concentrated hydrochloric acid added. The solution was refluxed for 15 min. and cooled. The product separated as a hydrochloride, yield 99%, m.p. 234–236° dec. The hydrochloride was dissolved in dilute hydrochloric acid and the solution made alkaline with 10% sodium hydroxide to precipitate the free base. The latter was recrystallized from benzene. The yield was 48%, m.p. 125–126°. This compound was previously made by a somewhat different method,[3] m.p. 126–127°.

*Anal.* Calcd. for $C_{14}H_{11}N_3$: C, 76.00; H, 4.98; N, 19.00. Found: C, 75.88; H, 4.97; N, 18.87.

Under the same conditions, acetone did not react with 1-aminobenzimidazole.

# Pyrimidobenzothiazine Derivatives. II. The Condensation of Isothiocyano Ketones and Aryl Amines

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The heating of equimolar mixture of 2-isothiocyano-2-methyl-4-pentanone with aryl amines, arylamino acids, and arylamino alcohols results in the formation of pyrimidines, benzothiazines, and pyrimidobenzothiazines, respectively.

The reaction of anthranilic acid (III) and 2-isothiocyano-2-methyl-4-pentanone (IV) has been reported[1] to yield a compound $C_{14}H_{14}N_2OS$ which may be represented by either I or II. Although I was preferred on the basis that on treatment with sodium hydroxide, the thiolactone ring opens up to give mercapto acid (VIII), additional information regarding the structure seemed desirable. Additional support for the proposed pyrimidobenzothiazine structure (I) can be gathered from the fact that the reaction of aryl amines (VI) with isothiocyano ketone (IV) leads to the formation of 2-mercaptopyrimidines,[2,3] while aryl amines with 2-mercapto-4,4,6-trimethyl-4*H*[1,3]-thiazine[4] result in the formation of 2-substituted thiazines (VII).

When I or the corresponding mercapto acid (VIII) is treated with alcoholic hydrochloric acid, a mixture of 2-thio-4-oxotetrahydroquinazoline[5] (XI) and 2-amino-4*H*-benzo[1,3]thiazin-4-one (XIa) is obtained.

This may be explained by considering a partial equilibrium between I and VIII. In either case the ring cleavage is occurring through the enamine[6–8] (IX, IXa) to the keto derivative and then to $\alpha,\beta$-unsaturated ketones (X) and imino derivatives (XI, XIa). Several additional pyrimidinebenzothiazines (I) were prepared

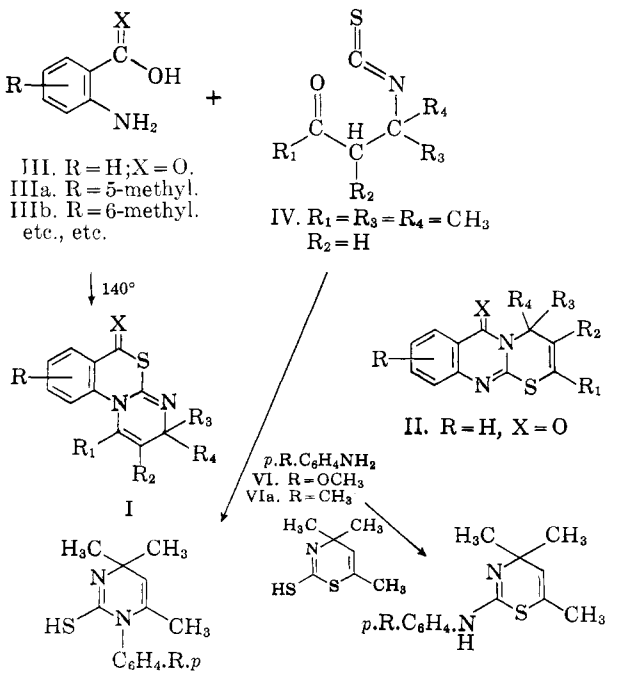



Figure 1

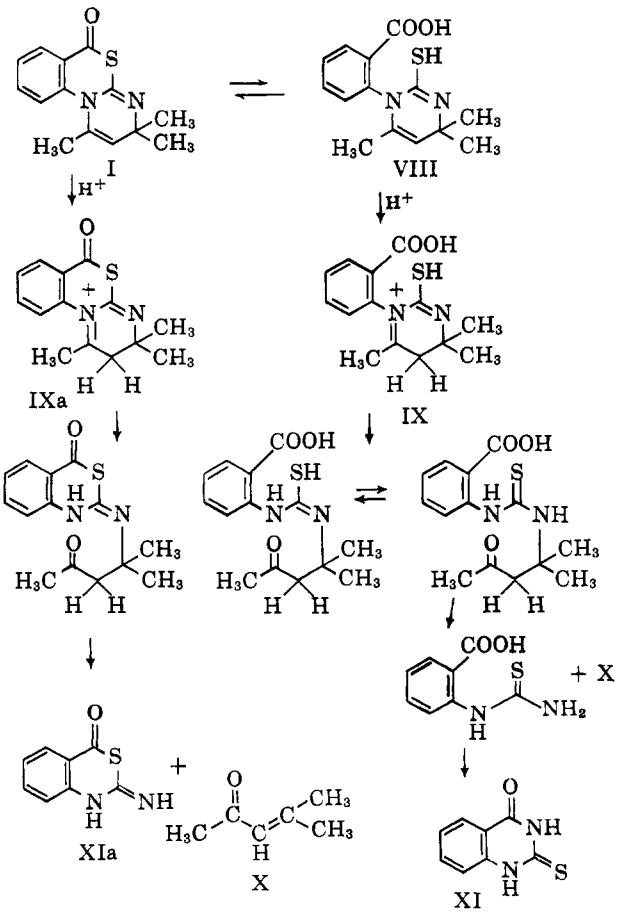



Figure 2

(1) N. Gill, N. K. Ralhan, H. S. Sachdev, and K. S. Narang, *J. Org. Chem.*, **26**, 966 (1961).

(2) R. A. Mathes, F. D. Stewart, and F. Swedish, *J. Am. Chem. Soc.*, **70**, 1452 (1948).

(3) R. A. Mathes, *ibid.*, **75**, 1747 (1953).

(4) J. E. Jenson and R. A. Mathes, *ibid.*, **77**, 5431 (1955).

(5) H. Rupe, *Ber.*, **30**, 1098 (1897).

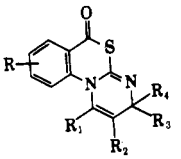
(6) G. Stork, R. Terrell, and J. Szmuszkovics, *J. Am. Chem. Soc.*, **76**, 2029 (1954).

(7) G. Stork and H. K. Landerman, *ibid.*, **78**, 5128 (1956).

(8) F. W. Heyl and M. E. Herr, *ibid.*, **75**, 1918 (1953).

TABLE I

PYRIMIDO[1,2-*a*][3,1]BENZOTHIAZINES

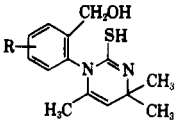


| S. no. | 2-Amino acid used | Product formed $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield, % | Solvent for crystallization | M.p., °C. | Formula | Analysis Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 5-Methyl-2-amino-benzoic acid | $C_2H_5$ | H | $CH_3$ | $CH_3$ | 74 | Dilute EtOH | 202 | $C_{16}H_{18}N_2OS$ | N 9.75 | N 9.91 |
| 2 | 6-Methyl-2-amino-benzoic acid | $C_2H_5$ | H | $CH_3$ | $CH_3$ | 63 | Dilute AcOH | 205 | $C_{16}H_{18}N_2OS$ | S 11.19 | D 11.52 |
| 3 | 5-Chloro-2-amino-benzoic acid | $C_2H_5$ | H | $CH_3$ | $CH_3$ | 65 | Dilute AcOH | 212 | $C_{15}H_{15}N_2SOCl$ | C 58.72<br>H 4.89<br>Cl 11.2 | C 58.77<br>H 5.08<br>Cl 10.96 |
| 4 | 5-Bromo-2-amino-benzoic acid | $C_2H_5$ | H | $CH_3$ | $CH_3$ | 71 | Dilute AcOH | 215 | $C_{15}H_{15}N_2SOBr$ | S 9.11 | S 8.62 |
| 5 | 5-Methoxy-2-amino-benzoic acid | $C_2H_5$ | H | $CH_3$ | $CH_3$ | 66 | EtOH | 215 | $C_{16}H_{18}N_2SO_2$ | S 10.59 | S 10.65 |
| 6 | 2-Aminobenzoic acid | $C_2H_5$ | H | $CH_3$ | $CH_3$ | 81 | Dilute AcOH | 206 | $C_{15}H_{16}N_2SO$ | N 10.29<br>S 11.76 | N 10.39<br>S 11.56 |
| 7 | 2-Aminobenzoic acid | OH | $COCH_3$ | $CH_3$ | $CH_3$[a] | 75 | Dilute AcOH | 205 | $C_{15}H_{14}N_2SO_3$ | C 59.6<br>H 4.63<br>N 9.27 | C 59.9<br>H 5.51<br>N 9.7 |

[a] On treatment with 10% sodium hydroxide it gave 5-acetyl-4,4-dimethyl-6-hydroxy-2-mercapto-1-(2-carboxy)phenylpyrimidine; m.p. 212°. *Anal.* Calcd. for $C_{15}H_{16}N_2SO_4$: S. 10.06. Found: S. 10.45.

TABLE II

2-MERCAPTO PYRIMIDINES



| S. no. | Benzyl alcohols used | Yield, % | Solvent for crystallization | M.p., °C. | Formula | Analysis Calcd. | Found |
|---|---|---|---|---|---|---|---|
| 1 | 2-Aminobenzyl alcohol | 88 | EtOH | 187 | $C_{14}H_{18}N_2OS$ | C 64.12<br>H 6.87 | C 63.93<br>H 6.93 |
| 2 | 5-Methyl-2-aminobenzyl alcohol | 59 | EtOH | 187 | $C_{15}H_{20}N_2OS$ | N 10.14 | N 10.58 |
| 3 | 4-Methyl-2-aminobenzyl alcohol | 75 | EtOH | 195 | $C_{15}H_{20}N_2OS$ | S 11.59 | S 11.74 |
| 4 | 3-Methyl-2-aminobenzyl alcohol | 34 | EtOH | 184 | $C_{15}H_{20}N_2OS$ | N 10.14 | N 9.99 |
| 5 | 4-Chloro-2-aminobenzyl alcohol (m.p., 140–142°) | 82 | Dilute AcOH | 207 | $C_{14}H_{17}N_2SOCl$ | N 9.5 | N 9.17 |
| 6 | 5-Chloro-2-aminobenzyl alcohol (m.p., 174°) | 64 | Dilute EtOH | 186 | $C_{14}H_{17}N_2SOCl$ | N 9.50<br>S 10.79 | N 9.45<br>S 11.20 |
| 7 | 5-Methoxy-2-aminobenzyl alcohol (m.p., 87°) | 48 | AcOEt | 186 | $C_{15}H_{20}N_2SO_2$ | N 9.59<br>S 10.93 | N 9.5<br>S 11.4 |

by the use of some novel isothiocyano ketones (IV) and various aminobenzoic acids (III, Table I).

Further studies in obtaining pyrimidobenzothiazines (I) were undertaken by the use of *o*-aminobenzyl alcohols (XII) in place of *o*-amino acids. Fair to good yields of the corresponding 2-mercaptopyrimidines (XIII; Table II) were obtained. Treatment with alcoholic hydrochloric acid resulted in the hydrolysis of the pyrimidine ring with subsequent ring closure to XIV (Table III), presumably by the same mechanism as submitted for VII.

The facile acid-catalyzed cleavage of the pyrimidine ring has been noted previously also in our laboratories.[9]

In a single case it was possible to isolate, in small amounts, the pyrimidobenzothiazine (I).

The use of concentrated sulfuric acid allowed I to be isolated in a fair yield (43%).

## Experimental[10,11]

1. **Pyrimidobenzothiazin-6-ones.**—An equimolar mixture of *o*-aminobenzoic acid and isothiocyano ketone was heated in an oil bath at 110°. The reaction mixture which liquifies at the bath temperature solidifies into a hard mass in about 9.5 hr. It was then cooled, neutralized with sodium bicarbonate and collected

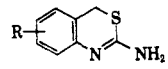
(9) N. Gill, N. K. Ralhan, H. S. Sachdev, and K. S. Narang, *J. Org. Chem.*, **26**, 968 (1961).

(10) The melting points are uncorrected.

(11) The analyses were performed by Drs. G. Weiler and F. B. Straus, Oxford, England.

TABLE III

2-AMINO[3,1]-4*H*-BENZOTHIAZINES. TREATMENT OF 2-MERCAPTOPYRIMIDINES (TABLE II) WITH HYDROCHLORIC ACID



| S. no. | 2-Mercaptopyrimidines | Yield, % | Solvent for crystallization (°C.) | M.p., °C. | M.f. | Analysis Calcd. | Analysis Found |
|---|---|---|---|---|---|---|---|
| 1[a] | 1-(2′-Hydroxymethylphenyl)-2-mercapto-4,4,6-trimethyl-1*H*,4*H*-pyrimidine. | 41 | Petroleum ether (60–80) | 136 | $C_8H_8N_2S$ | C 58.53<br>H 4.87 | C 58.59<br>H 4.85 |
| 2 | 1-(2′-Hydroxymethyl-4′-methylphenyl)-2-mercapto-4,4,6-trimethyl-1*H*,4*H*-pyrimidine. | 40 | Petroleum ether (60–80) | 159 | $C_9H_{10}N_2S$ | C 60.7<br>H 5.62 | C 61.0<br>H 6.08 |
| 3 | 1-(2′-Hydroxymethyl-5′-methylphenyl)-2-mercapto-4,4,6-trimethyl-1*H*,4*H*-pyrimidine. | 40 | Petroleum ether (60–80) | 132 | $C_9H_{10}N_2S$ | S 17.97 | S 18.3 |
| 4[b] | 1-(5′-Chlorophenyl-2′-hydroxymethylphenyl)-2-mercapto-4,4,6-trimethyl-1*H*,4*H*-pyrimidine. | 44 | AcOH + acetone | 257 | $C_8H_8N_2SCl_2$ | Cl 30.21<br>S 13.61 | Cl 30.71<br>S 14.1 |
| 5 | 1-(4′-Chlorophenyl-2′-hydroxymethylphenyl)-2-mercapto-4,4,6-trimethyl-1*H*,4*H*-pyrimidine. | 46 | Dilute EtOH | 150 | $C_8H_7N_2SCl$ | N 14.1 | N 14.32 |
| 6 | 1-(2′-Hydroxymethyl-4′-methoxyphenyl)-2-mercapto-4,4,6-trimethyl-1*H*,4*H*-pyrimidine. | 53 | $C_6H_6$ | 190 | $C_9H_{10}N_2SO$ | N 14.43 | N 14.1 |

[a] On treatment with concd. $H_2SO_4$, it gave 1,3,3-trimethyl-3*H*,6*H*-pyrimido[1,2-*a*][3,1]benzothiazine, m.p., 110°; the yield was 43%, from petroleum ether. On analysis N was found to be 11.78, while $C_{14}H_{16}N_2S$ requires N, 11.47. [b] 9-Chloro-1,3,3-trimethyl-3*H*,6*H*-pyrimido[1,2-*a*][3,1]benzothiazine was also separated, m.p. 151°; the yield was 17.0%, from dioxane. On analysis N was found to be 10.35, while $C_{14}H_{15}N_2SCl$ requires N, 10.01.

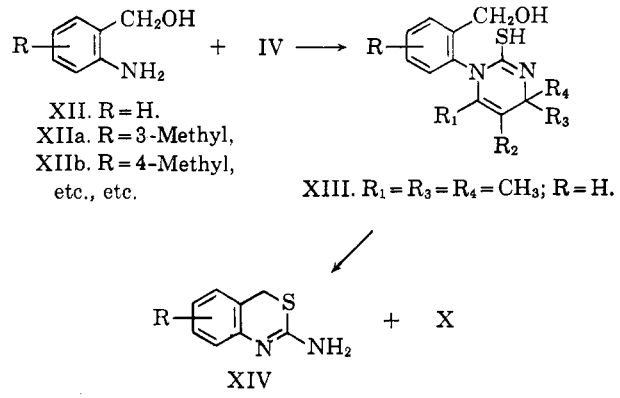



Figure 3

by suction. The solids were then crystallized from respective solvents (Table I).

**2. 2-Substituted aminothiazines.**—An equimolar mixture of 2-mercapto-4,4,6-trimethyl-4*H*[1,3]-thiazine[4] and the amine was heated in an oil bath at 140–145° for 8 hr.

VII was isolated by removing the impurities by ether and subsequent crystallization of the residue from acetic acid m.p. 182°; yield 55%.

*Anal.* Calcd. for $C_{14}H_{18}N_2OS$: N, 10.69; S, 12.22. Found: N, 10.95; S, 12.34.

VIIa is soluble in ether. The ether extract was concentrated and crystallized from dilute ethanol or dilute acetic acid, m.p. 169–170°; yield 40%.

*Anal.* Calcd. for $C_{14}H_{18}N_2S$: N, 11.46. Found: N, 11.02.

**3. 2-Mercaptopyrimidines.**[2,3]—V. R = $OCH_3$, m.p. 189°, and its mixture with VII melted at 175–180°. Va. R = $CH_3$, m.p. 191°.

**4. Treatment of VIII with Hydrochloric Acid.**—1-(2′-Carboxyphenyl)-2-mercapto-4,4,6-trimethyl-1*H*,4*H*-pyrimidine (7.0 g.) was dissolved in alcoholic hydrochloric acid (50 ml.) and refluxed for 10 hr. After removing the solvent, the residue was cooled, diluted with water, and filtered. The residue 1.8 g., m.p. 300°, was recrystallized from ethanol or acetic acid. It showed no depression in melting point upon admixture with 2-thio-4-oxotetrahydroquinazoline[5] (XI). The filtrate obtained above was concentrated, neutralized with 5% sodium hydroxide, and extracted with ether. The ether extract was dried and converted into the hydrochloride. Upon recrystallization from ethyl acetate it melted at 161–163° (1.2 g.) (XIa).

*Anal.* Calcd. for $C_8H_7N_2OSCl$: S, 14.91. Found: S, 14.50.

[5] The distillate obtained was treated with 2,4-dinitrophenylhydrazine, and a solid (0.3 g.) was obtained, m.p. 198–200° (ethanol), identical with the 2,4-dinitrophenylhydrazone of mesityl oxide.

4a.—I. R = H, X = O when subjected to similar procedure as VIII yielded 1.0 g. of XI, 2.55 g. of XIa, and 0.3 g. of 2,4-dinitrophenylhydrazone of mesityl oxide.

**5. 1-(2′-Hydroxymethyl)phenyl-2-mercaptopyrimidines (XIII).**—The following procedure was adopted for all alcohols. 2-Isothiocyano-2-methyl-4-pentanone (1.0 mole) and *o*-aminobenzyl alcohol (1.0 mole) were heated at 90–95°. A solid appeared within 20–25 min. The heating was continued until the solid had set into a hard mass. The total time of reaction was 1–3 hr. The solid was treated with ether and recrystallized from ethanol or acetic acid. The analyses and physical constants are reported in Table II.

**6. 1,3,3-Trimethyl-3*H*,6*H*-pyrimido[1,2-*a*][3,1]benzothiazine.**—1-(2′-Hydroxymethyl)phenyl-2-mercapto-4,4,6-trimethyl-1*H*,-4*H*-pyrimidine (2.0 g.) was dissolved in concentrated sulfuric acid (10 ml.) maintained at 10°. After 4 hr. the mixture diluted with cracked ice, neutralized with sodium carbonate, and extracted with ether. The solid obtained from the ethereal extract was recrystallized from petroleum ether; yield 0.8 g. (42.6%); m.p. 110°.

**7. Treatment of 1-(2′-Hydroxymethyl)phenylpyrimidines (XIII) with Hydrochloric Acid.**—1-(2′-Hydroxymethyl)phenylpyrimidine (XIII) (2.0 g.) was dissolved in hydrochloric acid (15 ml.) and heated on a steam bath for 5 hr. The acid was removed under vacuum; the residue diluted with water and neutralized with aqueous sodium hydroxide. The solid was filtered, washed with water, dried, and crystallized from petroleum ether or ethanol (Table III).

In the case of 1-(5′-chloro-2′-hydroxymethyl)phenyl-2-mercapto-4,4,6-trimethyl-1*H*,4*H*-pyrimidine, a solid separated from the hydrochloric acid, m.p. 257°; analysis indicated benzothiazine (no. 4, Table III). The solution after concentration, neutralization, and crystallization furnished the corresponding pyrimidobenzothiazine (see footnote *a*, Table III).