the temperature of the reaction zone or the time required for the gases to pass through it. We hope to make a study of the influence of these important factors later on.

Although a constant boiling fraction (b. p. about −48°) had been observed from the first,[5] repeated distillation of the product boiling from −50 to −40° at atmospheric pressure failed to separate it into pure components. However, on redistillation at elevated pressure, a pure compound was isolated, boiling at −38° at 1200 mm., and −48.5° at atmospheric pressure. It froze sharply at −103°, and had a molecular weight of 119. This was the hitherto unknown pentafluoroethane, CF_3CHF_2 (mol. wt. 120).

Anal. Calcd. for C_2HF_5: F, 79.2. Found: F, 79.0, 79.1.

When the material boiling in the range from −28 to −19° was distilled at reduced pressure, a fraction was isolated, boiling at −46 to −50° at 200 mm., which on redistillation at atmospheric pressure yielded another pure compound boiling from −23.5 to −22.5° with a molecular weight of 101–102. This was *sym*-tetrafluoroethane (b. p. −23°,[6] mol. wt. 102).

Anal. Calcd. for $C_2H_2F_4$: F, 74.5. Found: F, 74.5, 74.2.

Most of the product boiling above −19° consisted of a third pure compound, boiling at 3°, and freezing at −84°, with a constant molecular weight of 84. This was undoubtedly 1,1,2-trifluoroethane (b. p. 5°,[6] mol. wt. 84).

Anal. Calcd. for $C_2H_3F_3$: F, 67.8. Found: F, 67.8, 67.9.

(5) Calfee and Bigelow, THIS JOURNAL, **59**, 2072 (1937).
(6) Henne and Renoll, *ibid.*, **58**, 887, 889 (1936).

In addition to these compounds, a small amount of material was isolated boiling at −56 to −55°, and freezing at −132°, with a molecular weight of 103, but the quantity obtained was insufficient for analysis. Also, a constant boiling mixture, b. p. −19°, mol. wt. 92–98, was obtained, at times in considerable amounts, as well as small quantities of other materials, but these were not separated. No trace of ethyl fluoride (b. p. −38°) was found, even in a special run in which the ratio of fluorine to ethane was 2:6, although in this case over a quarter of the product boiled in the vicinity of 26° with a molecular weight of 70–75.

The writers are glad to express here their appreciation to Mr. Elbert H. Hadley for valuable assistance, and to the Duke University Research Council for a grant.

Summary

A study has been made of the influence of nitrogen dilution on the vapor-phase fluorination of ethane, and it has been found that a mixture of partially fluorinated ethanes can be obtained in excellent yield under suitable conditions.

Pentafluoroethane CF_3CHF_2, *sym*-tetrafluoroethane CHF_2CHF_2 and 1,1,2-trifluoroethane CHF_2CH_2F have been isolated from the reaction products boiling above −78°. The first of these is a new compound, and the others have not been prepared previously by direct fluorination.

DURHAM, NORTH CAROLINA RECEIVED JANUARY 19, 1940

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

The Synthesis of Some New Pyrimidines and Uric Acids fom Cystamine[1]

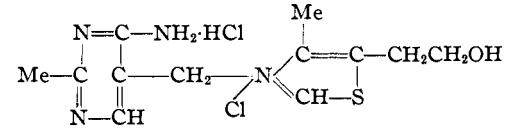
BY EDWARD JAMES MILLS, JR.,[2] AND MARSTON TAYLOR BOGERT

Attention recently has been directed increasingly to the important role played by various organic sulfur compounds concerned with vital physiological processes, and the present paper is a contribution in a field whose exploration seems to hold promise of interesting and perhaps useful results.

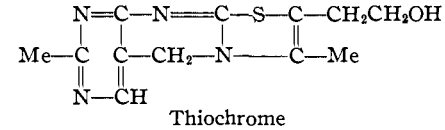
The great therapeutic value of Vitamin B_1, and its structural relationship to thiochrome, suggests the possibility of discovering other remedial drugs containing both the pyrimidine and thiazole nuclei, perhaps even when these two cycles have coalesced to a single bicyclic system with two atoms common to each of its constituent rings.

(1) Presented before the Organic Division at the Cincinnati Meeting of the American Chemical Society, April 8, 1940.
(2) E. R. Squibb & Sons Research Fellow at Columbia University, 1937–1939; present address, Department of Anatomy, College of Physicians and Surgeons, Columbia University, New York.

Fusion of the pyrimidine and thiazole, or of the purine and thiazole, cycles obviously will result in different structures depending upon the points of attachment of the two rings.

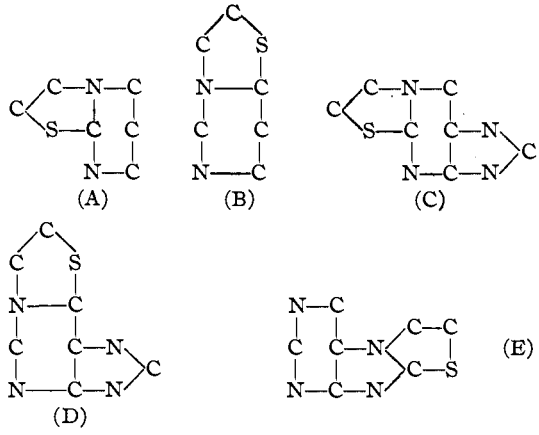


Vitamin B_1 hydrochloride



Thiochrome

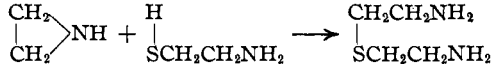
The polycyclic systems with which this communication deals are represented by skeletons (A), (B), (C) and (D):



For the synthesis of derivatives of (A), (B), (C) or (D), a convenient initial material is *beta*-mercaptoethylamine, and the Flow Sheets beyond show the progress made by utilizing that compound.

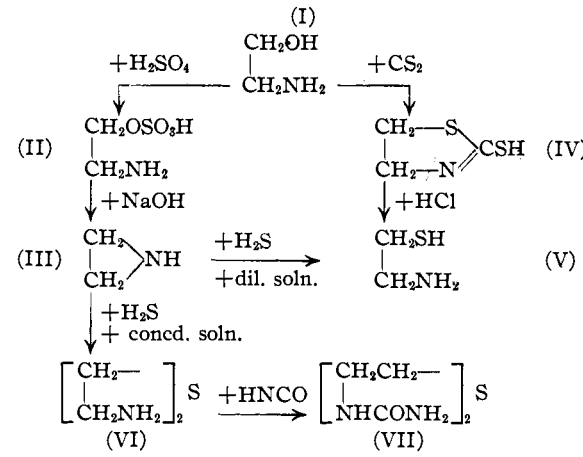
In 1936, Ochiai,[3] and Ochiai and Kitagawa,[4] prepared compounds containing the skeleton (E), but gave no information concerning their pharmacological properties.

The *beta*-mercaptoethylamine (V) required for our experiments was prepared by the hydrolysis of 2-mercaptothiazoline (IV), and also by the action of hydrogen sulfide upon a dilute solution of ethyleneimine (III). Of the two processes, the latter was the more satisfactory. The reaction in this case, as shown on Flow Sheet A, is a simple one, whether the cyclic (III), or the acyclic formula (CH_2=$CHNH_2$), be assigned to the imine. It was attempted by Gabriel and Eschenbach[5] many years ago, by passing hydrogen sulfide through ethyleneimine cooled to 0°, but their product was the sulfide (VI) and not the mercaptan (V) or its oxidation product the disulfide (VIII). It seems likely that this was due to a secondary reaction between the mercaptan first formed and the remaining unaltered imine.



A study of this problem and some preliminary experiments, convinced us that the conditions for optimum yields of the mercaptan (V) desired, or of the disulfide (VIII), would be (1) high concentration of hydrogen sulfide, (2) low concentration of the imine (III), and (3) low local concentration of the mercaptan (V) formed, to avoid the production of the monosulfide (VI). As described in detail beyond, the application of these conclusions resulted in yields of the mercaptoethylamine amounting to 85–95% of that calculated.

FLOW SHEET A



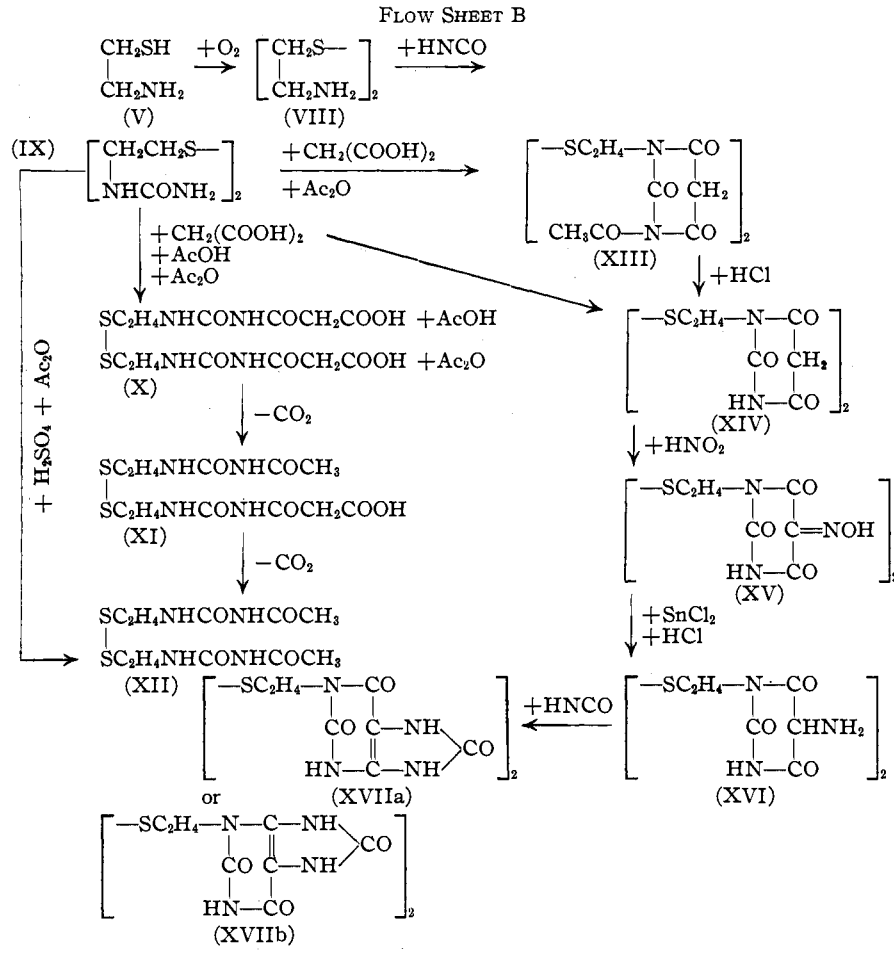
By oxidation, the mercaptan was easily converted into the disulfide (VIII) (cystamine or decarboxycystine), whose urea derivative (IX) may prove of interest if it should be found to possess hypoglycemic properties resembling those reported by Ackerman and Heinsen[6] for the analogously constituted diguanidino-diethyldisulfide. It is hoped that it also can be examined, together with its disulfoxide, to determine the effect, if any, upon the regulation of growth by cell proliferation, that phenomenon of natural chemical control of growth by sulfhydryl-disulfide–disulfoxide systems which has been studied so extensively and so ably by Hammett and his co-workers.[7]

The disulfide uric acid (XVII) also may merit attention in connection with cell proliferation studies, since it is structurally a uric acid with an alkyl disulfide side chain, or a cystamine in which the terminal nitrogen atoms form a part of two purine nuclei.

As will be observed, all of these compounds, as shown on Flow Sheet B, were retained in the stable disulfide form, to simplify purification and to avoid complications which would arise were a free mercapto group present. The reduction of the disulfide to the mercaptan was postponed purposely until it became necessary to reduce the disulfide uric acid (XVII) for the preparation of the *beta*-mercaptoethyl derivative and its cyclization product the thiazolidinouric acid.

(3) Ochiai, *Ber.*, **69B**, 1650 (1936).
(4) Ochiai and Kitagawa, *J. Pharm. Soc. Japan*, **56**, 979 (1936).
(5) Gabriel and Eschenbach, *Ber.*, **30**, 2497 (1897).
(6) Ackerman and Heinsen, *Z. physiol. Chem.*, **235**, 115 (1935).
(7) Hammett, *et al.*, *Protoplasma*, 1929–1933, numerous articles.

FLOW SHEET B



It has been learned that pyrimidines of type XIV, carrying either a *beta*-mercaptoethyl or an alkyldisulfide side chain in position 1, are very sensitive to alkaline solutions, the cycle tending to break open between positions 1 and 6, with formation of malonuric acids of the structure $RNHCONHCOCH_2COOH$. For this reason, the use of sodium ethylate as a condensing agent[8] in the preparation of these barbituric acids was not satisfactory.

This is in line with the findings of Aspelund and Skoglund,[9] who reported that 5,5,-1-trisubstituted barbituric acids were split by alkalies into both $RNHCONHCOCR_2COOH$ and $H_2NCONRCOCR_2COOH$, the former being produced in the larger quantity.

On the other hand, such pyrimidines are quite stable to acid solutions. The 3-acetyl derivative (XIII), for example, could be hydrolyzed readily to the unacetylated compound (XIV) by the action of hot 30% hydrochloric or sulfuric acid, without any apparent rupture of the pyrimidine cycle.

From the cystamine urea (IX), by condensation with malonic acid, in the presence of acetic acid and acetic anhydride, according to the method of Biltz and Wittek,[10] and Hepner and Frenkenberg,[11] the barbituric acid (XIV) was obtained, together with its acetyl derivative (XIII) and the dimalonuric acid (X). The latter (X) yielded the barbituric acid (XIV) when digested in glacial acetic acid solution with acetic anhydride; and the same product resulted when the acetyl derivative (XIII) of the barbituric acid was hydrolyzed by mineral acid.

Treatment of a mixture of the cystamine urea and malonic acid (IX) with acetic anhydride at 85–90°, also gave the acetylated barbituric acid (XIII).

The dimalonuric acid (X), when heated alone or with weakly acid solutions, lost first one and then a second mole of carbon dioxide, yielding successively the acetyl malonuric acid (XI) and then the diacetyl derivative (XII). The latter was also formed when the diureido disulfide (IX) was dissolved in acetic anhydride, a few drops of concentrated sulfuric acid added, and the mixture heated for three hours at 100°.

Grimaux[12] reported that when a mixture of urea and malonic acid was treated with phosphorus oxychloride, there resulted barbituric acid and an unidentified by-product, which latter was also formed when pure barbituric acid was

(8) Fischer, *Ann.*, **335**, 338 (1904).

(9) Aspelund and Skoglund, *Acta Acad. Aboensis, Math. et Phys.*, **10**, No. 10, 22 pp. (1937); *C. A.*, **31**, 6634 (1937).

(10) Biltz and Wittek, *Ber.*, **54**, 1035, 1046 (1921).

(11) Hepner and Frenkenberg, *ibid.*, **65**, 123 (1932).

(12) Grimaux, *Compt. rend.*, **88**, 85 (1879).

subjected to the action of phosphorus oxychloride. Conrad and Guthzeit,[13] repeating this work, concluded that this by-product was probably the 5-acetylbarbituric acid, arising from the decomposition of the malonic acid into carbon dioxide and acetic acid.

Sembritzky[14] has described a 1,3-diethyl-5-acetylbarbituric acid, produced by heating a mixture of diethylurea, malonic acid and phosphorus oxychloride in sealed tubes at 100°. Biltz and Wittek,[10] in developing their method of preparing N-alkylated barbituric acids from substituted ureas, malonic acid, and acetic anhydride, found that an excess of the latter led to the formation of acetylated barbituric acids. Using monomethylurea, malonic acid, acetic anhydride and sulfuric acid, they obtained what they believed to be the 1-methyl-5-acetylbarbituric acid, and prepared therefrom an oxime, a hydrazone and a phenylhydrazone. Further, acid hydrolysis of this acetyl derivative yielded no 1-methylbarbituric acid. These experimental observations led them to assign position 5 to the acetyl group. While such proof would be acceptable in the case of a 1,3-dialkylbarbituric acid, it is not so convincing for a monoalkylated acid, since the remaining NH group is easily acetylated and the resulting acetyl derivative is fairly resistant to de-acetylation by acids.

The acetyl derivative (XIII) obtained by us, when refluxed for six to eight hours with concentrated hydrochloric acid, gave the expected disulfide barbituric acid (XIV), while its sodium violurate was deep red. Based upon these experiments, and upon the analytical results for both (XIII) and (XIV), we believe that compound (XIII) carries its acetyl group in position 3 and not 5.

From the barbituric acid (XIV), the violuric acid (XV) was secured either by the action of sodium nitrite or, better, by treatment with isoamyl nitrite in acid solution.

For the reduction of violuric acids to uramils, such reagents as hydriodic acid,[10,15] hydrogen sulfide,[15] ammonium sulfide,[16,17] and sodium hydrosulfite,[18] have been used. Inasmuch as the uramil derivative was to be treated with cyanic acid, for conversion into the corresponding uric acid, the reducing agent employed had to be one which would attack only the isonitroso group and not the disulfide linkage. Such a selective reduction was accomplished by using stannous chloride and hydrochloric acid, with yields of the uramil about 50% of that calculated.

The experiments of Fruton and Clarke[19] have shown that, in solutions of *p*H 7, the reaction $RSSR \rightleftarrows 2RSH$ is a thermodynamically reversible system, the oxidation–reduction potential being a function thereof, independent of the substituents and equal to -0.23 volt for the reaction as written. Since the normal oxidation–reduction potential for the $Sn^{++++} \rightleftarrows Sn^{++}$ system equals $+0.13$ volt,[20] and since oximes and isonitroso compounds are irreversibly reduced to the amines by stannous chloride in hydrochloric acid solution,[21] it was concluded that no considerable reduction of the disulfide linkage would occur unless this reagent were used in large excess.

From this uramil (XVI), the uric acid derivative (XVII) was produced by the action of nitrourea, as a white crystalline solid, which remained unmelted at 350°. No intermediate pseudouric acid was detected. Apparently the urea group in position 5 of the pyrimidine cycle closed to the glyoxaline ring as soon as formed.

Manifestly, the method of synthesis does not enable us to decide whether the correct structure for the final product should be represented by (XVIIa) or (XVIIb). The synthesis of one or the other of these by a method which will resolve this uncertainty is now under way and the results will be reported later.

Preliminary experiments for the reduction of the disulfide uric acid (XVII) to the corresponding *beta*-mercaptoethyl derivative have been disappointing and, as it will be sometime before an additional supply of the disulfide can be synthesized, it has seemed to us desirable to record the results of our work to date. It remains to be ascertained also whether the *beta*-mercaptoethyl derivative so formed will close up spontaneously to a thiazolidinouric acid of (C) or (D) structure, or can be so cyclized by appropriate treatment.

Acknowledgments.—We are indebted to Drs. A. Wilbur Duryee and J. Nybor, of the New York Post Graduate Medical School, for the physiological tests with ethyleneimine reported in this

(13) Conrad and Guthzeit, *Ber.*, **15** 2845 (1882).
(14) Sembritzky, *ibid.*, **30**, 1816 (1897).
(15) Bayer, *Ann.*, **127**, 223 (1863).
(16) Traube, *Ber.*, **33**, 3040 (1900).
(17) Traube, *Ann.*, **331**, 74 (1904).
(18) Hepner and Fajersztejn, *Bull. soc. chim.*, [5] **4**, 854 (1937).
(19) Fruton and Clarke, *J. Biol. Chem.*, **106**, 667 (1934).
(20) Getman and Daniels, "Outlines of Theoretical Chemistry," John Wiley & Sons, Inc., New York, N. Y., 6th ed., 1937, p. 440.
(21) Gabriel, *Ber.*, **43**, 2494 (1910).

paper; and to Mr. Saul Gottlieb of our own Organic Laboratories, for the microanalyses which appear in the Experimental Part.

Experimental

beta-**Mercaptoethylamine** (V) was prepared from commercial ethanolamine (I) by two different routes: (a) *via* 2-mercaptothiazoline (IV), and (b) *via* ethyleneimine (III).

(a). **2-Mercaptothiazoline** was obtained from ethanolamine and carbon disulfide essentially as described by Knorr and Rössler,[22] and this in turn hydrolyzed to the mercaptoethylamine by the action of concentrated hydrochloric acid, as recorded by Gabriel and Leupold.[23] This gave a yield of hydrochloride practically equal to that calculated; white crystals, m. p. 70.2–70.7° (cor.); m. p. in the literature,[24] 70–72°. The free base, sublimed *in vacuo*, melted at 97–98.5°. Gabriel and Colman[25] gave the m. p. as 99–100°. It was further identified by oxidation in aqueous solution, with 30% hydrogen dioxide, to taurine.

Ethyleneimine (III) was prepared from commercial ethanolamine (I), by the process of Wenker.[26] The total yield of the intermediate *beta*-aminoethylsulfuric acid (II) was 85.9%; of the ethyleneimine from this, 25–30%, b. p. 54–56°. Wenker gives the b. p. as 55–56.5°.

This imine is strongly caustic and burns the skin. Inhalation of the vapors causes acute inflammation of the eyes, nose and throat, with symptoms resembling those of bronchitis. After two to three days, the irritation subsides and the tissues return to normal, without suffering any apparent permanent injury. Danehy and Pflaum[27] also have called attention to the toxicity of this compound.

Through the courtesy of Drs. A. Wilbur Duryee and J. Nybor, of the New York Post Graduate Medical School, some physiological experiments were carried out on a white rabbit, weighing 5.4 lb., to ascertain the effect of ethyleneimine upon the heart, since one of the authors (Mills) suffered some cardiac disorders while working with this substance.

The rabbit was subjected to an abdominal injection of 1 cc. of a *M*/6 solution of the imine in water (0.89 cc./100 cc. water). Electrocardiographic studies of this animal showed no marked cardiac changes.

After ten days, an intra-peritoneal injection of 2 cc. of a solution of 1.8 cc. of the imine in 100 cc. of water (*ca.* *M*/3) was given, and still no marked heart damage was detected. But within three days the rabbit died, and the post-mortem examination disclosed a gross hemorrhage of the lungs, congested and swollen kidneys, a flabby heart and a severe peritonitis.

A cooled solution of 91.1 g. (2.1 mols) of ethyleneimine in 819 cc. of absolute ethanol was added dropwise (three to four hours) to 200 cc. of chilled absolute ethanol surrounded by an ice pack, while a current of hydrogen sulfide was passed through the well stirred mixture. The solution was concentrated under reduced pressure to 50–75 cc., in the absence of air, to avoid oxidation of the mercaptan, and the concentrate well cooled. The mercapto amine separated as a white solid, which was air-dried, washed with petroleum ether and dried again, when it melted at 97–98.5° (cor.); yield, 139 g., or 85.5%. The free base had a disagreeable odor, and oxidized to the disulfide on standing in the air.

beta,beta'-**Diamino-ethylsulfide (Thioethylamine)** (VI).—When a 25% (or stronger) solution of ethyleneimine in 95% ethanol was treated with a stream of hydrogen sulfide, without either cooling or stirring, and the mixture was then concentrated under diminished pressure, the *beta, beta'*-diamino-ethylsulfide separated as a yellowish oil. It has been described by Gabriel and his collaborators.[28] Our product was identified by conversion into the corresponding compound, VII.

beta,beta'-**Diureido-ethylsulfide** (VII).—The crude thioethylamine (VI), in aqueous solution, was subjected to the action of nitrourea in excess.[29,30,31] After heating the solution at 100°, it was evaporated to dryness under reduced pressure, and the diureide (VII) crystallized from water. It formed white crystals, m. p. 221–222° (cor.).

Anal. Calcd. for $C_6H_{14}O_2N_4S$: C, 34.9; H, 6.8; N, 27.2. Found: C, 34.6; H, 6.5; N, 27.7.

Cystamine (*beta,beta'*-**Diamino-ethyldisulfide, Dithioethylamine**) (VIII).—The mercaptoethylamine was dissolved in slightly more than sufficient water, or 95% ethanol, to effect solution, and a current of oxygen was bubbled through until the solution no longer reduced a solution of iodine in potassium iodide, by which time the characteristic unpleasant odor of the mercaptan had disappeared. Concentration of this solution under reduced pressure yielded a thick oil. This was dehydrated by repeated addition of absolute ethanol and evaporated *in vacuo*, since the oil could not be distilled without decomposition.

Dihydrochloride.—An aqueous or alcoholic solution of the disulfide was mixed with an excess of alcoholic hydrochloric acid and the mixture evaporated to a small volume of viscous material under diminished pressure. Addition of a small amount of methanol, or ethanol (95% or absolute), precipitated the dihydrochloride as a white solid, which was removed and washed with a little chilled alcohol. More of the salt was recovered from the filtrate by similar treatment. The yield from the mercaptan was practically that calculated from the original imine, about 65%.

Anal. Calcd. for $C_4H_{14}N_2S_2Cl_2$: C, 21.3; H, 6.3; N, 12.4. Found: C, 21.6; H, 6.3; N, 12.2.

This salt when heated began to shrink at about 206° (cor.), and melted at 212–212.5° (cor.). Coblentz and Gabriel,[32] and Coblentz,[33] reported its m. p. as 203°, whereas Fruton and Clarke[19] found 214°.

beta,beta'-**Diureido-ethyldisulfide** (IX).—To one mol of the cystamine (VIII), in aqueous or alcoholic solution, 2.2 mols of nitrourea was added slowly, while heating care-

(22) Knorr and Rössler, *Ber.*, **36**, 1281 (1903).
(23) Gabriel and Leupold, *ibid.*, **31**, 2837 (1898).
(24) Gabriel, *ibid.*, **22**, 1139 (1889).
(25) Gabriel and Colman, *ibid.*, **45**, 1643 (1912).
(26) Wenker, THIS JOURNAL, **57**, 2328 (1935).
(27) Danehy and Pflaum, *Ind. Eng. Chem.*, **30**, 778 (1938).
(28) Gabriel, *Ber.*, **24**, 1114, 3100 (1891).
(29) Thiele and Lachmann, *Ann.*, **288**, 281 (1895).
(30) Davis and Blanchard, THIS JOURNAL, **51**, 1790 (1929).
(31) Carlton and Day, *J. Org. Chem.*, **1**, 552 (1936).
(32) Coblentz and Gabriel, *Ber.*, **24**, 1123 (1891).
(33) Coblentz, *ibid.*, **24**, 2132 (1891).

fully to control the reaction. After about an hour at 100°, the gas evolution ceased, and the solution was evaporated to dryness *in vacuo*. The residual solid was crystallized repeatedly from water or alcohol, in both of which it was quite soluble hot and very difficultly soluble cold. The pure compound formed white crystals, m. p. 166–167° (cor.).

Anal. Calcd. for $C_6H_{14}O_2N_4S_2$: C, 30.2; H, 5.9; N, 23.5. Found: C, 30.3; H, 5.8; N, 23.6.

Ethyldisulfide-*beta,beta'*-dimalonuric Acid (X).—By the usual sodium ethylate condensation of the diureido disulfide (IX) with malonic ester, in absolute ethanol solution at 105–110°, this dimalonuric acid was obtained, with small amounts (2–3%) of the dibarbituryl disulfide (XIV). A better method of preparing the dimalonuric acid follows.

A mixture of 4.7 g. of the diureido disulfide and 4.2 g. of malonic acid was dissolved in 25 cc. of glacial acetic acid at 50° and to this mixture, stirred under a reflux and protected from ingress of moisture, there was added slowly (thirty to sixty minutes) 9.2 g. of acetic anhydride, while the mixture was heated to 65–70°. This was followed by four hours of heating at 70–80°, and three hours at 80–90°, after which the mixture was permitted to cool. The yellowish precipitate of the dibarbituryl disulfide (XIV) (3%), m. p. 208.5–212.5° (cor.), was filtered out, and the filtrate concentrated *in vacuo* to a reddish oil. Treatment of this oil with hot absolute ethanol precipitated more of (XIV), but extracted the dimalonuric acid (X). The alcohol extract was concentrated *in vacuo* and the residual red oil crystallized repeatedly from hot water. A white crystalline solid was thus obtained, in a yield of 25–30%.

Anal. Calcd. for $C_{12}H_{18}O_8N_4S_2$: C, 35.1; H, 4.4. Found: C, 35.4; H, 4.6.

The behavior of this product on heating was significant. At 141–142° (cor.), it melted with evolution of carbon dioxide, recongealed, remelted at 150–151° (cor.), with evolution of a second mole of carbon dioxide, congealed again and finally melted with decomposition at 197.5–199° (cor.). With sodium nitrite, the compound gave a red salt.

***beta*-Acetylureido-ethyldisulfide-*beta'*-malonuric Acid (XI).**—When the dimalonuric acid (X) was warmed for a short time in slightly acidulated water, a white crystalline solid was obtained which, after recrystallization from warm water, melted at 150–151° (cor.), with evolution of gas, recongealed and then melted with decomposition at 197.5–199° (cor.). With sodium nitrite, it formed a red salt.

Anal. (of XI). Calcd. for $C_{11}H_{18}O_6N_4S_2$: C, 36.0; H, 4.9. Found: C, 35.5; H, 4.9.

***beta,beta'*-Diacetylureido-ethyldisulfide (XII).**—When an aqueous solution of (XI) was boiled, carbon dioxide was split out and a white solid obtained, which was repeatedly crystallized from boiling water, in which it was very difficultly soluble. The product began to shrink at 206° (cor.) and melted at 209–210° (cor.).

Another method of preparing the same compound consisted in dissolving the diureido disulfide (IX) in excess of acetic anhydride, adding a few drops of concentrated sulfuric acid, and heating the mixture for three hours at 100°, followed by removal of acetic acid and excess of acetic anhydride by concentration *in vacuo*. After repeated crystallization from water, the white powder began to shrink at 206° (cor.) and melted at 209–210° (cor.).

Anal. Calcd. for $C_{10}H_{16}O_4N_4S_2$: C, 37.2; H, 5.6; N, 17.4. Found: C, 37.8; H, 5.4; N, 17.0.

With sodium nitrite, the compound gave no color reaction, thus indicating the absence of a reactive malonic methylene group.

***beta,beta'*-Di-(1-barbituryl)-ethyldisulfide (XIV)** was prepared by three different methods.

(1) To a solution of 23.8 g. of the diureido disulfide (IX) and 20.9 g. of malonic acid in 100 cc. of glacial acetic acid at 50°, there was added dropwise, under a reflux, 40.8 g. of acetic anhydride, in the course of an hour, while the mixture was well stirred and protected from moisture. After eight hours of heating at 80–90°, the solution was concentrated *in vacuo* to a thick red oil, which was extracted with 200 cc. of boiling absolute ethanol. As the extract cooled, the dibarbituryl disulfide (XIV) separated as a pale yellow crystalline solid. It was filtered out, washed with chilled absolute ethanol, dried in a vacuum desiccator, and crystallized from water; yield, 9.8 g., or 26.2%; m. p. 216.8–218.8° (cor.).

Anal. Calcd. for $C_{12}H_{14}O_6N_4S_2$: C, 38.5; H, 3.8; N, 15.0. Found: C, 38.6; H, 4.0; N, 14.9.

Concentration *in vacuo* of the alcoholic filtrate from (XIV), yielded a large quantity of the dimalonuric acid (X), which was used in the preparation of (XIV) by the third method as noted beyond. Another by-product was the acetylated barbituric acid (XIII) described in the following pages.

The above process is based upon that of Biltz and Wittek[10] for the preparation of N-alkylated barbituric acids from substituted ureas, malonic acid, and acetic anhydride.

(2) A mixture of 1.9 g. of *beta,beta'*-di-(1-[3-acetylbarbituryl])-ethyldisulfide (XIII) with 25 cc. of concentrated hydrochloric acid was refluxed for two and one-half hours. The insoluble material was removed and refluxed for another two and one-half hours with a fresh 25-cc. lot of concentrated hydrochloric acid. The combined hydrochloric acid extracts were evaporated *in vacuo* to a pale yellow powder. This was crystallized four times from water, using Norit as a decolorizing agent, and then melted at 215.5–216.5° (uncor.); yield, 0.3 g., equivalent to 33%, after deducting the 0.9 g. of initial material (XIII) unaltered by the hydrochloric acid.

(3) To a solution of 1.9 g. of the dimalonuric acid (X), recovered from Method (1) above, in 25 cc. of glacial acetic acid, there was added slowly, with protection against absorption of moisture, 1.5 g. of acetic anhydride, while the mixture was heated under a reflux. After three hours of further heating at 80°, the warm solution was diluted with two volumes of water, which gave a solution sufficiently acid to precipitate the barbituric acid (XIV) desired, but not the initial dimalonuric acid (X). After standing for eighteen to twenty-four hours, the white precipitate was collected, washed free from acid, and crystallized twice from water, m. p. 211.5–214.5° (cor.). The mixed m. p. with an authentic sample of the barbituric acid (XIV), m. p. 216,8–218.8° (cor.), was 213–216.5°

(cor.); mixed m. p. with an authentic sample of the diacetylureido compound (XII), m. p. 209–210° (cor.), was 188–193° (uncor.); yield, 1 g., or 78.4%, after deducting 0.5 g. of unchanged initial material isolated from the acetic acid solution by evaporation *in vacuo*.

***beta,beta'*-Di-(1-[3-acetylbarbituryl])-ethyldisulfide (XIII).**—The diureidodisulfide (IX) was mixed with slightly more than the calculated amount of malonic acid, a small excess of acetic anhydride was added, and the mixture was heated at 70° for four hours. Acetic acid and excess of acetic anhydride were distilled off *in vacuo*, the residue treated with half the original quantity of acetic anhydride, the mixture heated for an hour at 70°, and acetic acid and acetic anhydride distilled off *in vacuo*. The oily residue was dissolved in 10% sodium hydroxide, and 10% hydrochloric acid added until the solution was acid to Congo-red. The orange-red precipitate was collected and purified by further precipitation from sodium carbonate and sodium bicarbonate solutions with 10% hydrochloric acid. A pale yellow product was thus obtained, in 80% yield, which was very slightly soluble in the usual neutral organic solvents. By reprecipitation with 10% hydrochloric acid from sodium bicarbonate solutions, and drying at 111° *in vacuo* for two and one-half hours, a pure compound was secured, which shrank at 214–217° (cor.) and melted at 219–223° (cor.).

Anal. Calcd. for $C_{16}H_{18}O_8N_4S_2$: C, 41.9; H, 4.0; N, 12.2. Found: C, 41.7; H, 4.3; N, 12.2.

***beta,beta'*-Di-(1-(violuryl)-ethyldisulfide (XV).**—A suspension of 1.1 g. of the barbituryl disulfide (XIV) in 20 cc. of water was treated slowly with 0.5 g. of sodium nitrite, with vigorous stirring. Upon completion of the addition, the pinkish solution was heated at 100° for thirty minutes, which changed its color to a purple, then cooled to room temperature, 1 cc. of concentrated sulfuric acid added, the mixture heated for an hour at 100° and then over a free flame until the red color was discharged. As the solution cooled, a yellow precipitate separated, which was filtered out, washed with cold water until acid-free, and dried *in vacuo* for twenty-four hours. There was thus obtained 1.1 g. (91% yield) of a yellow powder, which turned red at about 200°, and melted at 218.5–219.5° (cor.) with decomposition to a deep red liquid.

Difficulty was experienced in getting an analytically pure sample by this method, since inorganic salts or the sodium salt of the violurate, were carried down with the precipitate. Repeated crystallization from water, however, gave a practically pure product.

Anal. Calcd. for $C_{12}H_{12}O_8N_6S_2$: C, 33.3; H, 2.8. Found: C, 33.1; H, 3.0.

When the red solution of the sodium violurate stood for two to four days, the pyrimidine ring apparently broke open between positions 1 and 6, and no violuric acid (XV) could be recovered.

This violuric derivative (XV) was prepared also by the following process. A suspension of 2.4 g. of the barbituryl disulfide (XIV) in 50 cc. of 95% ethanol was cooled in an ice-bath, and 15 g. of isomamyl nitrite stirred in. After the careful addition of 0.5 cc. of concentrated hydrochloric acid, the mixture was stirred for fifteen to thirty minutes at 0°, one hour while warming up to room temperature, and thirty minutes at 40°. The solution was concentrated *in vacuo* to a small volume, cooled, the precipitate filtered out, washed twice with chilled 95% ethanol, and dried to a pale yellow powder, identical in m. p., and other respects, with the product of the first process; yield, 2.4 g., or 89%, and more was recovered from the filtrates. With sodium hydroxide or potassium hydroxide, it formed a purple isonitroso salt.

***beta,beta'*-Di-(1-uramilyl)-ethyldisulfide (XVI).**—To a solution of 1.1 g. of the violuric acid (XV) in 25 cc. of concentrated hydrochloric acid, there was added 1.9 g. of stannous chloride, and the mixture was heated at 100° for five hours. When the solution no longer reduced an iodine–potassium iodide solution, it was either evaporated to dryness at 100°, extracted with 60% ethanol, and precipitated by the addition of absolute ethanol; or absolute ethanol was added directly to the reduced solution. Cooling of either of these solutions gave a precipitate, which was filtered out and crystallized by dissolving it in a small amount of concentrated hydrochloric acid, reprecipitating with absolute ethanol and cooling to 0°. This precipitate was collected, washed with chilled absolute ethanol and dried *in vacuo* at 75° over phosphorus pentoxide for two hours. The pale yellow product shrank at 145°, turned reddish-brown at 155–160°, sintered at 170–171.5° and finally turned red and decomposed without showing any definite m. p.; yield, 55–60%.

Anal. Calcd. for $C_{12}H_{16}O_6N_6S_2$: C, 35.6; H, 4.0. Found: C, 35.2; H, 4.1.

With potassium hydroxide or sodium hydroxide, no color indicative of an isonitroso salt was obtained. The compound gave a positive murexide reaction.

1 (or 3)-(*beta*-Ethyldisulfide)-uric Acid (XVII).—A suspension of 0.4 g. of the above uramil (XVI) in 20 cc. of water was made faintly alkaline to litmus by the addition of dilute (10%) potassium hydroxide. To this there was added 0.25 g. of nitrourea, and the mixture was heated at 100° until the evolution of gas ceased. The nitrourea used contained sufficient sulfuric acid to change the reaction of the solution to the acid side, so it was filtered hot and cooled. The solid which precipitated was removed and crystallized from water. A white crystalline compound resulted, which was not melted, but only slightly charred, at 350°. Ignited on platinum foil, it left no ash. It dissolved in 5% sodium bicarbonate solution, was reprecipitated by hydrochloric acid, and gave a positive murexide reaction. For analysis, it was crystallized thrice from water and dried over phosphorus pentoxide *in vacuo* for two hours at 76°.

Anal. Calcd. for $C_{14}H_{14}O_6N_8S_2$: C, 37.0; H, 3.1; N, 24.7. Found: C, 36.9; H, 3.2; N, 24.9.

Summary

1. *beta*-Mercaptoethylamine is prepared most conveniently by passing hydrogen sulfide through an alcoholic solution of ethyleneimine. Some physiological tests on the toxicity of ethyleneimine are reported.

2. This mercaptan is easily oxidized to the corresponding disulfide (cystamine) by the action of air or oxygen upon its aqueous or alcoholic solution.

3. Cystamine is converted into the diurea by treatment with nitrourea.

4. This diurea when condensed with malonic acid, in the presence of acetic anhydride, yields the corresponding barbituric acid, as well as malonuric acid derivatives of cystamine and acetylation products.

5. From the disulfide barbituric acid, there have been obtained the corresponding violuric acid, uramil, and uric acid.

6. The latter is to be used as initial material for the preparation of *beta*-mercaptoethyl and thiazolidino uric acids.

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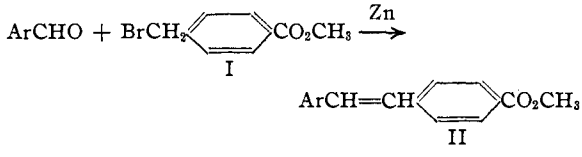
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Certain Carbalkoxystilbenes

BY REYNOLD C. FUSON AND H. G. COOKE, JR.

Carbalkoxystilbenes of the type $ArCH{=}CHC_6H_4CO_2R$, needed for certain studies on the reversibility of the Friedel–Crafts condensation, could not be found in the literature. It was necessary, therefore, to devise ways for synthesizing them. The present paper reports three such methods.

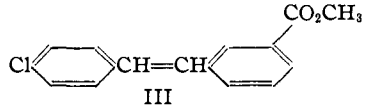
The first to be studied was the condensation of aromatic aldehydes with methyl α-bromo-*p*-toluate (I) by an adaptation of the Reformatsky reaction. This method was suggested by the vinylogous relationship between the α-bromo-*p*-toluates and bromoacetic esters. Experiments showed that the method could be used. Benzaldehyde, *p*-chlorobenzaldehyde and *p*-bromobenzaldehyde were condensed with methyl α-bromo-*p*-toluate to give the corresponding *p*-carbomethoxystilbenes (II).



I

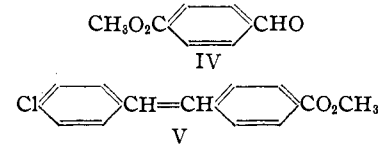
II

The activation of the bromine atom by the carbomethoxy group proved, however, not to be essential. Similar results were obtained with the *meta* isomer of the bromotoluate. *p*-Chlorobenzaldehyde condensed with methyl α-bromo-*m*-toluate to give 4-chloro-3′-carbomethoxystilbene (III).



III

This type of condensation was found to take place also with simple benzyl halides. Thus *p*-chlorobenzyl bromide condensed with methyl terephthalaldehydate (IV) to give 4-chloro-4′-carbomethoxystilbene, the product (V) being identical with that from methyl α-bromo-*p*-toluate and *p*-chlorobenzaldehyde. These two



IV

V

methods give about the same yields: approximately 20% of the theoretical. The former is preferable because the starting materials are less difficult to obtain.

The preparation of the α-bromotoluates[1] was accomplished by the method of Davis and Perkin.[2] The terephthalaldehydate was much more difficult to prepare. It was found that Mayer and Sieglitz's method[3] for α-naphthaldehyde could be applied successfully to methyl α-bromo-*p*-toluate to give methyl terephthalaldehydate.

After this work was completed Meerwein, Büchner and Emster[4] reported a new method for making substituted stilbenes from cinnamic acids and primary aromatic amines. For certain carbalkoxystilbenes this procedure proved to be superior to the methods already worked out. Applied to cinnamic acid and *p*-aminobenzoic esters it gave yields of 36 to 52%. The method gives low yields when applied to chlorocinnamic acids and consequently is not very helpful in making the halogen substituted stilbenes required in this work.

Experimental

Methyl α-Bromo-*p*-toluate.—Eighty-three grams of bromine was added slowly, with stirring, to 80 g. of *p*-

(1) Zal'kind, *J. Russ. Phys.-Chem. Soc.*, **46**, 508 (1914).
(2) Davis and Perkin, *J. Chem. Soc.*, **121**, 2202 (1922).
(3) Mayer and Sieglitz, *Ber.*, **55**, 1835 (1922).
(4) Meerwein, Büchner and Emster, *J. prakt. Chem.*, **152**, 237 (1939).