phenylethyl), 20429-55-4; **1a** (diperchlorate), 1020-94-6; **1b** (diperchlorate), 20445-47-0; **1c** (diperchlorate), 15567-89-2; **1d** (diperchlorate), 1083-67-6; **1e** (diperchlorate), 20429-72-5; **1f** (dichloride), 20429-73-6; **8b** (2 $HClO_4$), 20429-60-1; **8c** (2HCl), 20429-59-8.

Novel Reactions of 3-Unsubstituted 3-Isoxazolin-5-ones

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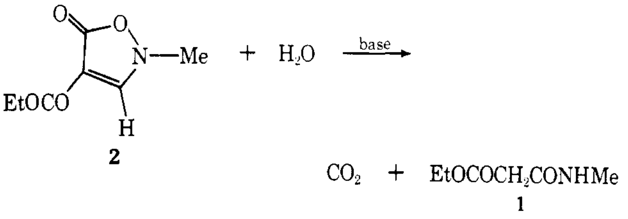
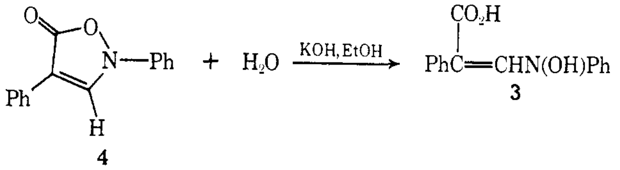
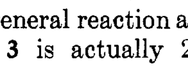
The reaction of 2,4-diphenyl-3-isoxazolin-5-one, **4**, and ethoxide gives ethyl 2-phenylmalonanilate, **7**, while that of 2-methyl-4-carbethoxy-3-isoxazolin-5-one, **2**, with acetate gives an enolic C-acyl derivative, **23** (R = Me). Both reactions may involve rearrangement of the normal ring-opening products.

The base-catalyzed ring opening of 3-unsubstituted 3-isoxazolin-5-ones was shown to involve abstraction of the proton from the 3-position and rupture of the N-O bond by Ulrich, Tilley, and Sayigh,[1] who obtained ethyl N-methylmalonamate, **1**, from the treatment of 2-methyl-4-carbethoxy-3-isoxazolin-5-one, **2**, with aqueous base. An alternative pathway for ring opening, cleavage of the ester function, had been proposed earlier by Rupe and Grünnolz,[2] who reported the isolation of 3-(N-hydroxy)anilinoatropic acid, **3**, from the reaction of 2,4-diphenyl-3-isoxazolin-5-one, **4**, with ethanolic potassium hydroxide. Fabbrini, Renzi, and Speroni[3] accepted this latter pathway for the formulation of the products in a related case, but later DeSarlo and Renzi[4] demonstrated that, in fact, fission of the N-O bond is a general reaction and that the product assigned structure **3** is actually 2-phenylmalonanilic acid, **5**.





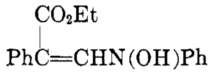


$$\overset{CO_2H}{|}\atop{PhCHCONHPh}$$

5

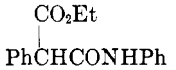
In the course of an independent study of isoxazolones, we also identified the product from **4** as **5**[5] and found, in addition, that the reactions of **4** and **2** with ethoxide and acetate ions, respectively, give ring-opening products of unexpected structure.

In support of the mode of ring opening they had proposed, Rupe and Grünholz[2] showed that the same compound, which they formulated as **6**, was obtained both from **4** and potassium hydroxide in ethanol and from esterification of the acid they thought to be **3**. In our reexamination of this work, we found, instead, that the product is ethyl 2-phenylmalonanilate, **7**, the ester of **5**.



$$\overset{CO_2Et}{|}\atop{PhC{=}CHN(OH)Ph}$$

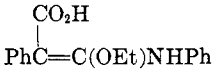
6



$$\overset{CO_2Et}{|}\atop{PhCHCONHPh}$$

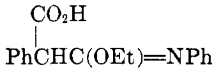
7

The possibility that ethoxide actually might attack the 5 position of **4** to give **6** is ruled out by the nmr spectrum of the compound, which lacks the characteristic low-field signals expected for the olefinic and hydroxyl protons of the vinylogous hydroxamic acid function of **6**.[7] Similarly, while the spectral properties are in complete accord with **7**, the tautomers **8** and **9**, which might be obtained directly from the ring opening with N-O bond rupture, are excluded by the absence of any nmr signal or ir band in the regions indicative of the carboxylic acid proton.[9]



$$\overset{CO_2H}{|}\atop{PhC{=}C(OEt)NHPh}$$

8



$$\overset{CO_2H}{|}\atop{PhCHC(OEt){=}NPh}$$

9

Our major interest in the 3-unsubstituted isoxazolones stemmed from the potential synthetic utility of the reaction with carboxylic acid anions. Specifically, the ring opening of **2** with carboxylate, followed by decarboxylation, would be expected to give **10** (or **11**) (Scheme I), which closely resembles the intermediates **12** (or **13**) in the isoxazolium salt method of peptide synthesis.[11]

Facile 6-center intramolecular acyl migrations are

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[1] H. Ulrich, J. N. Tilley, and A. A. Sayigh, *J. Org. Chem.*, **27**, 2160 (1962).

[2] H. Rupe and J. Grünholz, *Helv. Chim. Acta*, **6**, 102 (1923).

[3] L. Fabbrini, G. Renzi, and G. Speroni, *Chim. Ind.* (Milan), **43**, 1195 (1961).

[4] F. DeSarlo and G. Renzi, *Tetrahedron*, **22**, 2995 (1966).

[5] J. D. Jacobsen and J. V. Van Ornum,[6] unpublished results.

[6] National Science Foundation Undergraduate Research Participant, 1967.

[7] Both signals appear downfield from the aromatic proton signal in the related compound 3-(N-hydroxy)anilinoacrylophenone.[8] The conceivable nitrone tautomer of **6** also would have a low-field aldehydic signal and would be inconsistent with the NH band in the infrared spectrum.

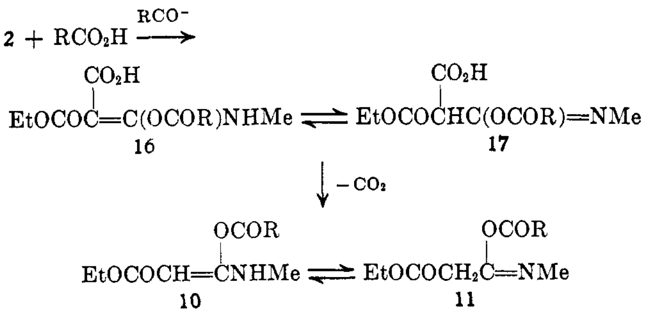
[8] R. B. Woodward, D. J. Woodman, and Y. Kobayashi, *J. Org. Chem.*, **32**, 388 (1967).

[9] The $=NH-^{+}$ ir band of the possible zwitterionic form of **9** also would appear at long wavelength, comparable with that of the carboxylic acid absorption.[10]

[10] K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 39.

[11] R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Amer. Chem. Soc.*, **83**, 1010 (1961); *Tetrahedron Suppl.*, **8**, 321 (1966).

SCHEME I



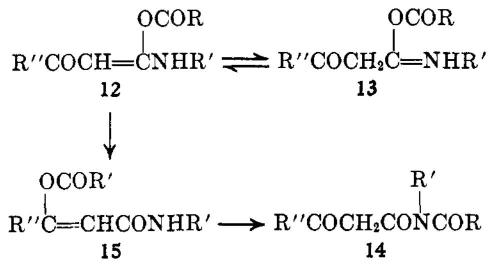
$$2 + \mathrm{RCO_2H} \xrightarrow{\mathrm{RCO^-}}$$

$$\underset{16}{\mathrm{EtOCO\overset{\overset{\textstyle CO_2H}{|}}{C}{=}C(OCOR)NHMe}} \rightleftharpoons \underset{17}{\mathrm{EtOCO\overset{\overset{\textstyle CO_2H}{|}}{C}HC(OCOR){=}NMe}}$$

$$\downarrow -\mathrm{CO_2}$$

$$\underset{10}{\mathrm{EtOCOCH{=}\overset{\overset{\textstyle OCOR}{|}}{C}NHMe}} \rightleftharpoons \underset{11}{\mathrm{EtOCOCH_2\overset{\overset{\textstyle OCOR}{|}}{C}{=}NMe}}$$

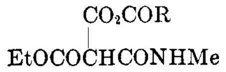
known to convert **12** (or **13**) to the imide **14** *via* the enol ester **15**.[7,12] Comparable rearrangements, beginning with **16** (or **17**) and decarboxylation, were anticipated to provide routes to **18**, **19**, **20**, **21**, and **22**, and, by analogy with the isoxazolium salt results, the ultimate, most stable product would be the imide **22**.



$$\underset{12}{\mathrm{R''COCH{=}\overset{\overset{\textstyle OCOR}{|}}{C}NHR'}} \rightleftharpoons \underset{13}{\mathrm{R''COCH_2\overset{\overset{\textstyle OCOR}{|}}{C}{=}NHR'}}$$

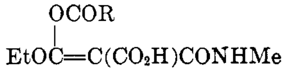
$$\downarrow$$

$$\underset{15}{\mathrm{R''\overset{\overset{\textstyle OCOR'}{|}}{C}{=}CHCONHR'}} \longrightarrow \underset{14}{\mathrm{R''COCH_2CO\overset{\overset{\textstyle R'}{|}}{N}COR}}$$



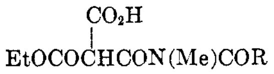
$\mathrm{EtOCO\overset{\overset{\textstyle CO_2COR}{|}}{C}HCONHMe}$

18



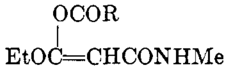
$\mathrm{EtO\overset{\overset{\textstyle OCOR}{|}}{C}{=}C(CO_2H)CONHMe}$

19



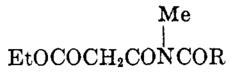
$\mathrm{EtOCO\overset{\overset{\textstyle CO_2H}{|}}{C}HCON(Me)COR}$

20



$\mathrm{EtO\overset{\overset{\textstyle OCOR}{|}}{C}{=}CHCONHMe}$

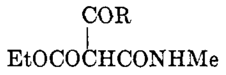
21



$\mathrm{EtOCOCH_2CO\overset{\overset{\textstyle Me}{|}}{N}COR}$

22

Ulrich, Tilly, and Sayigh[1] had treated **2** with aqueous sodium acetate, but they obtained **1**, which could have been formed by competitive attack by hydroxide or by hydrolysis of the product from attack by acetate. To avoid either complication, we combined **2** with acetic acid and triethylamine in chloroform. Monitoring by nmr revealed slow conversion of **1** to a single major product. Elemental analysis of the compound showed that decarboxylation had taken place, while hydrolysis to **1** indicated that the product was an acetyl derivative of **1**.[13] Surprisingly, however, the nmr spectrum rules out all of the anticipated structures in which the acyl group is attached to one of the heteroatoms. The spectrum includes the characteristic signals for the ethyl, acetyl, and -NHMe groups, together with a signal at extremely low field indicative of an enolic proton. The absence of an nmr signal for other hydrogen attached to carbon is inconsistent with all of the possible tautomeric forms of all of the candidates **10**, **11**, **21**, and **22**. The only remaining position for attachment of the acyl group is the central carbon, and an enol of the C-acyl isomer **23** (R = Me) satisfactorily accounts for the spectrum.



$\mathrm{EtOCO\overset{\overset{\textstyle COR}{|}}{C}HCONHMe}$

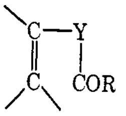
23

The formation of both unusual products **7** and **23** in these reactions can be rationalized as involving subsequent rearrangements of the expected, normal ring-opening products, although alternative mechanisms have not been excluded.

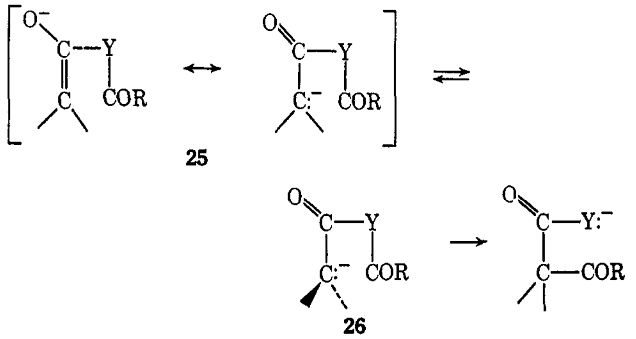
If the reaction of ethoxide and **4** gives **8** or **9** initially, conversion to **7** might be achieved by intramolecular alkylation of the carboxylate ion of either tautomeric intermediate or of the derived zwitterion.

In the case of reaction of **2** with acetate, migration of the acyl group to carbon could be the result of intermolecular processes in which one intermediate serves to acylate the central carbon of an anion from another intermediate or from **1**, although intermolecular reactions of that type are not observed to compete with the intramolecular rearrangements in the closely related reaction sequence leading to **14**.

A second possibility to account for **23** would be 4-center intramolecular acyl migration to carbon. Rearrangement of this type would not be expected for **19** and **21**, because of the stereoelectronic prohibition against acyl migration to terminal carbon in allyloid system **24** (where Y is a heteroatom).[15] However, the anions available in the basic reaction medium from **10** (or **11**), **16** (or **17**), **18**, **20**, and **22** might circumvent this difficulty, since the electron-withdrawing substituents in the ions (of the type **25**) could afford stabilization of the rotamer **26**, which has the proper geometry for acyl transfer. Again, this reaction was not observed either to compete with rearrangements leading to **14** in the studies with isoxazolium salts or to occur when **14** itself was subjected to basic conditions. It could be that the 4-center process is especially favorable in the present system, because of the availability of ions from **16** (or **17**), **18**, and **20**, still bearing the carboxyl group, which would have two electron-withdrawing substituents to stabilize **26**. Of these possibilities, **18** is particularly appealing as a precursor of **23**,



24



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[12] R. B. Woodward and R. A. Olofson, *J. Amer. Chem. Soc.*, **83**, 1007 (1961); *Tetrahedron Suppl.*, **7**, 415 (1966).

[13] Selective attack at the acetyl group rather than the amide or ester functions of **23** was expected by analogy with the results of basic hydrolysis of acetylmalonic acid diesters.[14]

[14] G. E. Lienhard and W. P. Jencks, *J. Amer. Chem. Soc.*, **87**, 3855 (1965).

[15] D. Y. Curtin and L. L. Miller, *ibid.*, **89**, 637 (1967).

since it would not be subject to competitive decarboxylation.

Experimental Section

Ethyl 2-Phenylmalonanilate (7).—A catalytic amount of Na metal was added to a suspension of 0.237 g (1.0 mmol) of 4 in 2 ml of absolute EtOH in a dry reaction vessel. The mixture was allowed to stand overnight, giving a yellow-green solution. Evaporation of the solvent and recrystallization of the residue from ethanol–water gave 0.080 g (30%) of the ester 7, mp 86°; ir (KBr) 3.01 (NH), 5.74 (ester C=O), 6.05 (amide I), and 6.56 μ (amide II); nmr τ 8.76 (t, 3, J = 7.0 Hz), 5.78 (q, 2, J = 7.0 Hz), 5.40 (s, 1), 2.74 (s, 10), and 1.04 (br, 0.96).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94; O, 16.94. Found: C, 71.96; H, 5.91; N, 4.96; O, 17.13.

Reaction of 2-Methyl-4-carbethoxy-3-isoxazolin-5-one (2) with Acetic Acid and Triethylamine.—The nmr spectrum was taken at intervals of a solution of 0.171 g (1.0 mmol) of 2, 0.14 ml (1.0 mmol) of Et_3N, and 0.05 ml (1.0 mmol) of HOAc in 0.80 ml of $CDCl_3$. After several days, no 2 remained, and the spectrum was that of an enol of 23 (R = Me) isolated below. Evaporation of the solvent and sublimation (0.25 mm at 25°) gave a pure sample of the product, mp 32–33°; ir 3.04, 5.97, and 6.38 μ; nmr τ 8.73 (t, 3, J = 7.0 Hz), 7.70 (s, 3), 7.06 (d, 3, J = 4.5 Hz), 5.93 (q, 2, J = 7.0 Hz), 1.42 (br, 1), −7.96 (s, 1).

Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48; O, 34.19. Found: C, 51.25; H, 7.02; N, 7.30; O, 34.06.

Stirring a sample of the product in water with a slight excess of sodium hydroxide resulted in hydrolysis to 1 (identified by nmr comparison with an authentic sample).

Registry No.—7, 20628-57-3; 23 (R = Me), 20628-58-4.

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A Novel Benzimidazole Reaction

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Received February 19, 1969

Reaction of benzimidazole with ethoxymethylenemalononitrile in ethanol produces **3a** instead of the expected **2** *via* further reaction of **2**. Thermal rearrangement of **4** also produces **3a**. The reaction of benzimidazole with ethoxymethylene compounds was extended to the preparation of **3b** and **3c**, **6a** and **6b**, **7a** and **7b**, and **8a** and **8b**. This reaction illustrates the principle of activation of imidazole rings toward nucleophilic attack by placing sufficiently electron-withdrawing substituents on the ring nitrogen atom.

Reaction of aliphatic and aromatic amines with ethoxymethylenemalononitrile (EMMN) leads to aminomethylenemalononitriles[1] (1). In the course of

$$RR'NH + EtOCH{=}C(CN)_2 \longrightarrow RR'NCH{=}C(CN)_2$$

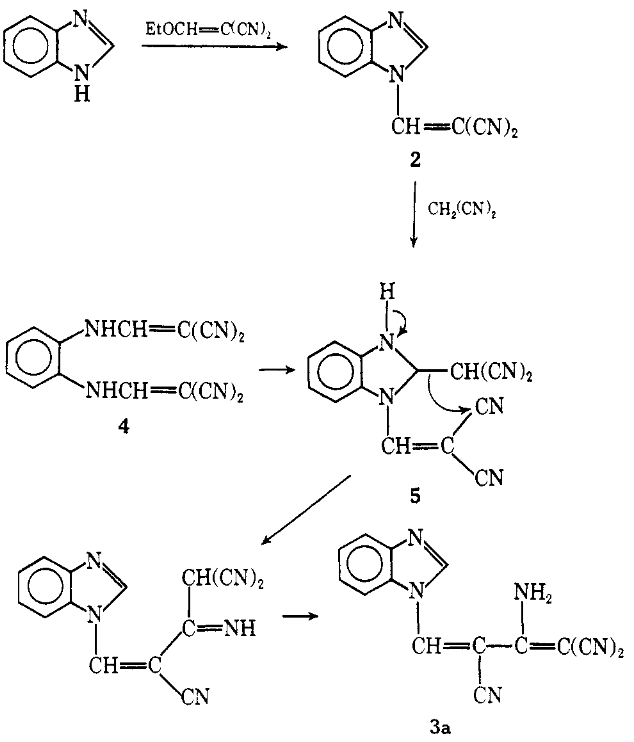
1

synthesis of benzimidazole derivatives for biological studies, we treated benzimidazole with EMMN. This report deals with the unexpected result of this reaction and with the extension of the reaction to a general synthesis of some novel imidazole and benzimidazole derivatives.

Reaction of benzimidazole with 1 equiv of EMMN in hot ethanol produced **3a** (76% yield based on EMMN) instead of the expected (1-benzimidazoyl)methylenemalononitrile (**2**) (see Scheme I). The structure of **3a** was determined by spectral means. The major features of the mass spectrum of **3a** consist of the parent ion at m/e 260, the base ion at m/e 118 (benzimidazole radical cation), and the lower mass region that is remarkably similar to that of benzimidazole itself. The uv spectrum (EtOH) of **3a** reveals the characteristic benzimidazole absorptions at 240 mμ (log ε 3.75), 273 (3.89), and 278 (3.50). The uv maxima (EtOH) reported[2] for benzimidazole itself are at 243 mμ (log ε 3.68), 272 (3.82), and 279 (3.81). The ir spectrum of **3a** reveals NH_2 and CN absorptions. The nmr spectrum (DMSO) of **3a** reveals the NH_2 signal at τ −1.91 (disappears upon addition of D_2O), the imidazole ring proton as a singlet at 0.42, the benzene ring protons as a multiplet centered at 2.25, and the aliphatic vinyl proton signal at 2.85.

The structure of **3a** was further indicated by an independent synthesis which started with reaction of *o*-phenylenediamine with 2 equiv of EMMN in ethanol at room temperature to give **4**. Thermal cyclization and intramolecular rearrangement of **4** in hot N,N-dimethylacetamide produced **3a** in 69% yield (Scheme I). Reaction of equimolar amounts of benzimidazole, EMMN, and malononitrile in ethanol also produces **3a** (92% yield); this is the preferred method.

Scheme I



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[1] A. A. Santilli, W. F. Bruce, and T. S. Osdene, *J. Med. Chem.*, **7**, 68 (1964).

[2] D. J. Rabiger and M. M. Joullié, *J. Org. Chem.*, **29**, 476 (1964).