Anal. Calcd. for $C_{29}H_{48}O_2$: neut. equiv., 428.0. Found: neut. equiv., 428.5.

One and a half gram of Fraction II was refluxed in 25 cc. of propylene glycol containing 2.5 g. of potassium hydroxide. After two hours of refluxing the solution was cooled, diluted with 400 cc. of water (clear solution) and acidified. The precipitate was filtered off, washed with water and dried. This substance, weighing 0.95 g. was dissolved in 20 cc. of methanol. After dilution with 100 cc. of water the mixture was extracted with petroleum ether. The petroleum ether was evaporated. The residue was twice crystallized from methanol. Three-tenths of a gram of large needles was obtained, m.p. 108–109°. No melting point depression was observed when mixed with the cholestane-6-acetic acid-γ-lactone, isolated from the *i*-cholesterylacetic acid rearrangement.

Interchange of Δ⁴-Cholestene-6-acetic Acid and Cholestane-6-acetic Acid-γ-lactone.—(a) Two-tenths of a gram of cholestane-6-acetic acid-γ-lactone was dissolved in 20 cc. of glacial acetic acid containing one-tenth of a cc. of concentrated sulfuric acid. The mixture was heated for one hour on the steam-bath, then diluted with a saturated sodium chloride solution. The precipitate was filtered off, washed with water and dissolved in about 20 cc. of boiling methanol. Crystals deposited in the cold and were separated from the liquid. After recrystallization from glacial acetic acid, 0.05 g. of a substance was obtained with a m.p. of 173–174°; mixed melting point with Δ⁴-cholestene-6-acetic acid 173–174°. From the methanol mother liquor 0.06 g. of unchanged cholestane-6-acetic acid-γ-lactone was isolated.

(b) Half a gram of Δ⁴-cholestene-6-acetic acid was treated with sulfuric acid in glacial acetic acid solution in an identical manner as the lactone. The acid treated product was first crystallized from glacial acetic acid. Unchanged Δ⁴-cholestene-6-acetic acid was recovered, yield, 0.25 g. From the mother liquor a solid was precipitated with saturated sodium chloride solution. This was twice crystallized from methanol. Cholestane-6-acetic acid-γ-lactone was obtained, m.p. 108–109°, yield, 0.1 g.

(c) Two-tenths of a gram of cholestane-6-acetic acid-γ-lactone was heated for eight hours to 205–210°.[5] The brown-colored product was three times recrystallized from methanol, m.p. 108–109°, mixed melting point with cholestane-6-acetic acid-γ-lactone 108–109°. The mother liquors yielded an additional amount of cholestane-6-acetic acid-γ-lactone.

Summary

i-Cholesterylacetic acid was prepared by pyrolysis of *i*-cholesterylmalonic acid and by alkaline hydrolysis of *i*-cholesteryl malonamide. The *i*-cholesterylacetic acid was rearranged in acid solutions. Two products were obtained; the Δ⁴-cholestene-6-acetic acid and the cholestane-6-acetic acid-γ-lactone. The mechanism of the *i*-cholesterylacetic acid rearrangement was shown to be different from the rearrangement mechanism of *i*-compounds connected by carbon-to-oxygen or carbon-to-nitrogen bonds to substituents in the six position.

i-Cholesterylmalonamide was also rearranged and the rearrangement products saponified. The same compounds were isolated as obtained from the *i*-cholesterylacetic acid rearrangement mixture.

CHICAGO, ILLINOIS RECEIVED AUGUST 12, 1948

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Amine Bisulfite Addition Products of Aldehydes and Ketones. I

BY ROGER ADAMS AND R. D. LIPSCOMB[1]

Aldehydes and ketones are frequently purified through their sodium bisulfite addition products. The adducts are seldom used for identification purposes since they usually do not have sharp melting or decomposition points and suffer the shortcoming of being essentially insoluble in organic solvents. Amine bisulfite addition products of aldehydes and ketones, which have been inadequately investigated, should be formed with equal ease. They offer several possibilities for utilization (1) as compounds for characterization of ketones and aldehydes; (2) for the resolution of aldehydes and ketones and (3) for the replacement of aldehyde and ketone adducts of sodium bisulfite as intermediates in various organic syntheses. The preparation of several representative tertiary amine bisulfites with typical aldehydes and ketones and the characterization of the adducts are described in this first communication.

The procedure usually followed for preparation of the amine bisulfites was to pass sulfur dioxide into the tertiary amines mixed with sufficient water to form the bisulfites. Invariably heat was evolved when sulfur dioxide was first introduced and in many of the conversions, a white solid was observed to separate. This white solid, probably the amine sulfite, gradually dissolved in the reaction mixture as the addition of sulfur dioxide was continued. Whether or not this solid was observed, the reaction mixture always became viscous during the intermediate stage of the conversion. In the final stages, the color of the solution changed to yellow or orange and the viscosity decreased. The reaction was no longer exothermic after the intermediate viscous stage had been reached. The volume of product was often nearly double the volume of starting materials. This volume increase was most noticeable during the latter stages of the reaction.

The resulting mixtures were obviously not pure amine bisulfites but complexes of amine bisulfites with sulfur dioxide. They are relatively stable to air oxidation over long periods of time, probably due to the presence of the excess sulfur dioxide. These mixtures were kept for several years in ordinary reagent bottles in a refrigerator; they may be kept in tightly closed containers at room tem-

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[1] An abstract of a thesis submitted in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry. General Aniline and Film Corporation Fellow, 1942–43.

TABLE I

TERTIARY AMINE BISULFITE ADDITION PRODUCTS OF ALDEHYDES AND KETONES

Bisulfite	Ketone or aldehyde	M. p., °C.	Composition, %			
			Carbon		Hydrogen	
			Calcd.	Found	Calcd.	Found
-Piperidine						
N-Methyl-	Cyclohexanone[b]	90–93	48.46	48.38	9.15	9.10
N-*n*-Butyl-	Cyclopentanone	118	54.69	54.60	9.51	9.26
N-*n*-Butyl-	Cyclohexanone	136			9.97[c]	9.41[c]
N-*n*-Butyl-	Benzaldehyde	89–90			9.73[c]	9.48[c]
N-*n*-Butyl-	Acetone	102	51.21	51.38	9.67	9.62
N-*n*-Butyl-	Methyl *n*-propyl ketone	69			10.35[c]	9.92[c]
N-*n*-Butyl-	2-Ethylhexanal	78[a]			....	....
N-Benzyl-	Cyclopentanone	94[a]			....	....
N-Benzyl-	Cyclohexanone	114			9.02[c]	8.95[c]
N-Benzyl-	Benzaldehyde	122–124			8.82[c]	8.52[c]
N-Benzyl-	Acetone	100	57.12	56.81	8.00	8.07
N-Lauryl-	Cyclohexanone	103	63.69	63.70	10.93	10.97
N-Lauryl-	Benzaldehyde	Oil				
N-Lauryl-	Acetone	95	58.35	58.35	11.02	10.49
N-Lauryl-	Methyl *n*-propyl ketone	81[a]				
N-Cetyl-	Cyclohexanone[b]	107	66.21	66.38	11.32	11.87
N-Cetyl-	Acetone	75–78	64.09	62.56	11.43	11.39
-Morpholine						
N-*n*-Butyl-	Cyclohexanone	118			9.98[c]	10.10[c]
N-*n*-Butyl	Benzaldehyde	114–117[a]				
N-*n*-Butyl-	Acetone	88–89			11.31[c]	11.25[c]
N-*n*-Butyl-	Methyl *n*-propyl ketone	85–87	50.1	50.0	9.38	9.10
N-Benzyl-	Acetone	103[a]				
Pyridine	Cyclohexanone	99			12.36[c]	12.40[c]
Pyridine	Acetone	85[a]				
Pyridine	Benzaldehyde	Oil				

[a] These compounds were, in general, less stable than the others, and decomposed sufficiently on standing a short time to vitiate the analyses. [b] These compounds gave analyses indicating the probable presence of a molecule of water of crystallization which was not removed by drying at 50–60° or by recrystallization from ether–ethanol mixtures. [c] % sulfur

perature. In open bottles at room temperature, sulfur dioxide is evolved, the color is gradually lost and the mixtures become more viscous. The amine bisulfite complexes are, in general, insoluble in ether and carbon tetrachloride, slightly soluble in benzene, soluble in methanol and ethanol and very soluble in chloroform and water. With an increase of the carbon content of the amine, the solubility of the amine bisulfite in benzene increases but the solubility in water decreases only slightly.

Bisulfites from trimethylamine, triethylamine, N-*n*-butylpiperidine, N-*n*-butylmorpholine, N-benzylpiperidine, N-methylpiperidine, N-laurylpiperidine, N-cetylpiperidine and pyridine were studied. The amine bisulfite complexes varied in color from yellow to orange, and in viscosity from the very limpid N-butylmorpholine bisulfite to the extremely viscous N-benzylmorpholine bisulfite. Several amines gave abnormal results and have not yet been further studied; dimethylaniline and sulfur dioxide reacted to form a red unstable liquid, triethanolamine gave an intermediate glass which could not be completely converted to the bisulfite, quinaldine and sulfur dioxide formed an orange powder, and tetrahydroquinoline an orange, low-melting crystalline solid.

The reaction of the amine bisulfites with aldehydes and ketones was carried out following a general procedure. The bisulfite reagent was mixed with a slight excess of the carbonyl compound. After crystallization started, the mixture was allowed to stand for some time at room temperature. In most cases where the aldehyde or ketone was reactive, mixing was followed immediately by evolution of heat and sulfur dioxide and an accompanying loss of orange color. Crystallization and loss of color often set in at once, or within a few minutes, although in a few instances as much as forty-eight hours was required for crystals to appear. Once crystallization had started, it was observed to proceed rapidly throughout the liquid. Only with the trimethylamine and triethylamine bisulfites and one or two others were "non-crystallizable oils" obtained with aldehydes and ketones, and these were not further investigated. As typical ketones and aldehydes, the following were used: acetone, cyclohexanone, cyclopentanone, benzaldehyde, methyl *n*-propyl ketone, and 2-ethylhexanal.

The addition products could often be obtained pure merely by alternately suspending the crystals in dry ether and collecting them on a filter. In general, they were recrystallized from absolute ethanol or ethanol–ether mixtures. They all formed well-defined small white needles or plates which possessed sharp melting points. Two of those studied indicated the probability of crystallization with one molecule of water of crystallization which was not removed by recrystallization from ethanol–ether mixtures or drying in air at 50–60°; at least the analyses conformed to this assumption. The N-lauryl- and N-cetylpiperidine bisulfite derivatives were much less soluble in water than the others presumably owing to the long hydrocarbon side-chain. At the same time they were the most stable of the compounds prepared. The stability of the adducts varied considerably. Gradual decomposition, in some cases, started within a few days but others showed no appreciable change over a period of many months. Like the sodium bisulfite addition products, these amine bisulfite addition products are readily decomposed by the action of dilute mineral acids or bases, and the amines are readily recovered.

The melting points of all the compounds prepared (Table I) were within the temperature range from 69 to 136°. A wider range would be preferable if the melting points are to be used for identification purposes. Other amine bisulfites more satisfactory from this standpoint may be found.

Experimental

Triethylamine and Trimethylamine Bisulfites.—A mixture of 0.22 mole of triethylamine and 0.55 mole of water was immersed in an ice-bath, and a stream of sulfur dioxide was passed slowly into the mixture for two hours. A strongly exothermic reaction at the beginning was followed by crystallization of a white solid in the upper amine layer. As the reaction progressed, the solid dissolved and the mixture became one phase, at first colorless, then yellow, and finally orange. The viscosity passed through a stage comparable to that of molasses, then decreased until the mixture was limpid.

This product did not form solid derivatives with acetone, benzaldehyde or *p*-chlorobenzaldehyde although reactions occurred with the evolution of heat.

The formation of trimethylamine bisulfite was essentially comparable except that the amine and water were used in molar ratios. The addition of acetone, cyclohexanone or benzaldehyde resulted in oils which could not be purified.

Alkylated Piperidines and Morpholines.—Piperidine and morpholine were alkylated by dissolving the amine (1.2 moles) in 125–200 ml. of dry benzene, and adding the appropriate alkyl halide (0.6 mole) dropwise with stirring at room temperature. When the addition was completed the mixture was stirred and warmed under reflux for several hours. The morpholine or piperidine hydrohalide, which precipitated from the solution, was collected on a filter and washed with benzene. Finally, the combined filtrate and washings were fractionally distilled to obtain the pure N-alkylamine.

The constants of these products, compared with those found in the literature, are shown in Table II.

N-*n*-Butylpiperidine Bisulfite.—N-*n*-Butylpiperidine, b. p. 67–67.5° (18 mm.), which contained one molecular equivalent of water was cooled in an ice-bath and sulfur dioxide was introduced. The gas inflow was continued for fifteen minutes after the upper layer had disappeared. The product was light orange and only slightly viscous.

In a similar manner, N-methylpiperidine and pyridine were converted to their bisulfites.

TABLE II

ALKYLATED PIPERIDINES AND MORPHOLINES

Amine	B. p., °C. (lit.)	B. p., °C. (found)	Ref
N-Methylpiperidine	105.9	105–107	2
N-*n*-Butylpiperidine	175.8	67–67.5 (18 mm.)	2
N-*n*-Laurylpiperidine	161 (5 mm.)	....	3
N-*n*-Cetylpiperidine	176–177 (1 mm.)	175–179 (1 mm.)	3
N-Benzylpiperidine	245	117–119 (13 mm.)	4
N-*n*-Butylmorpholine	67–68 (10 mm.)	67–67.5 (11 mm.)	5
N-Benzylmorpholine	135–136.5 (14mm.)	129–131 (13 mm.)	6

N-*n*-Butylmorpholine Bisulfite.—N-*n*-Butylmorpholine, b. p. 67–67.5° (11 mm.), was converted to its bisulfite in the same manner as described for the *n*-butylpiperidine. The intermediate viscosity, however, was much greater in this case and the final product was deeper orange in color.

N-*n*-Benzylpiperidine Bisulfite.—When sulfur dioxide was passed into N-*n*-benzylpiperidine, b. p. 117–119° (13 mm.), the reaction mixture became so viscous that when this stage was reached the gas was allowed to flow in a slow stream over the surface of the liquid for two days with occasional stirring. Toward the end the viscosity decreased.

N-*n*-Benzylmorpholine Bisulfite.—N-*n*-Benzylmorpholine, b. p. 129–131° (13 mm.), exhibited the same characteristics as *n*-benzylpiperidine when treated with sulfur dioxide. The viscosity was such that only by prolonged treatment with sulfur dioxide could part of it be converted to the bisulfite.

N-Lauryl- and N-Cetyl-piperidine Bisulfites.—When N-laurylpiperidine and N-cetylpiperidine were used, white solids formed as intermediates which made it necessary to pass the sulfur dioxide over the surface for a long period. The supernatant orange-colored liquid which formed on the surface was poured off from time to time until the conversion was complete.

Formation of Bisulfite Addition Products.—The general procedure consisted in addition of a slight excess of aldehyde or ketone to the amine bisulfite complex at room temperature. The color of the reagent was discharged completely only in the presence of an excess of the aldehyde or ketone. Usually, solution took place and the mixture became clear with a slight evolution of heat and a copious evolution of sulfur dioxide. In about one to five minutes the mixture had become colorless, and white crystals usually appeared. After fifteen minutes following solidification, dry ether was added and the crystals filtered. They were then recrystallized from absolute ethanol or absolute ethanol–ether mixtures and dried at 50°.

Some of the reaction mixtures required one hour or more before crystallization started; in particular, benzaldehyde, methyl *n*-propyl ketone or 2-ethylhexanal with N-*n*-butylpiperidine bisulfite, benzaldehyde with N-benzylpiperidine bisulfite and cyclohexanone with N-methylpiperidine bisulfite. The N-benzylmorpholine bisulfite was so insoluble as to require excess of acetone to take it into solution. Pyridine bisulfite and benzaldehyde did not decolorize, and no product crystallized.

The yields in practically all the reactions were entirely satisfactory, and losses by recrystallization were only slight.

Summary

A variety of tertiary amines, N-methyl-, N-*n*-butyl-, N-benzyl-, N-lauryl-, and N-cetyl-piperidines, N-butyl- and N-benzyl-morpholines were converted to their bisulfites. These bisulfites were allowed to react with representative aldehydes

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(2) Magnusson and Schierz, University of Wyoming, Pub., **7**, 1 (1940); *C. A.*, **34**, 6867 (1940).

(3) Stross and Evans, THIS JOURNAL, **64**, 2511 (1942).

(4) Clarke, *J. Chem. Soc.*, **99**, 1927 (1911).

(5) Blicke and Zienty, THIS JOURNAL, **61**, 771 (1939).

(6) Mason and Zief, *ibid.*, **62**, 1450 (1940).

and ketones; acetone, cyclopentanone cyclohexanone, methyl *n*-propyl ketone, benzaldehyde and 2-ethylhexanal.

The amine bisulfite adducts were characterized. In general they are white crystalline solids, readily crystallized from ethanol or ethanol–ether mixtures. Like the corresponding sodium bisulfite adducts, they are decomposed with acids or alkalies into the amines.

URBANA, ILLINOIS RECEIVED AUGUST 9, 1948

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Amine Bisulfites. II. Their Use as Resolving Agents for Aldehydes and Ketones

BY ROGER ADAMS AND JOHN D. GARBER[1]

The addition products formed from tertiary amine bisulfites and aldehydes or ketones have been described in the first communication.[2] The extension of this study to certain primary amine bisulfites has now been made. The bisulfites of benzylamine, *s*-butylamine, β-phenethylamine, α-phenethylamine, and β-naphthol phenylaminomethane have been allowed to react with acetone, cyclopentanone, cyclohexanone, 3-methylcyclohexanone, benzaldehyde, heptaldehyde, isovaleraldehyde and valeraldehyde. The reactions usually proceeded smoothly and the adducts are white crystalline compounds, readily purified from absolute ethanol or ethanol–water mixtures in the case of the higher molecular weight substances. The melting points range between 100 and 160° as shown in Table I. Although stereoisomers in certain of the adducts are possible one form predominated, for only a single substance was isolated in good yield.

The gradation in properties of the compounds listed in Table I is interesting. It was noticed that if the molecular weight of either the amine or carbonyl compound was increased, the salt-like properties of the bisulfite addition compound became more indefinite, and the solubility in water and ethanol decreased. The stability also was found to vary between wide limits, an observation which made the temperature of recrystallization an important factor. Thus, the *s*-butylamine bisulfite of *n*-valeraldehyde was formed in the usual manner, but the solid, after isolation, immediately began to evolve sulfur dioxide. It could be recrystallized, but by the time the sample was dry enough for analysis it was impure again. On the other hand, the addition compounds of β-naphthol phenylaminomethane bisulfite with most of the carbonyl compounds listed could be boiled in ethanol without appreciable decomposition.

When sulfur dioxide was allowed to bubble through an equimolar mixture of the amine and water, usually with the addition of a little ether or in certain cases of ethanol, a white precipitate was formed. This product, chiefly the amine sulfite, was not isolated, but the introduction of sulfur dioxide was continued until a homogeneous, yellow, viscous liquid was produced. It is postulated that the yellow color of the resulting product is due to a complex, perhaps of the type $(RNH_2)_x:(SO_2)_y$. Such a complex, in the presence of water and a suitable carbonyl compound, reacts to form an amine bisulfite addition compound. The evolution of sulfur dioxide in the latter reaction may be cited as evidence that y is greater than x. Moreover, Bright and Jasper[3] have shown that the 1:1 trimethylamine–sulfur dioxide complex is colorless.

The procedure for forming the adducts with aldehydes and ketones was essentially that previously described.[2] A few isolated experiments were unsuccessful. No reaction product could be isolated from the following combinations: camphor or carbethoxycyclohexanone and *dl*-α-phenethylamine bisulfite; glucose and *dl*-*s*-butylamine bisulfite; benzaldehyde and aniline bisulfite; propiophenone and benzylamine bisulfite (too unstable). In a few instances indicated in the table, no crystalline products formed.

If an optically active amine bisulfite were allowed to react with a racemic aldehyde or ketone, it is apparent that the product would be a mixture of four stereoisomers since a new asymmetric carbon holding the hydroxyl group would be introduced.

$$\underset{dl}{\mathrm{RCHO}} + \underset{d\text{ or }l}{\mathrm{R'NH_3SO_3H}} \longrightarrow \underset{dl\ dl\qquad d\text{ or }l}{\mathrm{RCHOHSO_3H_3NR'}}$$

Whether or not all four isomers are formed is of minor significance since the success in resolution will depend upon the ease of isolation of a single optically pure product. If this could be accomplished, a relatively simple method of resolving racemic aldehydes and ketones would be available.

Woodward, Kohman and Harris[4] have enumerated the known resolving reagents for ketones and aldehydes, most of which suffer the disadvantages of difficulty in preparation and of failure to give crystalline derivatives with many carbonyl compounds. They proposed a new reagent *l*-menthyl N-aminocarbamate, which was used by them merely to resolve *dl*-camphor, but which probably will prove to be a much more satisfactory general reagent than any of the others. Sobotka,

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[1] An abstract of a thesis submitted in partial fulfillment of requirements for the degree of Doctor of Philosophy, 1943.

[2] Adams and Lipscomb, THIS JOURNAL, **70**, 519 (1948).

[3] Bright and Jasper, *ibid.*, **65**, 1262 (1943).

[4] Woodward, Kohman and Harris, *ibid.*, **63**, 120 (1941).