TABLE 1

PROPERTIES OF 3-INDOLEACETAMIDES

3-Indoleacetamides	Formula	M.p.	$[\alpha]_D^{27}$	Yield %	Nitrogen % Calcd.	Nitrogen % Found	Neutralization Equivalent Calcd.	Neutralization Equivalent Found
N-(3-Indoleacetyl)-glycine	$C_{12}H_{12}N_2O_3$	86–87[a]		17	12.1	12.1	232	232
N-(3-Indoleacetyl)-DL-isoleucine	$C_{16}H_{20}N_2O_3$	102		34	9.7	9.9	288	290
N-(3-Indoleacetyl)-DL-methionine	$C_{15}H_{18}N_2O_3S$	169–171d		19	9.1	9.2	306	302
N-(3-Indoleacetyl)-L-tryptophan	$C_{21}H_{19}N_3O_3$	181–183	+14.56	9	11.6	11.7	361	358
N-(3-Indoleacetyl)-L-aspartic acid	$C_{14}H_{14}N_2O_5$	164.5d	−4.51	29	9.7	9.4	145	144
N-(3-Indoleacetyl)-L-glutamic acid	$C_{15}H_{16}N_2O_5$	162.5d	−10.57	20	9.3	9.3	151	152
N-(3-Indoleacetyl)-6-aminopurine	$C_{15}H_{12}N_6O$	242–244		30	28.8	28.5		
N-(3-Indoleacetyl)-*p*-aminobenzoic acid	$C_{17}H_{14}N_2O_3$	253–255d		45	9.5	9.6	294	296
N-(3-Indoleacetyl)-*m*-aminobenzoic acid	$C_{17}H_{14}N_2O_3$	246d		37	9.5	9.7	294	297

[a] *Cf.* reference 6.

dilute phosphoric acid. After standing for 1 hr. in the cold, the precipitate was collected by filtration. The product was further purified by recrystallizations from water coupled with carbon decolorizations. The yield of the recrystallized product was 380 mg., m.p. 86–87°.

Those 3-indoleacetamides, which possessed limited water solubility, were recrystallized from dilute ethanol or ethanol alone (adenine derivative). The yield of the recrystallized products was usually 25–30%.

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Structural Studies of the Isoximes of Weygand and Bauer

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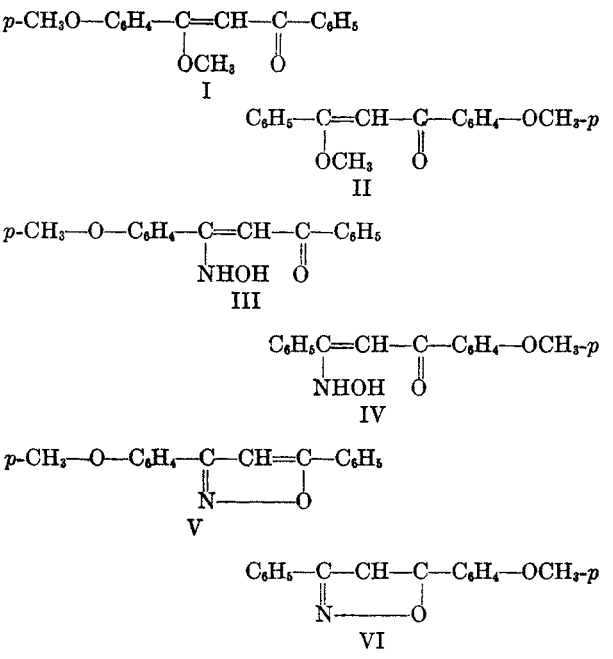
The infrared and ultraviolet spectra of the isoximes of Weygand and Bauer indicate that these substances are represented best as the more stable of the configurational isomers of the oximes. Chemical evidence points to facile rearrangement of the more stable isomers to the less stable forms which undergo ring closure with formation of isoxazoles.

Weygand and Bauer[2] reported that on treating the "A-ether" (I) and the "B-ether" (II) with hydroxylamine, they isolated compounds III and IV, respectively, which they called isoxime A and isoxime B. They showed that they obtained isoxazoles V and VI when they treated the isoximes with acids.



It is common knowledge that β-diketones yield isoxazoles when treated with hydroxylamine. Blatt[3] showed that methoxyamine hydrochloride, in contrast to the free base, adds to the ketonic carbonyl group. Barnes and Pinkney[4] showed that the free base, hydroxylamine, adds 1,4 to α,β-unsaturated ketones, and that in isoxazoline formation, nitrogen is found on the carbon atoms that was previously the carbonyl carbon. Blatt[3] showed that acetylenic ketones also add the free base, methoxyamine.

We believe that the structural formula III and IV should be designated as oximes with the following configurational formulas VII and VIII, and that these anti forms, on acidification, rearrange to the syn forms which then enolize and undergo

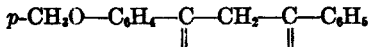
(1) In partial fulfillment of the requirements for the Master's degree.

(2) C. Weygand and E. Bauer, *Ann.*, **459**, 123 (1927).

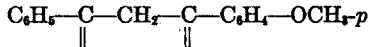
(3) A. H. Blatt, *J. Am. Chem. Soc.*, **61**, 3495 (1939).

(4) R. P. Barnes, G. Pinkney, and G. Phillips, *J. Am. Chem. Soc.*, **76**, 276 (1954).

ring closure with the formation of isoxazoles V and VI.



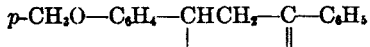
VII



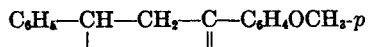
VIII

We have investigated the isoximes of Weygand and Bauer and have concluded that they are actually oximes. We believe that oximes VII and VIII are formed by 1,4-addition of hydroxylamine to ethers I and II with the elimination of methanol. These isoximes do not yield to ozonization.

p-Methoxybenzalacetophenone[5] and benzal-*p*-methoxyacetophenone[6] were converted into their respective isoxazolines IX and X by treatment with hydroxylamine in aqueous alcoholic solution in the presence of potassium hydroxide. These isoxazolines IX and X upon oxidation with chromic acid yielded the expected isoxazoles VI and V, respectively.

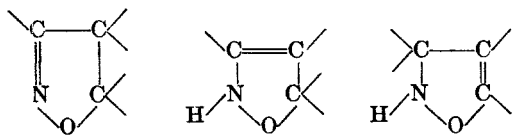


IX



X

We examined the infrared and ultraviolet spectra[7] of the isoximes. Recently, G. W. Perold[8] *et al.* observed no infrared absorption band in the N—H stretching region around 3300 cm.$^{-1}$ and on this basis assigned structure XI to isoxazoles rather than XII or XIII.



XI XII XIII

We also examined infrared absorption spectra for several compounds in the range 5.88–6.00 μ and around 3300 cm.$^{-1}$ In the 5.88–6.00 μ region we observed no absorption band for the isoximes of Weygand and Bauer. This region has been assigned to α,β-unsaturated ketones.[9]

(5) F. J. Pond and A. S. Shoffstall, *J. Am. Chem. Soc.*, 22, 666 (1900).

(6) H. Staudinger and N. Kon, *Ann.*, 384, 123 (1911).

(7) Infrared and ultraviolet spectra were measured by Messrs. J. E. Stewart and J. H. Gould of the National Bureau of Standards, Dept. of Commerce, Washington, D. C.

(8) G. W. Perold *et al.*, *J. Am. Chem. Soc.*, 79, 463 (1957).

(9) H. Gilman, *Organic Chemistry*, vol. 3, John Wiley & Sons, Inc., New York, p. 146.

Below are listed several ketones and their infrared and ultraviolet bands.

Compound	3500–3200 cm.$^{-1}$	5.88–6.00 μ
Isoxime A, III	3330	...
Isoxime B, IV	3300	...
N-methyl ether of isoxime A, XIV	...	...
II(*s*)	3580	6.01
Mes—C(=O)—C(=N)—CH$_2$—C$_6$H$_5$(*s*)[10]	3300	5.92
(OH, XV)		
Mes—C(=O)—C(=N)—CH$_2$—C$_6$H$_5$(*s*)[10]	3320	...
(O—CO)	Not developed	
Mes—C(=O)—CH$_2$—CH$_2$—C$_6$H$_5$(*l*)[10]	3400	5.85

s = Nujol mull. *l* = liquid

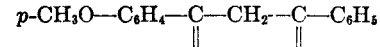
Ultraviolet Data

Compound	Absorption Band, Mμ	E_{max}
Isoxime A, III	270	1.92×10^4
Isoxime B, IV	260	1.50×10^4
XV	235	...

The infrared absorption in the region 5.88–6.00 μ (1700–1665 cm.$^{-1}$)[9] shows that compound II has a band at 6.01 μ, corresponding to α,β-unsaturated ketones. We obtained no absorption in this region for isoximes III and IV. This indicates that their structures could not be as represented.

We note that Perold[8] assigned an absorption band at 3300 cm.$^{-1}$ to N—H stretching. It is interesting to note that while the *N*-methyl ether of isoxime A, XIV, does not have an absorption band in this region, isoximes III and IV do.

Comparing the isoxime structures III and IV and the proposed configurational oxime formulas VII and VIII with the oxime structure XV, we find that isoximes III and IV and oxime XV all absorb in the range 3300–3340 cm.$^{-1}$ This band cannot be assigned to N—H stretching since the reference oxime XV does not have an N—H linkage. Instead, this band should be assigned to OH absorption. Hence the isoximes seem to be represented best as the configurational oximes VII and VIII. This is further confirmed by the fact that the *N*-methyl ether of isoxime A, XIV, showed no absorption in this region. And so the *N*-methyl ether of isoxime A is



XIV

(10) R. P. Barnes, *J. Am. Chem. Soc.*, 57, 937 (1935).

Ferguson and Barnes[11] reported that ultraviolet absorption in conjugated systems involving α,β-unsaturated carbonyl compounds ranges above 319 mμ, whereas these isoximes absorb at 260 and 270 mμ. This does not lend support to the isoxime structures.

EXPERIMENTAL

Preparation of isoxazolines IX *and* X. 3-phenyl-5-anisyl-isoxazoline (IX) and 3-anisyl-5-phenylisoxazoline (X) were prepared according to Blatt[12] and Barnes[13] by treating *p*-methoxybenzalacetophenone and benzal-*p*-methoxyacetophenone, respectively, with excess hydroxylamine in alcoholic potassium hydroxide.

	M.P., ° C.	Color	Analysis
IX	101–102°	White	Calcd. for $C_{16}H_{15}NO_2$: C, 75.88; H, 5.92. Found: C, 75.85; H, 6.00.
X	96°	White	Calcd. for $C_{16}H_{15}NO_2$: C, 75.88; H, 5.92. Found: C, 75.83; H, 6.02

Preparation of isoxazoles V *and* VI. Chromic acid oxidation[12,13] of isoxazolines IX and X yielded isoxazoles VI and V, respectively, identified by mixture melting points with samples obtained by acidification of isoximes IV and III.

Treatment of isoximes with ozone. Prolonged treatment of alcoholic solutions of isoximes III and IV gave no cleavage products. The isoximes were recovered unchanged.

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(11) L. N. Ferguson and R. P. Barnes, *J. Am. Chem. Soc.*, **70**, 3907 (1948).
(12) A. H. Blatt, *J. Am. Chem. Soc.*, **53**, 1140 (1931).
(13) R. P. Barnes, G. Pinkney, and G. McK. Phillips, *J. Am. Chem. Soc.*, **76**, 276 (1954).

Thiol Addition of Thiourea in Heterocyclic Ring Formation: Preparation of 5-Ethyl-6-phenyl-*meta*-thiazane-2,4-dione

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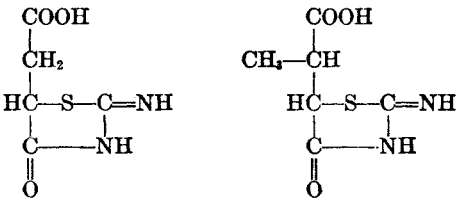
Received April 8, 1958

Thiourea has been made to undergo a thiol-type addition to a monobasic, α,β-unsaturated acid and to its ethyl ester. A simultaneous condensation between the carboxyl group of the acid and the amine group of thiourea has resulted in the formation of a derivative of the six-membered, sulfur containing heterocycles the *meta*-thiazanes.

Several reactions of thiourea that have been previously observed by other workers indicate that in some instances the thiol tautomer is the predominant reacting species. Thus, upon alkylating thiourea with hydrocarbon halides or with alkyl sulfates, *S*-alkyl- and *S*-arylthiouronium salts are formed.[1] Oxidation of thiourea in acid solution leads to the formation of dithiodiformamidine.[2] Andreasch[3] has reacted thiourea with maleic or fumaric acid to give I and with citraconic to give II (Fig. 1). These reactions were carried out by heating a fused mixture of the reactants either dry or with a small amount of water. The products obtained indicate that both a thiol addition of the thiourea to the unsaturated acid and a condensation, involving the elimination of water from the carboxyl group and from the amine group of the thiourea, occur. Attempts to repeat this reaction with such monobasic, unsaturated acids as oleic, crotonic, cinnamic, 2-phenyl-3-methylacrylic, and methacrylic were not successful. Either polymeric products were obtained or else amine addition by the thiourea occurred forming thiopyrimidines.[3,4] Thus with cinnamic acid, 4-phenyl-2-thio-6-ketopyrimidine was obtained.[4] However, a thiol addition reaction between thiourea and acrylic acid has been accomplished by hydrogen chloride catalysis in alcohol to give *S*-(β-carboxyethyl)-isothiouronium hydrochloride[5] without accompanying cyclization.



I Figure 1 II

In the present work, a sulfuric acid solution of thiourea was treated with the α,β-unsaturated acid *trans*-α-ethylcinnamic acid, and with its ethyl ester, and in both cases the same *meta*-thiazane derivative was obtained. This product which no longer contains unsaturation can only arise from a reaction where the thiol tautomer of thiourea adds to the unsaturated system, since the sulfur is part of the heterocyclic ring. The possible sequences of reactions which would result in such a product are shown in Fig. 2. Both the addition and the condensation reaction occur under the same conditions. Upon running the above reaction for shorter times and using the same

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(2) J. Boeseken, *Rec. trav. chim.*, **55**, 1040 (1936).
(3) R. Andreasch, *Monatsh.* **16**, 789 (1895); **18**, 56 (1897).
(4) H. Erlenmeyer and F. Heitz, *Helv. Chim. Acta*, **25**, 832 (1942).
(5) (a) E. H. Behringer and P. Zillikens, German Patent-Anm. B. **16741** (1951); (b) O. Bayer, *Angew. Chem.*, **61**, 236 (1949); (c) J. Houben, *Methoden der Organischen Chemie*, vol. IX, G. Thiele, Leipzig, Germany, 1955, p. 902.