Heterocyclic Rearrangements. Part X.[1] A Generalised Monocyclic Rearrangement

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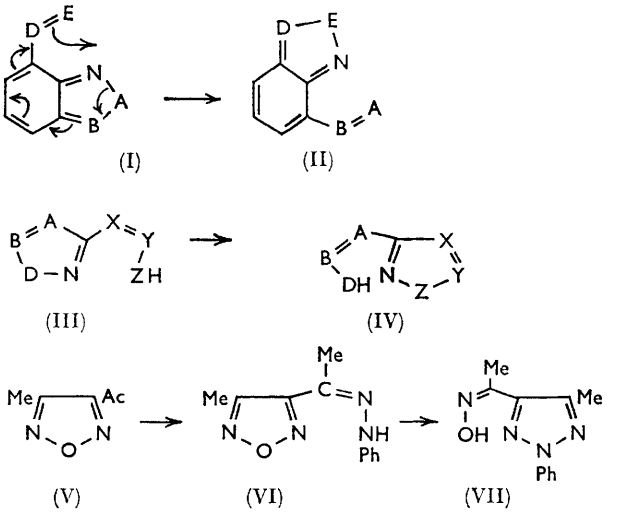
A new general class of rearrangements of substituted azoles (III) ⟶ (IV) has been recognised, scattered examples from the literature are collated, and further examples described.

RECENT Papers [2,3] in this Series have been concerned with the novel generalised rearrangement (I) ⟶ (II) which has led to new syntheses of benzotriazoles, benzofurazans, anthranils, and indazoles. We have now examined some analogous monocyclic rearrangements of type (III) ⟶ (IV). Possible combinations for ABD and XYZ (and the associated ring system) are: CCN (pyrazole); CNC (imidazole); NCC (imidazole); CCO (isoxazole); CNN (1,2,3-triazole); NNC (1,2,4-triazole); NCN (1,2,4-triazole); CNO (1,2,5-oxadiazole); NCO (1,2,4-oxadiazole); NNN (tetrazole). Hence there are at least 10^2 possible variations of this rearrangement (many more if sulphur is included). Of these 100 possibilities we have found eight described in the literature; as their mutual relationship has apparently not been previously recognised, we list them in the Table.

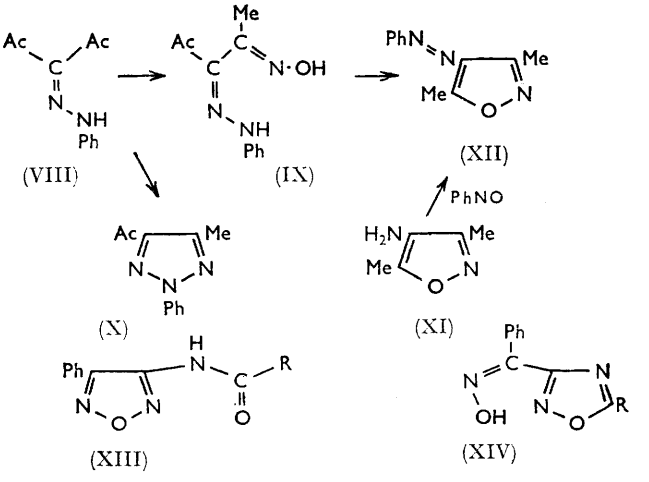
Examples of monocyclic rearrangements, (III) ⟶ (IV)

ABD	Starting ring	XYZ	Finishing ring	Ref.
CNO	1,2,5-Oxadiazole	CNO	1,2,5-Oxadiazole	4
CNO	1,2,5-Oxadiazole	CCO	Isoxazole	5
NCO	1,2,4-Oxadiazole	CNN	1,2,3-Triazole	6
NCO	1,2,4-Oxadiazole	CNO	1,2,5-Oxadiazole	7, 8
CCO	Isoxazole	CNN	1,2,3-Triazole	9, 10
CCO	Isoxazole	CNO	1,2,5-Oxadiazole	11—13
CCO	Isoxazole	NCN	1,2,4-Triazole	14
CCO	Isoxazole	NNN	Tetrazole	15

Rearrangement of a 1,2,5-*Oxadiazole.* — 3-Acetyl-4-methylfurazan (V) has been reported [16] to yield a phenylhydrazone (VI), m. p. 117°, but in our hands the initial phenylhydrazone, prepared as described,[16] had m. p. 106°; the structure was confirmed by the presence of the ν_{NH} at 3265 cm.$^{-1}$ (solid phase). However, by heating with copper (or in one instance on recrystallisation) this initial hydrazone was transformed into an isomer, m. p. 117°, which absorbed at 3325 cm.$^{-1}$. This product was a geometrical isomer of the phenylhydrazone (VI) (cf. the isomers of the phenylhydrazone of 3-benzoyl-4-methylfurazan [17]) rather than the triazole oxime (VII); however, both isomers (which had slightly different n.m.r. spectra in $CHCl_3$) were converted into (VII) by heating with sodio-dimethyl sulphoxide in dimethyl sulphoxide.



The first approach to an independent synthesis of the triazole oxime (VII) was the cyclisation of the oxime (IX) of 3-phenylhydrazonopentane-2,4-dione (VIII), but



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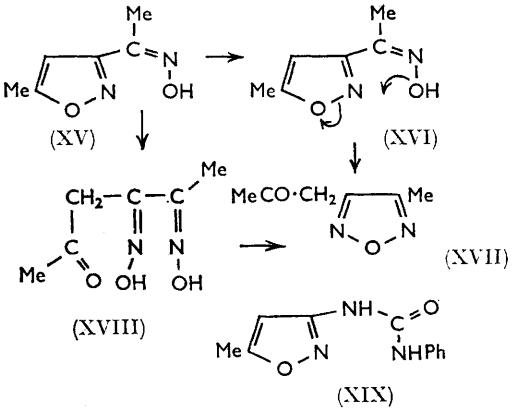
this yielded the azo-isoxazole (XII) (cf. ref. 18), the structure of which was proved by synthesis from the amino-isoxazole (XI). However, the hydrazone (VIII) was converted by ammonia–cupric acetate (cf. ref. 19) into the acetyl triazole (X), the oxime of which was identical with the product (VII) of the rearrangement mentioned above.

3-Acetamido- and 3-benzamido-4-phenylfurazan (XIII) were not rearranged to the 1,2,4-oxadiazole derivatives (XIV) on treatment with alkali, or on heating. The reverse of this rearrangement had previously been reported.[7,8]



Rearrangements of Isoxazoles.—3-Acetyl-5-methylisoxazole *p*-nitrophenylhydrazone smoothly rearranged on heating to yield 4-acetonyl-5-methyl-2-*p*-nitrophenyl-1,2,3-triazole (cf. refs. 9, 10).

It has been postulated [11–13] that previous examples of the rearrangement of oximino-isoxazoles to furazan ketones [cf. (XV) ⟶ (XVII)] proceed *via* open-chain poly-oxime intermediates [cf. (XVIII)]. This mechanism is supported for the aqueous base-catalysed reaction by the fact that (XV) does not rearrange on refluxing in potassium hydroxide–ethanol, potassium t-butoxide–t-butyl alcohol, or potassium hydroxide–dimethyl sulphoxide. However, the oxime (XV) smoothly rearranges to the ketone (XVII) on heating with copper powder, and this presumably is a reaction of type (XVI).

Attempts to induce rearrangement of the isoxazolylurea (XIX) and of 3-acetamido-5-methylisoxazole failed.

EXPERIMENTAL

3-Acetyl-4-methylfurazan (V).— Acetylmethylglyoxime (pentane-2,3,4-trione 2,3-dioxime) was prepared from isonitrosoacetylacetone and hydroxyammonium chloride essentially as described by Ponzio,[16] except that the reaction was complete in 3 hr. The product had m. p. 120° (decomp.) [lit., 141° (decomp.),[16] 128° (decomp.) [20]] (Found: C, 41·45; H, 6·0; N, 19·5. Calc. for $C_5H_8N_2O_3$: C, 41·7; H, 5·6; N, 19·4%). Acetylmethylglyoxime (14·4 g.) was heated to reflux with acetic anhydride (25 ml.) and sodium acetate (12·3 g.), then cooled, poured into water, and steam-distilled. Ether-extraction of the distillate, followed by distillation of the dried extracts, gave the furazan (6·3 g., 50%) as a colourless oil, b. p. 62°/16 mm. (lit.,[21] 76°/18 mm.).

3-Acetyl-4-methylfurazan Phenylhydrazone (VI).— Prepared by the published [16] method, this *derivative* (isomer A) had m. p. 106° (from ethanol) (Found: C, 60·9; H, 5·9; N, 25·6. $C_{11}N_{12}N_4O$ requires C, 61·1; H, 5·6; N, 25·9%). The product was converted into isomer B, m. p. 117° (lit.,[16] 117°), on melting with copper powder for 15 min., and on heating alone at 145° for 1 hr. (Found: C, 60·7; H, 5·8; N, 25·8%). Isomer A showed methyl absorptions at τ 7·49 and 7·6, isomer B at τ 7·36 and 7·69, in $CHCl_3$.

4-Acetyl-5-methyl-2-phenyl-1,2,3-triazole Oxime (VII).— The phenylhydrazone (VI) (either isomer) (1·0 g.) was heated in dimethyl sulphoxide (5 ml.) containing one equivalent of its sodio-derivative [22] for 2½ hr. at 140°. Cooling, dilution with water, neutralisation with dilute HCl, extraction with ether, and removal of the solvent, left the *triazole oxime* (0·6 g., 60%) which separated as fine white needles, m. p. 152—155° from ethanol–water (2 : 1) (Found: C, 61·4; H, 5·9; N, 25·7%).

3,5-Dimethyl-4-phenylazoisoxazole (XII).—(*a*) Hydroxyammonium chloride (1·35 g.) in water (3 ml.) was added to 3-phenylhydrazonopentane-2,4-dione (VIII) [23] (4·0 g.) in ethanol (10 ml.), and the mixture was heated to *ca.* 100° for 30 min. The hydrazone mono-oxime (IX) (2·2 g.) which separated on cooling was refluxed for 30 min. in acetic anhydride (15 ml.) containing sodium acetate (0·7 g.). Cooling and pouring into water liberated the *phenylazoisoxazole* (1·1 g., 55%) as a yellow oil, which after distillation (100°/0·1 mm.) partly solidified and crystallised from ethanol–water (2 : 1) as yellow plates, m. p. 42° (Found: N, 20·8. $C_{11}H_{11}N_3O$ requires N, 20·9%).

(*b*) Nitrosobenzene [24] (2·14 g.) and 4-amino-3,5-dimethylisoxazole [25] (2·24 g.) were dissolved in acetic acid (10 ml.) and the mixture was allowed to stand 15 hr. Addition of water precipitated an oil which was extracted with chloroform. The extracts were successively washed with 0·5N-hydrochloric acid and N-sodium hydroxde and dried. After removal of solvent, the residue (2·0 g., 50%) crystallised from aqueous ethanol and proved identical with the product from preparation (*a*).

3-Acetyl-4-methyl-2-phenyl-1,2,3-triazole (X).—Cupric acetate (10 g.) was added to 3-phenylhydrazonopentane-2,4-dione (VIII) [23] (10·2 g.) in ethanol (100 ml.). The mixture was saturated with ammonia, transferred to a sealed tube, and heated for 10 hr. at 120°. After cooling, cuprous oxide was removed by filtration, and hydrogen sulphide was passed through the filtrate to precipitate the dissolved copper salts. After heating to boiling with charcoal, the liquid was again filtered and concentrated *in vacuo* at 35—40°. The *acetyl triazole* (8·5 g., 84%), crystallised from aqueous ethanol as white needles, m. p. 54° (Found: C, 65·85; H, 5·7; N, 20·8. $C_{11}H_{11}N_3O$ requires C, 65·7; H, 5·5; N, 20·9%); $\nu_{C=O}$ 1690 cm.$^{-1}$ (Nujol mull). The oxime, prepared from the above ketone in aqueous ethanol in nearly quantitative yield, was identical (i.r., mixed m. p.) with the product of rearrangement of the oxadiazole phenylhydrazone.

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3-*Amino*-4-*phenylfurazan*.—This was prepared from isonitrosoacetophenone by the method of Angelico and Cusmano,[26] and had m. p. 97—99° (lit.,[26] 98°). It was converted into its acetyl derivative (XIII; R = Me) m. p. 186° (lit.,[7] 181—182°) and benzoyl derivative (XIII; R = Ph), m. p. 148° (lit.,[8] 148°) by standard procedures.

Attempted thermal rearrangement (XIII) ⟶ (XIV) of the two acyl derivatives (220°, 6 hr.) gave only the starting materials on work-up. Refluxing in toluene for 1 hr. in the presence of one equivalent of sodamide also gave only the unchanged acyl derivatives on acidification. Refluxing in aqueous alkali (2N, 15 min.), or in t-butanol with one equivalent of potassium hydroxide, merely caused hydrolysis to the amino-furazan.

3-*Acetonyl*-4-*methyl*-2-(p-*nitrophenyl*)-1,2,3-*triazole*.— 3-Acetyl-5-methylisoxazole *p*-nitrophenylhydrazone,[27] m. p. 222° (lit.,[27] 222—223°) (1·3 g.) was heated to its m. p. for 15 min. with copper powder (0·5 g.). The mixture was extracted with ethanol, giving the *acetonyl triazole* (1·0 g., 77%) as pale yellow needles, m. p. 144·5°, from ethanol (Found: C, 55·3; H, 4·8; N, 21·3. $C_{12}H_{12}N_4O_3$ requires C, 55·3; H, 4·65; N, 21·5%). Comparable yields were obtained when the *p*-nitrophenylhydrazone was heated alone at 230—240° for 3 hr. The phenylhydrazone formed brownish needles, m. p. 149—150°, from ethanol (Found: C, 61·4; H, 5·15; N, 24·2. $C_{18}H_{18}N_6O_2$ requires C, 61·7; H, 5·1; N, 24·0%).

3-*Acetyl*-5-*methylisoxazole Oxime* (XV).—This was prepared from the ketone,[27] and had m. p. 117° (lit.,[13,28] 117°).

3-*Acetonyl*-4-*methylfurazan* (XVII).—On fusion with copper powder (0·5 g.) for 15 min., the oxime (XV) (1·4 g.) isomerised to the acetonyl furazan (b. p. 68°/0·1 mm.) in 78% yield; $\nu_{C=O}$ 1720 cm.$^{-1}$. The semicarbazone of (XVII) had m. p. 189—190° (lit.,[13] 190°).

The oxime (XV) was recovered in over 90% yield after (*a*) heating to 130° for 2 hr., (*b*) refluxing in 5% ethanolic potassium hydroxide for 2 hr., (*c*) refluxing in 1M-potassium in t-butanol for 2 hr., and (*d*) heating with 1M-potassium hydroxide in dimethyl sulphoxide at 140° for 14 hr.

N-(5-*Methylisoxazol*-3-*yl*)-N′-*phenylurea* (XIX).—5-Methylisoxazole-3-carboxylic acid [27] was converted into the acid chloride, b. p. 60—62°/20 mm. (lit.,[29] 82—84°/14 mm.) and thence, by action of sodium azide in aqueous acetone, into the acid azide, m. p. 112° (decomp.) [lit.,[30] 112° (decomp.)]. The azide (0·7 g.) was refluxed for 10 min. in dry toluene, then aniline (2 ml.) was added and the solution was refluxed for a further hour. The *urea* (XIX) (0·85 g., 85%) separated on cooling, and crystallised from ethanol as needles, m. p. 186° (Found: C, 61·0; H, 5·1; N, 19·4. $C_{11}H_{11}N_3O_2$ requires C, 60·8; H, 5·1; N, 19·3%).

The urea (XIX) was unchanged after (*a*) heating at 195° for ½ hr., and (*b*) refluxing with 2N-potassium hydroxide in methanol for ½ hr. Fusion of the urea (1·0 g.) with copper powder (0·5 g.), followed by extraction with ethanol, gave *NN′*-diphenylurea (0·35 g., 66%), m. p. and mixed m. p. 235°, as the only product isolated.

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