d-limonene. The two compounds show the same strong infrared absorption band at 11.03 μ and the same medium strength bands at 8.05 and 8.18 μ.

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.41; H, 12.07.

***p*-Menthane-7-carbinol (VII)** was produced by hydrogenation of a mixture of about 75% IV and 25% V using Raney nickel at 1500–2000 pounds pressure. After removal of 7-methyl-3-ethyloctanol resulting from the hydrogenation of V at 110–116° at 10 mm., VII distilled at 126° at 10 mm., $n^{25}D$ 1.4700, d^{25}_4 0.9117. It was identified by oxidation with chromic acid–acetic acid to a mixture which partly solidified. The solid acid after several recrystallizations from pentane melted at 77–78° and its infrared spectrum was identical with that of a known[13] sample of *p*-menthane-7-carboxylic acid kindly furnished by Dr. L. A. Goldblatt. The liquid acids are thought to be a mixture of the *cis–trans* isomers of this acid which indicates that the VII is a mixture of the two possible *cis–trans* alcohols.

Alloöcimene dimer[7] is readily produced by heating alloocimene at about 200° and its ultraviolet spectrum has been studied.[10] This work was repeated. Alloöcimene was heated at 205° for 10 hours and 40 minutes at which time the product contained about 17% unchanged alloöcimene by ultraviolet absorption analysis. This result was in good agreement with Fuguitt[14] who reported 19% unchanged alloöcimene after heating alloöcimene under the same conditions of time and temperature. The partly polymerized product was distilled at about 5 mm. pressure through a short column and fractions of dimer, b.p. 155–156°, were collected and examined. All fractions showed λ_{max} 241–242 mμ and the extinction coefficient (α) of the fractions ranged from 88 to 110.6. The dimer is further characterized by infrared absorption bands at 10.15, 10.36, 11.54, 11.63 and 11.87 μ.

Alloöcimenecarbinol (V) was polymerized by heating at 205° for 10 hours and 40 minutes. The viscous product was shown by infrared analysis to have retained the hydroxyl group. Its ultraviolet spectrum was determined in methanol since the product was partly insoluble in isooctane. The spectrum showed two absorption maxima, λ_{max} 242, α 65, and λ_{max} 276, α 78. From these data and the known extinction coefficient for V, it was calculated that the partly polymerized V contained approximately 31% unreacted V and 69% polymerized V, and that the polymerized V possessed an extinction coefficient, α, of about 79. The infrared spectrum of this crude mixture of V and its polymer showed with certainty only one absorption band which appeared to be common with that of alloöcimene dimer, a band at 10.15 μ.

Isomerization of Nopyl Acetate.—Nopyl acetate was heated at 240° for 5.5 hours. The isomerized product contained free acetic acid equivalent to decomposition of about 0.8% of the nopyl acetate. The product was fractionated at 10 mm. and the fractions were analyzed by ultraviolet and infrared methods.

There was formed no β-pinene or other low boiling terpenes. The first fractions boiling over the range 109–132.5° were rich in acetates showing λ_{max} 264 mμ and believed to be alkyl cyclohexadiene carbinol acetates resulting from cyclization of alloöcimenecarbinol acetate. The quantity of these conjugated cyclic acetates was estimated to be 10% of the original nopyl acetate. There was also present in these fractions nopyl acetate amounting to 5% of the starting material.

Dipentene-7-carbinol acetate was obtained in about 55% yield, b.p. 134° at 10 mm., $n^{25}D$ 1.4775. Its identity was apparent from comparison of its infrared spectrum with that of limonene and dipentene-7-carbinol, all of whose major absorption bands are common except, of course, for the acetate or hydroxyl absorptions.

Alloöcimenecarbinol acetate was obtained in about 15% yield; b.p. 140° at 10 mm., $n^{25}D$ 1.526; extinction coefficient for the purest fraction, α 173, λ_{max} 279 mμ. The major infrared absorption bands of the acetate coincide with those common to alloöcimene and alloöcimene carbinol. It was estimated from spectrophotometric data that purity of the best fraction was only about 85%, the remainder chiefly dipentene-7-carbinol acetate.

The distillation residue amounted to 15% of the charge and was estimated to contain 28% alloöcimenecarbinol acetate and 15% alloöcimenecarbinol polymer acetate, the latter showing λ_{max} 241.

Acknowledgment.—The authors wish to express their appreciation to Dr. Philip Sadtler for providing the infrared absorption spectra shown in Fig. 1.

JACKSONVILLE, FLORIDA

(14) R. F. Fuguitt Thesis, University of Florida, May 1943.

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

The Preparation of Some 1-Alkylamino- and Dialkylaminoalkylaminothiaxanthones[1]

BY S. ARCHER AND C. M. SUTER

RECEIVED MARCH 8, 1952

The preparation of an extensive series of 1-alkyl and dialkylaminoalkylaminothiaxanthones was undertaken as part of a study on the chemotherapy of schistosomiasis. The compounds were prepared by condensing a 1-chlorothiaxanthone with a substituted alkylenediamine at atmospheric pressure. The required 1-chlorothiaxanthones were obtained by (a) condensing a thio- or dithiosalicylic acid with a 1-halo-4-methylbenzene; (b) treating a chlorothiophenol with an appropriately substituted *o*-chlorobenzoic acid followed by ring closure of the resulting *o*-arylmercaptobenzoic acid with sulfuric acid and (c) condensing 2,4-dichloronitrobenzene with a thiosalicyclic acid, followed by conversion of the resulting acid to the corresponding acid chloride and cyclizing with the aid of aluminum chloride. A modified mechanism for the condensation of dithiosalicylic acid with benzene and its congeners is proposed.

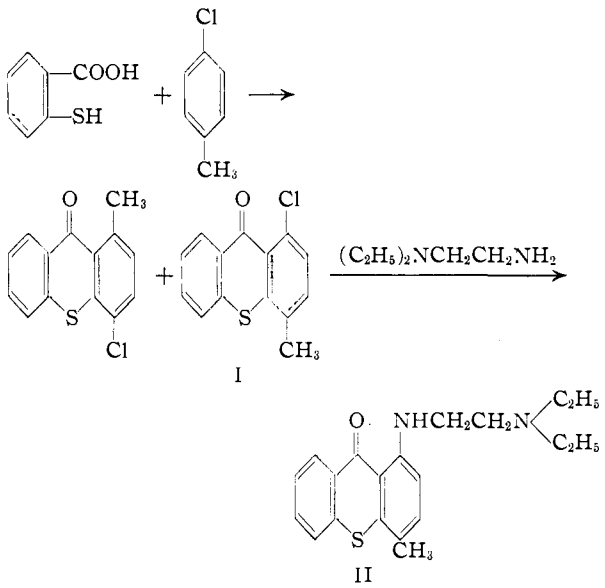
Several years ago it became of interest to prepare a sample of Miracil D (II), a new orally effective schistosomicidal drug, which was developed in Germany during the recent war. The method of preparation[2] consisted of condensing diethylaminoethylamine with 1-chloro-4-methylthiaxanthone (I). The intermediate chlorothiaxanthone, I, was obtained mixed with the 4-chloro-1-methylthiaxanthone according to the procedure of Ullmann and Glenck[3] who treated thiosalicylic acid with *p*-chlorotoluene in sulfuric acid. The 1-chloro isomer, I, is sufficiently reactive to condense with an amine at elevated temperatures.

When this work was repeated it was found that in small scale runs it was possible to duplicate the results already reported; however, on a larger scale

(1) The numbering system of the thiaxanthones used throughout this paper follows current *Chemical Abstracts* usage. This differs from the system used by the English and German workers in that the sulfur atom is numbered 5 in one case and 10 in the other. The compound which Mauss (ref. 4) named 1,6-dichloro-4-methylthioxanthone corresponds to 1,7-dichloro-4-methylthiaxanthone here. The minor difference in spelling should be noted.

(2) Office of the Publication Board, Department of Commerce, Washington, D. C., Report No. 981.

(3) F. Ullmann and O. v. Glenck, *Ber.*, **49**, 2487 (1916).



I

II

the reaction mixture turned dark and afforded only intractable tars. It was found possible to effect the condensation between the diamine and the thiaxanthone mixture consistently and in reproducible yield at atmospheric pressure. This reaction proved to be a general one so that a large variety of compounds could be prepared.

Although it was reported that about seventy compounds had been prepared[2] only the structure of Miracil D was revealed. Accordingly, it was decided to prepare compounds having varying structures and evaluate their schistosomicidal activity in these laboratories. During the course of this work several papers bearing directly on the problem have appeared. In the paper of Mauss[4] the chemistry of Miracil D and its congeners was reported in some detail. It was rather surprising and gratifying that our work duplicated that of the German worker only to a slight extent. Hawking,[5] Kikuth,[6] Vogel[7] and Alves[8] have described the toxicological and chemotherapeutic properties of Miracil D. It appears from this work that the toxic dose of this drug is so close to the curative dose that the compound cannot be considered more than a promising lead in the oral treatment of schistosomiasis.

The first method we employed for the synthesis of the 1-chlorothiaxanthones was discovered by Smiles[9] who found that thiosalicylic acid and dithiosalicylic acid condense with certain substituted aromatic hydrocarbons in sulfuric acid to furnish thiaxanthones. For *p*-chlorotoluene Ullmann[3] used about 90% sulfuric acid but the more concentrated acid has been found to be a superior condensing agent. We studied the use of both thio- and dithiosalicylic acids in the reaction with *p*-chlorotoluene. The readily available crude dithio acid furnished the thiaxanthone mixture in yields comparable to those obtained with thiosalicylic acid. Condensations were also run with 5-chlorothiosalicylic acid, 5,5′-dimethyldithiosalicylic acid, 3,3′-dichloro- and 3,3′-dimethyldithiosalicylic acids. These intermediates were all prepared by the usual procedure from the corresponding anthranilic acids.[10] The 5,5′-dimethyldithio acid and 5-chlorothiosalicylic acid condensed with *p*-chlorotoluene to give thiaxanthone mixtures in which a substantial portion of the 1-chloro isomer was present. Both 3,3′-dimethyl- and 3,3′-dichlorodithiosalicylic acids afforded chlorothiaxanthones which failed to react with dibutylaminoethylamine. Authentic specimens of 1-chloro-4,6-dimethylthiaxanthone and 1,6-dichloro-4-methylthiaxanthone were prepared by condensing the appropriate potassium *o*-chlorobenzoate with 5-chloro-2-methylthiophenol. The *o*-phenylmercaptobenzoic acids were cyclized in sulfuric acid. The thiaxanthones so obtained condensed with dibutylaminoethylamine to furnish the desired 1-(2-dibutylaminoethylamino)-thiaxanthones. This reaction served to locate the position of the chlorine atom with respect to the carbonyl group. The melting points of the thiaxanthone from 3,3′-dimethyldithiosalicylic acid, presumably 1,6-dimethyl-4-chlorothiaxanthone, and authentic 1-chloro-4,6-dimethylthiaxanthone were widely divergent. On the other hand, 4,6-dichloro-1-methylthiaxanthone (from 3,3′-dichlorodithiosalicylic acid) and 1,6-dichloro-4-methylthiaxanthone melted close to each other. The mixed melting point lay between the melting points of the individual compounds. This is not surprising since a mixture of 1-chloro-4-methylthiaxanthone and the 4-chloro-1-methyl isomer does not give a depression in melting point on admixture.

The isomeric dichloromethylthiaxanthones may be differentiated by their chemical properties, infrared spectrum and behavior on crystallization. One isomer forms buff-colored crystals whereas the other separates as yellow needles. Apparently unidirectional condensation occurs when the disulfide group is situated between two ortho substituents.

Another instance of largely unidirectional condensation was noted with 3,4-dimethylbromobenzene. When this bromoxylene was condensed with thiosalicylic acid the resulting thiaxanthone gave very little acid-soluble material when treated with dibutylaminoethylamine. In 3,4-dimethylbromobenzene the position ortho to the bromine and para to the methyl is the most highly activated; it is to be expected that the reaction would be initiated at that point.

There has been some previous consideration of the mechanism whereby dithiosalicylic acids condense with benzene and its derivatives. Smiles[11,12] proposed the mechanism for the reaction shown in the equations.

He was unable to determine whether thiosalicylic acid was oxidized to the sulfenic acid by way of dithiosalicylic acid. However, it has long been

(4) H. Mauss, *Chem. Ber.*, **81**, 19 (1948).

(5) (a) F. Hawking and W. F. Ross, *Brit. J. Pharm.*, **3**, 167 (1948). (b) D. M. Blair, F. Hawking, C. V. Meeser and W. F. Ross, *ibid.*, **4**, 68 (1949).

(6) W. Kikuth and R. Gonnert, *Ann. Trop. Med. and Parasit.*, **42**, 256 (1949).

(7) H. Vogel and W. Minning, *ibid.*, **42**, 268 (1949).

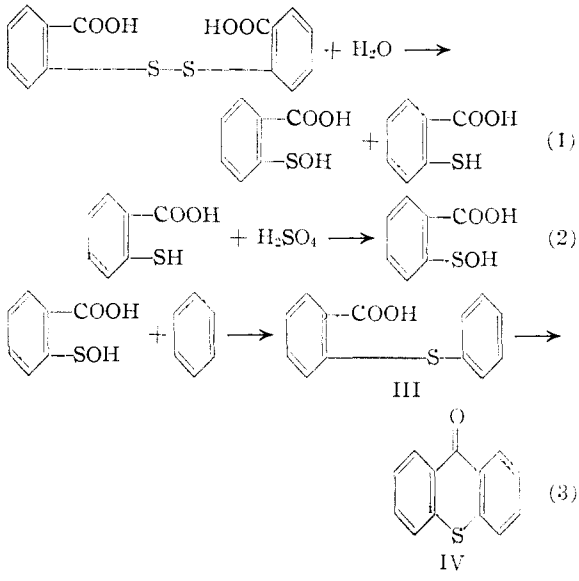
(8) W. Alves, *ibid.*, **44**, 34 (1950).

(9) E. K. Davies and S. Smiles, *J. Chem. Soc.*, **97**, 1290 (1909).

(10) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 580.

(11) E. G. Marsden and S. Smiles, *J. Chem. Soc.*, **99**, 1354 (1911).

(12) W. G. Prescott and S. Smiles, *ibid.*, **99**, 640 (1911).



known that mercaptans can be oxidized to disulfide in sulfuric acid[13] and we have found that thiosalicylic acid is converted to the dithio acid in sulfuric acid almost quantitatively under conditions that correspond to those required for the condensation.

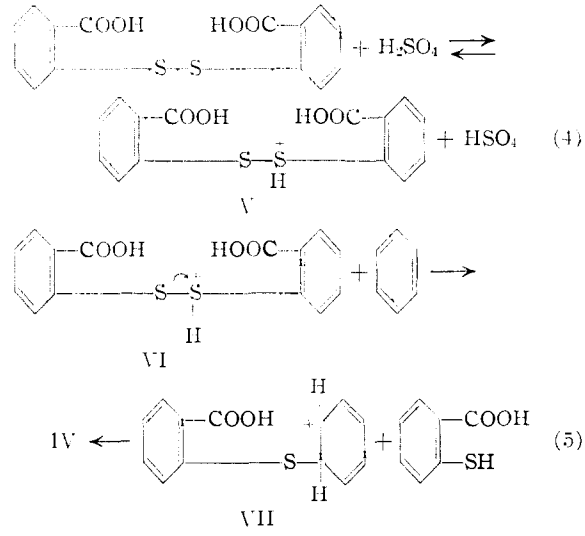
Experimental evidence is at hand to support the formation of a sulfide as the first step in the elaboration of the heterocyclic ring. It is fairly well established that benzoic acid does not condense with benzene in sulfuric acid but that ring closures such as III to IV do occur in this medium. Smiles[11] prepared a mixed sulfide from bis-(4-dimethylaminophenyl) disulfide and a phenol in sulfuric acid. Thus, a disulfide without a carboxyl group can condense with a benzene derivative.

The structures of thiaxanthones formed by the condensation also indicate that sulfide formation is the first step. Smiles[14] reported only one thiaxanthone, namely, 1-methyl-4-methoxythiaxanthone from the reaction between thiosalicylic acid and *p*-tolyl methyl ether. Ullmann[3] obtained only 1-chloro-2-methyl-4-methoxythiaxanthone from the interaction of 3-methyl-4-chloroanisole and thiosalicylic acid. This particular thiaxanthone was obtained in about 75% yield and was shown to consist largely if not exclusively of the 1-chloro isomer since it reacted with aniline to form the 1-anilinothiaxanthone in 85% yield. Since the position ortho to the methoxyl groups is more susceptible to attack by electrophilic agents than the other possible reaction sites it is apparent that the sulfur function condensed first. In the case of *p*-chlorotoluene this difference in susceptibility is not as marked as in the anisoles so that mixtures of thiaxanthones are frequently obtained. The exceptions, as noted above, occur when 3,3′-substituted dithiosalicylic acids are used, but here steric factors may supervene. *p*-Dichlorobenzene, which does not react with cationoid reagents as readily as *p*-chlorotoluene or *p*-chloroanisole, does not condense with thiosalicylic acid under the conditions of the experiment. This order of reactivity parallels that in the Friedel–Crafts ketone synthesis.

(13) J. Stenhouse, *Ann.*, **149**, 250 (1869).
(14) K. C. Roberts and S. Smiles, *J. Chem. Soc.*, **132**, 863 (1929).

In the Smiles formulation, water is required to hydrolyze dithiosalicylic acid to the sulfenic acid and thiosalicylic acid (equation 1). This reaction seemed improbable and was tested experimentally. When the condensation was carried out between pure dithiosalicylic acid and *p*-chlorotoluene in 96% sulfuric acid the reaction was very sluggish and at the end of 90 minutes the yield of thiaxanthone mixture was only 26%. However, in 101% sulfuric acid the reaction was so vigorous that cooling was required and in the same time the yield was 81%. This was almost the maximum obtainable.

In view of this result it seems necessary to modify Smiles' mechanism for the reaction by replacing the sulfenic acid with another type of reactive structure as shown.

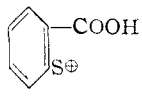


Since the disulfide group is less acidic than the carboxyl group, the former adds a proton reversibly to furnish the conjugate, V, (equation 4). In the presence of an acceptor for V the polarization indicated by the expression, VI,[15] occurs and condensation of the sulfur function with the aromatic compound takes place as in equation (5). The thiosalicylic acid which is formed is oxidized to the dithiosalicylic acid.

According to equation (4), the addition of bisulfate ion should drive the equilibrium to the left and thereby decrease the reaction rate. When 100% sulfuric acid previously saturated with potassium bisulfate was the condensing agent the yield at the end of 90 minutes was 40% and the reaction was only mildly exothermic. A control run without the added salt furnished the thiaxanthone mixture in 83% of the theoretical yield.

The experiments cited support the modified mechanism and render it unlikely that the dithio acid reacts *via* a sulfenic acid intermediate. Analogously it is improbable that thiosalicylic acid con-

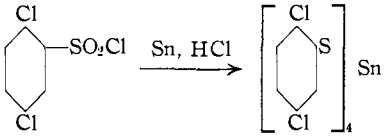
(15) Complete polarization of VI with charge separation gives thiosalicylic acid and the ion



The latter may be the reactive intermediate. Since little is known about the behavior of such ions we do not wish to imply a temporal existence for such a species and prefer to use the polarized expression VI.

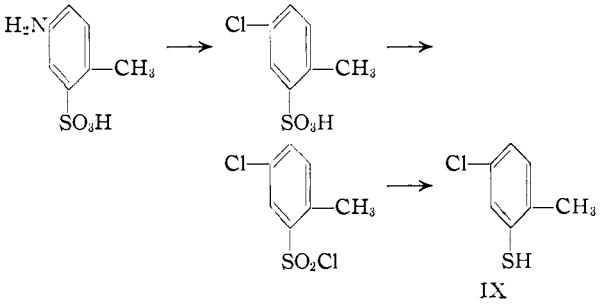
denses according to the Smiles mechanism. The mercapto acid is first oxidized to the disulfide since this is a one electron oxidation, whereas the direct oxidation to the sulfenic acid involves the removal of two electrons.[16,17]

A number of the 1-chlorothiaxanthones were prepared by the condensation of appropriately substituted potassium *o*-chlorobenzoates with either 5-chloro-2-methylthiophenol or 2,5-dichlorothiophenol, followed by cyclization of the intermediate *o*-phenylmercaptobenzoic acids in sulfuric acid. The 2,5-dichlorothiophenol was prepared by reduction of 2,5-dichlorobenzenesulfonyl chloride with tin and hydrochloric acid.[18] Usually the thiophenol was separated from the reaction mixture by steam distillation. In one experiment this operation was omitted; the thiophenol was extracted from the acid with ether. On standing the solution deposited yellow crystals, the analysis of which agreed well for tin tetra-(2,5-dichlorothiophenolate) (VIII). Wuyts[19] prepared a similar compound from diphenyl disulfide with the same reducing mixture.



VIII

Several methods were investigated for the preparation of 5-chloro-2-methylthiophenol (IX). Chien and Kuan[20] reported the preparation of this compound by the method of Dosser and Richter.[21] They stated that IX melted at 80–81° when crystallized from ethanol. The corresponding bromo compound was reported to be a liquid boiling at



IX

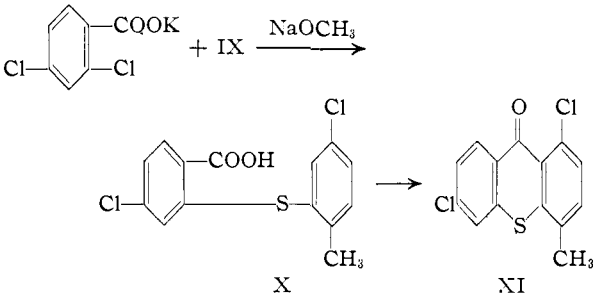
107–108° (2 mm.). In their purification procedure the Chinese workers did not extract their product with base. We prepared IX by four different methods, at least two of which involved isolation by alkaline extraction. In no instance did our material correspond in properties to those reported by Chien and Kuan.[20] A sample of the disulfide corresponding to IX was found to be only slightly soluble in ethanol and to melt at 81.3–82.7°. Evidently these workers had this disulfide rather than an authentic specimen of 5-chloro-2-methylthiophenol.[23a]

Treatment of 5-chloro-2-methylphenylmagnesium bromide with sulfur furnished IX in moderate yield. The thiophenol IX was also prepared in a sequence which required the conversion of 2-amino-4-chlorotoluene to 5-chloro-2-methylbenzenesulfinic acid[22] followed by reduction to the thiol.

Chlorosulfonation of *p*-chlorotoluene yielded a mixture of sulfonyl chlorides[23,23a] which were reduced without separation to IX and the isomeric 2-chloro-5-methylthiophenol. This mixture was suitable for further work since the isomer gives rise to a 4-chlorothiaxanthone which does not react with an amine. In our hands the best method for preparing IX consisted of converting 2-amino-4-chlorotoluene to the xanthate and then hydrolyzing this ester with potassium hydroxide to give the thiol in 60% over-all yield.[24] A neutral fraction was obtained which was apparently 5-chloro-2-methylphenyl ethyl sulfide.

The 3-substituted *o*-chlorobenzoic acids were prepared by the isatin synthesis. The proper amines were converted to the isatins, these oxidized to the anthranilic acids and the latter then subjected to a Sandmeyer reaction. 2-Chloro-5-methylbenzoic acid was prepared from *p*-toluidine in this way. The 4-methyl- and 4-methoxy-2-chlorobenzoic acids were made from the corresponding 2-nitrobenzonitriles.

The condensation of the potassium *o*-chlorobenzoates and the thiophenols were generally effected about 200° using a molar ratio of 1 sodium methoxide:1 potassium salt:2.5 thiophenol. The yields of the arylmercaptobenzoic acids were quite good and it was possible to recover some of the excess thiophenol by steam distillation. In a few successful reactions it was possible to double the amount of potassium salt having present only a 25% excess of thiophenol. However, the yields were lower when this proportion was used. Thus, where potassium 2,4-dichlorobenzoate and IX were allowed to react



X XI

(16) L. Michaelis and C. V. Smythe, *Ann. Rev. Biochem.*, **7**, 1 (1938).

(17) R. B. Woodward and R. H. Eastman, THIS JOURNAL, **68**, 2231 (1946).

(18) J. Stewart, *J. Chem. Soc.*, **121**, 2555 (1922).

(19) H. Wuyts and A. Vangindertaelen, *Bull. soc. chim. Belg.*, **30**, 328 (1921).

(20) S. L. Chien and H. T. Kuan, *J. Chinese Chem. Soc.*, **4**, 355 (1936).

(21) R. C. Dosser and G. H. Richter, THIS JOURNAL, **56**, 1132 (1934).

(22) M. S. Shah, C. T. Bhatt and D. D. Konga, *J. Chem. Soc.*, 1375 (1933).

(23) W. D. Wynne, *ibid.*, **61**, 1078 (1892). (a) After this paper was written, J. M. Sharp, *ibid.*, 2961 (1951), reported the preparation of the thiol, IX, by the same series of reactions which differed in experimental detail. He obtained the thiol IX in 63–73% yield based on *p*-chlorotoluene. Oxidation with iodine furnished the corresponding disulfide m.p. 80–81°. No details of the experiment were given. Condensation with potassium *o*-chlorobenzoate yielded 2'-carboxy-5-chloro-2-methyldiphenyl sulfide in 88% yield. Cyclization to 1-chloro-4-methylthiaxanthone was accomplished in 90% yield. Our results (*vide infra*) suggest that the thiophenol prepared this way contained some of the isomeric 2-chloro-5-methylthiophenol.

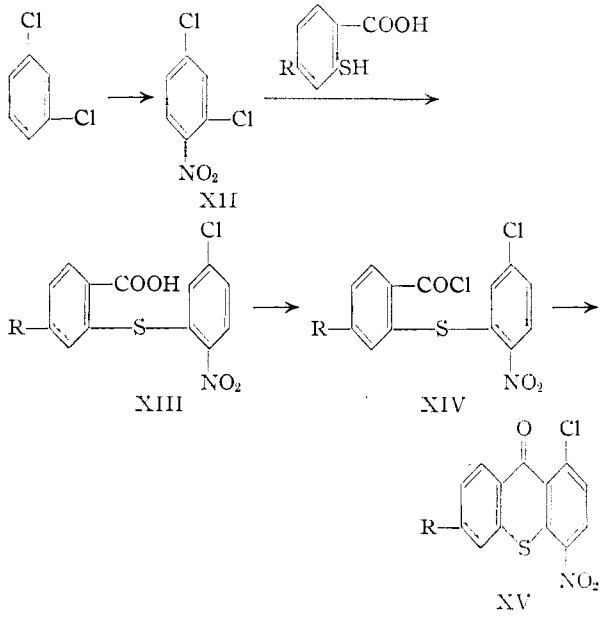
(24) D. S. Tarbell and D. K. Fukushima, *Org. Syntheses*, **27**, 81 (1947).

in the molecular ratio of 1:2.5 the yield of X was 90%. When the amount of potassium salt was doubled the yield fell to 82%.

The ring closures of the 2-(5-chloro-3-methylphenylmercapto)-benzoic acids were carried out in sulfuric acid at steam-bath temperatures whereas the 2-(2,5-dichlorophenylmercapto)-benzoic acids were cyclized at 120–130°. The yield of XI from potassium 2,4-dichlorobenzoic acid was 82%.

Pure 1,7-dichloro-4-methylthiaxanthone (XI) melted at 196–197°. Mauss[4] obtained XI mixed with 4,7-dichloro-1-methylthiaxanthone from 4-chlorothiosalicylic acid and *p*-chlorotoluene. The mixture melted at 182–183°. When the mixed thiophenols obtained from the chlorosulfonation and reduction of *p*-chlorotoluene were allowed to react with potassium 2,4-dichlorobenzoate and the crude product then cyclized a thiaxanthone mixture was obtained which melted at 188°.[23a]

1-Chloro-4-nitrothiaxanthone (XV, R = H) and 1,7-dichloro-4-nitrothiaxanthone (XV, R = Cl) were prepared according to the scheme



The acid (XIII, R = H) was previously prepared in poor yield by condensing 3,4-dinitrochlorobenzene with thiosalicylic acid[25] because the evolved nitrogen oxides oxidize the mercapto acid. Hodgson[26] found that the chlorine ortho to the nitro group in XII was replaced when treated with sodium methylmercaptide. Condensation of XII with thiosalicylic acid in the presence of sodium ethoxide gave the acid (XIII, R = H) in excellent yield.

Ring closure to the thiaxanthone (XV, R = N) was performed *via* the intermediate acid chloride, XIV, with the aid of aluminum chloride.[25] The properties of XIII and XV agreed with those reported.[25]

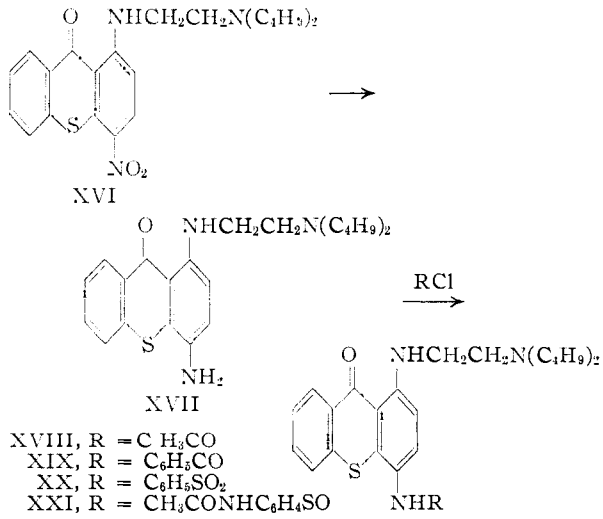
Most of the alkyl and dialkylaminoalkylamines were prepared by literature methods or were available from work on the anti-malarial problem. The hydroxyalkylaminoalkylamines were prepared from ethylenediamine and the alkylene oxide according to Kitchen and Pollard.[27] The 1-dialkylamino-2-propylamines were obtained by reductive amination of the corresponding dialkylaminoacetones.[28]

The N-alkyl-N-hydroxyalkylaminoethylamines were prepared from bromoethylphthalimide and the alkylhydroxyalkylamines. The new diamines are listed in Table I.

In our early experiments the original procedure for condensing diethylaminoethylamine with the 1-chlorothiaxanthones was used.[2] It was noted that the copper was unnecessary,[29] the temperature could be lowered to a point where the reaction could be run at atmospheric pressure and that the pyridine could be eliminated.[30,30a] We preferred to use the pyridine in the reactions involving some of the less accessible diamines since it tended to conserve these compounds. In the reactions involving diamylamino and dihexylamino derivatives it was mandatory to omit the copper catalyst. When present intractable mixtures were encountered.

In the processing of the reaction mixtures which contained non-basic material it was found expedient to dissolve the non-volatile components in acetic acid and throw out the neutral fraction with water rather than to extract with dilute acetic acid.[2] The acetic acid treatment was omitted when the reaction products were completely acid soluble. When it was anticipated that the desired hydrochloride would be slightly soluble in alcohol the entire mixture was taken up in this solvent and then treated with excess dry hydrogen chloride.

Several hydrochlorides resisted crystallization until water was added. The resulting salts ap-



XVIII, R = CH_3CO
XIX, R = C_6H_5CO
XX, R = $C_6H_5SO_2$
XXI, R = $CH_3CONHC_6H_4SO$

(25) F. Mayer, *Ber.*, **43**, 584 (1910).

(26) H. H. Hodgson and F. W. Handley, *J. Chem. Soc. Ind.*, **46**, 435T (1927).

(27) L. J. Kitchen and C. B. Pollard, *J. Org. Chem.*, **8**, 342 (1943). Dr. A. R. Surrey of this Institute prepared 2,3-dihydroxypropylaminoethylamine. The properties of this compound will be reported by him.

(28) D. S. Breslow, *et al.*, THIS JOURNAL, **68**, 100 (1946).

(29) H. Mauss (ref. 4) found that copper was unnecessary.

(30) B. F. Tullar (private communication) condensed 1-chloro-4-methylthiaxanthone with dibutylaminoethylamine without pyridine. (a) P. Gaillot and J. Gaudechon, Union of S. Africa Patent Application No. 2587/51 (Oct. 3, 1951) prepared 1-(2-dibutylaminoethylamino)-4-methylthiaxanthone from 2-dibutylaminoethylamine and the Ullmann-Glenck thiaxanthone mixture in refluxing quinoline. Their hydrochloride melted at 160–161°. Sharp (ref. 23a) prepared the same substance by Mauss' method. He reported the m.p. of the hydrochloride to be 167–169°.

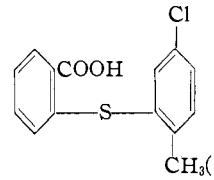
TABLE I

PROPERTIES OF THE N-HYDROXYALKYLAMINOETHYLAMINES, $R^1R^2NCH_2CH(R)NH_2$

R	Alkyl groups R^1	Alkyl groups R^2	B.p., °C.	B.p., Mm.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
H	C_2H_5	$HOCH_2CH_2$	72–72.5	0.4	$C_6H_{16}N_2O$	21.20	21.10
H	n-C_4H_9	$HOCH_2CH_2$	145–147.5	21	$C_8H_{20}N_2O$	17.42	17.08
CH_3	C_2H_5	$HOCH_2CH_2$	69–70.5	0.4	$C_7H_{18}N_2O$	19.27	19.01
H	C_2H_5	$(CH_3)_2COHCH_2$	79–80	3.0	$C_8H_{20}N_2O$	17.42	17.21
H	C_2H_5	$CH_3CHOHCH_2$	102–103	8.0	$C_7H_{18}N_2O$	19.16	18.68
H	CH_3	$CH_3CHOHCH_2$	81–83	2.0	$C_6H_{16}N_2O$	21.20	20.50
H	C_4H_9	$CH_3CHOHCH_2$	109–111	3.0	$C_9H_{22}N_2O$	16.07	15.93

TABLE II

PROPERTIES OF THE SUBSTITUTED *o*-PHENYLMERCAPTOBENZOIC ACIDS



Acid	M.p., °C. (cor.)	Solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
5-NO_2-2′-Me-5′Cl	237.9–239.3	EtOH	$C_{14}H_{10}ClNO_4S$	51.74	51.79	3.11	3.06		
4-Cl-2′,5′-diCl	228.6–229.4	EtOH	$C_{13}H_7Cl_3O_2S$	46.80	46.55	2.10	2.40	9.61	9.66
5-NO_2-2′,5′-diCl	255–256.4	HOAc	$C_{13}H_7Cl_2O_4NS$					9.32	9.33
4-Cl-2′-Me,5′Cl	199.6–201	Benzene	$C_{14}H_{10}Cl_2O_2S$	53.68	53.60	3.21	3.38		
4-MeO-2′Me-5′Cl	194.6–195.8	Benzene	$C_{15}H_{13}ClO_3S$	58.34	58.64	4.24	4.31	11.49[a]	11.73[a]
4-Me-2′Me-5′Cl	191.4–192.4	EtOH	$C_{15}H_{13}ClO_2S$					10.95	10.98
4-Cl-2′-NO_2,5′Cl	210–211	HOAc-H_2O	$C_{13}H_7Cl_2NO_4S$					4.07[b]	4.02[b]

[a] Chlorine analysis. [b] Nitrogen analysis.

TABLE III

PROPERTIES OF THE 1(OR 4)-HALOTHIAXANTHONES

Thiaxanthone	Method	Solvent	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
1,4-diCl	H	HOAc	175.5–176.8[b]	$C_{13}H_6Cl_2OS$					11.40	11.38
1-Cl,2,4-diMe	J	EtOH-H_2O	144–147[c]	$C_{15}H_{11}ClOS$					11.60	11.60
1,7-diCl,4-Me	I	HOAc	196–197[d]	$C_{14}H_8Cl_2OS$	57.1	57.5	2.71	2.91		
1-Cl,4-NO_2	G[a]	HOAc	202–205							
1,4,7-triCl	H[a]	HOAc	227.8–228.6[b]	$C_{13}H_5Cl_3OS$	49.48	49.49	1.60	1.90		
1-Cl,4-Et[e]	J	HOAc	71–75	$C_{15}H_{11}ClOS$					11.67	11.86
1-Cl,4,6,8-triMe	I	HOAc	203–205	$C_{16}H_{13}ClOS$					11.08	10.30
1,4-diCl,6,8-diMe	H	HOAc	216.3–217.4[b]	$C_{15}H_{10}Cl_2OS$	58.24	58.18	3.26	3.35		
1,4-diCl,7-Me	H	HOAc	202–203.1[b]	$C_{14}H_8ClOS$	56.77	56.71	2.73	2.94		
1-Cl,4-Me,8-NO_2	I	None[f]	293–293.8[b]	$C_{14}H_8ClNO_3S$					10.50	10.87
1-Cl,4,7-diMe	I[a]	HOAc-H_2O	147.8–148.8[b]	$C_{15}H_{11}ClOS$	65.56	65.47	4.04	4.35		
1-Cl,4-Me,7-MeO	I	HOAc	188–190.1[b]	$C_{15}H_{11}ClO_2S$					11.03	11.08
4-Br,1,2-diMe	J	HOAc	129.9–133.8[b]	$C_{15}H_{11}BrO_2S$					10.04	10.33
1,6-diCl,4-Me	I[a]	HOAc	190.2–191.2[b]	$C_{14}H_8Cl_2OS$					10.84	11.41
4,6-diCl,1-Me	J[g]	HOAc-H_2O	193.6–194.6	$C_{14}H_8Cl_2OS$					10.84	10.79
1,4-diCl,8-NO_2	H	Pyridine	>300	$C_{13}H_5Cl_2NO_3S$					9.83	10.08
1-Cl,4,8-diMe	J[g]	HOAc	152–153	$C_{15}H_{11}ClOS$	65.56	66.38	4.04	3.89		
1,8-diCl,4-Me	J	HOAc	193.5–195	$C_{14}H_8Cl_2OS$					10.84	10.85
1-Cl,4,6-diMe	I[a]	HOAc	183.1–183.7[b]	$C_{15}H_{11}ClOS$					11.62	11.71
4-Cl,1,6-diMe	J[g]	HOAc	151–153	$C_{15}H_{11}ClOS$					11.62	11.91
1,7-diCl,4-NO_2	G	HOAc	245.5–246.3	$C_{13}H_5Cl_2NO_3S$					4.39[h]	4.27

[a] Details of the method used for this experiment are in the Experimental part. [b] Corrected. [c] Mauss (ref. 4) reported m.p. 143–144°. [d] Mauss (ref. 4) reported that the mixture of 1,7-dichloro-4-methylthiaxanthone and 4,7-dichloro-1-methylthiaxanthone melted at 182–183°. [e] Prepared by T. R. Lewis from thiosalicyclic acid and *p*-chloroethylbenzene. This is probably an isomer mixture. [f] This compound was insoluble in all of the common solvents. [g] The dithio acid was used here. [h] Nitrogen analysis.

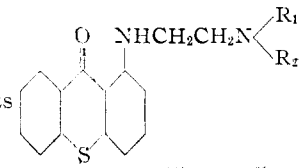
peared to be hydrates which readily lost water on drying at 75°. Dihydrochlorides of some bases were obtained but only when there were at least three methylene groups separating the nitrogen atoms in the side chain.

The chlorine atom in the thiaxanthone (XV, R = H) was sufficiently active to condense with the diamine in boiling ethanol. In order to investigate the effect of changes in the 4-position on schistosomicidal activity, the nitro group in XVI was reduced and the amine XVII then acylated as shown in the equation.

It was found best to reduce XVI as the hydrochloride with iron powder. The base, XVII, was a low-melting but nicely crystalline solid, capable of forming both mono- and dihydrochlorides. The salts were separated by taking advantage of the fact that the monohydrochloride was insoluble in

TABLE IV

PROPERTIES OF THE 1-(HYDROXYALKYLAMINOETHYLAMINO)-THIAXANTHONES



Thiaxanthone	R_1	R_2	Method	Solvent	M.p., °C. (cor.)	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
4-Me	$HOCH_2CH_2$	H	B	EtOH-H_2O	266.2–269	$C_{18}H_{20}N_2O_2S\cdot HCl$			8.79	8.57
4-Me	$CH_3CHOHCH_2$	H	B	EtOH	204–206	$C_{19}H_{22}N_2O_2S\cdot HCl$	7.39	7.16	8.46	8.53
4-Me	$HOCH_2HOCHCH_2$	H	B[a]	EtOH	207.8–208.4	$C_{19}H_{22}N_2O_3S\cdot HCl$	7.10	6.81	8.12	8.30
4-Me	$(CH_3)_2COHCH_2$	H	B[a]	EtOH	227.7–228.5	$C_{20}H_{24}N_2O_2S\cdot HCl$	7.13	6.77	8.16	8.25
4-Me	$CH_3CH_2CHOHCH_2$	H	B	EtOH-Et_2O	206–207.7	$C_{20}H_{24}N_2O_2S\cdot HCl$	7.13	6.76	8.16	8.12
4-Me	$CH_3CHOHCH_2$	CH_3	B	EtOH-Et_2O	144.4–146.1	$C_{20}H_{24}N_2O_2S\cdot HCl$	7.13	6.92	8.16	7.88
4-Me-α-Me	$HOCH_2CH_2$	C_2H_5	B	EtOH	152–154	$C_{21}H_{26}N_2O_2S\cdot HCl$	6.89	7.27	7.88	7.20
4-CH_3	$HOCH_2CH_2$	n-C_4H_9	B	EtOH-Et_2O	135–139	$C_{22}H_{28}N_2O_2S\cdot HCl$	6.65	6.40	7.62	7.91
4-CH_3	$CH_2CHOHCH_2$	n-C_4H_9	B	EtOH-Ac[b]	158.7–162	$C_{23}H_{30}N_2O_2S\cdot HCl$	6.44	6.40	7.37	7.32
4-CH_3-7-Cl	$CH_2CH_2CHOHCH_2$	H	D	EtOH	227.8–239	$C_{20}H_{23}ClN_2O_2S\cdot HCl$	6.56	6.27	7.50	7.30
4-CH_3-7-Cl	$(CH_3)_2COHCH_2$	H	D	EtOH	231–234	$C_{20}H_{23}ClN_2O_2S\cdot HCl$	6.56	6.61	7.50	7.50
4-CH_3-7-Cl	$HOCH_2CH_2$	C_2H_5	D[a]	EtOH	218–220.8	$C_{20}H_{23}ClN_2O_2S\cdot HCl$	6.56	6.86		
4-CH_3-7-Cl	$CH_3CHOHCH_2$	CH_3	C	EtOH	198.5–199.9	$C_{20}H_{23}ClN_2O_2S\cdot HCl$	6.56	6.37	7.51	7.69
4-CH_3-7-Cl	$CH_3CHOHCH_2$	C_2H_5	C	EtOH	188.3–190.3	$C_{21}H_{25}ClN_2O_2S\cdot HCl$	6.35	6.05	7.27	7.37
4-CH_3-7-Cl	$CH_3CHOHCH_2$	n-C_4H_9	C	Ac-MeOH[b]	161.6–163.8	$C_{23}H_{29}ClN_2O_2S\cdot HCl$	5.97	5.75	6.83	6.67
4-CH_3-7-Cl	$(CH_3)_2COHCH_2$	C_2H_5	D[a]	EtOH-Et_2O	201–202.2	$C_{22}H_{27}ClN_2O_2S\cdot HCl$	6.16	5.86	7.03	7.12
4,7-diMe	$HOCH_2CH_2$	C_2H_5	D	EtOH	186.1–187.8	$C_{21}H_{26}N_2O_2S\cdot HCl$	6.89	6.60	7.88	8.00
4-Me-7-MeO	$HOCH_2CH_2$	C_2H_5	D	EtOH	198.4–200.8	$C_{21}H_{26}N_2O_3S\cdot HCl$	6.16	6.37	7.05	7.00
4-Me-6-Cl	$HOCH_2CH_2$	C_2H_5	D	EtOH-Et_2O	220.1–221.7	$C_{20}H_{30}ClN_2O_2S\cdot HCl$	6.56	6.43	7.50	7.67
4-Cl	$HOCH_2CH_2$	C_2H_5	D	EtOH	209.1–211.2	$C_{19}H_{21}N_2O_2S\cdot HCl$	6.78	6.64	7.76	7.63
4-CH_3	$HOCH_2CH_2$	C_2H_5	B	EtOH	187.4–188.8	$C_{20}H_{24}N_2O_2S\cdot HCl$	7.13	7.21	8.16	8.47
4,7-diCl	$HOCH_2CH_2$	C_2H_5	D	EtOH	200.6–202.4	$C_{19}H_{20}Cl_2N_2OS\cdot HCl$	6.26	6.33	7.16	7.08
4-NO_2-α-Me	$HOCH_2CH_2$	C_2H_5	E	EtOH	226–228	$C_{20}H_{23}N_3O_4S\cdot HCl$			7.32	7.34

[a] Experiment described in detail. See experimental part. [b] Ac, acetone.

acetone. The base, XVII, was acylated in pyridine solution with benzoyl chloride, benzenesulfonyl chloride and *p*-acetamidobenzenesulfonyl chloride to furnish the thiaxanthones, XIX, XX and XXI, respectively. The acetylation which gave XVIII was carried out with acetic anhydride.

Biological Results.—The screening procedure which was employed was developed by Berberian, Dennis and Freele[31] of this Institute. The primary criterion of drug activity was the per cent. reduction of viable worms in infected mice compared with untreated controls. Rather than acute toxicities, chronic five-day toxicities were determined since it was anticipated that the drugs would be administered clinically in divided doses over a period of a few days. The lethal dose (LD_{50}) of Miracil D determined in this way was found to be 280 mg./kg. The effective dose which killed 50% of the adult worms was about 55 mg./kg. The relatively low therapeutic index (LD_{50}/ED_{50}) found in these laboratories is in line with the findings of others.[5,8] It was our intention to find a drug which was considerably less toxic and at least as effective as Miracil D.

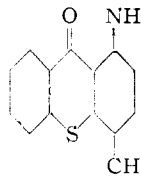
To determine the effect of nuclear substitution, 2-dibutylaminoethylamine was condensed with a variety of thiaxanthones (Table V). To study the effect of side-chain variation, the diamines were condensed with 1-chloro-4-methylthiaxanthone and in some cases with 1,7-dichloro-4-methylthiaxanthone.

The most effective thiaxanthones were those substituted in the 4-position with a methyl group and in the 7-position with hydrogen, methyl, methoxyl and chlorine.

When the number of carbon atoms between the nitrogen atoms in the side-chain exceeded two, the activity of the drug dropped precipitously. Thus, 1-(3-diethylaminopropylamino)-4-methylthiaxanthone was inactive, but the isomeric 1-(2-diethylaminopropylamino)-4-methylthiaxanthone was about equal to Miracil D in effectiveness.

All homologs of Miracil D from the dimethyl through dihexyl compounds were less active than the parent substance. However, the marked drop in toxicity of 1-(2-dibutylaminoethylamino)-4-methylthiaxanthone more than compensated for the activity loss, so that the therapeutic ratio was quite favorable.

It was observed that the thiaxanthone, XXII, was a feebly active schistosomicidal drug but that its homologs, XXIII and XIV, were about as active as Miracil D.



XXII, R = R′ = H
XXIII, R = H; R′ = CH_3
XXIV, R = R′ = CH_3

These observations prompted us to prepare a series of 4-methylthiaxanthones substituted in the 7-position with chlorine, methyl and methoxyl and in the 1-position with N-alkyl-N-hydroxyalkylaminoethylamino groups. When this was done a marked increase in activity and a decrease in toxicity was achieved. Compounds with therapeutic indices about ten times greater than Miracil D were found in this group.

Experimental[32]

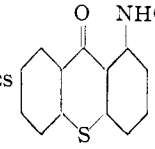
The first six experiments described below illustrate the methods used for preparing the 1-di-(alkylamino)-alkylaminothiaxanthones. The compounds are listed in Tables IV, V and VI.

(31) D. Berberian, E. W. Dennis and H. Freele, to be published. We wish to thank our colleagues for their excellent coöperation and making the biological results available to us.

(32) Analyses were carried out under the supervision of Messrs. M. E. Auerbach and K. D. Fleischer.

TABLE V

PROPERTIES OF THE DIBUTYLAMINOETHYLAMINOTHIAXANTHONE HYDROCHLORIDES



Thiaxanthone	Method	Solvent	M.p., °C. (cor.)	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
4-Me	A[a]	Acetone	166.4–167.4[i]	$C_{24}H_{32}N_2OS\cdot HCl$	6.47	6.25	7.44	7.52
4-Me	A[a]	Ac–ether[j]	142–144.4	$C_{24}H_{32}N_2OS\cdot C_2H_5SO_3H$	5.53	5.60	12.66	12.90
4,7-diMe	D	Acetone	153.5–154.7	$C_{25}H_{34}N_2OS\cdot HCl$	6.27	6.19	7.17	7.46
4,8-diMe	C[b]	Acetone	154.4–155.6	$C_{25}H_{34}N_2OS\cdot HCl\cdot 5H_2O$[d]	6.14	5.88	7.02	6.82
4,6-diMe	C[a,b]	Acetone	173.1–174.3	$C_{25}H_{34}N_2OS\cdot HCl$[e]			7.17	7.00
4,6,8-triMe	C	Ac–ether	164.3–165.5	$C_{26}H_{36}N_2OS\cdot HCl$	6.08	6.06	6.95	6.90
4-Et	C[b]	Ac–ether	125–127	$C_{25}H_{34}N_2OS\cdot HCl$	6.27	6.11	7.17	6.97
4-Me-α-Me	C	Ac–ether	192–193.5	$C_{25}H_{34}N_2OS\cdot HCl$	6.27	5.97	7.17	6.82
6-Cl-4-Me	C	Alc–ether[k]	204.1–205	$C_{24}H_{31}ClN_2OS\cdot HCl$	5.99	5.79	6.86	7.02
7-Cl-4-Me	C	Alc–ether	164.4–165.5	$C_{24}H_{31}ClN_2OS\cdot HCl$[f]	5.99	5.72		
8-Cl-4-Me	C[c]	Alc–Ac	196–197.2	$C_{24}H_{31}ClN_2OS\cdot HCl$	5.99	5.82	6.84	6.58
4-Me-8-NO_2	C	Alcohol	246.6–247.1	$C_{24}H_{31}ClN_2OS\cdot HCl$			6.84	6.74
4-Cl-6,8-diMe	C[b]	Acetone	184.5–185.9	$C_{25}H_{33}ClN_2OS\cdot HCl$	5.82	5.96	6.66	6.75
4,7-diCl	C	Acetone	163.2–164	$C_{23}H_{28}Cl_2N_2OS\cdot HCl$	5.74	5.91	6.57	6.76
4-Cl	C	EtOAc	127.6–129.7	$C_{23}H_{29}ClN_2OS\cdot HCl\cdot H_2O$[g]	6.19	6.48		
4-Cl-6-Me	C[b]	Ac–ether	140.2–142	$C_{24}H_{31}ClN_2OS\cdot HCl$	6.00	5.72	6.86	6.80
4-Cl-8-NO_2	C	Ethanol	251.5–253	$C_{23}H_{28}ClN_3O_3S\cdot HCl$[h]			6.43	6.71
4-NO_2-7-Cl[a]		Ethanol	196.2–197.8	$C_{23}H_{28}ClN_3O_3S\cdot HCl$	8.43	8.53	6.43	6.51
4-NO_2[a]		Ethanol–ether	220–221.5	$C_{23}H_{29}N_3O_3S\cdot HCl$	9.00	9.14	6.91	6.91
4-NH_2[a]		Ethanol	245–248	$C_{23}H_{31}N_3OS\cdot HCl$			7.44	7.07
4-C_6H_5CONH[a]		Ethanol	273.5–275.5	$C_{30}H_{35}N_3O_2S\cdot HCl$	7.81	7.66	5.96	6.15
4-CH_3CONH[a]		Ethanol	224–226	$C_{25}H_{33}N_3O_2S\cdot HCl$	8.83	8.96	6.73	6.65
4-$AcNHC_6H_4SO_2NH$[a]		Ethanol	246–247.7	$C_{31}H_{28}N_4O_4S_2\cdot HCl$	8.88	8.77	10.16	10.12
4-$C_6H_5SO_2NH$[a]		EtOH–ether	202.8–203.6	$C_{29}H_{35}N_3O_3S_2\cdot HCl$	7.31	7.45	11.15	11.06

[a] Experiment described in detail. See experimental part. [b] Crystallization of the hydrochloride occurred when ice was added. [c] The gummy hydrochloride crystallized when triturated with acetone. [d] *Anal.* Calcd.: H_2O, 2.08. Found: H_2O, 2.08. [e] *Anal.* Calcd.: C, 67.16; H, 7.89. Found: C, 67.29; H, 7.92. [f] *Anal.* Calcd.: C, 61.65; H, 6.90. Found: C, 61.60; H, 6.70. [g] *Anal.* Calcd.: C, 61.08; H, 6.68; H_2O, 3.83. Found: C, 61.29; H, 6.73; H_2O, 3.71. [h] *Anal.* Calcd.: C, 55.42; H, 5.86. Found: C, 55.67; H, 5.71. [i] See ref. 30. [j] Ac, acetone. [k] Alc, alcohol.

TABLE VI

PROPERTIES OF MISCELLANEOUS 1-(ALKYLAMINOALKYLAMINO)-THIAXANTHONE HYDROCHLORIDES

Thiaxanthone substituent	Side-chain	Method	M.p., °C. (cor.)	Solvent	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
4-Me	$(CH_3)_2NCH_2CH_2NH$	B	230–231.5	EtOH	$C_{18}H_{26}N_2OS\cdot HCl$	8.03	8.00	9.19	9.10
4-Me	$(C_2H_5)_2NCH_2CH_2NH$	A[a]	199.6–200.6	EtOH	$C_{20}H_{24}N_2OS\cdot HCl$	7.43	7.29		
4-NO_2	$(C_2H_5)_2NCH_2CH_2NH$	E	264.8–265.2	EtOH	$C_{19}H_{21}N_3O_3S\cdot HCl$			7.86	7.72
4-CH_3-7-Cl	$(C_2H_5)_2NCH_2CH_2NH$	D	250.5–251.3[b]	EtOH	$C_{20}H_{23}ClN_2OS\cdot HCl$			7.80	7.99
4,7-diMe	$(C_2H_5)_2NCH_2CH_2NH$	D	202–203	EtOH	$C_{21}H_{26}N_2OS\cdot HCl$	7.17	7.01	8.20	8.12
4-NO_2-7-Cl	$(C_2H_5)_2NCH_2CH_2NH$	E	276–277	EtOH	$C_{19}H_{20}ClN_3O_3S\cdot HCl$	9.50	9.74	7.25	7.28
4-CH_3	$(C_2H_5)_2NCH_2CH(CH_3)NH$	B	227.2–228.6	EtOH–Et_2O	$C_{21}H_{26}N_2OS\cdot HCl$	7.17	7.13	8.20	8.11
4-CH_3	$(n\text{-}C_3H_7)_2NCH_2CH_2NH$	B	155.8–157.6	EtOH–Et_2O	$C_{22}H_{28}N_2OS\cdot HCl$	6.92	6.97	7.92	7.56
4-CH_3	$(i\text{-}C_4H_9)_2NCH_2CH_2NH$	B(ice)[f]	151.8–153.4	MeOH–Et_2O	$C_{24}H_{32}N_2OS\cdot HCl$	6.47	6.02	7.44	7.20
4-CH_3	$(n\text{-}C_5H_{10})_2NCH_2CH_2NH$	F	156.8–157.6	Acetone	$C_{26}H_{36}N_2OS\cdot HCl$	6.08	5.80	6.75	7.00
4-CH_3	$(n\text{-}C_6H_{12})_2NCH_2CH_2NH$[a]		135.2–136.4	Acetone	$C_{28}H_{40}N_2OS\cdot HCl$	5.73	5.75	6.55	6.43
4-CH_3	$(C_2H_5)_2NCH_2CH_2CH_2NH$	A	164–165[c]	MeOH–Et_2O	$C_{21}H_{28}N_2OS\cdot HCl$	9.07[d]	8.97	8.20	8.31
2,4-diMe	$(C_2H_5)_2NCH_2CH_2CH_2NH$	A	211–212	EtOH–Et_2O	$C_{22}H_{28}N_2OS\cdot 2HCl$	6.59	6.30	7.53	7.49
4-Me-8-Cl	$(C_2H_5)_2NCH_2CH_2CH_2NH$	A	166.8–167.2	EtOH	$C_{21}H_{25}N_2OS\cdot 2HCl$	6.07	5.95	6.94	6.80
4-Me	$CH_3CH_2CH_2NHCH_2CH_2CH_2NH$	B	221.4–222.4	EtOH	$C_{20}H_{24}N_2OS\cdot HCl$	7.43	7.40	8.51	8.42
4-Me	$(C_3H_7)_2NCH_2CH_2CH_2NH$	B	210.4–212	EtOH–Et_2O	$C_{23}H_{30}N_2OS\cdot HCl$	6.69	6.63	7.65	7.73
4-Me	$(C_4H_9)_2NCH_2CH_2CH_2NH$	B	174.6–176.2	Acetone	$C_{25}H_{34}N_2OS\cdot HCl$	6.27	6.31	7.17	7.20
4-Me	$(i\text{-}C_4H_9)_2NCH_2CH_2CH_2NH$	B	183.6–185.4	EtOH–Et_2O	$C_{25}H_{34}N_2OS\cdot HCl$	6.27	6.31	7.11	6.73
4-Me	$(C_5H_{11})_2NCH_2CH_2CH_2NH$[a]		128.8–130.0	Acetone	$C_{27}H_{38}N_2OS\cdot HCl$	5.70	5.90	7.40	7.62
4-Me	$(C_6H_{13})_2NCH_2CH_2CH_2NH$[a]		135.2–136.8	Acetone	$C_{29}H_{42}N_2OS\cdot HCl$	5.57	5.65		
4-Me	$(C_2H_5)_2N(CH_2)_4NH$	B	153–155.0	EtOH–Et_2O	$C_{22}H_{28}N_2OS\cdot 2HCl$	6.35	6.23	7.26	7.14
4-Me	$(C_4H_9)_2N(CH_2)_4NH$	B	136.2–138.2	Ac[e]–Et_2O	$C_{26}H_{36}N_2OS\cdot HCl$	6.08	5.94	6.95	6.70
4-Me	$(C_2H_5)_2NCH_2CH_2CH_2CH(CH_3)NH$	A	144–145.2	EtOH–Et_2O	$C_{23}H_{30}N_2OS\cdot 2HCl$	6.29	6.29	7.20	7.19
3,4-diMe	$(C_2H_5)_2NCH_2CHOHCH_2NH$	A	216–217.4	EtOH–Et_2O	$C_{22}H_{28}N_2O_2S\cdot 2HCl$	6.12	6.00	7.01	7.06
4-Me	$(C_2H_5)_2NCH_2CHOHCH_2NH$	A	220.8–222.2	EtOH–Et_2O	$C_{21}H_{26}N_2O_2S\cdot HCl$	6.90	6.85	7.70	7.88
4-Me-8-Cl	$(C_2H_5)_2NCH_2CHOHCH_2NH$	A	214–215.2	EtOH	$C_{21}H_{25}ClN_2O_2S\cdot HCl$	6.20	6.20	7.26	7.26
4-Me	$Et(HOCH_2CH_2)NCH_2CH_2CH_2NH$	B	183–184.4	EtOH	$C_{21}H_{28}N_2O_2S\cdot HCl$	6.89	6.78	7.88	8.05
4-Me	$C_5H_{10}NCH_2CH_2NH$	B	260.7–262.3	EtOH	$C_{21}H_{24}N_2OS\cdot HCl$	7.20	7.14	8.24	7.93
4-Me	$O(CH_2CH_2)_2NCH_2CH_2NH$	B	257.5–259.5	EtOH	$C_{20}H_{22}N_2O_2S\cdot HCl$	7.18	7.06	8.20	8.20

[a] Experiment described in detail. See Experimental part. [b] Mauss (ref. 4) reported m.p. 246–247°. [c] Mauss (ref. 4) reports m.p. 173°. [d] Chlorine analysis. [e] Ac, acetone. [f] Ice added to induce crystallization of the crude hydrochloride.

1-(2-Dibutylaminoethylamino)-4-methylthiaxanthone Hydrochloride. (Method A).—The following is a general procedure first used for preparing Miracil and related compounds. It is a modification of the method of Mauss.[2,4]

A mixture of 20 g. of 1-chloro-4-methylthiaxanthone and its isomer, 25 g. of dibutylaminoethylamine and 40 g. of pyridine was heated under reflux for 18 hours. Then the mixture was allowed to cool and treated with a few ml. of 50% potassium hydroxide. The whole was steam distilled to remove the volatile bases. The residue was cooled and the supernatant liquid was carefully decanted. The residue was boiled with 500 ml. of 10% acetic acid and filtered. The insoluble residue was boiled again with two 100-ml. portions of 10% acetic acid; the solid was filtered after each extraction. The acid filtrates were combined and made alkaline. The thiaxanthone was collected in chloroform. After drying, the solution was concentrated *in vacuo* and the residue dissolved in dry ether. It was filtered and the filtrate was treated with a slight excess of alcoholic hydrogen chloride. The solid was filtered and dried, wt. 11.0 g. It was crystallized from acetone and dried at 75° for at least 24 hours. It melted at 166.4–167.4° (cor.).

The salt was sparingly soluble in cold water but readily soluble in hot water and can be recrystallized from this solvent. A sample of the hydrochloride was dissolved in warm water and the solution was made alkaline with sodium carbonate solution. The base was taken up in chloroform. The solution was concentrated to dryness and the residue dissolved in ether. A slight excess of ethanesulfonic acid (95%) was added. A gum separated which solidified on scratching. The salt was purified by recrystallization from acetone–ether.

The ethanesulfonate was very soluble in cold water.

1-(2-[2,3-Dihydroxypropyl]-aminoethylamino)-4-methylthiaxanthone Hydrochloride (Method B).—The following procedure was found to be more convenient than the one just described. It was applicable in cases where separation from non-basic material was necessary. It was not used when a tertiary hydroxyl was present in the final product.

A mixture of 30 g. of 1-chloro-4-methylthiaxanthone and its isomer, 15 g. of 2-(2,3-dihydroxypropylamino)-ethylamine and 15 g. of dry pyridine was heated under reflux for 18 hours. The dark red solution was cooled, treated with a few ml. of 50% potassium hydroxide and steam distilled. The residue was cooled and filtered. The solid was dissolved in a minimum quantity of boiling glacial acetic acid and the solution was diluted with six volumes of water. The suspension was heated to boiling and filtered. The insoluble material was washed with water, pressed dry and discarded. The filtrate was made basic. The oil that separated was collected in chloroform and processed as in method A from this point. There was obtained 12.0 g. of the desired hydrochloride.

1-(2-Dibutylaminoethylamino)-4,6-dimethylthiaxanthone Hydrochloride. (Method C.)—A mixture of 7.0 g. each of 1-chloro-4,6-dimethylthiaxanthone, dibutylaminoethylamine and pyridine was refluxed for 16 hours. The solution was cooled, treated with 50% potassium hydroxide and steam distilled. The residue was dissolved in chloroform, dried and concentrated. The oil that remained was dissolved in ether, filtered and treated with alcoholic hydrogen chloride. A gum separated. The ether was decanted. Ice was added and the material crystallized. After recrystallization from acetone–ether the product weighed 7.3 g. It was probably a hydrate since it melted at 132–134° (uncor.). After one more crystallization from acetone, the salt was dried for three days at 80°. It then melted at 173.1–174.3° (cor.).

In most instances the addition of ice to induce crystallization was unnecessary. The places where this operation was required are noted in the Tables.

7-Chloro-1-(2-N-ethyl-2-N-(2-hydroxyethyl)-aminoethylamino)-4-methylthiaxanthone Hydrochloride (Method D).—A mixture of 29 g. of 1,7-dichloro-4-methylthiaxanthone, 28 g. of 2-N-ethyl-N-(2-hydroxyethyl)-aminoethylamine and 25 g. of pyridine was refluxed for 18 hours. The solution was cooled to 80° and treated with 100 ml. of absolute ethanol. The solution was boiled and filtered. To the hot filtrate there was added 100 ml. of 25% alcoholic hydrogen chloride. On cooling the hydrochloride separated. It was filtered, washed with three 20-ml. portions of cold ethanol and dried; wt. 31.5 g. It was recrystallized from absolute alcohol; wt. 24.9 g., m.p. 218–220.8° (cor.).

1-(2-Dibutylaminoethylamino)-4-nitrothiaxanthone Hydrochloride (Method E).—A suspension of 8.0 g. of 1-chloro-4-nitrothiaxanthone in 8.0 g. of dibutylaminoethylamine and 75 ml. of absolute ethanol was refluxed for eight hours. The alcohol was removed and the residue dissolved in a minimum amount of hot acetic acid. The solution was treated with 5 volumes of water and filtered. The filtrate was made basic. The crystalline base was filtered and recrystallized from ethanol; wt. 7.0 g. It melted at 95–97° (uncor.).

Anal. Calcd. for $C_{23}H_{29}N_3O_3S$: N, 9.83; S, 7.49. Found: N, 10.18; S, 7.20.

The hydrochloride was prepared by dissolving the base in ethanol, adding alcoholic hydrogen chloride and throwing out the salt with ether. It was collected on a filter and recrystallized from ethanol, m.p. 219.5–220.8° (cor.).

1-(2-[2-Hydroxy-2-methylpropyl]-aminoethylamino)-4-methylthiaxanthone Hydrochloride (Method F).—Thirty grams of 1-chloro-4-methylthiaxanthone and its isomer, 20 g. of 2-(2-hydroxy-2-methylpropylamino)-ethylamine and 15 g. of pyridine were refluxed for 18 hours. The mixture was treated with a few ml. of 50% potassium hydroxide and steam distilled. The residue was cooled and filtered. It was boiled with 250 ml. of acetone and filtered. The extraction was repeated. The acetone filtrates were concentrated to dryness. The residue was taken up in ether and filtered. The filtrate was treated with alcoholic hydrogen chloride. The solid that separated was removed and crystallized twice from absolute alcohol; wt. 10 g., m.p. 227.7–228.5° (cor.).

1-Diethylamino-ethylamino-4-methylthiaxanthone Hydrochloride (Miracil D).[2,4]—One hundred grams of mixed 1,4-chloromethylthiaxanthones, 54 g. of diethylaminoethylamine and 54 g. of pyridine were refluxed for 20 hours. The temperature at the boiling point was 121° initially and 123° at the end of the reaction period. The mixture was processed as in method A above, to furnish 41 g. of pure hydrochloride, m.p. 199.6–200.6° (cor.). In pilot experiments it was found that the addition of copper powder has little or no effect on the yield.

In one experiment in which the reaction mixture was heated at 190° for four hours in an autoclave there was obtained some Miracil D from 13.0 g. of thiaxanthone. However, when repeated on a larger scale we obtained intractable tars in 173-g. and 150-g. runs.

7-Chloro-1-(2-dibutylaminoethylamino)-4-nitrothiaxanthone Hydrochloride.—A mixture of 12 g. of 1,7-dichloro-4-nitrothiaxanthone, 15 g. of dibutylaminoethylamine and 250 ml. of absolute alcohol was boiled under reflux for six hours. Then an excess of alcoholic hydrogen chloride was added and boiling was continued for one-half hour. The reaction mixture was filtered to remove a small amount of insoluble material. On cooling crystals separated from the filtrate. They were collected on a filter and recrystallized from 95% ethanol; wt. 10.0 g. After one more crystallization the salt melted at 196.2–197.8° (cor.).

7-Chloro-1-(2-ethyl-[2-hydroxy-2-methylpropyl]-aminoethylamino)-4-methylthiaxanthone Hydrochloride.—A mixture of 11 g. of 1,7-dichloro-4-methylthiaxanthone, 9.0 g. of 2-(N-ethyl-N-[2-hydroxy-2-methylpropyl]-amino)-ethylamine and 10.0 g. of pyridine was refluxed for 18 hours. The whole was dissolved in 75 ml. of absolute ethanol and treated with an excess of alcoholic hydrogen chloride. The dark red solution was kept at 5° overnight. The crystals that separated were filtered off and not further investigated. The filtrate was diluted with ether. A gum separated which soon solidified. After three crystallizations from ethanol–ether the product melted at 201–202.2° (cor.); wt. 4.5 g.

1-(3-Diamylaminopropylamino)-4-methylthiaxanthone Hydrochloride.—Thirty grams of the mixture of 1-chloro-4-methylthiaxanthone and its isomer, 20 g. of di-N-amylaminoethylamine and 20 g. of pyridine were heated under reflux for 20 hours before being made alkaline with dilute potassium hydroxide and steam distilled. The residue was dissolved in chloroform, separated from the aqueous layer and concentrated to dryness. The oil that remained was dissolved in ether and filtered. The filtrate was treated with a solution of dry hydrogen chloride in alcohol. The salt that separated was filtered. It was dissolved in warm chloroform, filtered and the filtrate diluted with an equal volume of ether. The crystals that separated on standing were

recrystallized from acetone; wt. 10.0 g., m.p. 128.6–130.6° (cor.).

When the reaction was carried out in the presence of metallic copper a very dark reaction mixture resulted. We were unable to obtain a pure product from this run.

1-(2-Dihexylaminoethylamino)-4-methylthiaxanthone Hydrochloride.—Twenty grams of di-N-hexylaminoethylamine, 30 g. of 1-chloro-4-methylthiaxanthone and the isomer and 20 g. of pyridine were refluxed 20 hours. After the usual steam distillation, residual oil was separated from the water by decantation and then extracted with hot acetone. The extract was taken to dryness. The residue was covered with absolute ether and allowed to stand at room temperature for two hours. The ethereal extract was filtered and then treated with dry hydrogen chloride in alcohol. An oil separated. The ether was removed and the hydrochloride stirred with ice. It solidified almost immediately. It was filtered and dried; wt. 14.7 g. After one recrystallization from acetone the product melted at 87–91° (uncor.). It was probably a hydrate since after one more crystallization and drying at 65° for three days the melting point rose to 135.2–136.4° (cor.). An experiment was carried out in which a small amount of copper was added to the reaction mixture. A dark solution resulted from which no pure product could be secured.

1-(3-Dihexylaminopropylamino)-4-methylthiaxanthone Hydrochloride.—A mixture of 30 g. of isomeric chloromethylthiaxanthones, 22 g. of 1-dihexylaminopropylamine and 25 ml. of pyridine was refluxed for 20 hours. After the usual steam distillation the residue was cooled. The solid was filtered and ether extracted. The extract was concentrated to dryness. It was dried by azeotropic distillation with chloroform. The gum was converted to the hydrochloride in ether solution. The partly gummy solid was converted to well-defined crystals by boiling a short time with ether. The product was filtered and recrystallized from acetone. After one more recrystallization the salt melted at 135.2–136.4° (cor.).

1-(2-Dibutylaminoethylamino)-4-aminothiaxanthone Hydrochloride.—A mixture of 57.0 g. of 1-(2-dibutylaminoethylamino)-4-nitrothiaxanthone, and 29 g. of *ferrum reductum* was suspended in a solution of 500 ml. of 90% ethanol and 12.2 ml. of concentrated hydrochloric acid (if only 1.2 ml. of acid was used no reduction occurred). The reaction mixture was stirred vigorously under reflux for four hours. A slight excess of 10% sodium carbonate solution was added and the dark mixture was filtered (Filtercel). On cooling the base crystallized. It was filtered and dried; wt. 39 g. (75%). On further crystallization from alcohol it melted at 64–66° (uncor.). It was dissolved in ether and treated with alcoholic hydrogen chloride. A mixture of mono- and dihydrochlorides separated. The crystals were filtered and leached with boiling acetone in which solvent the monohydrochloride is only slightly soluble. The insoluble residue was crystallized from absolute alcohol. It melted at 245–248° (uncor.).

1-(2-Dibutylaminoethylamino)-4-benzamidothiaxanthone Hydrochloride.—Eight grams of the 4-aminothiaxanthone in 80 ml. of pyridine was cooled in ice and treated dropwise with 1.8 ml. of benzoyl chloride. The flask was stoppered and allowed to stand at room temperature for five days. The reaction mixture was poured into water and the crystalline base collected on a filter. After drying at 65° the product was suspended in alcohol, treated with hydrogen chloride, heated to boiling and filtered. On cooling the hydrochloride separated; m.p. 273.5–275.5° (uncor.), wt. 4.2 g.

1-(2-Dibutylaminoethylamino)-4-acetamidothiaxanthone Hydrochloride.—When 2.0 ml. of acetic anhydride was substituted for the benzoyl chloride in the above experiment there was obtained 7.2 g. of the 4-acetamidothiaxanthone after recrystallization from ethanol; m.p. 194–197° (uncor.). Acetyl analysis revealed that monoacetylation had occurred.

Anal. Calcd. for $C_{25}H_{33}N_3O_2S$: CH_3CO, 9.78. Found: CH_3CO, 9.41.

The hydrochloride was prepared in the usual way in ethanol. Seven grams of the base yielded 6.5 g. of pure hydrochloride, m.p. 224–226° (cor.) after recrystallization from ethanol.

4-(*p*-Acetamidobenzenesulfonamido)-1-dibutylaminoethylaminothiaxanthone Hydrochloride.—Ten grams of the aminothiaxanthone was dissolved in 100 ml. of pyridine and cooled to 5°. Then 5.83 g. of pure *p*-acetamidobenzenesulfonyl chloride was added portion-wise with stirring. When all had been added the red reaction mixture was allowed to stand overnight at room temperature. It was poured into water and allowed to stand until the gum that separated turned crystalline. It was filtered and dried; wt. 14.2 g. After recrystallization from dilute ethanol with the aid of charcoal there was obtained 11.0 g.

The base was converted to the hydrochloride in ethanol; wt. 10.5 g. It melted at 246–247.7° (cor.) after two recrystallizations from alcohol.

4-Benzenesulfonamido-1-(2-dibutylaminoethylamino)-thiaxanthone Hydrochloride.—The compound was obtained in a similar manner from benzenesulfonyl chloride. Eight grams of the aminothiaxanthone yielded 3.8 g. of purified hydrochloride, m.p. 202.8–203.6° (cor.).

Dibutylaminoacetone.—A modification of the method of Hauser[29] was used. A solution of 181 g. of dibutylamine in 75 ml. of dry ether was added dropwise to a stirred solution of 63 g. of chloroacetone in 75 ml. of ether. The addition required one hour. The mixture was then refluxed for three hours more. Then sodium chloride was added and the mixture was filtered. The filter cake was washed with ether and the combined filtrates distilled. The amino ketone, which boiled at 111–112° (18 mm.) weighed 77 g. (59%).

Anal. Calcd. for $C_{11}H_{23}NO$: N, 7.57. Found: N, 7.48.

N-Ethyl-N-(2-hydroxyethylamino)-acetone.—From 63 g. of chloroacetone in 75 ml. of ether and 125 g. of ethylaminoethanol in 75 ml. of ether, there was obtained 56 g. (54%) of the desired product. The hydrochloride of ethylaminoethanol separated as an oil that was recovered in a separatory funnel. The aminoacetone boiled at 48–49° (1 mm.).

Anal. Calcd. for $C_7H_{15}NO_2$: N, 9.60. Found: N, 10.06.

2-Aminopropyldibutylamine.—A solution of 75 g. of dibutylaminoacetone in 350 ml. of 15% methanolic ammonia was treated with Raney nickel catalyst and reduced at 640 p.s.i. at 75° in five hours. The catalyst was filtered off and the filtrate distilled first at atmospheric pressure and then at 0.9 mm. The diamine boiled at 59° (0.9 mm.); wt. 55 g. (73%).

Anal. Calcd. for $C_{11}H_{26}N_2$: N, 15.03. Found: N, 14.81.

N-(2-Aminopropyl)-N-ethylaminoethanol.—A solution of 94 g. of N-ethyl-N-(2-hydroxyethyl)-aminoacetone in 500 ml. of 15% methanolic ammonia was hydrogenated at 70° at 450 p.s.i. in the presence of Raney nickel catalyst. Reduction was complete in seven hours. The catalyst was filtered and the filtrate distilled. After a forerun, b.p. 64–69° (0.4 mm.), wt. 18.4 g., the pure diamine was obtained, b.p. 69–70.5° (0.4 mm.), wt. 56.3 g. (59%).

2-(2-Hydroxybutylamino)-ethylamine.—The general procedure of Kitchen and Pollard[27] was followed. Twenty-seven grams of 1,2-epoxybutane prepared by the method used for 2,3-epoxybutane[33] was added dropwise with stirring to 135 g. of ethylenediamine which was heated to 60°. After all the oxide had been added the mixture was heated to 75°, held there three hours and then distilled. There was recovered 108 g. of ethylenediamine. This product boiled at 102° (3 mm.), wt. 36.3 g.

Anal. Calcd. for $C_6H_{16}N_2O$: N, 21.20. Found: N, 20.70.

Ethyl 2-Hydroxy-2-methylpropylamine.—To a solution of ethylamine in methanol (1450 ml. of 25.6%) which was cooled to 5° there was added 144 g. of isobutylene oxide dropwise with stirring. The temperature rose to 40° during the addition. The mixture was stirred for 16 hours at room temperature and then distilled. The amine boiled at 76–77° (40 mm.), wt. 177 g. (77%).

Anal. Calcd. for $C_6H_{15}NO$: N, 11.95. Found: N, 11.58.

The hydrobromide which was obtained from the interaction of β-bromoethylphthalimide and the above amine was crystallized from alcohol–ether and melted at 174.3–175.3° (cor.).

Anal. Calcd. for $C_6H_{15}NO \cdot HBr$: N, 7.07. Found: N, 6.96.

γ-Dibutylaminobutyronitrile.—A solution of 45 g. of potassium cyanide in 150 ml. of water was added to 325 ml. of ethanol. Then 125 g. of 1-dibutylamino-3-chloropro-

(33) C. E. Wilson and H. J. Lucas, THIS JOURNAL, 58, 2396 (1936).

pane[34] was added and the mixture stirred under reflux for 12 hours. Excess potassium carbonate was added and the solution extracted with ether. The extract was concentrated and the residue dissolved in ether and dried over Drierite. The solution was filtered and distilled. The fraction b.p. 91–94° (0.8 mm.) was analyzed; wt. 100.3 g. (82%), $n^{25}D$ 1.4412.

Anal. Calcd. for $C_{12}H_{24}N_2$: C, 73.41; H, 12.32; N, 14.27. Found: C, 73.26; H, 12.17; N, 14.02.

γ-Dibutylaminobutylamine.—To a solution of 525 g. of methanolic ammonia (6-7%) there was added 99.0 g. of γ-dibutylaminobutyronitrile and Raney nickel catalyst. The reduction proceeded at 500 p.s.i. and 78° in 12 hours. The catalyst was filtered and the filtrate concentrated and distilled to furnish 75.2 g. (75%) of the diamine, b.p. 54–55° (1.0 mm.), $n^{25}D$ 1.4472.

Anal. Calcd. for $C_{12}H_{28}N_2$: N, 13.77. Found: N, 13.96.

Butyl 2-Hydroxypropylamine.—A solution of 145 g. of butylamine in 400 ml. of methanol was heated to boiling. The source of heat was removed and 112 g. of propylene oxide was added at such a rate that gentle reflux was maintained. After all had been added the solution was heated for an additional hour and then distilled, first at atmospheric pressure to remove the solvent and then at 20 mm. The fraction, b.p. 98–100°, which weighed 134 g. (52%) was analyzed. There was also obtained 75 g. of a higher boiling oil which presumably was the tertiary amine, butyl-di-(2-hydroxypropyl)-amine.

Anal. Calcd. for $C_7H_{17}NO$: N, 10.67. Found: N, 10.62.

1-(N-Butyl-N-(2-aminoethyl)-amino)-2-propanol.—A mixture of 102 g. of β-bromoethylphthalimide, 109 g. of 2-hydroxypropylbutylamine and 240 ml. of dry xylene was refluxed for ten hours. The mixture was cooled and filtered. The filtrate was concentrated to remove xylene and the residue dissolved in 400 ml. of ethanol. The solution was heated to boiling with stirring and treated with 32 g. of 85% hydrazine hydrate. After three hours it was concentrated to dryness. The complex was dissolved in water and made acid with hydrochloric acid. The phthalhydrazide was filtered, pressed dry and washed with a liberal quantity of water. The combined filtrates were taken to dryness. The diamine hydrochloride was dissolved in a minimum quantity of water and then treated with solid potassium hydroxide until the oil layer which separated did not increase in size. The latter was separated and the aqueous part extracted with ether. The combined oil layers were dried over potassium hydroxide and distilled. The product boiled at 105–106.5° (3 mm.); wt. 35 g. (53%).

All the compounds listed in Table I were prepared by this method or minor variants thereof, with the exception of N-ethyl-N-(2-hydroxyethyl)-amino-2-propylamine. It was made by reductive amination of the corresponding acetone.

4-Chloro-2-(methyl-5-chlorophenylmercapto)-benzoic Acid.—Three grams of sodium was dissolved in 60 ml. of methanol and the solution heated to 90°. At this temperature 54 g. of 2-methyl-5-chlorothiophenol, 30 g. of potassium 2,4-dichlorobenzoate and 0.5 g. of copper powder were added. The whole was carefully heated to 215°. It was held there for 20 minutes. During this time the contents of the flask solidified. After cooling to 100°, dilute sodium carbonate was added to the mixture. The suspension was boiled and filtered. The filtrate was ether extracted and then acidified. A slightly gummy solid separated. It was filtered, pressed dry and washed with ligroin; wt. 33.4 g. The filtrate was extracted with ether. All the extracts were combined and extracted with 10% potassium hydroxide. The base layer was acidified and extracted with ether. The solvent was removed and the residue was steam distilled. The steam distillate gave 13.0 g. of recovered thiophenol, b.p. 115° (19 mm.). The non-volatile residue was filtered and dried. It weighed 3.6 g. making the total yield of desired acid 37 g. or 90.5% of the theoretical yield. The analytical sample was purified by recrystallization from benzene. It melted at 199.6–201.0° (cor.).

In the above experiment the ratio of sodium, potassium salt and thiophenol was 1:1:2.5. When this ratio was changed to 1:2:2.6, the yield of desired product fell to 82%. However, liquefaction of the reaction mixture occurred at a lower temperature and heating to 200° was all that was required to cause solidification of the mixture to occur. When the sodium was omitted no reaction occurred.

1,7-Dichloro-4-methylthiaxanthone; 4,7-Dichloro-1-methylthiaxanthone. Mixture from Mixed Thiophenols.—To a solution of 3.80 g. of sodium in 65 ml. of methanol there was added 66 g. of a mixture of 5-chloro-2-methylthiophenol and 2-chloro-5-methylthiophenol (prepared by chlorosulfonation of *p*-chlorotoluene followed by reduction), 70 g. of potassium 2,4-dichlorobenzoate and 0.3 g. of copper powder. The mixture was heated carefully. At 155° the mass liquefied as the temperature rose spontaneously to 162°. It was heated to 210° and held there for 15 minutes. The whole was allowed to cool and then was treated with dilute sodium carbonate solution. The suspension was heated to boiling and filtered. The filtrate was acidified and then steam distilled. After all the volatile material came over (mostly recovered thiophenol) the residue was cooled, filtered and washed with ligroin. After air drying there was obtained 88 g. of a gray crystalline solid. This mercapto acid mixture was cyclized with the aid of 880 g. of sulfuric acid at 95° for two hours. It was poured in water and filtered. The yellow solid was heated with dilute ammonia for one hour and filtered. It was washed with water and alcohol. After drying at 80° the product weighed 66 g. A sample was recrystallized from acetic acid and was analyzed; m.p. 188.3–188.7° (cor.).

Anal. Calcd. for $C_{14}H_6Cl_2OS$: C, 57.0; H, 2.71. Found: C, 56.4; H, 2.71.

Ethyl 2-(2-Methyl-5-chlorophenylmercapto)-5-nitrobenzoate.—To a solution of 1.7 g. of sodium in 250 ml. of absolute alcohol there was added 17.0 g. of ethyl 2-chloro-5-nitrobenzoate and 11.8 g. of 5-chloro-2-methylthiophenol. The mixture was stirred under reflux for six hours. It was poured in ice and allowed to stand. After one hour the solid was removed by filtration and dried; wt. 25 g. A portion was recrystallized from ethanol; m.p. 93.6–94.2° (cor.).

Anal. Calcd. for $C_{16}H_{14}ClNO_4S$: S, 9.13. Found: S, 9.26.

The acid was obtained by saponification in aqueous potassium hydroxide. It was purified by recrystallization from ethanol; m.p. 237.9–239.3°.

2-(2,5-Dichlorophenylmercapto)-5-nitrobenzoic Acid.—A solution of 2.3 g. of sodium in 150 ml. of dry alcohol was treated with 17.9 g. of 2,5-dichlorothiophenol and 21.3 g. of methyl 2-chloro-5-nitrobenzoate. After being stirred and refluxed for two hours the reaction mixture was poured on ice. After about an hour the ester was filtered and dried; wt. 36 g.

Twenty-eight grams of the crude ester was refluxed with a solution of 30 ml. of 50% potassium hydroxide in 400 ml. of 50% ethanol for 30 minutes. The clear solution was made acid and filtered. There was obtained 23 g. of the acid which after recrystallization from acetic acid melted at 255–256.4° (cor.).

2-(5-Chloro-2-nitrophenylmercapto)-benzoic Acid.—A solution of 2.3 g. of sodium, 7.7 g. of thiosalicylic acid and 9.6 g. of 2,4-dichloronitrobenzene in 100 ml. of absolute ethanol was boiled under reflux for 16 hours. The solution was concentrated to dryness and the mixture was then taken up in water and ether extracted. The aqueous portion was acidified and filtered. The crude acid was recrystallized from dilute ethanol to yield 12.5 g. (81%) of the desired product, m.p. 187–190° (uncor.).[35]

1-Chloro-4-nitrothiaxanthone (Method G).—A suspension of 29 g. of 2-(5-chloro-2-nitrophenylthio)-benzoic acid in a solution of 15 ml. of thionyl chloride and 100 ml. of benzene was refluxed for 45 minutes. The solvents were removed *in vacuo*. Then 75 ml. of benzene was added to the residue and the process repeated. The crude acid chloride was dissolved in 75 ml. of fresh benzene and the solution treated with 15 g. of aluminum chloride. The catalyst was added portionwise in the course of one-half hour. The dark mixture was boiled for 1.5 hours before being poured into iced dilute hydrochloric acid. The cold suspension was filtered and sucked as dry as possible. The filter cake was washed with ligroin. It was suspended in dilute ammonium hydroxide and steam was passed into the suspension. The yellow solid was filtered, washed thoroughly with water and then alcohol and dried, wt. 25 g. (92%).

(34) E. C. Whitmore and R. Adams, *ibid.*, **67**, 735 (1945).

(35) Mayer (ref. 25) reported m.p. 188–189°.

Material of this quality was satisfactory for coupling with amines. A pure sample was obtained by recrystallization from acetic acid; m.p. 201–202.5° (uncor.). Mayer[25] reported the melting point as 204–205°.

1,4,7-Trichlorothiaxanthone (Method H).—A solution of 7.0 g. of 4-chloro-2-(2,5-dichlorophenylthio)-benzoic acid in 70 g. of sulfuric acid was heated and stirred at 120–130° for one hour. The cooled solution was poured into water and filtered. The yellow solid was suspended in dilute ammonia and heated to boiling. After ten minutes the solid was filtered, washed with water and then acetone and dried; wt. 5.2 g. (78%). The acids prepared from 2,5-dichlorothiophenol were cyclized at 120–130°. Those prepared from 2-methyl-5-chlorothiophenol were cyclized at 95–100°.

1-Chloro-4,7-dimethylthiaxanthone (Method I).—Ten grams of crude 2-(5-chloro-2-methylphenylmercapto)-4-methylbenzoic acid and 100 g. of sulfuric acid were stirred and heated on the steam-bath for 90 minutes and then worked up as above. There was obtained 8.5 g. of the desired thiaxanthone. The over-all yield from potassium 2-chloro-4-methylbenzoate was 83%.

1,6-Dichloro-4-methylthiaxanthone.—This was obtained in 64% yield from the phenylmercapto acid. After recrystallization from dilute acetic acid it melted at 190.2–191.2° (cor.). The crystals were bright yellow in color. The thiaxanthone obtained from 3,3′-dichlorodithiosalicylic acid melted at 193.8–194.2°. The crystals were buff-colored. The mixed melting point fell between the melting points of the individual compounds.

1-Chloro-4,6-dimethylthiaxanthone.—This compound was obtained by ring closure of the corresponding acid. The over-all yield was 72% based on potassium 2-chloro-3-methylbenzoate. The compound melted at 183.1–185.9° (cor.) after recrystallization from acetic acid. The isomeric thiaxanthone obtained from 3,3′-dimethyldithiosalicylic acid melted at 151–153°.

2,5-Dichlorothiophenol and Tin Tetra-(2,5-dichlorothiophenolate).—A mixture of 234 g. of 2,5-dichlorobenzenesulfonyl chloride, 450 g. of tin and 1000 ml. of hydrochloric acid was heated to reflux. After 15 minutes a vigorous reaction ensued which was controlled by removing the heat source. After three hours of heating the mixture was cooled and extracted with ether. On standing yellow prisms separated from the solution. These were filtered and the filtrate was distilled to yield 65 g. of the required 2,5-dichlorothiophenol, b.p. 132° (29 mm.).[18] The crystals were purified by recrystallization from chloroform–Skelly B.

Anal. Calcd. for $C_{24}H_{12}Cl_8S_4Sn$: C, 34.69; H, 1.46; Sn, 14.29. Found: C, 34.49; H, 1.58; Sn, 14.12.

In other runs the reaction mixture was subjected to steam distillation rather than ether extraction. The usual yield was 66–70% of the theoretical based on the sulfonyl chloride.

2-Methyl-5-chlorothiophenol. A. Xanthate Method.—To a mixture of 150 ml. of hydrochloric acid and 150 g. of ice there was added 109 g. of 2-amino-4-chlorotoluene (Eastman Kodak Co. practical grade). The suspension was kept at 0–5° and diazotized with 56 g. of sodium nitrite dissolved in 125 ml. of water. After all the nitrite had been added the solution was stirred for one hour and filtered through Filtercel.

A solution of 144 g. of potassium ethylxanthate in 150 ml. of water was stirred and heated to 60°. The clear diazonium solution was added dropwise while the temperature was kept between 55–60°. Within this temperature range the decomposition proceeded smoothly and without the crackling noise that accompanied the addition at a higher temperature. When all the solution of the diazonium salt had been added the mixture was kept at 70–80° for one hour.

The red xanthate layer was removed and the aqueous solution was ether extracted. The combined oil layers were concentrated. The residue was dissolved in 400 ml. of alcohol, heated to boiling and treated portionwise with 175 g. of potassium hydroxide pellets. The suspension was refluxed ten hours. The alcohol was removed *in vacuo* and the resultant gummy mass shaken with one liter of water and ether extracted. The ether layer was dried and concentrated. The neutral oil was distilled. It boiled at 140–142° (21 mm.), $n^{25}D$ 1.5744. The analysis indicated that it was ethyl 5-chloro-2-methylphenyl sulfide.

Anal. Calcd. for $C_9H_{11}ClS$: Cl, 19.05; S, 17.24. Found: Cl, 19.15; S, 16.65.

The alkaline aqueous layer was acidified carefully in the hood. The oil that separated was gathered in ether, dried and distilled. There was obtained 63 g. of 5-chloro-2-methylthiophenol (54%), b.p. 126–128° (30 mm.).

Anal. Calcd. for C_7H_7ClS: S, 20.21. Found: S, 19.70.

In other runs of similar size the yields were 62, 61 and 56%. Some simplification in method without loss in yield was achieved by adding the potassium hydroxide as a 50% solution rather than as pellets.

B. Sulfinate Procedure.[22]—A solution of 50 g. of 2-amino-4-chlorotoluene was prepared in 150 g. of sulfuric acid and 500 ml. of water. It was kept at 0 to 5° and diazotized with a solution of 26.5 g. of sodium nitrite in 125 cc. of water. After being stirred for one hour longer 400 g. of 50% sulfuric acid was added and the temperature lowered to −5°. Sulfur dioxide was bubbled through and then 75 g. of copper powder, previously washed with alcohol, ether and dried, was added over a two-hour period. The whole was stirred and allowed to warm to room temperature overnight. It was filtered. The filter cake was leached thoroughly with ether and the filtrate extracted with the same solvent. The ether was removed and the residue covered with petroleum ether. The solid that formed was filtered and dried, 141.6 g.

A mixture of 63 g. of the sulfinic acid, 180 g. of tin and 600 ml. of hydrochloric acid was allowed to stand at room temperature for one hour before being refluxed for three hours. The mixture was steam distilled. The distillate was ether extracted. The oil layer was washed with water, dried over Drierite and distilled. The thiophenol boiled at 130° (35 mm.); wt. 22 g. (39%, based on 2-amino-4-chlorotoluene).

C. Grignard Procedure.—The required 2-bromo-4-chlorotoluene was prepared by a Sandmeyer reaction from 2-amino-4-chlorotoluene. A Grignard reagent in 500 ml. of dry ether was prepared from 123 g. of 2-bromo-4-chlorotoluene and 14.4 g. of magnesium. While kept under nitrogen the Grignard reagent was treated with 15.0 g. of sulfur over a 45-minute period. It was stirred for two hours more. It was poured into ice-water previously acidified with hydrochloric acid. The ether layer was separated. The aqueous layer was washed with ether. The combined extracts were washed with water, dried and distilled. After a small forerun in which the odor of *p*-chlorotoluene was readily discernible, the thiol was collected. It boiled at 126–129° (30 mm.), wt. 28 g. (29%).

In another experiment, the thiophenol was extracted from the ether solution with dilute potassium hydroxide. The basic solution was acidified and the oil gathered in ether, dried and distilled. This work-up definitely illustrates the nature of the thiophenol and definitely eliminates the possibility that we had a disulfide.

D. Sulfonyl Chloride Procedure.—To 350 g. of chlorosulfonic acid, 116 g. of *p*-chlorotoluene was added dropwise in two hours while the temperature was maintained at 25–30°. After two hours more the whole was poured on ice. The oil which separated soon solidified. It was taken up in carbon tetrachloride, washed with cold water and dilute sodium carbonate and then taken to dryness. The residue weighed 140 g.

The sulfonyl chloride was added dropwise to a suspension of 1500 g. of ice and 268 ml. of sulfuric acid kept at 0 to −10°. Then 250 g. of zinc dust (anal. reagent) was added portionwise in 30 minutes. The cooling bath was withdrawn and after the reaction mixture warmed to room temperature it was heated on the steam-bath for ten hours.

It was steam distilled. The distillate was extracted with chloroform. The solvent was removed and the residue distilled to yield 66 g. of the thiophenol, b.p. 74–76° (1 mm.). The yield was 46% based on *p*-chlorotoluene.[23a]

2-Amino-3,5-dimethylbenzoic Acid.—The procedure described below was used for all the isatins used in this work. Sixty grams of 2,4-dimethylaniline was converted to isonitrosoacet-2,4-dimethylanilide by the procedure described in "Organic Syntheses." The crude anilide was dissolved in 1 *N* sodium hydroxide, filtered to remove tarry by-products and the filtrate was made acidic. The crystals were filtered, washed with water and dried, wt. 69 g.

The crude isonitrosoacetxylidide was added portionwise to 500 g. of sulfuric acid at 60–70°. The dark mixture was heated at 80° for ten minutes, and poured in water. The crude 5,7-dimethylisatin was filtered, washed with water and dried; wt. 53 g. It was of suitable purity to be used

in the oxidation step. The isatin was dissolved in a solution of 48 g. of sodium hydroxide in 630 ml. of water at 25°. The stirred solution was treated with 79 ml. of Superoxol dissolved in 320 ml. of water. The dropwise addition required about one hour. The mixture was stirred for three hours more, filtered and made faintly acidic. The crystalline solid was filtered and dried. The analytical sample was crystallized first from dilute ethanol and then benzene–ligroin; m.p. 193.4–194.6° (cor.).

Anal. Calcd. for $C_9H_{11}NO_2$: N, 8.46. Found: N, 8.33.

2-Chloro-3,5-dimethylbenzoic Acid.—Twenty-two grams of the above acid was dissolved in 120 ml. of 6 *N* hydrochloric acid and diazotized with the aid of 9.5 g. of sodium nitrite in 30 ml. of water. The diazonium solution was added to a solution of 16.0 g. of cuprous chloride in hydrochloric acid at 5°. The reaction was completed by warming the mixture at 60° for one hour. There was obtained 20.4 g. of the chloro acid. After two crystallizations from benzene–ligroin the acid melted at 138.3–139.9° (cor.).[36]

Anal. Calcd. for $C_9H_9ClO_2$: Cl, 19.22. Found: Cl, 19.40.

2-Chloro-3-methylbenzoic Acid.—This was obtained in 85% yield from 2-amino-3-methylbenzoic acid.[37] After two crystallizations from dilute ethanol it melted at 138–140° (uncor.).

Anal. Calcd. for $C_8H_7ClO_2$: C, 56.32; H, 4.14. Found: C, 56.48; H, 4.04.

2,4-Dichloronitrobenzene.—Fuming nitric acid (360 g., d. 1.52) was stirred vigorously at 20–30° while 73 g. of *m*-dichlorobenzene was added dropwise over a period of one hour. After all had been added stirring was continued for 90 minutes longer. The mixture was poured in ice-water and allowed to stand until the ice had melted. The crystalline material was filtered, washed with water and recrystallized from ethanol. After drying over sulfuric acid, the product weighed 76 g. (80%).[38]

2-Nitro-4-methylbenzoic Acid.—Sixty grams of 3-nitro-4-aminotoluene furnished 62 g. of 4-methyl-2-nitrobenzonitrile by the method of Morgan and Coulson.[39] The nitrile was suspended in 120 ml. each of water, acetic acid and sulfuric acid. After refluxing for six hours the suspension was cooled and poured in ice-water. The solid was filtered and dissolved in dilute sodium carbonate. After filtration to remove some tar the solution was acidified to furnish 38.8 g. of the nitro acid. After recrystallization from water there was obtained 29.6 g. of pure nitro acid.[40]

Reduction of 29 g. of the above acid in dilute ammonia was carried out in the presence of Raney nickel catalyst. The anthranilic acid was precipitated by acidification to *p*H 5. **The 2-amino-4-methylbenzoic acid** melted at 151–153°.[41]

4-Chlorothiosalicylic Acid.—The method described in reference 10 for the preparation of thiosalicylic acid was used: 41.6 g. of 2-amino-4-chlorobenzoic acid furnished 15.0 g. of the acid after recrystallization from dilute acetic acid.

Anal. Calcd. for $C_7H_5ClO_2S$: S, 17.00. Found: S, 17.52.

5-Chlorothiosalicylic Acid.—Eighty-six grams of 2-amino-5-chlorobenzoic acid gave 22 g. of 5-chlorothiosalicylic acid by the same method; m.p. 188–190° (uncor.) after recrystallization from dilute ethanol.

Anal. Calcd. for $C_7H_5ClO_2S$: S, 17.00; Cl, 18.81. Found: S, 16.51; Cl, 18.30.

The same procedure except for the omission of the reduction step was used for preparing 3,3′-dichloro-5,5′-dimethyl- and 3,3′-dinethyldithiosalicylic acid in yields of 91, 84 and 64%, respectively. The crude acids were used directly in the condensations with *p*-chlorotoluene.

1-Chloro-4-methylthiaxanthone and 4-Chloro-1-methylthiaxanthone (Method J).[3]—A mixture of 150 ml. of *p*-chlorotoluene and 1500 ml. of sulfuric acid was stirred vigorously at 25–30° as 60 g. of pure thiosalicylic acid was added. The mixture turned dark red, sulfur dioxide was evolved and the temperature usually rose about ten to fifteen degrees. Stirring was continued for about 16 hours at room temperature and then the mixture was held at 60° for two hours. The solution was poured into ice-water and filtered. The yellow solid was suspended in dilute ammonia and steam was passed into the suspension for 30 minutes. Then the solid was collected on a filter and washed successively with water, alcohol and acetone. On drying there was obtained 83 g. (81%) of the thiaxanthone mixture suitable for use in the condensation with the diamines. It melted at 142–145° (uncor.). Upon crystallization from acetic acid the melting point was raised slightly to 145–147°. The loss on crystallization was about 20%. When *p*-dichlorobenzene was substituted for the *p*-chlorotoluene no thiaxanthone was obtained.

In another experiment 159 g. of crude dithiosalicylic acid was condensed with 750 ml. of *p*-chlorotoluene in the presence of 1250 ml. of sulfuric acid. The temperature rise upon the addition of the dithio acid was about five degrees. At the end of the reaction the mixture was poured into ice-water and the suspension steam distilled to remove excess *p*-chlorotoluene. The solid was collected and treated as above. There was obtained 175 g. (65%) of the thiaxanthone mixture, m.p. 138–142°.

2,2′-Dimethyl-5,5′-dichlorodiphenyl Disulfide.—Four grams of 2-methyl-5-chlorothiophenol was dissolved in 40 ml. of 75% acetic acid and a solution of 1.74 *N* iodine in potassium iodide was added dropwise with vigorous stirring until a permanent iodine color remained. The crystals that had separated were collected and recrystallized from ethanol; wt. 2.7 g. After two more crystallizations the compound melted at 81.3–82.7° (cor.).

Anal. Calcd. for $C_{14}H_{12}Cl_2S_2$: S, 20.35. Found: S, 20.20.

Oxidation of Thiosalicylic Acid with Sulfuric Acid.—Five grams of thiosalicylic acid was suspended in 50 ml. of 96% sulfuric acid and the mixture was kept at 50–60° for six hours. Sulfur dioxide was evolved throughout the reaction. The red suspension was poured in water, filtered and thoroughly washed with water. After drying at 75° the product weighed 4.96 g. The acid formed a bispiperidinium salt which after recrystallization from ethanol did not depress the m.p. of an authentic specimen.

Piperidinium Dithiosalicylate.—One hundred grams of crude dithiosalicylic acid was suspended in boiling alcohol and treated with a slight excess of piperidine. The turbid solution was treated with charcoal and filtered. The cooled filtrate deposited yellow crystals which after two more recrystallizations from ethanol were analytically pure; m.p. 211.5–215.4° (cor.).

Anal. Calcd. for $C_{24}H_{32}N_2O_4S_2$: N, 5.87. Found: N, 5.65.

A white free acid was obtained by acidification of a hot aqueous solution of the above salt. The substance was filtered, washed with water and dried.

The condensations described below were carried out with this purified dithiosalicylic acid and a good grade of *p*-chlorotoluene. The 100–101% sulfuric acid was prepared by treating the 96% acid with the appropriate quantity of fuming sulfuric acid (25% SO_3). The acid was titrated before use.

The Condensation of Dithiosalicylic Acid and *p*-Chlorotoluene. A. 101% Sulfuric Acid.—One hundred milliliters of 101% sulfuric acid was treated with 8.0 g. of pure dithiosalicylic acid at 25°. The mixture was cooled to 22° and 25 ml. of *p*-chlorotoluene was added with vigorous stirring. Within one minute the temperature rose to 30°. The mixture was cooled in an ice–alcohol bath, but the temperature rose until it reached 43°. When the temperature fell to 40° the cooling bath was removed and stirring continued until a total of 1.5 hours had elapsed.

The red solution was poured into water and the yellow crystals collected on a filter. The crude thiaxanthone mixture was boiled with dilute ammonia for 15 minutes and then was filtered. It was washed with water and dried at 100°,

(36) The above method was used to prepare the following acids: 2,3-dichlorobenzoic acid, E. Hope and G. C. Riley, *J. Chem. Soc.*, **123**, 2478 (1923); 2-chloro-4-methylbenzoic acid, A. Claus and N. Davidsen, *J. prakt. Chem.*, [2] **39**, 491 (1889); 2-chloro-5-methylbenzoic acid, A. Claus, *ibid.*, [2] **46**, 27 (1896); 2-chloro-4-methoxybenzoic acid, F. Ullmann and C. Wagner, *Ann.*, **355**, 368 (1907).

(37) W. Findeklee, *Ber.*, **38**, 3553 (1905).

(38) This is a more convenient procedure than that reported by E. Roberts and E. E. Turner, *J. Chem. Soc.*, **127**, 2011 (1925).

(39) G. T. Morgan and E. A. Coulson, *ibid.*, 2556 (1929).

(40) W. A. Noyes, *Am. Chem. J.*, **10**, 474 (1888).

(41) F. Mayer and H. Günther, *Ber.*, **63**, 1458 (1930), reported m.p. 155–155.5°.

wt. 11.1 g. (81%). It melted at 145–147° (Ullmann[2] reported the m.p. as 148–148.5° for the recrystallized mixture).

When the reaction time was extended to 18 hours the yield was 87%.

B. **96% Sulfuric Acid.**—The same quantities of the same reagents were used except that an equivalent volume of 96% sulfuric acid was substituted for the one of greater strength. No temperature rise occurred when the *p*-chlorotoluene was added to the mixture of the acids. The whole was heated to 30° and the reaction allowed to proceed for 90 minutes as the temperature fell gradually.

At the end of this time the mixture was processed as above. Only 3.6 g. (26%) of the thiaxanthone mixture was obtained, m.p. 137–142°. On acidification the ammoniacal extract furnished 5.1 g. of almost pure dithiosalicylic acid.

C. **100% Sulfuric Acid Saturated with Potassium Bisulfate.**—One hundred milliliters of 100% (rather than 101%) sulfuric acid was stirred for one hour with 50 g. of fused potassium bisulfate. The suspension was cooled to 21° and treated first with 8.0 g. of pure dithiosalicylic acid and then with 25 ml. of *p*-chlorotoluene. After five minutes the temperature rose to 32° and reached the maximum, 40°, after 13 minutes. After 1.5 hours the mixture was worked up in the usual way. There was obtained 5.4 g. (40%) of the thiaxanthone mixture.

The control run was carried out with the identical reagents, except that the potassium bisulfate was omitted. Prior to the addition of the dithio acid and the *p*-chlorotoluene, the sulfuric acid was stirred for one hour to simulate the above experiment as closely as possible. When the *p*-chlorotoluene was added to the stirred mixture of acids at 21° the temperature rose to 30° in 45 seconds. The whole was cooled in an ice–alcohol bath but the temperature continued to rise until it reached 35°. After 1.5 hours the solution was poured into water and processed as usual. The neutral fraction weighed 11.3 g. (83%).

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[CONTRIBUTION FROM THE RESEARCH LABORATORY, GENERAL CIGAR CO., INC.]

The Chemistry of Tobacco Fermentation. I. Conversion of the Alkaloids. A. The Formation of 3-Pyridyl Methyl Ketone and of 2,3′-Dipyridyl

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Nicotine and minor tobacco alkaloids are converted in the leaves of cigar tobacco into various 3-substituted pyridine compounds, including 3-pyridyl methyl ketone and 2,3′-dipyridyl.

Decrease of Alkaloids in Tobacco Leaves during Fermentation.—Probably the most characteristic chemical effect in the fermentation[1] of certain cigar tobaccos[2] is the substantial decrease of their alkaloid contents.[3] The nicotine initially present in these tobaccos decreases in regular fermentation by about 30 to 50% and in a recently developed, more effective, fermentation procedure by as much as 80 to 95%. Since volatilization from the leaves accounts for not more than about 8% of the total nicotine loss, considerable amounts of nicotine must be converted during fermentation into other products. Besides its industrial significance, this conversion of nicotine is of general interest in view of the mild conditions (temperature 43 to 54°, *p*H range 5.6 to 6.8) at which it occurs.

Prior to any studies of the catalytic or enzymic mechanism of this alkaloid degradation within the tobacco leaves, more detailed information is needed on its chemistry, and particularly on the transformation products derived from the alkaloids. A search was undertaken for these products[4] in our laboratory, using as a starting material well fermented[5] Pennsylvania Seedleaf tobacco.[2]

Solvent extraction of this tobacco discloses the presence of various newly formed 3-substituted pyridine derivatives in addition to small amounts of unchanged alkaloids. Although the former have not all been identified, the total amount of pyridine nitrogen in the extracted fractions can be estimated by a combination of the following methods: (1) Kjeldahl determination of the nitrogen contained in silicotungstate precipitates, (2) ultraviolet absorption measurements, and (3) oxidation to nicotinic acid and determination of the latter.

Quantitative Correlation between the Pyridine Derivatives in Tobacco Leaves before and after Fermentation.—Table I represents a survey of the pyridine derivatives found in thoroughly fermented samples and of the method used in separating them. In four fractions, obtained by extracting successively with different selective solvents, about 87% of the pyridine originally present in the leaves as a moiety of nicotine can be recovered, partly as unchanged nicotine, and partly as a component of newly formed pyridine compounds (Table I, column 10). This indicates that the pyridine ring remains practically intact during the fermentation. Of these fractions, 1 and 2 are each again separated into two subfractions by liquid–liquid extraction with organic solvents at specific *p*H's.

(1) A process in which the cured tobacco leaves, moistened with selected amounts of water, are kept at temperatures of about 45° with periodical aerations. See W. G. Frankenburg, *Advances in Enzymology*, **10**, 325 (1950).

(2) Particularly "filler" tobaccos, such as Pennsylvania Seedleaf, U. S. type 41.

(3) Nicotine represents about 90% of the total alkaloids in these tobaccos.

(4) As a part of general investigations concerning the conversions of all the nitrogenous leaf components during the fermentation of cigar tobacco.

(5) The tobacco samples used had on the average nicotine contents of 4.2% before and of 0.7% after fermentation (0.72% and 0.12% nicotine nitrogen, respectively).