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2-METHYLISOXAZOLIN-5-ONES—II

RING-OPENING BY BASES

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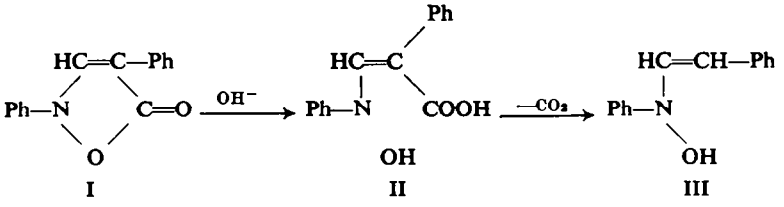
Abstract—N-methylisoxazolin-5-ones without substituents in position 3 undergo alkaline ring-opening in the cold, yielding N-methyl monoamides of C-substituted malonic acid, whereas 3-substituted compounds react only by heating with alkali yielding corresponding ketones, or with hydrazines yielding substituted pyrazolin-5-ones.

RUHEMANN[1] and Claisen[2] found that 2-methyl-4-carbethoxyisoxazolin-5-one decomposes to methylamine, CO_2 and malonic acid by boiling in alkaline solution. Recently, Ulrich *et al.*[3] observed that ring-opening with 5% aqueous sodium hydroxide occurs even at room temperature, the reaction being exothermic, yielding malonic acid N-methylamide ethyl ester.

The ring-opening of 2,4-diphenylisoxazolin-5-one (I) with alcoholic sodium hydroxide was interpreted by Rupe [4]according to the scheme:

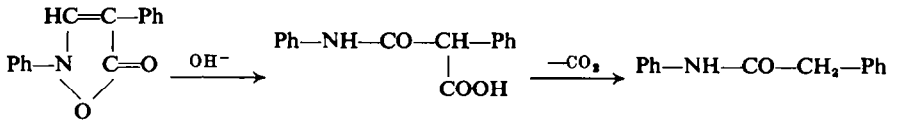


The fact that compound I could not be obtained from II was assumed due to isomerization of II to the *trans* form and on this basis, the hydrolysis of 2-methyl-4-phenyl-isoxazolin-5-one was interpreted.[5]

No doubt was expressed by Rupe regarding the structure of III since he also obtained[6] this substance by condensing phenylbenzoylacetaldehyde (VI) with phenylhydroxylamine and subsequent debenzoylation of the product (VII).

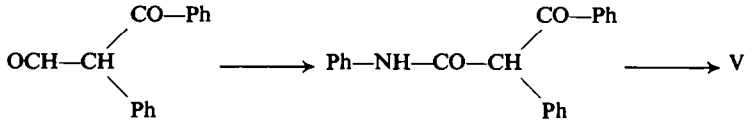
Actually, the products derived from 2,4-diphenylisoxazolin-5-one by alkaline hydrolysis and by subsequent decarboxylation are phenylmalonic acid monoanilide (IV) and phenylacetanilide (V).[7] Therefore, the ring-opening follows the route

[1] S. Ruhemann, *Ber. Dtsch. Chem. Ges.* **30**, 1086 (1897).
[2] L. Claisen, *Ber. Dtsch. Chem. Ges.* **30**, 1481 (1897).
[3] H. Ulrich, J. N. Tilley and A. A. Sayigh, *J. Org. Chem.* **27**, 2160 (1962).
[4] H. Rupe and J. Grünholz, *Helv. Chim. Acta* **6**, 102 (1923).
[5] L. Fabbrini, G. Renzi and G. Speroni, *La Chim. e l'Ind.* **43**, 1195 (1961).
[6] H. Rupe and R. Wittwer, *Helv. Chim. Acta* **5**, 205 (1922).
[7] F. F. Blicke and H. Zinnes, *J. Amer. Chem. Soc.* **77**, 4849 (1955); B. C. Redmon, U.S. 2782231, *Chem. Abstr.* **51**, 10571c (1957).



I IV V

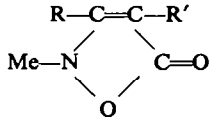
indicated by Ulrich *et al.* for the 2-methyl-4-carbethoxyisoxazolin-5-one. Moreover, the intermediate benzoylated compound obtained by Rupe should be VII instead of the N-(β-benzoyl) phenylvinyl-N-phenylhydroxylamine reported. In fact phenyl-benzoyl acetanilide (VII)[8] may be debenzoylated to phenylacetanilide (V) under the



VI VII

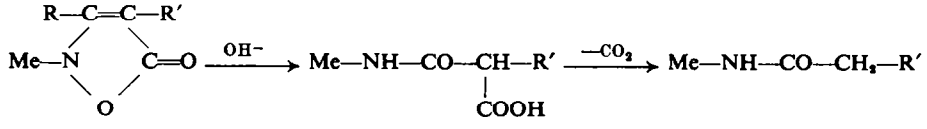
conditions indicated by Rupe. This reaction was not investigated further and perhaps some rearrangement occurs.

During the investigation on N-methylisoxazolin-5-ones (VIII),* it was found that



VIII

compounds having no substituents in position 3 (VIII: R = H; R′ = Me, Ph, *p*-Br–C_6H_4) can be easily hydrolysed by alkaline solutions even at room temperature. This process leads to the N-methylmonoamides of corresponding malonic acids (IX: R′ = Me, Ph, *p*-Br–C_6H_4). As this behaviour is analogous to that of 2,4-



VIII, R = H IX X

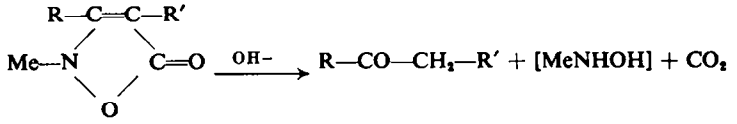
diphenylisoxazolin-5-one, alkaline ring-opening of N-substituted isoxazolin-5-ones with a free 3 position always follows this path.

3-Substituted N-methylisoxazolin-5-ones are unaffected by bases at room temperature. According to Ulrich *et al.*,[3] no methylamine is evolved on treating 2,3-dimethyl-isoxazolin-5-one-4-carboxylic acid with boiling 50% sodium hydroxide solution. This is considered by these Authors as proof of the suggested mechanism for ring-opening of isoxazolin-5-ones unsubstituted in position 3, i.e. attack at carbon 3, subsequent migration of H from 3 to 4, and eventual electronic rearrangement of the so formed ion. It was observed that this acid decomposes with evolution of both

* See preceding paper for its preparation.

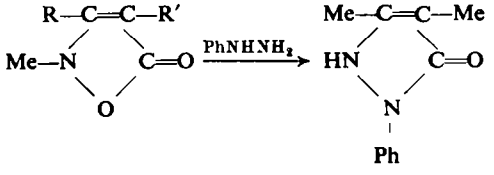
[8] H. Wieland and S. Bloch, *Ber. Dtsch. Chem. Ges.* **37**, 2528 (1904); L. Wolff, *Liebigs Ann.* **394**, 46 (1912); W. Wislicenus, H. Eichert and M. Marquardt, *Ibid.* **436**, 93 (1924).

methylamine and ammonia on boiling in even dilute sodium hydroxide solution. Except 2-methyl-3-phenyl-4-bromoisoxazolin-5-one, all 3-substituted compounds (VIII: R = Me, Ph; R′ = H, Me, Ph), on prolonged heating with dilute sodium hydroxide undergo ring-opening with formation of ketones XI:



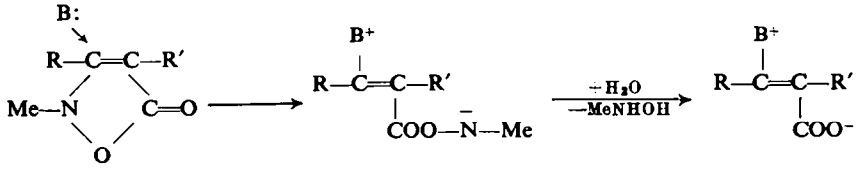
VIII, R ≠ H XI

This behaviour was observed by Kohler and Blatt[9] in 2-methyl-3,4-diphenylisoxazolin-5-one. Such a difference in reactivity between 3-substituted and 3-unsubstituted compounds towards alkaline solutions is analogous to the behaviour of isoxazole derivatives.[10] In the ring-opening of 2-methylisoxazolin-5-ones the base attacks carbon 3 even if this position is occupied. The reaction of 2,3,4-trimethylisoxazolin-5-one (VIII: R = R′ = Me) with phenylhydrazine gives 1-phenyl-3,4-dimethylpyrazolin-5-one (XII) by attack on position 3 by the more basic nitrogen of the phenylhydrazine, while an analogous attack on carbon 5 should yield the isomer 1-phenyl-4,5-dimethylpyrazolin-3-one:



VIII, R = R′ = Me XII

The ring-opening of 2,3-disubstituted isoxazolin-5-ones could therefore be interpreted as a nucleophilic substitution on the carbon 3, with subsequent detachment of a CH_3NHOH molecule:



By acidification, cyclization to pyrazolin-5-one occurs when B = ph—NH—NH_2, whereas decarboxylation and ketone formation occurs when B = OH^-.

The bromo derivative VIII (R = Ph, R′ = Br) exhibits exceptional behaviour if heated in alkaline solution, yielding 3-phenylisoxazolin-5-one, thus showing that in this case a demethylation at the N atom occurs. An investigation of this reaction is in progress.

[9] E. P. Kohler and A. H. Blatt, *J. Amer. Chem. Soc.* **50**, 504 (1928).

[10] A. Quilico, in A. Weissberger: *The Chemistry of Heterocyclic Compounds* Vol. 17; p. 44. Wiley, N.Y. (1962)

EXPERIMENTAL

Action of bases on 2-substituted 3-unsubstituted isoxazolin-5-ones

Anilide of phenyl-malonic acid (IV) *and phenyl-acetanilide* (V). Decomposition of I, according to Rupe,[4] gave a small amount of IV, which was mainly decarboxylated to V. Both compounds were identified by comparison of IR spectra with those of authentic samples.[7]

Methylmalonic acid N-*methylmonoamide* (IX: R′ = Me). 15% NaOHaq (16·3 ml) was added dropwise to VIII (R = H, R′ = Me; 6·9 g; molar ratio 1:1), the temp being at 20–30°. The solution was concentrated in a dessiccator, the residual oil treated with anhydrous MeOH and acidified with gaseous HCl. After removing NaCl, the concentrated solution yielded 2·75 g (ca. 35%) of a product, m.p. 110–120°. It was recrystallized several times from AcOH and then washed with ether; m.p. 118–122° (dec.). It is very soluble in water and alcohol, almost insoluble in ligroine and acetone. (Found: C, 45·79; H, 6·86; N, 10·80; calc. for $C_5H_9NO_3$ (131·1): C, 45·80; H, 6·92; N, 10·68%.)

Decarboxylation of IX: R′ = Me. Compound IX(R′ = Me) was heated at 135–140° in an oil bath, until evolution of CO_2 ceased. The IR spectrum of the resulting liquid was identical with that of the N-methylpropionamide.[11]

Phenylmalonic acid N-*methylmonoamide* (IX: R′ = Ph). A suspension of VIII(R = H, R′ = Ph; 1 g) in NaOHaq (20 ml) was refluxed for 1½ hr. From the resulting solution, acidified in the cold with conc. HCl, phenylmalonic acid N-methylmonoamide[13] separated, yield 78%; m.p. 116–117° (dec) after crystallization from water. Decarboxylation of this acid yielded the methylamide of phenylacetic acid (X: R′ = Ph).[13]

N-methylamide ethylester of phenylmalonic acid. Compound IX(R′ = Ph) was esterified by boiling in alcohol with conc. HCl (1:1 mixture). The solvent was then removed, the residue treated with water and cooled, yield 68%; m.p. 86–88° from ligroine. (Found: C, 65·15; H, 6·69; N, 6·64; calc. for $C_{12}H_{15}NO_3$ (221·3): C, 65·14; H, 6·83; N, 6·33%.)

p-*Bromophenylmalonic acid* N-*methylmonoamide* (IX: R′ = *p*-Br–C_6H_4). A suspension of 2-methyl-4-(*p*-bromophenyl)isoxazolin-5-one (3 g) in 1N NaOH (60 ml) was refluxed for ½ hr. The resulting solution, after standing, was acidified with dil. H_2SO_4 to give a precipitate of *p*-bromophenylmalonic acid N-methylmonoamide; yield 62% of crude product, m.p. 129–130° (dec) after crystallization from water, not heated above 70°. (Found: mol. wt. 264 (Rast); C, 44·10; H, 3·68; Br, 30·00; N, 5·45; calc. for $C_{10}H_{10}BrNO_3$ (272·1): C, 44·13; H, 3·70; Br, 29·37; N, 5·15%.)

p-*Bromophenylacetic acid* N-*methylamide* (X: R′ = *p*-Br–C_6H_4).

(1) *By decarboxylation.* The N-methylmonoamide of *p*-bromophenylmalonic acid was heated at 135° until gaseous evolution was no more observed. The resulting liquid solidified on cooling; m.p. 124–126° after crystallization from water; yield 74% of crude product.

(2) *By synthesis.* *p*-Bromophenylacetic acid was chlorinated with $SOCl_2$[13] and the chloride (b.p. 118–120°/3 torr) treated with methylamine in anhydrous ether. The white precipitate was treated with water to remove the methylamine hydrochloride and recrystallized from water: m.p. 122–124°. Its IR spectrum is identical to that of a sample obtained according to Ref. 1. (Found: C, 47·13; H, 4·45; Br, 35·18; N, 6·40; calc. for $C_9H_{10}BrNO$ (228·1): C, 47·39; H, 4·42; Br, 35·05; N, 6·14%.)

Action of bases on 2,3-disubstituted isoxazolin-5-ones

Alkaline hydrolysis. A suspension of VIII (R = Me, R′ = $COOC_2H_5$) in 15% NaOHaq was refluxed up to dissolution with evolution of basic vapours. The mixture was then fractionally distilled: acetone and EtOH were identified in the distillate. By passing the gaseous reaction products through HClaq and then concentrating under vacuum, a mixture of NH_4Cl and methylamine hydrochloride was obtained, which were separated by crystallization from anhydrous alcohol.

Compound VIII (R = Me, R′ = H; 0·1 moles) was heated (2 hr) with 15% NaOHaq (0·25 moles). By fractional distillation acetone was collected (yield 50%).

Alkaline hydrolysis of VIII (R = R′ = Me) yielded methylethyl ketone.

[11] G. R. Leader, J. F. Gormley, *J. Amer.Chem. Soc.* **73**, 5731 (1951).
[13] H. J. Taverne, *Rec. Trav. Chim.* **16**, 34 (1897).
[13] L. R. Cerecedo and C. P. Sherwin, *J. Biol. Chem.* **62**, 222 (1924).

A mixture of VIII (R = Ph, R′ = H; 1 g) and 20% NaOHaq (10 ml) was refluxed for several hr, until gaseous evolution ceased, and acetophenone separated.

By a similar procedure, methylbenzylketone, propiophenone and desoxybenzoin were obtained from VIII (R = Me, R′ = Ph), VIII(R = Ph, R′ = Me) and VIII (R = R′ = Ph). respectively.

Reaction of 2,3,4-*trimethylisoxazolin-5-one* (VIII: R = R′ = Me) *with phenylhydrazine.* A mixture of VIII (R = R′ = Me; 1 g) and phenylhydrazine (1·6 g) was heated at 140° for ca. 2½ hr (until gaseous evolution ceased). The reaction mixture was then acidified with 1:1 AcOH and extracted with ether. After drying, the ether was evaporated: the residue yielded XII as long needles: m.p. 117–124° (0·15 g). After several washings with ether, m.p. 126–130°, and mixed with an authentic sample.[14]

Reaction of 2,4-*dimethyl*-3-*phenylisoxazolin*-5-*one* (VIII: R = Ph, R′ = Me) *with hydrazine.* A mixture of VIII (R = Ph, R′ = Me; 0·78 g) with 85% hydrazine hydrate solution (8 ml) was refluxed for ½ hr . The water and the excess of hydrazine were evaporated until a resinous residue was obtained, which solidified by standing for one day over H_2SO_4 in a dessiccator, yield 0·74 g (crude); m.p. 213–216° (from alcohol). The compound was identified as 3-phenyl-4-methylpyrazolin-5-one.[15]

Action of aqueous NaOH *on* 2-*methyl*-3-*phenyl*-4-*bromoisoxazolin*-5-*one* (VIII: R = Ph, R′ = Br). The bromo derivative was kept 2 hr in boiling 5% NaOHaq (molar ratio 1:5). The resulting solution gave on acidification a crude solid, m.p. 135–142° (dec); yield 27% ca.; (from EtOH, m.p. 147–149° with dec). By comparison of the IR spectrum it was found to be 3-phenyl-isoxazolin-5-one. Little amounts of acetophenone and benzonitrile were isolated by steam distillation.

[14] L. Knorr and A. Blank, *Ber. Dtsch. Chem. Ges.* **17**, 2050 (1884).
[15] K. v. Auwers and H. Mauss, *J. Prakt. Chem.* [2] **110**, 206 (1925).