crystallized from benzene–light petroleum in colorless crystals, m.p. 71–72°.

Anal. Calcd. for $C_{17}H_{20}O_5S$: C, 60.7; H, 6.0; S, 9.52; OCH_3, 18.45. Found: C, 60.57; H, 6.16; S, 10.87; OCH_3, 17.0.

4-Methoxystyrene.—A mixture of 4-methoxycinnamic acid (50 g.), pure quinoline (150 ml.) and copper powder (5 g.) was slowly distilled in such a rate that a drop distilled over every 2 seconds. The distillate was dissolved in ether, extracted with ice-cold dilute hydrochloric acid, then with cold sodium carbonate solution, and dried (Na_2SO_4). Ether was evaporated in a nitrogen atmosphere, and the product distilled in a vacuum to give 4-methoxystyrene as a colorless oil, b.p. 51–52° (1 mm.)[3] (23–25 g.).

4-Methoxystyrene Bromohydrin (VI).—A solution of 4-methoxystyrene dibromide (20 g.) [prepared according to Guss,[6] using carbon tetrachloride instead of ether and chloroform] in acetone (100 ml.) was diluted with water (100 ml.) and stirred for 1 hour at room temperature. Water (200 ml.) was added, and the mixture extracted with ether, washed with cold dilute sodium hydrogen carbonate solution, and dried (Na_2SO_4). Ether was evaporated at room temperature to leave a pale yellow oil, which could not be purified by distillation as it was decomposed on heating (yield nearly quantitative).

4-Methoxystyrene Oxide (VII).—The bromohydrin (10 g., *ca.* 0.0435 mole) was dissolved in methyl alcohol (50 ml.) and treated with a solution of potassium hydroxide (2.5 g., *ca.* 0.446 mole) in methyl alcohol (50 ml.). The mixture was allowed to stand for 10–15 minutes with occasional shaking. It was diluted with ice-cold water, extracted with ether, and dried (K_2CO_3). The removal of the ether at room temperature in a nitrogen atmosphere left a nearly colorless oil, which solidified when cooled in ice and melted at room temperature. The product might be a mixture of the oxide and its dimerization product, the dioxane, and being unstable could not be purified by vacuum distillation.[4]

2-(4′-Methoxyphenyl)-2-methoxyethanol (IV).—The oxide (5 g.) was dissolved in methyl alcohol (25 ml.) containing two drops of concentrated sulfuric acid. The mixture was allowed to stand at room temperature for 2 hours, diluted with water, extracted with ether, washed with sodium hydrogen carbonate, and dried (Na_2SO_4). Evaporation of the ether left an oil which could not be obtained in a crystalline form by crystallization (*cf.* first method). It was repeatedly extracted with hot light petroleum (b.p. 30–60°), and separated from the insoluble fraction by decantation. The solvent was evaporated at room temperature and the remaining alcohol (*ca.* 3 g.) was converted into the tosylate in the usual manner. The product (*ca.* 3.5 g.) was pressed on a piece of unglazed clay to remove traces of a low melting material. It was crystallized from benzene–light petroleum (b.p. 30–60°) to give colorless crystals, m.p. 71–72°, undepressed on admixture with an authentic specimen.

Anal. Calcd. for $C_{17}H_{20}O_5S$: C, 60.7; H, 6.00; S, 9.52. Found: C, 61.22; H, 6.27; S, 8.5.

Action of Perbenzoic Acid on 4-Methoxystyrene.—A stirred solution of perbenzoic acid (11.8 g., 0.086 mole) in chloroform (100 ml.) was cooled in a freezing mixture and treated dropwise with a solution of 4-methoxystyrene (11.0 g., 0.082 mole) in chloroform (50 ml.). The temperature was not allowed to rise above 0°. After the addition was completed, the mixture was kept in a freezing mixture for one hour, then allowed to stand in a refrigerator for 24 hours. The chloroform solution was washed with cold potassium carbonate solution to remove the benzoic acid, dried (Na_2SO_4), and the chloroform removed under reduced pressure. The product was distilled in a vacuum, and the fraction which boiled at 70° (3 mm.) was rejected. Distillation was interrupted and the residue (*ca.* 10 g.) which failed to solidify was treated with *p*-toluenesulfonyl chloride (10 g.) in pyridine (10 ml.), left overnight and worked up as usual. On crystallization from methyl alcohol the **tosylate of 1-(4′-methoxyphenyl)-ethanediol-1,2 monobenzoate** was obtained in nearly colorless crystals, m.p. 113–114°.

Anal. Calcd. for $C_{23}H_{22}O_6S$: C, 64.78; H, 5.20; S, 7.51. Found: C, 64.54; H, 5.26; S, 7.65.

On hydrolysis of the benzoate with alcoholic alkali it gave benzoic acid and 1-(4′-methoxyphenyl)-ethanediol-1,2, m.p. 81–82°. Fodor and Kovács[5] gave m.p. 82°.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.25; H, 7.20. Found: C, 63.8; H, 7.31.

(3) C. Walling and K. B. Wolfstirn, THIS JOURNAL, **69**, 852 (1947).

(4) C. O. Guss, *ibid.*, **74**, 2562 (1952).

(5) G. Fodor and Ö. Kovács, *ibid.*, **71**, 1047 (1949).

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Acetylation and S-Alkylation of Ethylene Thiourea[1]

BY JOHN E. BAER[2] AND ROBERT G. LOCKWOOD

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Although a number of alkylisothioureas have been reported,[3] few S-alkyl derivatives of ethylene thiourea (2-alkylmercapto-2-imidazolines) are known. The methyl,[4] ethyl[4] and carboxymethyl derivatives[5] were prepared some years ago. Recently a series of substituted 2-benzylmercaptoimidazolines were synthesized by Easton, Hlynsky and Foster.[6a] This paper reports the preparation of a series of 2-alkylmercapto-2-imidazolines. The impure salts tended to be hygroscopic. Perhaps for this reason numerous attempts to prepare the amyl derivative yielded only crude material melting at about 60°. The compounds that were prepared are shown in Table I.

About a year after the present work was done, two reports[6a,b] cited the melting point of the benzyl derivative as 172°. Redetermination of the melting point indicated that our sample had undergone transformation to the 172° isomer upon long standing. We subsequently found an earlier report confirming the 147° melting point.[6c] The polymorphism which Donleavy noted for S-benzylthiuronium chloride[7] appears to hold for 2-benzylmercaptoimidazoline hydrochloride. The alkyl derivatives, like ethylene thiourea itself, are slowly decomposed by prolonged heating with acid or alkali, to yield, at least in part, the corresponding mercaptan. The bases tend to be unstable, hygroscopic and not easily crystallizable. The pK_a of the butyl derivative was found by potentiometric titration of the hydrobromide salt with alkali to be 9.0.

Attempts to condense ethylene thiourea with β-chloropropionitrile, β-chloro- or β-bromopropionic acid, or corresponding esters were without success although ethyl chloroacetate reacted easily. From the condensation of ethylene chlorobromide with ethylene thiourea, I and II were obtained, m.p. 167° and about 270°, respectively. I, which contained chlorine and bromine and had the correct carbon and hydrogen content, was converted to a base, m.p. 64°, containing chlorine but not bromine.

(1) This work was carried out principally in 1950 under a grant from the Research Corp., and was presented at the A.C.S. Meeting in Miniature, Phila., Jan. 29, 1953.

(2) Pharmacology Section, Sharp & Dohme Division, Merck & Co., Inc., West Point, Pa.

(3) T. B. Johnson and J. M. Sprague, THIS JOURNAL, **58**, 1348 (1936).

(4) W. Schacht, *Arch. Pharm.*, **235**, 451 (1897).

(5) T. B. Johnson and C. O. Edens, THIS JOURNAL, **63**, 3527 (1941); *ibid.*, **64**, 2706 (1942).

(6) (a) N. R. Easton, A. Hlynsky and H. Foster, *ibid.*, **73**, 3507 (1951); (b) S. R. Aspinall and E. J. Bianco, *ibid.*, **73**, 602 (1951); (c) J. Walker, *J. Chem. Soc.*, 1996 (1949).

(7) J. J. Donleavy, THIS JOURNAL, **58**, 1004 (1936).

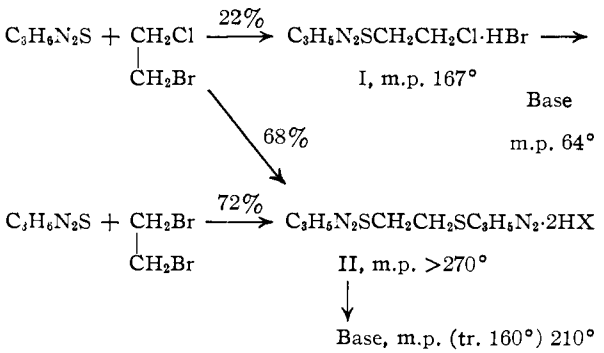
TABLE I

2-ALKYLMERCAPTO-2-IMIDAZOLINES

R	Salt	M.p. of salt, °C.	Analyses of salt, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	M.p. of base, °C.
C_2H_5–	HI	113–114.5[a]	23.3	23.9	4.3	4.4	55–60
n-C_3H_7–	HBr	95–95.5	32.0	32.1	5.8	5.9	73–74
i-C_3H_7–	HBr	135–135.5	32.0	32.3	5.8	6.0	106–108
n-C_4H_9–	HBr	116.5–117	35.2	35.3	6.3	6.4	55–57.5
$C_6H_5CH_2$–	HCl	147–147.5[b]	52.5	52.8	5.7	5.7	69–69.5
$ClCH_2CH_2$–	HBr	165–167	24.5	24.4	4.1	4.3	64
$C_2H_5OCOCH_2$–	HCl	140–141	37.4	37.4	5.8	5.9	
C_2H_4:[c]			41.7	41.8	6.1	6.1	(160) 210

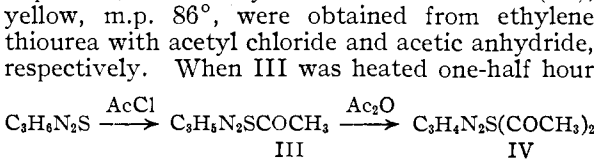
[a] Reported m.p. 157°.[4] [b] Reported m.p. 172°.[6a,b] [c] Analytical data for base.

II, also containing chlorine and bromine as a double salt, was converted to a base which was stable, crystallizable to analytical purity and contained no halogen. This same base was obtained from the condensation product of ethylene thiourea with ethylene bromide (II, HX = HBr) in good yield. Since our preparation of the base it has been described in a patent.[8]

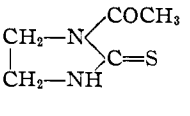


Acetylation of Ethylene Thiourea.—Thiourea may be acetylated on the sulfur atom with acetyl chloride in the cold. When heated for several hours in boiling toluene, acetylisothiourea is rearranged to N-acetylthiourea.[9] Under suitable conditions, a diacetyl derivative of thiourea may be obtained.[10] Study of the acetylation reaction was extended to the behavior of ethylene thiourea with acetic anhydride and acetyl chloride.

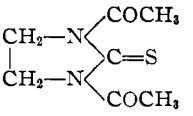
Monoacetylimidazolidine-2-thione (III), white, m.p. 165°, and diacetylimidazolidine-2-thione (IV), yellow, m.p. 86°, were obtained from ethylene thiourea with acetyl chloride and acetic anhydride, respectively. When III was heated one-half hour



in acetic anhydride, IV was produced. Both compounds were quantitatively hydrolyzed to ethylene thiourea in acid. Neither compound was altered by refluxing in xylene for several hours. Neither compound reacted with sodium nitroprusside in ammonium hydroxide. Both compounds reacted with warm lead nitrate solution; IV reacted with silver nitrate to produce a black precipitate, presumably the metal sulfide. The ultraviolet absorption spectra of the compounds are similar, and unlike the spectra of ethylene thiourea or 2-butylmercaptoimidazoline. The difference in the spectra of III and IV is in accord with an increase in resonance without profound change in structure. The hydrolysis of III and IV to ethylene thiourea, rather than to thioacetic acid and ethylene urea, together with the other properties described, make it likely that III is 1-acetylimidazolidine-2-thione and IV is 1,3-diacetylimidazolidine-2-thione.



III



IV

Dixon, Werner and Kohmann all prepared a diacetylthiourea which was yellow in color, but did not agree whether this was an N,N′ or an N,S-diacetyl compound. It is probable that IV is an analogous compound in the ethylene thiourea series. In the acetylation of ethylene thiourea with acetyl chloride there was some evidence of a compound which melted at about 140°. This might have been the S-acyl compound which, under the conditions of the reaction, was converted to the N-acyl compound.

Experimental

2-Alkylmercaptoimidazolines.—Two grams (0.02 mole) of ethylene thiourea and a slight molar excess of the appropriate alkyl halide were refluxed in 20 ml. of ethanol for 1 to 3 hours. Evaporation of the solvent under reduced pressure yielded either the crystalline salt or a sirup that crystallized slowly in the cold. The salts were recrystallized from alcohol or alcohol–acetone. No attempt was made to secure maximum yields; actual yields varied from 50 to 90%. Condensations of isopropyl bromide and benzyl chloride also were carried out in sodium ethoxide solution, but poor yields (35%) of the bases were obtained by this procedure. When concentrated aqueous solutions of the salts were made alkaline with 10% sodium hydroxide, the corresponding bases were precipitated.

1-Acetylimidazolidine-2-thione (III).—Ethylene thiourea (5.1 g., 0.05 mole) was suspended in acetyl chloride (7.2 ml., 0.1 mole) and 15 ml. of glacial acetic acid, and the mixture was refluxed for 3 hours. The crystalline material (3.2 g.) was washed promptly and thoroughly with petroleum ether to remove excess acetyl chloride, then was recrystallized from 95% ethanol; yield 2.4 g. (35%), m.p. 161–163°. The compound gave a negative test for ethylene thiourea with copper sulfate in concentrated hydrochloric acid.[5]

Anal. Calcd: C, 41.64; H, 5.59; N, 19.43. Found: C, 41.67; H, 5.72; N (Kjeldahl), 19.44.

(8) E. B. Knott and J. Morgan, U. S. Patent 2,514,650 (July 11, 1950); *C. A.*, **45**, 1889 (1951).

(9) M. L. Moore and F. S. Crossley, THIS JOURNAL, **62**, 3273 (1940).

(10) (a) E. F. Kohmann, *ibid.*, **37**, 2130 (1915); (b) E. A. Werner, *J. Chem. Soc.*, **109**, 1128 (1916); (c) A. E. Dixon and J. Taylor, *ibid.*, **117**, 720 (1920).

1-Acetylimidazolidine-2-thione (100 mg., 0.07 mole) was warmed with 0.7 ml. of 0.1 *N* hydrochloric acid in water until the aqueous phase had evaporated (4 hours). The residue, weighing 71.7 mg. (101%), had the same melting point and mixed melting point as authentic ethylene thiourea.

1,3-Diacetylimidazolidine-2-thione (IV).—Ethylene thiourea (5.1 g., 0.05 mole) was dissolved in 20 ml. of acetic anhydride. The solution turned yellow almost at once and it was refluxed for three hours. The mixture was evaporated to dryness under reduced pressure and the crude needles recrystallized from 10 ml. of methanol; yield 7.35 g. (79%), m.p. 85–87°. The compound was slightly soluble in water; it gave a negative test with copper sulfate in hydrochloric acid.

Anal. Calcd.: C, 45.14; H, 5.41; N, 15.04; S, 17.22. Found: C, 45.18; H, 5.34; N (Kjeldahl), 15.08; S, 17.09.

One gram of III was refluxed for one-half hour with 5 ml. of acetic anhydride. Evaporation to dryness yielded yellow needles of IV, m.p. 84–85.5°.

1,3-Diacetylimidazolidine-2-thione (93 mg., 0.05 mole) was warmed with 0.5 ml. of 0.1 *N* hydrochloric acid in water until the aqueous phase had evaporated (4 hours). The residue, weighing 52.0 mg. (102%) had the same melting point and mixed melting point as authentic ethylene thiourea.

Ultraviolet Spectra.—Spectra were measured in ethanol at appropriate dilutions with a Beckman DU spectrophotometer. Wave lengths of maxima and molar absorptivity were found as follows: ethylene thiourea, 235 mμ (15,000); 2-*n*-butylmercaptoimidazoline HCl, 222 mμ (10,500); acetylimidazolidinethione, 235 mμ (12,500), 270 mμ (11,000), shoulder at 325 mμ (80); diacetylimidazolidinethione, 252 mμ (20,000), 288 mμ (11,000), 375 mμ (54).

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Unsymmetrically N-Substituted Piperazines. IV. N-Alkyl Derivatives

BY RICHARD BALTZLY

RECEIVED JULY 27, 1953

While alkylation of piperazine by lower alkyl halides gives mixtures from which mono-N-alkyl derivatives are not readily separated, the use of higher alkyl halides permits relatively facile isolation of pure products. Two mono-N-alkylpiperazines have been reported previously, the *n*-lauryl[1] and the *n*-decyl[2] derivatives. The former of these, which possesses considerable antibacterial potency, was also found to have marked fungistatic and fungicidal action. Since infections with pathogenic fungi have aroused increased interest in recent years, several related mono-N-alkylpiperazines were prepared. In this series optimal activity was observed with the decyl and lauryl derivatives.

As 2,5-dimethylpiperazine had become available commercially a somewhat parallel series of N-alkyl derivatives was also prepared from this base. The peak of activity was now found associated with the lauryl and tetradecyl compounds. As between members of the two series having the same N-alkyl group, the 2,5-dimethyl compound was never inferior and usually substantially more active, and, at the same time, less toxic. This difference in toxicity was appreciable after injection (intraperitoneally) and very marked on oral administration which suggests possible use against *Monilia* infections of the digestive tract.

(1) R. Baltzly, J. S. Buck, E. Lorz and W. Schoen, THIS JOURNAL, **66**, 263 (1944).

(2) K. E. Hamlin, A. W. Weston, F. E. Fischer and R. J. Michaels, Jr., *ibid.*, **71**, 2731 (1949).

Microbiological tests in buffered solutions indicate that the fungicidal entity both with these and with related piperazine derivatives (*e.g.*, N-methyl-N′-(*p*-chlorobenzhydryl)-piperazine) is the monocation, activity is greater at *p*H 7–8 than at *p*H 6 or *p*H 5.[3]

The 2,5-dimethylpiperazine used as starting material is preponderantly (over 90%) the *trans* form. The mono-N-alkyl derivatives of such a centrosymmetrical substance should be capable of optical activity. So far none has been resolved.

Three carbamates (II, VI and VIII) and two guanidines (IV and X) were prepared from the corresponding N-alkylpiperazines. Compounds II and VI had hypnotic activity of a low order.

Experimental

The physical properties and analytical data of the compounds reported are shown in Table I. Most of the mono-N-alkylpiperazine dihydrochlorides crystallized from ethanol–ether mixtures in fine platelets. In the cases of the higher members (IX, XVII and XVIII) these platelets were rather waxy and the crystals, once obtained, were sparingly soluble in water. A mono hydrochloride was prepared from XII but its physical properties discouraged further work with mono-cationic salts. Melting points over 220° are uncorrected and may be regarded as only approximate. Some of them are decomposition points and others are attended by decomposition and are markedly dependent on minor variations in technique. Hamlin, Weston and co-workers[2] have reported the melting point of V as 271–274°. The writer has obtained the figure shown in Table I on their material as well as our own but would not expect either value to be duplicated by a third party.

Alkylations.—Ideally these reactions would be best performed in a one-phase system at a *p*H favoring predominance of the mono-valent cation (*p*H 7–8). With benzyl chloride yields of monobenzylpiperazine as high as 72% have been obtained in this fashion. With the higher alkyl halides the ideal conditions are not attainable since the alkyl halides have sparing solubility even in hot alcohol and the reaction takes an inordinate time if the halide is added slowly enough to prevent separation of layers. Buffering is also rather unsatisfactory. Piperazine forms rather insoluble phosphates and while acetates give good buffering, the acetate ion reacts appreciably with the alkyl halide. Thus use of acetate buffer results in small loss through formation of dialkylpiperazine but leaves a considerable neutral fraction, presumably alkyl acetate. On a scale large enough to justify recovery of materials, the most convenient and economical procedure is to employ 2 to 3 equivalents of the piperazine and to ignore buffering possibilities.

The separation of products is greatly facilitated by the facts that the mono-N-alkylpiperazines of these molecular dimensions are more readily extracted from ether by dilute acid than are the dialkyl derivatives and that the dihydrochlorides of the latter are sparingly soluble in water. The general procedure has been to extract the total ether-soluble material with successive portions of dilute hydrochloric acid until crystals began to form. At this point an excess of hydrochloric acid would be added to the ethereal layer and the precipitated solid would be filtered off and washed with ether and water. The washings would then be partitioned, the aqueous layer added to the previous acid extracts and the ethereal layer evaporated. Except when acetate buffers were used in the reactions this neutral residue was generally quite small (less than 5% of the starting halide). The aqueous layers were then basified strongly, the basic oil was taken into ether and dried over potassium carbonate. On distillation, the monoalkylpiperazines came over rather sharply leaving only small residues (1 to 2 cc.) of less volatile material. No attempt was made to investigate further the N,N′-dialkylpiperazines separated in working up the reaction mixtures. The following experiment is given in detail to exemplify the methods used.

(3) The results of the microbiological studies will be reported in more detail by Dr. Marion B. Sherwood of these laboratories.