

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

S. no.	Anthranilic acid used	Compound formed	Yield, %	M.p., °C.	Molecular formula	Calcd., %	Found, <sup>a</sup> %
1	Anthranilic acid	2,4,4-Trimethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline 10-one	77	247-248	C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> OS	C 65.19 H 5.51 N 10.85 S 12.40	65.52 5.60 10.42 12.15
2	3-Methylantranilic acid	2,4,4,8-Tetramethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline-10-one	56	227	C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> OS	N 10.30	10.30
3	4-Methylantranilic acid	2,4,4,7-Tetramethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline-10-one	44	188	C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> OS	N 10.29 S 11.76	10.53 12.10
4	5-Methylantranilic acid	2,4,4,6-Tetramethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline-10-one	58	267	C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> OS	N 10.29	10.43
5	4-Chloroantranilic acid	7-Chloro-2,4,4-trimethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline-10-one	50	243	C <sub>14</sub> H <sub>13</sub> Cl <sub>2</sub> N <sub>2</sub> OS	N 9.57	9.30

<sup>a</sup> 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.<sup>2</sup>

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

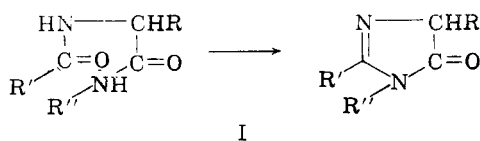
## 1,2,4-Substituted 5(4H)-Imidazolones<sup>1</sup>

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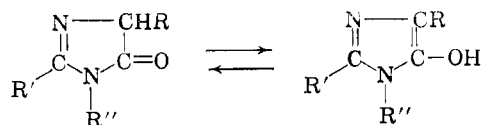
The possible presence of five-membered heterocycles, oxazolones, oxazolines, and imidazolones in proteins has been suggested as being important to the biological activity of proteins. Oxazolones are internal anhydrides of acyl amino acids, oxazolines are lactones involving serine, and 5(4H)-imidazolones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



The resemblance of these latter compounds to imidazole, which is thought to be somehow involved in the activity of hydrolytic enzymes, is of

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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).<sup>2</sup> Another type of imidazolones described 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<sup>3</sup> 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<sup>4</sup> 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,

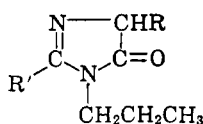
(2) E. S. Schipper and A. R. Day, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, ed., J. Wiley & Sons, Inc., New York, N. Y. 1960, p. 248.

(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).

TABLE I  
 AMINO ACIDS ALKYLAMIDES

Compound	Yield, %	M.p., °C.		Mol. formula	Carbon, %		Hydrogen, %		Nitrogen, %	
		or b.p., °C.			Calcd.	Found	Calcd.	Found	Calcd.	Found
<i>d,l</i> -Alanine <i>n</i> -propylamide	74	75/0.03 mm.		C <sub>8</sub> H <sub>14</sub> N <sub>2</sub> O						
<i>d,l</i> -Alanine <i>n</i> -propylamide picrolonate	..	198-199		C <sub>15</sub> H <sub>22</sub> N <sub>6</sub> O <sub>6</sub>	48.72	48.82	5.62	5.87	21.31	20.80
<i>l</i> -Leucine <i>n</i> -propylamide	81	91/0.1 mm.		C <sub>9</sub> H <sub>2</sub> N <sub>2</sub> O						
<i>l</i> -Leucine <i>n</i> -propylamide picrolonate	..	238		C <sub>19</sub> H <sub>28</sub> N <sub>6</sub> O <sub>6</sub>	52.28	52.37	6.47	6.76	19.26	19.01
<i>d,l</i> -Phenylalanine <i>n</i> -propylamide	64	129/0.05 mm.		C <sub>12</sub> H <sub>18</sub> N <sub>2</sub> O	69.86	69.83	8.79	9.41	13.58	13.36
<i>d,l</i> -Phenylalanine <i>n</i> -propylamide picrolonate	..	212		C <sub>22</sub> H <sub>26</sub> N <sub>6</sub> O <sub>6</sub>	56.16	56.48	5.57	5.77	17.86	17.66

 TABLE II  
 IMIDAZOLONES


R'	R	Yield, %	M.p., °C.		Mol. formula	Carbon, %		Hydrogen, %		Nitrogen, %	
			or b.p., °C.			Calcd.	Found	Calcd.	Found	Calcd.	Found
CH <sub>2</sub> CH <sub>2</sub>	CH <sub>3</sub> <sup>a</sup>	54	76-77/0.2 mm.		C <sub>9</sub> H <sub>15</sub> N <sub>2</sub> O						
CH <sub>2</sub> CH <sub>2</sub>	CH <sub>3</sub> Picrolonate	..	181		C <sub>19</sub> H <sub>24</sub> N <sub>6</sub> O <sub>6</sub>	52.77	53.01	5.59	5.69	19.44	19.36
CH <sub>3</sub>	CH <sub>3</sub> } CHCH <sub>2</sub>	70	88/0.2 mm.		C <sub>11</sub> H <sub>20</sub> N <sub>2</sub> O	67.30	66.90	10.27	10.25	14.27	13.59
CH <sub>3</sub>	CH <sub>3</sub> } CHCH <sub>2</sub>	..	191		C <sub>21</sub> H <sub>28</sub> N <sub>6</sub> O <sub>6</sub>	54.77	54.34	6.13	6.64	18.25	18.03
CH <sub>3</sub>	CH <sub>3</sub> } CHCH <sub>2</sub>	68	99/0.1 mm.		C <sub>13</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub>	65.51	65.76	9.31	9.58	11.76	12.07
CH <sub>3</sub>	CH <sub>2</sub> } CHCH <sub>2</sub>	55	118/0.3 mm.		C <sub>14</sub> H <sub>18</sub> N <sub>2</sub> O						
CH <sub>3</sub>	CH <sub>2</sub> } CHCH <sub>2</sub>	..	189		C <sub>24</sub> H <sub>26</sub> N <sub>6</sub> O <sub>6</sub>	58.29	57.92	5.30	5.68	17.00	16.62
	Picrolonate										

<sup>a</sup> R' = CH<sub>3</sub>. R = CH<sub>3</sub> gave a product, the analytical data of which fell slightly outside analytical limits.

leucine and phenylalanine the reactions proceeded smoothly and gave good yields of imidazolones.

### Experimental

Ethyl orthoacetate and propionate are commercially available.

**Preparation of Amino Acids Alkylamides.**—Amino acid ethyl ester hydrochloride, 0.1 mole, was dissolved in 0.5 mole of the alkylamine (*n*-propylamine in our case), and left at room temperature for 4-6 days. Excess of amine was partly recovered through distillation. The residual mass was dissolved in a minimum amount of methanol and a theoretical amount of a methanolic solution of sodium methoxide added. The reaction mass was concentrated to a thick sirup and the alkylamides extracted into acetone to eliminate sodium chloride. After evaporation of the solvent, the residual oil was distilled in vacuum. Amino acid alkylamides are thick, colorless or slightly colored oils

having an amine smell. The results are given in Table I. The compounds were identified through their picrolonates.

**Preparation of 5(4H)-Imidazolones.**—The general procedure was that used by Brunken and Bach. Amino acid *n*-propylamide, 20 mmoles was mixed with 23 mmoles of an ortho ester and after addition of 1 drop of acetic acid, the solution was gently heated until the reaction started. Temperature was maintained at 110-120° for 1-1.5 hr. The reaction mixture was then fractionally distilled under vacuum. Imidazolones are colorless or slightly yellow oils, very soluble in organic solvents and also soluble in water except for the derivative of phenylalanine.

**Preparation of 1-*n*-Propyl-2-methyl-4-isobutyl-5-acetoxymidazole.**—(Enol acetate of imidazolone). Imidazolone, 25 mmoles, was heated on a steam bath with 15 ml. of acetic anhydride for 1.5 hr. Excess acetic anhydride was distilled under water pump vacuum and the residue fractionated, giving a thick almost colorless oil.

The results are given in Table II. The compounds were identified through their picrolonates.