. portions of chloroform. The chloroform was evaporated, the *p*-aminobenzoate taken up in 5 cc. of alcohol, diluted with 50 cc. of ether and dry hydrogen chloride passed through the solution until precipitation was complete. The dihydrochloride was recrystallized from 95% alcohol: yield 50% of theoretical.

All attempts to prepare aromatic esters of II have failed.

The benzoates and *p*-nitrobenzoates are white crystalline solids soluble in alcohol and chloroform. Their hydrochlorides are only slightly soluble in cold water and alcohol. The *p*-aminobenzoates are light yellow when first prepared but darken on standing. They are soluble in alcohol, ether, chloroform, etc. Their dihydrochlorides

TABLE I

Compound	Series	M. p. (corr.), °C. Base	M. p. (corr.), °C. Hydrochloride	B. p. (corr.), °C. 15 mm.	B. p. (corr.), °C. 757 mm.	Density 0/4	Density 25/4	Refract. index at 25°
Alcohol	I	35.5	162–163	130 (10 mm.)				
	II	45	173–174					
	III	54	175.5					
	IV	55	188					
Acetate	I	..	149.5	144	269	1.1247	1.1107	1.4990
	II	..	135–136					
	III	22.3	147			1.3161	1.2965	1.4852
	IV	..	145					
Propionate	I	− 1.0	132.6	155	277.7	1.1000	1.0841	1.4948
	II	..	161–162					
	III	43–44	183–184			1.2502	1.2356	Solid
Butyrate	I	..	129	166	284.7	1.0778	1.0615	1.4912
	II	..	158.5					
	III	21.6	146			1.1997	1.1841	1.4840
Valerate	I	..	128.3	176.6	291	1.0588	1.0427	1.4883
	II	..	149–150					
	III	25	144			1.1666	1.1523	1.4823
Caproate	I	..	121.5	186.8	297	1.0425	1.0290	1.4861
	II	..	140					
	III	25	141–142			1.1610	1.1443	1.4845
Heptoate	I	..	118.6	196.6	...	1.0285	1.0159	1.4849
	II	..	156–157					
	III	27	142.5			1.1529	1.1369	1.4830
Benzoate	I	66–67	224					
	III	125.5	174					
	IV	..	183.5					
p-Nitrobenzoate	I	63	219					
	III	167	222					
	IV	77	218					
p-Aminobenzoate	I	136	237 (dihydrochloride)					
	III	148.6	238 (dihydrochloride)					
	IV	..	219 (dihydrochloride)					

form light tan crystals soluble in water and alcohol. They do not melt sharply, decomposing with the evolution of gas.

β,β′-Dibromodiethyl Sulfide, V, Sulfoxide, VI, and Sulfone, VII[6]

V.—A mixture of 976 g. of thiodiglycol and 400 cc. of water was cooled in ice and saturated with hydrogen bromide. The reaction mixture was then warmed to about 80° and more hydrogen bromide gas passed in until the reaction was complete. On cooling V solidified in the bottom of the flask. The aqueous layer was poured off, the solid product washed with cold water and recrystallized from ether: yield 95% of theoretical, melting point 32–34°.

VI.—To 992 g. of V in a three-liter flask fitted with a dropping funnel and reflux condenser and cooled to 0°, 1500 cc. of concentrated nitric acid was added slowly with shaking. The reaction was quite violent at first and about one hour was required for the addition of the first 250 cc. of acid. The remainder of the acid was added, 250 cc. at a time, at thirty-minute intervals. The reaction mixture was allowed to come to room temperature and was then left overnight. The products were poured slowly with vigorous stirring into four liters of water. VI settled out, was washed several times with water and recrystallized from 95% alcohol: yield 70% of theoretical, melting point 100°.

VII.—A mixture of 500 g. of V and 2500 cc. of water, 182 g. of chromic acid and 240 cc. of concentrated sulfuric acid was heated on the steam-bath for six hours. The solution was cooled and VII filtered off. It was washed free of chromium salts with hot water and recrystallized from 95% alcohol: yield 70% of theoretical, melting point 111–112°.

The relative ease of reaction of V, VI and VII with primary amines is the same as that found by Cashmore and McCombie[4] for the corresponding β,β′-dichloro compounds. Addition of a solution of monoethanolamine in chloroform to a solution of VII in chloroform produced sufficient heat to cause the solvent to boil. Direct addition of the amine to dry VII produced enough heat to char the products. When chloroform solutions of VI and monoethanolamine are mixed, a noticeable rise in temperature

(6) Steinkopf, Herold and Stohr prepared β,β′-dibromodiethyl sulfide from thiodiglycol and phosphorus tribromide, *Ber.*, **53B**, 1007–1012 (1920). Lewin and Tschulkoff prepared the sulfoxide and sulfone by oxidation of the sulfide with perbenzoic acid, *J. prakt. Chem.*, **128**, 171 (1930).

TABLE II

ANALYSES

Compound	Series	Sulfur analyses, % Base Calcd.	Base Found	Hydrochloride Calcd.	Hydrochloride Found	Chlorine analyses, % Calcd.	Chlorine Found
Alcohol	I	21.70	21.89	17.36	17.25	19.30	19.27
	II			16.02	16.10	17.80	17.90
	III	17.87	17.99	14.90	15.10	16.50	16.52
	IV			16.15	16.36	17.92	18.05
Acetate	I	16.93	16.71	14.21	14.40	15.75	15.73
	II			13.25	13.41	14.72	14.75
	III	14.48	14.61	12.45	12.60	13.80	14.01
	IV					14.80	14.85
Propionate	I	15.75	15.51	13.37	13.59	14.81	14.60
	II			12.54	12.74	13.90	13.65
	III	13.05	13.27	11.82	12.10	13.28	13.10
Butyrate	I	14.73	14.85	12.62	12.34	14.00	13.80
	II			11.90	12.28	13.38	13.05
	III	12.85	12.82	11.18	10.96	12.45	12.28
Valerate	I	13.87	14.12	11.98	11.72	13.28	13.22
	II			11.32	11.65	12.52	12.45
	III	12.16	12.37	10.80	11.05	11.85	11.70
Caproate	I	13.08	13.31	11.38	11.67	12.62	12.58
	II			10.76	10.92	12.52	12.45
	III	11.55	11.81	10.25	10.58	11.33	11.28
Heptoate	I	12.37	12.52	10.85	11.05	12.01	11.94
	II			10.27	10.47	11.40	11.55
	III	11.00	11.30	9.79	10.01	10.85	10.92
Benzoate	I	12.73	12.48	11.17	11.42	12.36	12.35
	III	11.31	11.35	10.03	10.21	11.12	11.05
	IV					17.76	11.88
p-Nitrobenzoate	I	10.81	11.10	9.62	9.81	10.67	10.50
	III	9.78	10.04	9.02	9.21	9.74	9.90
	IV					10.22	10.29
p-Aminobenzoate	I	12.02	11.80	9.43	9.55	21.00	21.20
	III	10.73	11.02	8.65	8.62	19.10	18.75
	IV					20.10	19.7

occurs but no rise was noticed in the same reaction with V. However, when aniline was added to dry V and the mixture warmed above the melting point of V the reaction proceeded violently.

The properties and analyses of all new compounds prepared are listed in Tables I and II.

Pharmacological Properties

I, III and IV and all of their esters with the exception of the *p*-nitrobenzoates have been tested by Dr. David I. Macht in friendly coöperation.[7] The toxicity of none of the compounds is very great but the members of series III are in general more toxic than those of series I. Toxicity, as determined by tests on Lupinus Albus seedlings, goldfish and tadpoles, increases with the molecular weight in the aliphatic esters but there seems to be an alternation in the esters with even and odd numbers of carbon atoms similar to that shown by the melting points. When injected in doses of 10 to 15 mg. per kg. weight into cats, it was found that all the compounds of series I produce an immediate fall in blood pressure and slight inhibition of respiration. This depressant action increases progressively with the length of the ester chain among the aliphatics but the effect is of short duration and circulation becomes normal after a few minutes. The benzoates of I and III are less toxic than aliphatic esters of equal molecular weight and act more like the lower esters. None of the compounds of series III reveals definite local anesthetic action and only the benzoate of I shows appreciable effect. The latter compound also has the greatest effect on blood pressure and respiration.

The benzoate of IV possesses the most pronounced local anesthetic activity of all compounds studied, being about as effective as procaine when applied to the surface.

(7) David I. Macht, *Proc. Soc. Exp. Biol. Med.*, 234-236 (1933).

Summary

Four new alcohols, thiomorpholine-γ-4-propanol, thiomorpholine-4-ethanol, its oxide and its dioxide have been prepared. A series of esters has been prepared from each of these alcohols and their properties have been studied.

New and more satisfactory preparations of β,β'-dibromodiethyl sulfide, sulfoxide and sulfone have been carried out and their reactions with monoethanolamine studied.

Thiomorpholine derivatives have been shown to be only slightly toxic. The aromatic esters have shown local anesthetic properties similar to those of the corresponding morpholine derivatives.

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[CONTRIBUTION NO. 280 FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF PITTSBURGH]

Preparation and Properties of β-Monoglycerides

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

The β-monoglycerides of fatty acids, together with the analogous unsymmetrical diglycerides, have offered the greatest difficulties in preparation of any of the related glycerol esters. The tendency of an aliphatic acyl group to shift from the beta to the alpha position while preparations are under way was first pointed out by Fischer.[1] Aromatic acyl groups were later fixed in the beta position by Helferich and Sieber,[2,3] who prepared the β-monobenzoate and the β-mono-(*p*-nitrobenzoate) of glycerol, using as an intermediate the α,α'-di-(triphenylmethyl) ether. This method proved unsuitable, however, for the preparation of fatty acid β-glycerides, because of the rapid migration of the acyl group to an alpha position[4] during the removal of the ether groups. The first successful method for the preparation of a fatty acid β-monoglyceride was developed by Bergmann and Carter.[5] They prepared the acetyl, benzoyl, and palmityl esters of 1,3-benzylideneglycerol and succeeded in reducing these to the corresponding β-monoglycerides.

In the present investigation (essentially by the method of Bergmann and Carter) we have prepared the β-glycerol esters of capric, lauric, myristic, palmitic and stearic acids, and have determined their constants for identification.

Since the preparation of mixed unsymmetrical triglycerides by treating α-monoglycerides with acyl chlorides had proved satisfactory,[6,7,8] we investigated the procedure for the preparation of symmetrical mixed triglycerides, using β-monoglycerides as intermediates. A specific study was then made of the factors which influence migration from the beta to the alpha position. In an alcoholic solution of $N/20$ hydrochloric acid at room temperature, β-monopalmitin underwent complete rearrangement to the more stable alpha isomer in twenty-four hours, but in solutions more dilute than $N/200$ there was no significant rearrangement during the same time interval. Higher concentrations (approximately $\times$ 2) of ammonium hydroxide gave similar results.

When the pure β-monopalmitin was held slightly above its melting point for a period of one hour, there was no significant change in structure, but prolonged heating induced a change which did not involve a similar complete transition.

Further evidence of the formation of a cyclic intermediate compound during the change from one isomer to the other has been provided recently by Hibbert and Greig.[9]

Experimental

1,3-Benzylidene glycerol was prepared essentially as described by Hibbert and Carter.[10] It was purified by crystallization first from benzene and heptane (1:1) and then from warm water. A yield of 22% was obtained, m. p. 84°.

Preparation of Esterified Acetals.—The preparation of 2-palmityl-1,3-benzylidene glycerol is given as an example of the method used for the entire series. To a cooled solution of 18 g. of 1,3-benzylidene glycerol in 25 cc. of dry pyridine (cautiously to avoid overheating) 25 g. of palmityl chloride was added. After standing at 20° for twenty-four hours it was washed repeatedly with 200 cc. of ice water until all pyridine was removed. The finely powdered

(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) Jackson and King, THIS JOURNAL, **55**, 678 (1933).
(5) Bergmann and Carter, *Z. physiol. Chem.*, **191**, 211 (1930).
(6) Fischer, Bergmann and Barwind, *Ber.*, **53**, 1589 (1920).
(7) Roche, Averill and King, THIS JOURNAL, **51**, 866 (1929); **54**, 365 (1930).
(8) Robinson, Roche and King, *ibid.*, **54**, 705 (1932).
(9) Hibbert and Greig, *Can. J. Research*, **4**, 254 (1931).
(10) Hibbert and Carter, THIS JOURNAL, **51**, 1601 (1929).