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	H	Br	Found C	H	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 (1930)

(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.

TABLE II

N,N-DIALKYL-α-HYDROXYAMIDES

Formula	Name	Solvent halogen[a]	Yield, %	B. p./mm. and/or m. p. °C.	Mm.
$C_{11}H_{21}O_2N$	N,N-Diethyl-1-hydroxycyclopentaneacetamide	B, Br	13.5	94–95	0.1
$C_{11}H_{23}O_2N$	N,N-Diethyl-3,4-dimethyl-3-hydroxyvaleramide	B, Br	55	74–75	.1
$C_{11}H_{23}O_2N$	N,N-Diethyl-3-hydroxy-3-methylcaproamide	T, Br	52	94–95	.2
$C_{12}H_{23}O_2N$	N,N-Diethyl-1-hydroxycyclohexaneacetamide	B, T; Br	60	94–95	.2
$C_{12}H_{25}O_2N$	N,N-Dipropyl-3-hydroxy-3-methylvaleramide	B, T; Br	48	95–96	.3
$C_{12}H_{25}O_2N$	N,N-Diethyl-3-hydroxy-3,4,4-trimethylvaleramide	B, Br	69	97	.6
$C_{13}H_{19}O_2N$	N,N-Diethyl-3-hydroxy-3-phenylpropionamide	B, E; Br	58	137–138	.1
$C_{13}H_{25}O_2N$	N,N-Diethyl-1-hydroxycyclohexane-α-methylacetamide	T, Br	30	108–109	.1
$C_{13}H_{25}O_2N$	N,N-Diethyl-1-hydroxy-4-methylcyclohexaneacetamide	B, T; Br	59	104–105	.3
$C_{13}H_{26}O_2N$	N,N-Diethyl-1-hydroxy-4-methylcyclohexaneacetamide	B, T; Cl	32	.....	..
$C_{13}H_{27}O_2N$	N,N-Diethyl-3-hydroxy-4-methyl-3-isopropylvaleramide	B, Br	39	108–109	.6
$C_{13}H_{27}O_2N$	N,N-Diisopropyl-1-hydroxycyclohexaneacetamide	B, T; Br	42	106	.4
$C_{14}H_{19}O_2N$	N,N-Diethyl-β-anisylacrylamide[c]	B, E; Br	55	167–170	.4
$C_{16}H_{23}O_2N$	N,N-Diisopropyl-β-anisylacrylamide[c]	B, E; Br	30	163–165	.4
				M. p. 68.7–69.9	
$C_{16}H_{33}O_2N$	N,N-Diethyl-2-*n*-butyl-4-ethyl-3-hydroxycaproamide	B, E; Br	43	124–125	.3
$C_{17}H_{27}O_2N$	N-Methyl-N-phenyl-4-ethyl-3-hydroxycaprylamide	B, E; Br	76	135–136	.3
$C_{17}H_{27}O_2N$	N-Methyl-N-phenyl-4-ethyl-3-hydroxycaprylamide	B, T; Cl	24	144–146	.6
$C_{18}H_{37}O_2N$	N,N-(Mixed)-diamyl-4-ethyl-3-hydroxycaproamide	B, E; Br	65	144–146	.3
$C_{19}H_{21}O_2N$	N-Ethyl-N-phenyl-3-hydroxy-5-phenylvaleramide	B, Br	38	M. p. 109–109.5	
$C_{19}H_{23}O_2N$	N,N-Diethyl-3,3-diphenyl-3-hydroxypropionamide	B, T; Br	53	M. p. 92.6–93.6	

possible to obtain consistently yields above 65% of the calculated amount by adding an ether solution of the desired dialkylamine (2 moles) slowly to an ether solution of the desired bromoacyl halide (1 mole) cooled to −15°. The N,N-disubstituted-α-haloamides prepared in this way are listed in Table I; all of the bromoamides are strongly lachrymatory and sternutatory.

All of the amides listed in Table I were used successfully. It was noted, however, in the only two cases studied in which the disubstituted amides were related to high homologs of acetic acid, that yields obtained were considerably lower than those obtainable from corresponding acetamides. Thus, N,N-diethyl-α-bromocaproamide gave only a 43% yield of hydroxyamide when it reacted with 2-ethylbutyraldehyde; on the other hand, N,N-diamylbromoacetamide reacted with the same aldehyde and yielded 65% of the calculated amount of the expected hydroxyamide. A similar comparison can be made between yields obtained in the reaction of cyclohexanone with N,N-diethyl-α-bromopropionamide and N,N-diethyl-α-bromoacetamide, respectively. Branching of the alkyl groups attached to nitrogen appeared, from the very limited evidence available, to cause lower yields.

The reaction appears to be applicable to aliphatic or aromatic aldehydes and to most ketones. Worthy of note is the fact that we were unable to use furfural successfully as the carbonyl-bearing component. This finding is difficult to explain inasmuch as furfural participates normally in the usual form of the Reformatsky reaction. Nine ketones were investigated and all were converted to the expected hydroxyamide. Five aldehydes were studied; with the exception noted above, all participated in the reaction, but in the case of anisaldehyde the hydroxyamide underwent spontaneous dehydration.

The behavior of three alicyclic ketones, cyclohexanone, 4-methylcyclohexanone and cyclopentanone, was studied. The reaction proceeded satisfactorily with the first two but only poorly with the third. In four different attempts to bring about reaction between cyclopentanone and N,N-diethylbromoacetamide, the yield of desired product was never above 14%. Cyclic ketones in general appeared to form more insoluble zinc complexes than was the case with other carbonyl compounds investigated and vigorous stirring was necessary to prevent the separated zinc complex from coating the zinc alloy and stopping the reaction. It was found expedient to employ larger quantities of solvent in such cases to minimize this difficulty. In order to study steric effects in this reaction, methyl isopropyl ketone, diisopropyl ketone and pinacolone were used with N,N-diethylbromoacetamide in a series of similar reactions. All of the reactions occurred satisfactorily; the yields obtained were, respectively, 39, 69 and 55% of the calculated amounts. It is noteworthy that diisopropyl ketone, a substance which Conant and Blatt[10] found would react additively only with methylmagnesium iodide among various Grignard reagents studied, participates additively in the modified Reformatsky reaction to a considerable extent.

Several experiments in which attempts were made to substitute α-chloroamides for the corresponding α-bromoamides indicated that yields

(10) Conant and Blatt, THIS JOURNAL, 51, 1227 (1929).

TABLE II (*Continued*)

Sp. gr. 25°/25°	$n^{25}D$	MR Obs.	MR Calcd.	Analyses,[b] % Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
1.005	1.4743	55.7	56.3	66.33	10.56		65.95 65.89	10.80 10.57	
0.9477	1.4548	57.5	58.5	65.67	11.54		65.30 65.13	11.68 11.51	
0.9402	1.4530	57.7	58.5	65.67	11.54		65.47 65.17	11.57 11.65	
1.005	1.4787	60.1	60.9	67.70	10.80	6.63	66.84 66.94	10.40 10.55	6.60 6.53
0.9327	1.4524	62.2	63.1	66.98	11.63		66.54 66.82	11.73 11.60	
0.9442	1.4577	62.4	64.2	66.66	12.04		66.54 66.29	11.78 11.71	
1.060	1.5265	64.1	63.1	70.59	8.60		70.04 70.25	8.68 8.59	
0.9978	1.4795	64.7	65.5	68.72	11.02		68.64 68.40	11.21 10.60	
0.9872	1.4760	64.9	65.5	68.72	11.02		68.23 68.43	10.83 11.11	
....	1.4770	..	..	...	...		... ...	... ...	
0.9520	1.4641	66.4	67.7	68.12	11.79		67.51 67.50	11.90 11.70	
....	1.4774	..	..	69.71	11.22		69.48 69.43	10.84 10.86	
1.068	1.5902	73.6	68.4	72.10	8.15		71.40 71.65	8.09 8.30	
....	....	..	..	73.56	8.81		73.66	9.18	
0.9303	1.4635	80.4	81.6	70.85	12.18		70.06 70.29	12.24 12.38	
0.9959	1.5079	82.9	81.6	73.65	9.75		74.29 74.01	9.80 10.08	
....	1.5078								
0.9105	1.4594	89.8	90.8	72.24	12.37		71.81 71.88	12.23 12.44	
....	....	..	..	77.29	7.13		76.80 76.54	7.14 7.13	
....	....	..	..	76.77	7.75		77.00 76.96	8.01 8.12	

[a] B = benzene; E = ether; T = toluene. Cl and Br refer to the halogen in the haloamide used. [b] Microanalyses by Miss E. Werble. [c] The hydroxyamide suffered dehydration during preparation.

obtainable from chloro compounds were considerably smaller than those from the corresponding bromoamides.

The dehydration of N,N-diethyl-β,β-diphenylhydracrylamide proceeds smoothly in the presence of 99% formic acid; it is probable that the other hydroxyamides described could be similarly converted to the corresponding unsaturated compounds.

Experimental

The aldehydes and ketones used were purified by usual methods.

Preparation of α-Haloamides.—An ether solution of the appropriate α-haloacyl halide was cooled to −15°, and an ether solution of 2 equivalents of the desired amine was added to the well-stirred solution at such a rate that the temperature of the mixture did not exceed −10°. After the reaction was complete, enough cold water was added to dissolve the precipitated amine hydrochloride. The organic layer was separated and washed successively with dilute phosphoric acid, dilute potassium carbonate and finally with saturated brine until neutral. After removal of the ether by distillation, the product was purified by distillation under diminished pressure, or by recrystallization.

The compounds prepared are found in Table I,

Preparation of N,N-Disubstituted-α-hydroxyamides.—The calculated quantity of turnings of zinc–copper alloy (8% copper) and a crystal of iodine were added to a 500 ml., three-necked flask for experiments in which 0.2 to 0.25 mole of reactants were employed. The flask was fitted with a reflux condenser, stirrer and dropping funnel and was protected from atmospheric moisture by drying tubes; before use the apparatus was flamed until dry while a stream of dry air was drawn through it. A small quantity (*ca.* 15 ml.) of a solution of the α-haloamide and the aldehyde or ketone in 100–150 ml. of the solvent listed in Table II was added, stirring was begun and the mixture was heated under reflux until the reaction started (usually within 15 min.). After the initial reaction had subsided, the remainder of the solution of reactants was added at such a rate that gentle refluxing occurred (*ca.* one hour). The mixture was then heated under reflux for one hour, cooled and poured onto 200 ml. of cold 10% sulfuric acid. Copper and unused zinc were removed by filtration, whereupon the organic layer was washed in turn with 5% solutions of sulfuric acid and potassium carbonate and finally with saturated brine until neutral. After the solution had been dried, the solvent was removed by distillation, and the product was purified by distillation or crystallization.

The compounds prepared and certain pertinent data are listed in Table II.

Dehydration of N,N-Diethyl-β,β-diphenylhydracrylamide.—The method used was similar to one already described.[11] The amide (3 g.) in 20 ml. of 99% formic acid was heated on a steam-bath for fifteen minutes. The cooled reaction mixture was poured into water, the product was extracted with benzene and the benzene solution was washed with 5% potassium carbonate and then with water until neutral. Evaporation of the benzene yielded a solid which was purified by recrystallization from petroleum ether (60–80°). Purified for analysis the compound melted at 83.6–84.3°. *Anal.* Calcd. for $C_{19}H_{21}NO$: C, 81.72; H, 7.53. Found: C, 81.87, 81.99.; H, 7.46, 7.47.

α,β-Dibromo-N,N-diethyl-β-anisylacrylamide.—Prepared from a solution of N,N-diethyl-β-anisylacrylamide in carbon tetrachloride by the addition of a 5% solution of bromine in the same solvent, and recrystallized from benzene–petroleum ether (1:1), the analytical sample melted at 122–122.8°. To obtain reproducible melting points, it was found necessary to heat the melting-point bath to 115° before inserting the capillary. *Anal.* Calcd. for $C_{14}H_{19}Br_2NO_2$: C, 42.75; H, 4.84. Found: C, 43.16, 42.86; H, 5.03, 5.23.

α,β-Dibromo-N,N-diisopropyl-β-anisylacrylamide.—Prepared as above, the analytical sample melted at 139–140°. *Anal.* Calcd. for $C_{16}H_{23}Br_2NO_2$: Br, 38.01. Found: Br, 37.70, 38.05.

(11) Bachmann and Edgerton, THIS JOURNAL, **62**, 2971 (1940).

Summary

1. The substitution of N,N-disubstituted-α-halomides for α-haloesters in the Reformatsky reaction has been studied and shown to be practical.
2. Sixteen different hydroxyamides prepared by this method are described.
3. Anisaldehyde reacted with two α-haloamides to yield the unsaturated relative of the expected hydroxyamide.
4. It was found impossible to isolate the expected product when furfural was one of the reactants.

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[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Certain N-Alkyl, N-Carboxyalkyl and N-Hydroxyalkyl Derivatives of 4,4′-Diaminodiphenyl Sulfone

BY ERNEST L. JACKSON

Numerous derivatives of 4,4′-diaminodiphenyl sulfone (I) have been reported[1] since the observation of the antibacterial activity of this sulfone by Buttle, *et al.*,[2] and by Fourneau, *et al.*[3] Among the amino substituted derivatives the results of biological studies[4] indicate the desirability of the presence of one free amino group and suggest the superiority of the alkyl type of substituent. The present paper reports the synthesis of a number of derivatives having an alkyl, carboxyalkyl or hydroxyethyl group substituted in one of the amino groups. Several similar derivatives of 4-amino-4′-nitrodiphenyl sulfone (II) were prepared both for use as intermediates in the synthesis of some of the derivatives of I and also for tests of their antibacterial activity, since compound II is known to show considerable bacteriostatic activity.

Two methods were employed in the preparation of the crystalline derivatives of I shown in the table: (1) direct alkylation or carboxyalkylation of I, an excess of I being used to minimize substitution in the second amino group of the molecule; (2) alkylation or hydroxyethylation of II and subsequent reduction of the nitro group of the product by iron and 1.5% hydrochloric acid in ethanol solution. The first method, the success of which depends on efficient separability of the product from I, was applied to the preparation of compounds IV and X–XIV. As alkylation and carboxyalkylation agents, ethyl iodide was used for the preparation of IV, the appropriate *n*-alkyl bromide for XII–XIV, bromoacetic acid for X and β-bromopropionic acid for XI. In the case of the glycine and β-alanine derivatives, separation from excess I was effected by removal of the carboxyl compounds as the water-soluble sodium salts. The acids required further purification, which was accomplished readily through the crystalline pyridine salts. The ethyl derivative crystallized from the ethylation solution at the end of the reaction. The difference in solubility of the *n*-butyl, *n*-amyl and *n*-tetradecyl derivatives in 2.5–5% hydrochloric acid as compared with I provides a convenient method of separation. Compounds IV and XIV were prepared also by the second method, which was the way the β-hydroxyethyl (VII) and benzyl (XVII) derivatives were obtained. The yields of amino derivatives in the reduction of the nitro compounds were excellent, 90% in one case.

The hydroxyethylation of II by reaction with 2-bromoethanol proceeds at a slow rate in boiling cellosolve solution to produce compound VI in a yield of 30–35%. Prolonged duration of the reaction results in a secondary reaction involving the hydroxyethyl group of the initial product (VI), as shown by the formation of both the β-hydroxyethyl (VII) and ethyl (IV) derivatives in the reduction of the mixture resulting from the hydroxyethylation reaction under certain conditions. Although the mechanism of the formation of IV in the two-step process has not been established, it seems possible that the compound might result from the reduction of 4-nitro-4′-β-bromoethylaminodiphenyl sulfone, which could be produced by the reaction of VI with the hydrobromic acid accumulated in the hot hydroxyethylation reaction solution. The direct hydroxyethylation of I by the reaction of 2-bromoethanol and I in equimolecular proportions at 100° produced a mixture from which only crystalline 4,4′-bis-(β-hydroxyethylamino)-diphenyl sulfone (VIII) was isolated. During the progress of this investigation Heymann and Heidelberger[1] reported the preparation of VIII, in low yield, through a pressure reaction of ethylene oxide with I followed by isolation of the product as the crystalline N,N′-dinitroso derivative. 2-Bromoethanol possesses advantages over ethylene oxide for the preparation of VIII, since

(1) For references see: Roblin, Williams and Anderson, THIS JOURNAL, **63**, 1930 (1941); Heymann and Fieser, *ibid.*, **67**, 1979 (1945); Heymann and Heidelberger, *ibid.*, **67**, 1986 (1945); Jackson, *ibid.*, **68**, 1438 (1946).

(2) Buttle, Stephenson, Smith, Dewing and Foster, *Lancet*, **232**, 1331 (1937).

(3) Fourneau, Tréfouël, Nitti, Bovet and Tréfouël, *Compt. rend.*, **204**, 1763 (1937); **205**, 299 (1937).

(4) (a) Smith, Jackson and McClosky, *Am. Rev. Tuberc.*, **53**, 589 (1946); **55**, 366 (1947); (b) Youmans and Doub, *ibid.*, **54**, 287 (1946); Youmans, Feldman and Doub, *ibid.*, **54**, 295 (1946); (c) Smith, McClosky, Jackson and Bauer, *Proc. Soc. Exptl. Biol. Med.*, **64**, 261 (1947); see also Heymann and Fieser, ref. 1.