0° the mixture was poured onto ice and the product extracted into pentane. Pure camphene (1.0 g.) was obtained and identified by its infrared spectrum and by vapor phase chromatography on a 5-ft. silver nitrate column.

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Pyrimidobenzothiazine Derivatives. I

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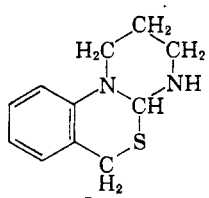
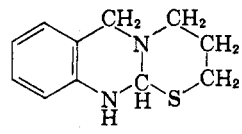
Ring systems I and II appear to be quite interesting from the point of view of potential antibacterial activity. Moreover, neither is known in the literature:

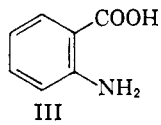


I

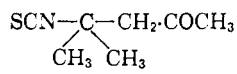


II

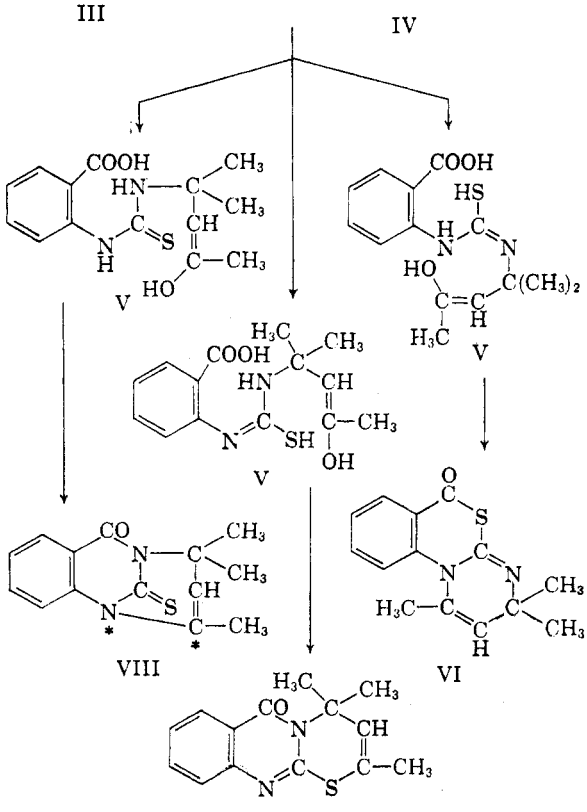
The present investigation records a study of the condensation between anthranilic acids (III) and



III



IV



V

V

V

VIII

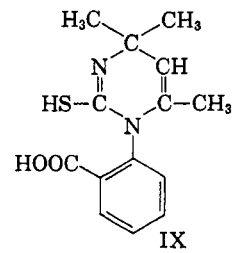
VI

VII

4-isothiocyano-4-methyl-2-pentanone (IV). The first step would lead to the formation of the intermediate (V) which could cyclize in three different ways giving rise to VI, VII, or VIII.

So far the condensation of IV with various anthranilic acids has given only one product in each case (Table I). The model of VIII shows that C and N (marked *) cannot approach near enough for cyclization.

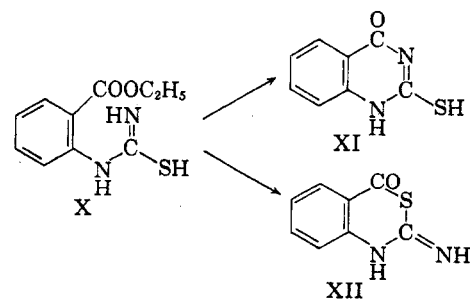
The structure (VI) appears to be the most probable for the products given in Table I. To gain further information on the structure a reaction between anthranilic acid and the isothiocyano ketone (IV) was carried out in sodium bicarbonate solution at 50°. The product obtained on acidification was an acid (m.p. 185–90°). The same acid was obtained by prolonged treatment (twelve hours) of the condensation product of III, R = H, and IV with sodium hydroxide at room temperature followed by acidification. This obviously would have the structure IX.



IX

Repeated crystallization of the acid (IX) gives back the ring closed compound. Ring opening with dilute alkali in the cold indicates that the product obtained by the condensation of anthranilic acid with IV probably has the assigned structure (VI).

2 - Carbethoxyphenylthiourea (X) on warming readily gives 2-thio-4-oxotetrahydroquinazoline (XI)[1] in good yields; the isomeric thiazine (XII) derivative has not so far been isolated. This also indicates that in the present case VII is probably formed.



X

XI

XII

The formation of VI in the present case indicates that the pyrimidine ring system is formed first giving rise to the intermediate IX and this is followed by the formation of the thiazine ring system. It is significant that the sodium salt of this inter-

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

TABLE I

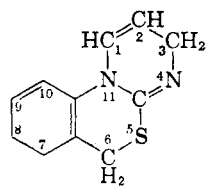
PYRIMIDO[1,2-*a*][3,1]BENZOTHIAZINES

No.	2-Amino Acid or 2-Aminonitrile used	Product	Yield,[a] %	Solvent of Crystallization	M.P.	Formula	Analyses[a] Found, %	Calcd.
1	Anthranilic acid	1,3,3-Trimethyl-3*H*,6*H*-pyrimido[1,2-*a*][3,1]-benzothiazine-6-one	55	Dil. acetic acid	208	$C_{14}H_{14}N_2OS$	S, 11.95	S, 12.4
2	3-Methylanthranilic acid	1,3,3,10-Tetramethyl-3*H*,6*H*-pyrimido-[1,2-*a*][3,1]benzo-thiazine-6-one	50	Dil. acetic acid	255	$C_{15}H_{16}N_2OS$	S, 11.7 N, 10.0	S, 11.76 N, 10.29
3	4-Methylanthranilic acid	1,3,3,9-Tetramethyl-3*H*,-6*H*-pyrimido[1,2-*a*][3,1]benzothiazine-6-one	52	Dil. acetic acid	215	$C_{15}H_{16}N_2OS$	N, 10.08	N, 10.29
4	6-Methylanthranilic acid	1,3,3,7-Tetramethyl-3*H*,-6*H*-pyrimido[1,2-*a*][3,1]benzothiazine-6-one	50	Dil. acetic acid	220	$C_{15}H_{16}N_2OS$	N, 9.96	N, 10.29
5	5-Methoxyanthranilic acid	8-Methoxy-1,3,3-trimethyl-3*H*,6*H*-pyrimido[1,2-*a*][3,1]benzo-thiazine-6-one	58	Dil. acetic acid	198	$C_{15}H_{16}N_2O_2S$	S, 10.53	S, 11.00
6	5-Chloroanthranilic acid	8-Chloro-1,3,3-trimethyl-3*H*,6*H*-pyrimido-[1,2-*a*][3,1]-benzo-thiazine-6-one	41	Glacial acetic acid	230	$C_{14}H_{13}ClN_2OS$	Cl, 12.15	Cl, 12.14
7	2-Amino-4-chloro-benzonitrile hydrochloride	9-Chloro-1,3,3-trimethyl-6-imino-3*H*,6*H*-pyrimido-[1,2-*a*][3,1]-benzothiazine	54	Glacial acetic acid	292	$C_{14}H_{14}ClN_3S$	S, 10.61	S, 10.94
8	2-Aminobenzonitrile hydrochloride	1,3,3-Trimethyl-6-imino-3*H*,6*H*-pyrimido-[1,2-*a*][3,1]-benzo-thiazine hydrochloride	63	Glacial acetic acid	295	$C_{14}H_{15}N_3S.HCl$	N, 14.70	N, 14.31

[a] The yields and the analyses reported are as obtained by Method A.

mediate (IX) is formed if the reaction between anthranilic acid and IV is carried out in sodium bicarbonate solution.

Nomenclature[2]:



XIII

The structure VI is a derivative of the ring system XIII; the latter would be named as 3*H*,6*H*-pyrimido[1,2-*a*] [3,1]benzothiazine and consequently the VI wouid be called 3*H*,6*H*-pyrimido-[1,2-*a*] [3,1]benzothiazine-6-one. Further work in the line is in progress.

Antibacterial tests[2]:

1,3,3 - Trimethyl - 3*H*,6*H* - pyrimido[1,2 - *a*] [3,1]benzothiazine-6-one was found to act adversely on the growth of *s-paratyphi* in dilutions of 1:5000 while 1,3,3-trimethyl-9-chloro-6-imino-3*H*,6*H*-pyrimido [1,2-*a*][3,1]benzothiazine has a bacteriostatic effect on the strains of *s-schottmuelleri*, *s-typhi*, *E. coli*, and *Sh. Sonnei* at a dilution of 1:1000.

(2) We are indebted to Leonard T. Capell, Nomenclature Director and Executive Consultant, Chemical Abstract Service, for his helpful suggestions in connection with nomenclature and to the Director, Central Drug Research Institute, Lucknow (India) for the antibacterial test.

EXPERIMENTAL

1,3,3-Trimethyl-3H,6H-pyrimido[1,2-a][3,1]benzothiazin-6-one. Method A. A mixture of 4-isothiocyano-4-methyl-2-pentanone (5.0 g.) and anthranilic acid (4.3 g.) was heated in an oil bath at 110°. The reaction mixture which liquefies at the bath temperature solidifies into a hard mass in about 0.5 hr. It was then cooled, neutralized with sodium bicarbonate, and collected by suction. Crystallization from dilute ethanol or acetic acid furnished rectangular shining needles, m.p. 207°.

Method B. An equivalent mixture of anthranilic acid and 4-isothiocyano-4-methyl-2-pentanone was placed in a three necked flask, water (5 c.c. for each gram of anthranilic acid used) was then added to make a thin suspension which was vigorously stirred at a bath temperature of 60–70° for about 12 hr. The product was cooled to room temperature and treated with sodium bicarbonate solution to remove unchanged anthranilic acid. The product was collected by suction and crystallized from dilute ethanol. Its melting point and the melting point on admixture with the product obtained by method A was the same.

Method C. An equivalent mixture of anthranilic acid and 4-methyl-4-isothiocyano-2-pentanone was dissolved in diethyl ether and allowed to stand for about 60 hr. The solid was collected by suction and repeatedly washed with ether. The product so obtained was pure and crystalline; m.p.

207–208°. Admixture with the product obtained by method A did not depress the melting point.

The yield of pure products as obtained by the three methods was 55%, 60%, and 95% respectively.

1-(2'-Carboxyphenyl)-2-mercapto-4,4,6-trimethyl-1,4-dihydropyrimidine. 4-Isothiocyano-4-methyl-2-pentanone (5 g.) was added to a mixture of anthranilic acid (4.5 g.) in sodium bicarbonate solution. The mixture was warmed to 50° for 3 hr. when disappearance of the oily layer indicated completion of the reaction. The sodium salt (8.5 g.) was salted out with the help of saturated sodium chloride solution and crystallized from brine. A sample of 1-(2'-carboxyphenyl)-2-mercapto-4,4,6-trimethyl-1,4-dihydropyrimidine was obtained by acidification of the pure sodium salt solution, washed with water, and after drying in vacuum at 20° had the following analysis.

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.87; H, 5.79. Found: C, 61.13; H, 5.98.

1,3,3-Trimethyl-6-imino-3H,6H,-pyrimido[1,2-a][3,1]-benzothiazine. A mixture of 4-isothiocyano-4-methyl-2-pentanone (1.02 g.) and *o*-aminobenzonitrile hydrochloride (1 g.) was placed in a hard glass test tube and heated in an oil bath, the temperature being maintained at 110° for 45 min. The reaction mixture turned into a liquid which solidified in about 25 min. into a hard solid. The resulting hydrochloride on crystallization from glacial acetic acid furnished a crystalline solid, m.p. 295°; yield 1.2 g. (63.3%).

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Studies in Thiazolopyrimidines. I. A Case of Michael Retrogression

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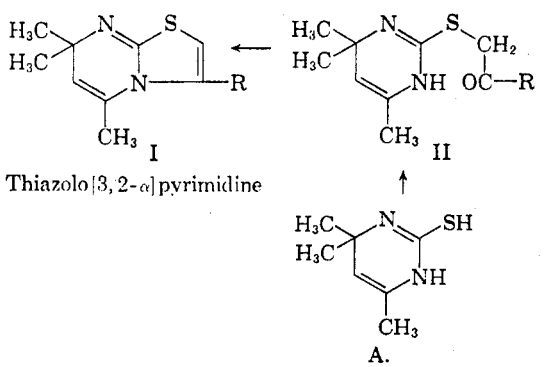
Several thiazole and pyrimidine derivatives are physiologically important. To obtain the compounds for antibacterial evaluation, the synthesis of thiazolopyrimidines (I) by ring closure of II was undertaken.



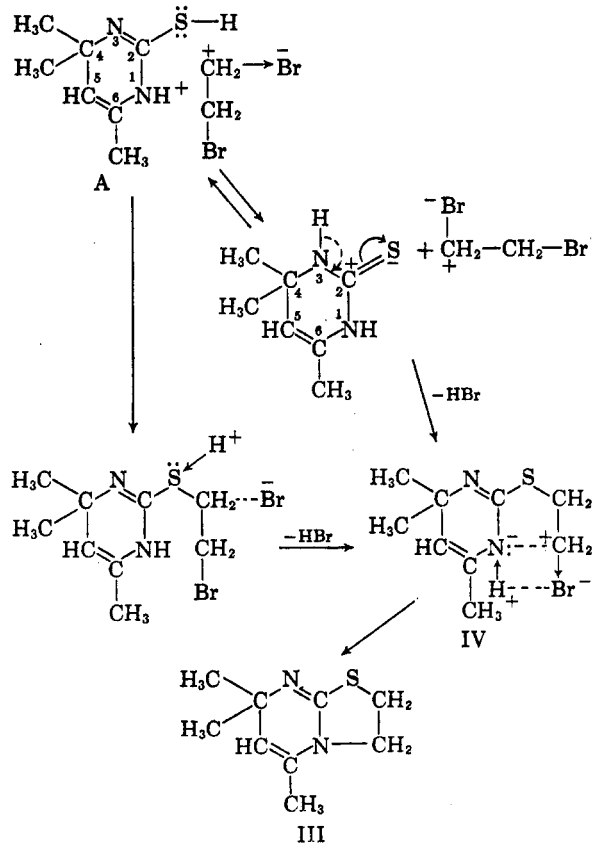
I — Thiazolo[3,2-*a*]pyrimidine

II

A.

However, the condensation of 2-mercapto-4,4,6-trimethyl-1,4-dihydropyrimidine[1] (A) with ω-bromoacetophenone and with *p*-methoxy-ω-bromoacetophenone in boiling ethanol furnished solids which on treatment with base and crystallization gave 2-amino-4-phenylthiazole and 2-amino-4-(*p*-methoxyphenyl)thiazole respectively. These were identified through analyses as well as by undepressed mixed melting points with authentic samples. The enthanolic filtrates after separation of the solids, referred to above, were treated in each case with 2,4-dinitrophenylhydrazine, and the 2,4-dinitrophenylhydrazone of mesityl oxide was isolated from each filtrate and its structure confirmed by comparison with an authentic sample.

On the other hand 2-mercaptopyrimidine (A) readily condensed with ethylenedibromide to give III, the structure being confirmed through undepressed mixed melting point with the product obtained by cyclization of 1-(β-hydroxyethyl)-2-mercapto-4,4,6-trimethyl-1,4-dihydropyrimidine.[2] The formation of III by the condensation of ethylene dibromide and 2-mercaptopyrimidine (A) shows that H attached to N at 3 is more mobile; the formation of intermediate products could be visualized to take place as follows:



A — III — IV

The essential difference between the intermediate in the case of the two ω-haloacetophenones (II. R = C_6H_5, *p*-$CH_3OC_6H_4$) and the intermediate in the case of ethylene dibromide (IV) is that the former contains a C = O group which plays a central part in the Michael Retrogression. The mech-

(1) Roger A. Mathes, Floyd D. Stewart, and Frank Swedish, Jr., *J. Am. Chem. Soc.*, 70, 1452 (1948).

(2) Roger A. Mathes, *J. Am. Chem. Soc.*, 75, 1747 (1953).