temperature was 165–169°. Vacuum distillation of the reaction residue resulted in collection of a 31% yield of a viscous liquid, b.p. 122–140° (*ca.* 0.2 mm.). Elution chromatography on Merck aluminum oxide gave a separation into two fractions. The first fraction was eluted with benzene and benzene–ether mixtures and the second fraction was eluted with methanol. The ratio of first to second fraction was *ca.* 1.6:1. Both fractions were further purified by vacuum distillation: first fraction, b.p. 128–131° (0.4 mm.), $n^{25}D$ 1.5036; second fraction, b.p. 126–127° (0.1 mm.), $n^{25}D$ 1.4966. Neither product could be made to crystallize. The analytical results show both products to be somewhat impure. However, it is clear that they are 1:1 adducts.

Anal. Calcd. for $C_{13}H_{18}O_4N_2$: C, 58.63; H, 6.81; N, 10.52; mol. wt., 266. Found for the first fraction: C, 59.27; H, 7.35; N, 10.38; mol. wt., 271. Found for the second fraction: C, 58.96; H, 7.34; N, 10.40; mol. wt. 270.

A solution of the first fraction product in carbon tetrachloride rapidly decolorized a solution of bromine in carbon tetrachloride. The second fraction product decolorized bromine much more slowly.

Acknowledgment.—E. L. A. is indebted to the National Science Foundation for a post-doctoral fellowship under which this research was initiated. D. L. W. was a recipient of a National Science Foundation grant for teacher training through research participation. The n.m.r. spectra were kindly determined by Mr. Bernard J. Nist of the University of Washington.

Studies in Thiazinoquinazolines

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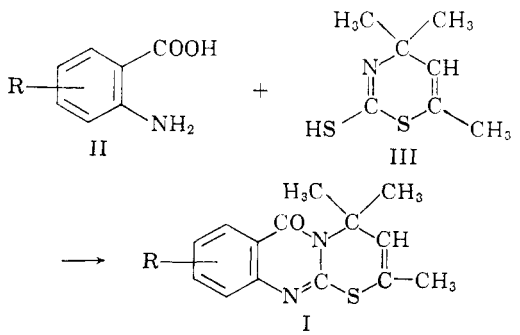
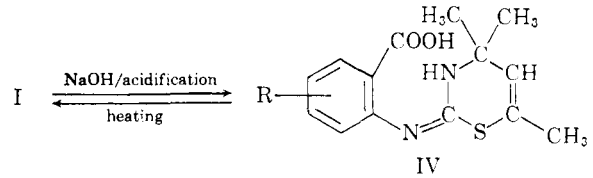
Received January 31, 1961

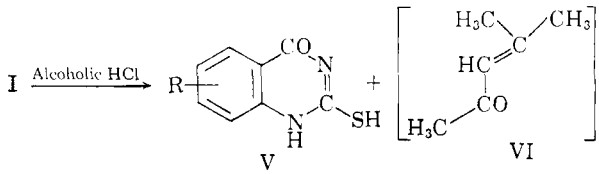
Thiazinoquinazolines (I), a new heterocyclic system which incorporates the physiologically active rings as thiazine and quinazoline present in febrifugine and methylene blue, respectively, have been prepared by a very simple method, which involves a condensation between 2-mercapto-4,4,6-trimethyl 4H-1,3-thiazine (III)[1] and the requisite anthranilic acids (II). This new ring system is quite stable towards cold alkali and remains unaffected for a number of days in 5% sodium hydroxide. The quinazoline ring opens to furnish IV on prolonged heating with 5% sodium hydroxide at 60–70°. The acid (IV) is transformed back to I on either heating in the dry state or refluxing in alcohol.



II III I

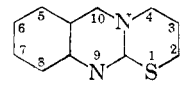


IV



V VI

These thiazino-quinazolines are also insoluble in aqueous hydrochloric acid and undergo a degradation to V and VI on refluxing in alcoholic hydrochloric acid.



VII

The parent ring system (VII) can be named 1,3-thiazino[2,3-b]quinazoline and thus I will be 2,4,4-trimethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline-10-one.

Antibacterial Results.—On preliminary testing the compounds no. 1, 2, 3, 4, 5 (Table I) have proved bacteriosidal to the strains of proteus vulgaris at a dilution of 1:5000.

Experimental

1. **1,3-Thiazino[2,3-b]quinazolines (Table I).**—An equimolar mixture of 2-mercapto-4,4,6-trimethyl-4H-1,3-thiazine and the requisite anthranilic acid was heated in an oil bath at 120–125° for 4 hr.; the completion of the reaction is indicated when hydrogen sulfide no longer evolves. The slurry was cooled, neutralized with sodium carbonate, filtered, and the residue thoroughly washed with water. In all cases it could be crystallized from dilute ethanol or acetic acid.

2. **Treatment of I with Alkali and Isolation of IV.**—Thiazinoquinazoline (I) (R = H) was taken in 5% sodium hydroxide and heated at 60–70° for 5 hr. The solution was acidified with acetic acid and the resulting precipitate purified by dissolving in sodium hydroxide and reprecipitation and finally crystallization from dilute ethanol. The product melted at 290°.

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 64.61; H, 6.1; N, 10.77. Found: C, 64.23; H, 5.9; N, 10.90.

3. **Treatment of I with Alcoholic Hydrochloric Acid; Isolation of 2-Thio-4-keto-tetrahydroquinazoline (V).**—I (R = H) was dissolved in ethanol and saturated with dry hydrochloric acid. The solution then refluxed over a steam bath for 8 hr. The solvent was removed by dis-

(1) J. E. Jansen and R. A. Mathes, *J. Am. Chem. Soc.*, **77**, 5431 (1955).

TABLE I

1:3-THIAZINO[2:3-b]QUINAZOLINES

S. no.	Anthranilic acid used	Compound formed	Yield, %	M.p., °C.	Molecular formula		Calcd., %	Found,[a] %
1	Anthranilic acid	2,4,4-Trimethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline 10-one	77	247–248	$C_{14}H_{14}N_2OS$	C	65.19	65.52
						H	5.51	5.60
						N	10.85	10.42
						S	12.40	12.15
2	3-Methylanthranilic acid	2,4,4,8-Tetramethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline-10-one	56	227	$C_{15}H_{16}N_2OS$	N	10.30	10.30
3	4-Methylanthranilic acid	2,4,4,7-Tetramethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline-10-one	44	188	$C_{15}H_{16}N_2OS$	N	10.29	10.53
						S	11.76	12.10
4	5-Methylanthranilic acid	2,4,4,6-Tetramethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline-10-one	58	267	$C_{15}H_{16}N_2OS$	N	10.29	10.43
5	4-Chloroanthranilic acid	7-Chloro-2,4,4-trimethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline-10-one	50	243	$C_{14}H_{13}Cl_2N_2OS$	N	9.57	9.30

[a] N tested by Dumas method.

tillation and the residue crystallized from glacial acetic acid. It melted at 285° and was confirmed to be 2-thio-4-keto-tetrahydroquinazoline by comparison with an authentic sample.[2]

Acknowledgment.—The authors are thankful to Dr. K. S. Narang, reader, Panjab University, Chemistry Department, for his valuable guidance and the Director, Central Drug Research Institute, for testing the compounds.

(2) H. Rupe, *Ber.*, **30**, 1097 (1897).

1,2,4-Substituted 5(4H)-Imidazolones[1]

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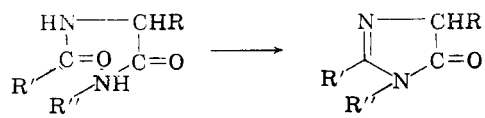
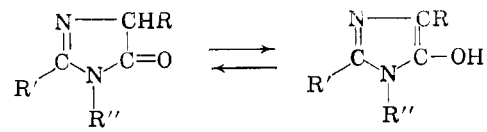
Received February 16, 1962

The possible presence of five-membered heterocycles, oxazolones, oxazolines, and imidazolones in proteins has been suggested as being important to the biological activity of proteins. Oxazolones are internal anhydrides of acyl amino acids, oxazolines are lactones involving serine, and 5(4H)-imidazolones are internal condensation products of tripeptides (or acyl amino acid amides).



I

The resemblance of these latter compounds to imidazole, which is thought to be somehow involved in the activity of hydrolytic enzymes, is of some theoretical interest. 5(4H)-Imidazolones are tautomeric with 5-hydroxyimidazoles and under favorable circumstances the enolic form may be stable. This appears to be the case for corresponding oxazolones when R′ = *p*-nitrophenyl.



The enolate anion may be an active nucleophile. It was of interest to prepare imidazolones of the general structure I, of which no members had previously been reported.

Until recently all methods for the preparation of imidazolones applied mostly to those which are not substituted in the position one (R″ = H).[2] Another type of imidazolonscribe deed in the literature contains a side chain linked to carbon four *via* a double bond. These "unsaturated" imidazolones correspond to the "unsaturated" oxazolones which are more stable than the "saturated" derivatives. These compounds do not form enols and are not derivatives of natural amino acids.

Karrer and Granacher[3] prepared "unsaturated imidazolones" and an imidazolone derived from hippurylamide by direct dehydration, but the method did not work with hippuryl ethylamide.

In 1956 a method was devised for the easy preparation of N-substituted 5(4H)-imidazolones. Brunken and Bach[4] condensed ortho esters with substituted glycine amides. The amides were prepared from glycine ethyl ester hydrochloride and the appropriate amine. When applied in the present instance to N-substituted amides of alanine,

(1) This work was supported by the Division of Research Grants and Fellowships of the National Institutes of Health, U.S. Public Health Service, Grants No. B-573 C13 and B-3304.

(2) E. S. Schipper and A. R. Day, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, ed., J. Wiley & Sons, Inc., New York, N. Y. 1960, p. 248.

(3) P. Karrer and C. Granacher, *Helv. Chim. Acta*, **7**, 763 (1924); C. Granacher and M. Mahler, *ibid.*, **10**, 246 (1927).

(4) J. Brunken and G. Bach, *Ber.*, **89**, 1363 (1956).