[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PANJAB UNIVERSITY]

THIAZOLOQUINAZOLINE DERIVATIVES. III.[1] SYNTHESES OF ALKYL AND ARYL DERIVATIVES

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The presence of a thiazolidine structure in the penicillins (I) is well established. Furthermore, the antimalarial alkaloid febrifugine (II) (1) has been proven to contain a quinazolone system. Therefore it was thought desirable to synthesize compounds having both the above systems fused together and to study their chemotherapeutic properties. As a result a number of derivatives of the thiazoloquinazoline III have been prepared and have been tested for their therapeutic value. In previous papers (2) the ring system III has been called 10:11 thiopegan (2) but *Chemical Abstracts* nomenclature will be used here.

In Part I (3) 2-carbethoxyphenylthiourea (IV, R = H) was condensed with α-haloketones and ethylene dibromide and the structures (V, R = H; R′, R″ = various groups) and (VI, R = H) were assigned to the products respectively.

The method developed in this laboratory for building up derivatives of this ring system has now been extended to the syntheses of (V, R = CH_3, R′, R″ = various groups) (Table I) and VI, R = CH_3) by the condensation of 4-methyl-2-carbethoxyphenylthiourea (IV, R = CH_3) with α-haloketones and ethylene dibromide respectively.

It should be pointed out that the products obtained in the present investigation have been assigned the linear structures on the basis of the observations of Traumann (4) on the condensation of phenylthiourea with chloroacetone, which gave exclusively 2-anilino-4-methylthiazole. However, the angular structures VII and VIII remain a possibility. This point and the mechanism of the reaction are under investigation.

EXPERIMENTAL

Ethyl 5-methylanthranilate hydrochloride was prepared by the method used previously for the synthesis of ethyl anthranilate hydrochloride (3). The yield from 50 g. of 5 methylanthranilic acid was 60.0 g. It crystallized from acetone in fine, colorless needles, m.p. 184°.

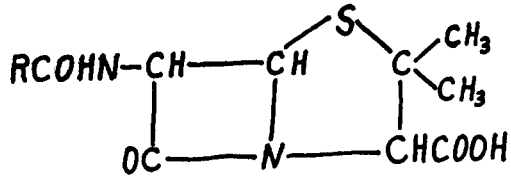
Anal. Calc'd for $C_{10}H_{14}ClNO_2$: N, 6.51. Found: N, 6.85.

4-Methyl-2-carbethoxyphenylthiourea (IV, R = CH_3). Ethyl 5-methylanthranilate hydrochloride (50 g.) was added to a concentrated aqueous solution of 75.0 g. of potassium thiocyanate and the mixture was pulverized to a paste. It was filtered after two hours, washed with water, and crystallized from 10% ethanol in light brown plates and needles, m.p. 106–107° (yield, 30–40 g.).

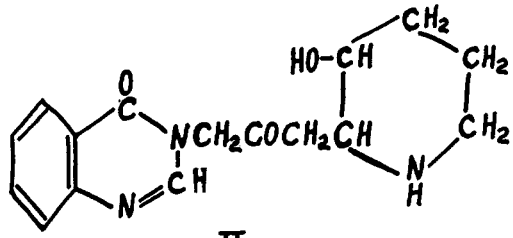
Anal. Calc'd for $C_{11}H_{14}N_2O_2S$: N, 11.76. Found: N, 11.60.

Substituted 7-methyl-5H-thiazolo[2,3-b]quinazolin-5-ones (V). An alcoholic solution of an α-haloketone (1 mole) was added to 2-carbethoxy-4-methylphenylthiourea (1 mole) dissolved in the minimum amount of ethanol. The mixture was refluxed on the water-bath for 5 hours. The residue, after distilling off the solvent, was made alkaline with 20% so-

[1] This is Thiopegan Derivatives. III. For previous papers, see (2, 3).



I R = various side chains



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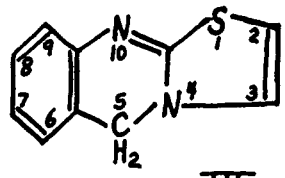

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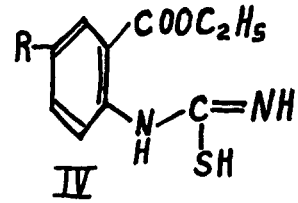

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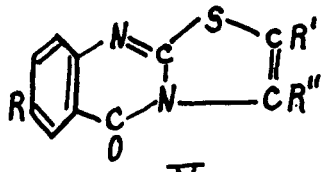

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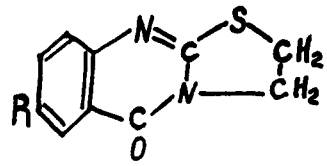

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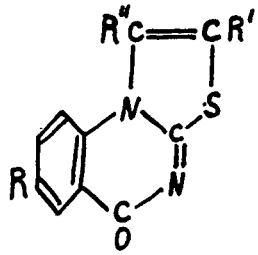
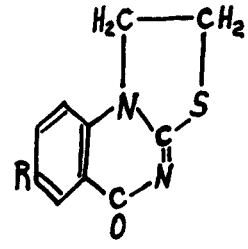


VII



VIII

TABLE I

CONDENSATION OF 2-CARBETHOXY-4-METHYLPHENYLTHIOUREA WITH α-HALOKETONES; FORMATION OF 7-METHYL-5*H*-THIAZOLO[2,3-*b*]QUINAZOLIN-5-ONES (V)

No.	Haloketone used	Product (V)		Solvent of Crystallization	M.P., °C.	Yield, %	Empirical Formula	Analyses			
								Calc'd		Found	
		R′	R″					N	H	N	H
1	Monochloroacetone	H	CH_3	(a) EtOH	(a) 307–308	43	$C_{12}H_{10}N_2OS$	12.17		11.80	
				(b) 30% EtOH	(b) 180–181[a]	12	$C_{12}H_{10}N_2OS$	12.17		12.10	
2	Methyl α-chloroethyl ketone	CH_3	CH_3	30% EtOH	280	73	$C_{13}H_{12}N_2OS$	11.47		11.20	
3	α-Bromoacetophenone	H	C_6H_5	Benzene	264	82	$C_{17}H_{12}N_2OS$	9.60		9.51	
4	*p* - Methyl - α - bromo-acetophenone	H	*p*-$CH_2C_6H_5$	Ethyl acetate	254	80	$C_{18}H_{14}N_2OS$	9.13		9.21	
5	*p* - Methoxy - α - bromo-acetophenone	H	*p*-$CH_3OC_6H_5$	Benzene	244	70	$C_{18}H_{14}N_2O_2S$	8.69		8.66	
6	*p* - Chloro - α - bromo - acetophenone	H	*p*-ClC_6H_5	Ethanol	326	70	$C_{17}H_{11}ClN_2OS$	62.48[b]	3.37	62.54[b]	3.35

[a] This may be the isomer with the angular structure. It should be noted that condensation of IV (R = H) with monochloroacetone also gave two isomeric products (3) which were analyzed for C, H, N, and S.

[b] This is a value for carbon.

dium hydroxide solution. The products were collected, washed with water, dried, and crystallized from various solvents (Table I).

7-Methyl-2,3-dihydro-5H-thiazolo[2,3-b]quinazolin-5-one (VI, R = CH_3). A mixture of 10 g. of 2-carbethoxy-4-methylphenylthiourea and 100 g. of ethylene dibromide was refluxed at 140–150° (oil-bath) for 1½ hours. After cooling the solid was collected with suction and washed with hot, glacial acetic acid to remove 6-methyl-4-keto-2-thiotetrahydroquinazoline (5). The product (9.5 g.) crystallized from ethanol in white shining plates, m.p. 305°.

Anal. Calc'd for $C_{11}H_{11}BrN_2OS$: N, 9.36. Found: N, 9.70.

The *free base* was liberated from a hot aqueous solution of its hydrobromide by basification with sodium carbonate solution. It crystallized from ethanol in colorless needles, m.p. 270°.

Anal. Calc'd for $C_{11}H_{10}N_2OS$: N, 12.84. Found: N, 13.20.

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SUMMARY

Several thiazoloquinazolines have been synthesized in order that their antibacterial properties might be tested. 2,3-Dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one hydrobromide and its 7-methyl derivative have been found to be active in antimalarial tests using *Plasmodium gallinaceum* in chicks.

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