

[CONTRIBUTION FROM STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Alkamine Esters and Amides of Some Amino-alkylmercaptobenzoic Acids¹BY JOHN J. DONLEAVY² AND PAUL C. CONDIT³

Previous communications from this Laboratory⁴ have described alkamine esters of alkylmercaptobenzoic and phenylcarbamic acids. Both of these groups of compounds were active as local anesthetics.^{4,5}

In an extension of their work on esters of alkylmercaptobenzoic acids, Donleavy and English also made a brief study of the alkamine esters of amino-alkylmercaptobenzoic acids.⁶ For the synthesis of these compounds it was necessary to prepare the corresponding nitro-alkylmercaptobenzoic acids. These intermediates proved to be difficult to synthesize by the diazotization technique used for the simpler alkylmercaptobenzoic acids. The present investigation was therefore undertaken in an effort to develop general methods of synthesis by which alkamine esters of benzoic acids containing both an amino and an alkylmercaptobenzoic group attached to the nucleus could be prepared in good yields and a high state of purity from readily obtainable starting materials.

It has long been known that a nuclear halogen atom is labilized by negative substituents, such as the nitro group, in the *o*- and *p*- positions.⁷ Such a halogen atom can be replaced under relatively mild conditions by reaction with basic reagents, and the method has been used in the past for the introduction of sulfur-containing groups into aromatic nuclei.^{7c,8} It seemed possible that this reaction might be used to prepare nitro-alkylmercaptobenzoic acids and their derivatives.

It was found that either the methyl ester or the amide of 3-nitro-4-chlorobenzoic acid reacts with sodium mercaptides to give the corresponding 3-nitro-4-alkylmercaptobenzoic compounds in 85-95% yields. The reaction is carried out in refluxing alcohol and appears to be applicable to any sodium mercaptide. The sodium salt of 3-nitro-4-chlorobenzoic acid likewise reacts in the same sense with sodium mercaptides when aqueous alcohol is used as a medium. The 3-nitro-4-alkylmercaptoben-

zoic acids are obtained from the salts in equally good over-all yields. These acids and their derivatives are all bright yellow solids which crystallize unusually well in the form of fine needles or occasionally plates. The color of these compounds deepens to a red-orange in basic solution.

Upon treatment with thionyl chloride, the 3-nitro-4-alkylmercaptobenzoic acids are quantitatively converted to their acid chlorides, which are yellow, crystalline solids of unusual stability. Refluxing with methanol converts the acid chlorides to the methyl esters in about 90% yields. There is little to choose between this method of synthesis of the methyl esters and the one described in the previous paragraph. The 3-nitro-4-alkylmercaptobenzoyl chlorides react very sluggishly with ammonia, however, and the best synthesis for the amides of these acids is by the direct metathetical reaction of sodium mercaptides with 3-nitro-4-chlorobenzamide.

The acid chloride of 3-nitro-4-methylmercaptobenzoic acid was treated with β -diethylaminoethanol and the hydrochloride of the corresponding alkamine ester obtained in a 65% yield. Dioxane proved to be a much more convenient solvent for this reaction than the conventional ether or benzene. Reduction of the nitro group in the β -diethylaminoethyl ester of 3-nitro-4-methylmercaptobenzoic acid or in its hydrochloride presented unexpected difficulties. Although some reduction took place catalytically, none of the desired β -diethylaminoethyl ester of 3-amino-4-methylmercaptobenzoic acid was found among the products. It is possible that this difficulty was the result of traces of impurities, although the hydrochloride of the nitro compound was recrystallized from acetone before the catalytic reduction was attempted. The nitro compound can be reduced by shaking with powdered zinc and glacial acetic acid at room temperature, but large quantities of by-products are formed and the yield of the desired amine is less than 20%.

It was found, on the other hand, that the amides or the methyl esters of 3-nitro-4-alkylmercaptobenzoic acids are reduced smoothly to the corresponding amino compounds by hydrogenation over Adams catalyst⁹ and that the yields in this case are quantitative. The only precautions necessary are careful purification of the materials to be reduced and the use of a comparatively large quantity of the catalyst. Without this excess catalyst, insoluble orange condensation or polymerization products are formed and these cannot be further hydrogenated.

Considering the difficulty encountered in the reduction of the β -diethylaminoethyl ester of 3-

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(4) J. J. Donleavy and J. English, Jr., *THIS JOURNAL*, **63**, 220, 2965 (1940); J. J. Donleavy, U. S. Patent 2,173,827 (1939).

(5) H. R. Hulpien, J. H. Kitchel and J. H. Weatherby, *J. Pharmacol.*, **63**, 395 (1940).

(6) James English, Jr., Doctoral dissertation, Yale University, 1936; J. J. Donleavy, U. S. Patent 2,321,468 (1943).

(7) (a) F. Beilstein and A. Kurbatow, *Ann.*, **197**, 75 (1879); (b) J. J. Blanksma, *Rec. trav. chim.*, **30**, 399 (1901); (c) T. Wohlfahrt, *J. prakt. Chem.*, [2] **66**, 551 (1902).

(8) R. W. Bost, J. O. Turner and R. D. Norton, *THIS JOURNAL*, **54**, 1985 (1932).

(9) R. Adams, "*Org. Syn.*," **8**, 93 (1928).

nitro-4-methylmercaptobenzoic acid, it seemed advisable to prepare the amides or the methyl esters of the 3-amino-4-alkylmercaptobenzoic acids and to convert these intermediates to the desired alkamine esters by alcoholysis. The alcoholysis of either of these intermediates goes satisfactorily with dry hydrogen chloride as a catalyst. The purity of the products and the yields (70–75%) are slightly better when the methyl esters are used. The number of alkamine esters that could be prepared was limited by the fact that the higher members of the series cannot be distilled without extensive decomposition. Attempts were made to purify these compounds by precipitation of the hydrochlorides from ethereal extracts of the undistilled bases, but the products so obtained were too impure to be recrystallized. The distilled bases, on the other hand, formed well-defined monohydrochlorides which could be recrystallized from absolute alcohol. The yields of the hydrochlorides from the bases were substantially quantitative, but unless particular care was taken, the recrystallization loss was apt to be large.

The alkamine amides of the 3-amino-4-alkylmercaptobenzoic acids were made by aminolysis of the methyl esters with β -diethylaminoethylamine. Since these products were viscous oils which resisted all attempts at direct purification, their hydrochlorides were precipitated and recrystallized from a mixture of absolute alcohol and dry ether. The dihydrochlorides rather than the monohydrochlorides are the stable derivatives in this series. Yields varied from 30 to 85%, depending largely upon the difficulty of recrystallization.

The methylmercapto series of compounds was the most intensively investigated and these have been used as examples in the Experimental part to follow. The procedures used and the yields obtained were similar for the other three series studied. None of the compounds for which detailed data are given in the following section has been previously described in the literature.

Experimental

Starting Materials.—3-Nitro-4-chlorobenzoic acid was prepared from 4-chlorobenzoic acid¹⁰ by the method of Montagne.¹¹ 3-Nitro-4-chlorobenzoyl chloride was made from the acid by the use of thionyl chloride and was converted to the methyl ester and amide in the customary way. The yield for each of the steps given was 95% or better. The melting points of the materials, after purification, checked those given by Montagne.¹¹ In most cases, the compounds were used in further synthesis without recrystallization.

3-Nitro-4-methylmercaptobenzoic Acid.—Ten grams of sodium bicarbonate and 24.5 g. of 3-nitro-4-chlorobenzoic acid were dissolved in 350 cc. of 50% alcohol. Carbon dioxide was evolved. Four and eight-tenths grams of sodium hydroxide dissolved in 36 cc. of water was added to 350 cc. of 95% alcohol, and 12 g. of methyl mercaptan, prepared according to the directions of Shildneck and Windus,¹² was bubbled into the mixture. The two solu-

tions were then heated to boiling, mixed and refluxed for one hour. The solvent was removed by distillation under diminished pressure, and the residue, consisting of sodium chloride and the orange sodium salt of 3-nitro-4-methylmercaptobenzoic acid, was dissolved in the minimum amount of warm water. The resulting solution was acidified with concentrated hydrochloric acid, and the 3-nitro-4-methylmercaptobenzoic acid which precipitated was filtered from the solution after thorough cooling. Recrystallization of the crude product from 95% alcohol and concentration of the mother liquor to half volume yielded 23 g. of the pure acid.

3-Nitro-4-methylmercaptobenzamide.—Twenty-four grams of 3-nitro-4-chlorobenzamide dissolved in 350 cc. of boiling 95% alcohol was added to a hot solution of sodium methyl mercaptide, prepared as above, and the mixture was refluxed for one hour. The alcohol was then removed by distillation under diminished pressure, and the solid residue treated with 200 cc. of water containing a few drops of hydrochloric acid, in order to remove the sodium chloride and any excess alkali that was present. The crude product (24 g.) was oven-dried to free it of traces of mercaptan, and recrystallized from 95% alcohol. The yield of pure 3-nitro-4-methylmercaptobenzamide was 22 g.

3-Nitro-4-methylmercaptobenzoyl Chloride.—Ten grams of 3-nitro-4-methylmercaptobenzoic acid was added to 75 cc. of thionyl chloride and heated to boiling in a flask attached to a reflux condenser. The acid dissolved as the reaction proceeded and hydrogen chloride was evolved. Refluxing was continued for one hour, and the excess thionyl chloride was removed by distillation under diminished pressure. The residual solid was recrystallized from high-boiling petroleum ether. The yield of 3-nitro-4-methylmercaptobenzoyl chloride was quantitative.

The Methyl Ester of 3-Nitro-4-methylmercaptobenzoic Acid.—The methyl esters of the 3-nitro-4-alkylmercaptobenzoic acids may be prepared by exactly the technique described for the amides, using the methyl ester of 3-nitro-4-chlorobenzoic acid as the starting material. They may also be prepared from the acid chlorides as follows:

Two and one-tenth grams of 3-nitro-4-methylmercaptobenzoyl chloride was added to 30 cc. of methyl alcohol and warmed on the steam-bath. The acid chloride dis-

TABLE I

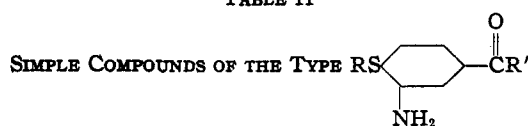
COMPOUNDS OF THE TYPE		Analyses, %			
R—	—R'	M. p., °C.	Element	Calcd.	Found
CH ₃ —	—OH	240	N	6.57	6.63
C ₂ H ₅ —	—OH	231	N	6.17	6.16
<i>n</i> -C ₃ H ₇ —	—OH	234	N	5.80	5.70
C ₆ H ₅ CH ₂ —	—OH	216	N	4.84	4.85
CH ₃ —	—Cl	111	N	6.06	6.22
C ₂ H ₅ —	—Cl	102	N	5.71	5.69
<i>n</i> -C ₃ H ₇ —	—Cl	94	C	46.24	46.21
			H	3.85	3.72
C ₆ H ₅ CH ₂ —	—Cl	129	N	4.56	4.57
CH ₃ —	—NH ₂	209	S	15.10	15.38
C ₂ H ₅ —	—NH ₂	214	N	12.39	12.38
<i>n</i> -C ₃ H ₇ —	—NH ₂	187	N	11.67	11.56
CH ₃ —	—OCH ₃	117	N	6.17	6.20
C ₂ H ₅ —	—OCH ₃	130	N	5.81	5.93
<i>n</i> -C ₃ H ₇ —	—OCH ₃	97	C	51.76	51.53
			H	5.10	5.02
C ₆ H ₅ CH ₂ —	—OCH ₃	138	N	4.62	4.69

(10) H. T. Clarke and E. R. Taylor, "Org. Syn.," 10, 20 (1930).

(11) P. J. Montagne, *Rec. trav. chim.*, 19, 46 (1900).

(12) P. R. Shildneck and W. Windus, "Org. Syn.," 12, 52 (1932); 14, 54 (1934).

TABLE II



R—	—R'	M. p., °C.	B. p., °C.	n_D	N Analyses, %	
					Calcd.	Found
CH ₃ —	—NH ₂	166	15.38	15.34
C ₂ H ₅ —	—NH ₂	156	14.29	14.31
<i>n</i> -C ₃ H ₇ —	—NH ₂	118	13.33	13.24
CH ₃ —	—OCH ₃	61	170 at 4 mm.	7.11	7.10
C ₂ H ₅ —	—OCH ₃	liquid	180 at 4 mm.	1.5936 at 23°	6.63	6.40
<i>n</i> -C ₃ H ₇ —	—OCH ₃	24	182 at 6 mm.	1.5936 at 24.5°	6.22	6.06
C ₆ H ₅ CH ₂ —	—OCH ₃	76–78	234 at 4.5 mm.	5.13	4.97

solved to give a clear yellow solution, a rapid evolution of hydrogen chloride took place, and a precipitate of the ester formed. Sufficient methyl alcohol was added to redissolve the precipitate, refluxing was continued for a few minutes, the solution was filtered through a hot funnel and the product was allowed to crystallize. After removal of this product by filtration, the mother liquor was concentrated to half volume, and a second batch of pure product was obtained. The total yield of the pure methyl ester of 3-nitro-4-methylmercaptobenzoic acid was 2.1 g.

The melting points and analyses of the 3-nitro-4-alkylmercaptobenzoic acids and of their amides, methyl esters and acid chlorides are recorded in Table I.

The Hydrochloride of the β -Diethylaminoethyl Ester of 3-Nitro-4-methylmercaptobenzoic Acid.—Four and six-tenths grams of 3-nitro-4-methylmercaptobenzoyl chloride was dissolved in 100 cc. of dry dioxane, and the solution was placed in a three-necked flask fitted with a mechanical stirrer and a dropping funnel. Two and thirty-four hundredths grams of β -diethylaminoethanol, dissolved in another 100-cc. portion of dry dioxane was added over a period of one and one-half hours, and stirring was continued for two hours after the addition was completed. Throughout this procedure, the temperature of the reaction mixture was kept between 40 and 50°. The hydrochloride of the β -diethylaminoethyl ester of 3-nitro-4-methylmercaptobenzoic acid (6 g.) precipitated during the course of the reaction and was filtered from the dioxane when the reaction was finished. Upon recrystallization from dry acetone, 4.5 g. of the non-hygroscopic, yellow hydrochloride was obtained. It melted sharply at 171°.

Anal. Calcd. for C₁₄H₂₁O₄N₂SCl: N, 8.05. Found: N, 8.15.

3-Amino-4-methylmercaptobenzamide.—Five grams of 3-nitro-4-methylmercaptobenzamide was suspended in 250 cc. of alcohol, and 0.5 g. of platinum oxide catalyst⁹ was added. The mixture was then shaken with hydrogen under a pressure of 25 lb. until no more of the gas was absorbed. This required about two and one-half hours, and a colorless solution with a blue fluorescence resulted. The solution was warmed to dissolve any precipitated product, filtered and the alcohol removed by distillation under diminished pressure. The product was recrystallized from water, Norite being used to remove the last traces of colloidal catalyst. It was obtained as long, white needles. The yield was quantitative.

The Methyl Ester of 3-Amino-4-methylmercaptobenzoic Acid.—Twenty-five grams of the methyl ester of 3-nitro-methylmercaptobenzoic acid was suspended in 250 cc. of alcohol and 2.5 g. of platinum oxide catalyst⁹ was added. The reduction, filtration and removal of the solvent were carried out exactly as in the case of the amide. The residual oil was transferred to a small Claisen flask and distilled under diminished pressure. The methyl ester of 3-amino-4-methylmercaptobenzoic acid was obtained as a clear yellow oil which distilled at 170° at a pressure of 4 mm. and gradually solidified at

room temperature. The yield was 18 g. Upon recrystallization from alcohol the product was obtained in the form of pure white, feathery needles.

The physical constants and analyses of the amides and methyl esters of the 3-amino-4-alkylmercaptobenzoic acids prepared in this manner are recorded in Table II.

The β -Diethylaminoethyl Ester of 3-Amino-4-methylmercaptobenzoic Acid (Method I).—Dry hydrogen chloride was bubbled through 5 cc. of β -diethylaminoethanol until gelation set in. The salt was dissolved in an additional 30 cc. of the amino-alcohol and 8 g. of the methyl ester of 3-amino-4-methylmercaptobenzoic acid added. The mixture was heated at 175° for one hundred and twenty-five hours in a flask fitted with a short reflux air-condenser. The excess β -diethylaminoethanol was removed by distillation under diminished pressure, and the residual bases were freed of hydrogen chloride with cold aqueous sodium bicarbonate and extracted with ether. After drying the extract with anhydrous sodium sulfate, the ether was removed in the customary manner, and the residue distilled under diminished pressure. The β -diethylaminoethyl ester of 3-amino-4-methylmercaptobenzoic acid (8.25 g.) was obtained as a viscous, yellow oil which distilled at 218° at a pressure of 5 mm. This ester was converted to its monohydrochloride by treatment in ether solution with 1.25 molecular proportions of dry hydrogen chloride. The hydrochloride precipitated and was recrystallized from absolute alcohol. The yield was 6.75 g.

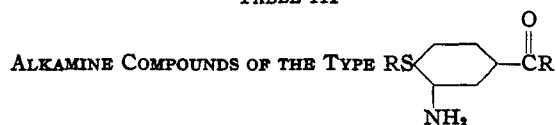
Method II.—Five grams of 3-amino-4-methylmercaptobenzamide was alcoholized in exactly the same manner that was employed for the methyl ester. Five grams of the free base was obtained by distillation of the ether extract. Its physical characteristics and those of its hydrochloride proved it to be identical with the material obtained by Method I.

Method III.—Seven grams of the hydrochloride of the β -diethylaminoethyl ester of 3-nitro-4-methylmercaptobenzoic acid was dissolved in cold water and treated with aqueous sodium bicarbonate. The free base was extracted with ether, dried over anhydrous sodium sulfate and the ether removed. The residue was dissolved in 100 cc. of glacial acetic acid and shaken for five hours at room temperature with 20 g. of powdered zinc. The excess zinc was removed by filtration and most of the acetic acid by vacuum distillation. The residue was then treated with aqueous sodium bicarbonate and worked up exactly as in Method I. Distillation of the crude base left a large quantity of tar in the distilling flask, and the yield of material boiling in approximately the proper range was less than 20%. A sample was redistilled for analysis.

Anal. Calcd. for C₁₄H₂₂O₂N₂S: N, 9.93. Found: N, 9.72.

The β -Diethylaminoethylamide of 3-Amino-4-methylmercaptobenzoic Acid.—Three grams of the methyl ester of 3-amino-4-methylmercaptobenzoic acid was dissolved in 2.5 g. of β -diethylaminoethylamine, and the mixture was heated at 160° for ten hours in a flask fitted with a short reflux air-condenser. The excess amine was then

TABLE III



R—	—R'	B. p., °C.	M. p., °C.	Hydrochloride		Remarks	
				mole HCl mole base	N Analyses, % Calcd. Found		
CH ₃ —	—OCH ₂ CH ₂ N(C ₂ H ₅) ₂	218 at 5 mm.	168–172	1	8.79	8.71
C ₂ H ₅ —	—OCH ₂ CH ₂ N(C ₂ H ₅) ₂	218–223 at 4 mm.	118–123	1	8.43	8.38
<i>n</i> -C ₃ H ₇ —	—OCH ₂ CH ₂ N(C ₂ H ₅) ₂	230–234 at 4 mm.	190–194	1	8.09	8.21
CH ₃ —	—OCH ₂ CH ₂ CH ₂ N(C ₂ H ₅) ₂	215–218 at 4 mm.	175–179	1	8.43	8.24	Hygroscopic
C ₂ H ₅ —	—OCH ₂ CH ₂ CH ₂ N(C ₂ H ₅) ₂	230–235 at 4 mm.	166–171	1	8.09	8.04	Hygroscopic
CH ₃ —	—NHCH ₂ CH ₂ N(C ₂ H ₅) ₂	196–200	2	11.86	11.93	Hygroscopic
C ₂ H ₅ —	—NHCH ₂ CH ₂ N(C ₂ H ₅) ₂	149–151	2	11.44 ^a	11.36	Hygroscopic
<i>n</i> -C ₃ H ₇ —	—NHCH ₂ CH ₂ N(C ₂ H ₅) ₂	145–149	2	11.02	11.09	Hygroscopic
C ₆ H ₅ CH ₂ —	—NHCH ₂ CH ₂ N(C ₂ H ₅) ₂	197–201	2	9.77	9.72	Hygroscopic

^a Anal. Calcd.: Cl, 19.07. Found: Cl, 18.80.

removed by distillation under diminished pressure, and the residual oil was dissolved in dry ether. Three molecular proportions of dry hydrogen chloride dissolved in ether was added dropwise with stirring, and the reaction mixture was allowed to stand in the refrigerator for several days in order to harden the precipitate. The dihydrochloride was dissolved in absolute alcohol, and dry ether which contained dry hydrogen chloride was added until the solution became faintly cloudy. The dihydrochloride crystallized on cooling, and was filtered from the solution, triturated with dry ether, and transferred to an Abderhalden drier. The yield was 3.25 g.

The properties of the alkamine esters and amides prepared and of their hydrochlorides are given in Table III.

All nitrogen analyses were run by the semi-micro Kjeldahl method, carbon and hydrogen by semi-micro combustions, and sulfur by the Parr-bomb method. The analysis for ionizable chlorine reported in the footnote to Table III was run gravimetrically.

Summary

1. Methods for the preparation of 3-nitro-4-alkylmercaptobenzoic acids and their simple esters, amides and acid chlorides have been developed. Examples of these compounds with four different alkylmercaptobenzoyl groups have been described.

2. The methyl esters and the amides of these acids have been reduced catalytically to the corresponding 3-amino-4-alkylmercaptobenzoic acid derivatives.

3. Five alkamine esters and four alkamine amides of the 3-amino-4-alkylmercaptobenzoic acids have been prepared from the methyl esters or amides and have been converted to their hydrochlorides for characterization.

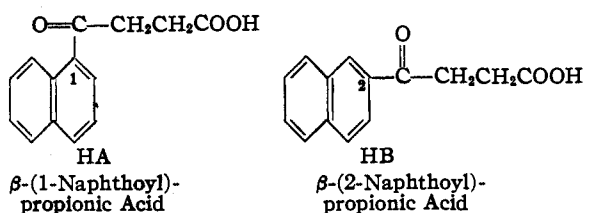
NEW HAVEN, CONNECTICUT RECEIVED MARCH 4, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE OHIO STATE UNIVERSITY]

Separation of Isomers. β -(2- and β -(1-Naphthoyl)-propionic Acid; their Ionization Constants and Solubilities and Method of Separation¹

BY M. S. NEWMAN, ROBERT B. TAYLOR, THOMAS HODGSON AND A. B. GARRETT

The mixture of isomeric naphthoylpropionic acids



formed by the Friedel-Crafts condensation of succinic anhydride with naphthalene, is difficult to separate. We have found that if a solution of the sodium salts of these two acids is treated with mineral acid insufficient to liberate all of the acids, almost pure β -(2-naphthoyl)-propionic acid (here-

(1) The material herein presented is taken in part from the M.S. Theses of R. B. T. and T. H.

inafter called HB, its isomer, HA) is precipitated. Successive additions of acid precipitate further amounts of HB until a point is reached after which further additions of acid precipitate HA and HB in nearly constant ratio.

This behavior is similar to that involved in the Mohr titration of chloride ion using the chromate ion as the indicator in which the chloride ion precipitates until the ratio of $[\text{Cl}^-]^2/[\text{CrO}_4^{2-}] = 5 \times 10^{-9}$ at which point the two precipitate together.

However, in the case of these organic acids the values of the ionization constants are necessary, as well as the values of the solubilities, to determine the ionic precipitation ratio which we shall call K . This ratio, K , can be evaluated from the ionization constants K_A and K_B from HA and HB giving

$$\frac{[\text{A}^-]}{[\text{B}^-]} = \frac{K_A}{K_B} \times \frac{[\text{HA}]}{[\text{HB}]} = K \quad (1)$$