Transformations of Imidazo- and Pyrimido-pyrimidines into Pyrazoles

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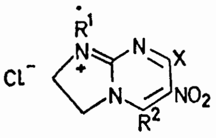
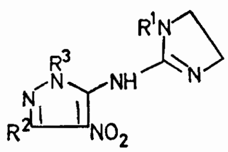
Summary 7-Substituted amino-2,3-dihydro-5-methyl-6-nitroimidazo[1,2-*a*]pyrimidines and similar pyrimido-pyrimidines are very readily cleaved by hydrazine and substituted hydrazines to give a wide range of highly substituted pyrazoles; isoxazoles similarly result from cleavage by hydroxylamine.

HIGH yields of substituted pyrazole derivatives have resulted from reactions of hydrazine or substituted hydrazines with the imidazopyrimidines (**1**)[1,2] and similar pyrimidopyrimidines (**3**).[2] Thus, treatment of hydrochlorides of the imidazopyrimidines (**1**; R^1=H; R^2=Me; X = NMe_2, pyrrolidinyl, piperidyl, or morpholino) with cold hydrazine hydrate gave the pyrazole (**2**; R^1 = R^3 = H; R^2 = Me) in 60—90% yield. Analogous reactions were undergone by other imidazopyrimidines (**1**; R^1 = R^2 = Me, X = NMe_2 and **1**; R^1 = R^2 = H, X = NMe_2), while the dihydropyrimidopyrimidine (**3**) similarly yielded a pyrazole (**4**).



(1)



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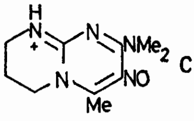

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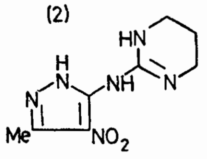

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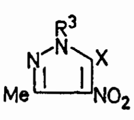

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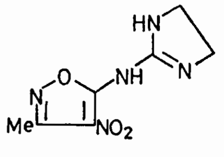
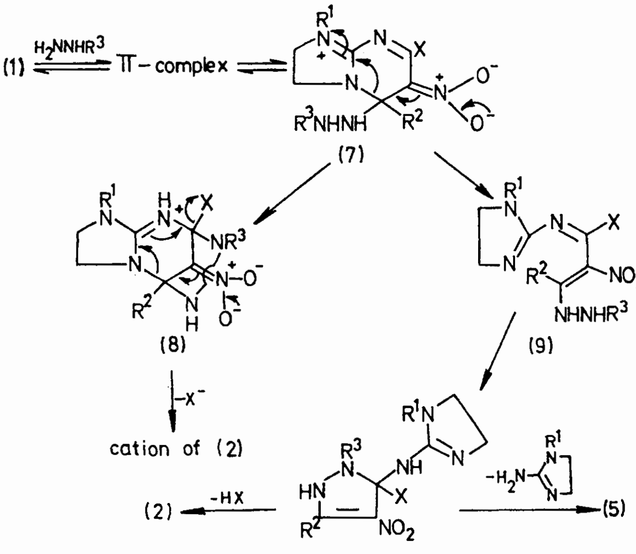


(6)

The transformations took a different course when the 7-dialkylamino-imidazopyrimidines (**1**; R^1 = H, R^2 = Me, X = NMe_2, pyrrolidinyl, piperidyl, or morpholino) were treated with hydrazine hydrate in boiling propan-2-ol for a short time, since 3-substituted aminopyrazoles (**5**; R^3 = H; X = NMe_2, pyrrolidinyl, piperidyl, or morpholino) were then isolated, in *ca.* 50% yield. 7-Alkylamino-compounds (**1**; R^1 = H; R^2 = Me; X = NHMe, NHEt, $NHCH_2Ph$, or $NHCH_2CH_2OH$) also yielded similar pyrazoles (**5**; R^3 = H, X = NHMe, NHEt, $NHCH_2Ph$, or $NHCH_2CH_2OH$) but only after a much longer reaction time.



SCHEME

The dimethylamino-compound (**1**; R^1 = H; R^2 = Me; X = NMe_2) and methyl- or phenyl-hydrazine gave *N*-substituted pyrazoles (**2**; R^1 = H; R^2 = Me; R^3 = Me or Ph) while the dimethylamino-compound and hydroxylamine gave the isoxazole (**6**). The latter was assigned the 5-substituted amino-structure (**6**) rather than the isomeric

3-substituted amino-structure because it was acidic like other 5-aminoisoxazoles.[3a] 3-Aminoisoxazoles show aromatic amine characteristics.[3b] The *N*-methyl- and *N*-phenyl-pyrazoles were assigned the 1-substituted structures (**2**) on the basis of u.v. spectra and ionisation constants.

The orientations of the products (**2**; $R^1 = H$; $R^2 = Me$; $R^3 = Me$ or Ph) and the isoxazole (**6**) have an important bearing on the mechanism of the reactions. The orientation of the products plus the isolation, under milder conditions, of examples of π-complexes and substituted hydrazine adducts suggest that the reactions proceed by interaction of the imidazopyrimidine and reagent to give a π-complex and then attack at position 5 of the imidazopyrimidine by the amino-group of the reagent. The resulting adduct (**7**) undergoes cyclisation either before or after cleavage of the 4,5-bond (Scheme). Loss of the 7-substituent or the 2-aminoimidazole unit completes the reaction. The way in which the nature of the products depends on reaction temperature suggests that imidazoylaminopyrazoles (**2**) may be formed *via* the more ordered intermediate (**8**) and the alkyl- or dialkylamino-pyrazoles (**5**) *via* the less ordered intermediate (**9**).

Ring cleavages of simple pyrimidines[4] and fused pyrimidines[5] by hydrazine are fairly common but the present reactions are remarkable for the ease with which they occur, the range of products which can be obtained, and the way the nature of the products may be changed by small changes in reaction conditions.

Satisfactory analyses and ^{1}H n.m.r. spectra have been obtained for all compounds mentioned.

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[3] (a) A. Quilico in 'The Chemistry of Heterocyclic Compounds,' ed. A. Weissberger, vol. 17, Interscience, 1962, pp. 135 and 139; (b), p. 73.

[4] See for example; F. Lingens and H. Schneider-Bernlöhr, *Angew. Chem. Internat. Edn.*, 1964, **3**, 379; *Annalen*, 1965, **686**, 134; F. Baumbach, H. G. Henning, and G. Hilgetag, *Z. Chem.*, 1964, **4**, 67; H. C. van der Plas and H. Jongejan, *Tetrahedron Letters*, 1967, 4385; M. E. C. Biffin and D. J. Brown, *J. Chem. Soc.* (*C*), 1968, 2159.

[5] See for example; N. J. Leonard and W. V. Ruyle, *J. Org. Chem.*, 1948, **13**, 903; E. C. Taylor, *J. Amer. Chem. Soc.*, 1952, **74**, 1651; J. Clark and G. Neath, *J. Chem. Soc.* (*C*), 1966, 1112; F. Baumbach, H. G. Henning, and G. Hilgetag, *Z. Chem.*, 1962, **12**, 369.