SYNTHESES OF HETEROCYCLES BASED ON N-SUBSTITUTED AMIDINES AND YLIDENEMALONONITRILES (REVIEW)

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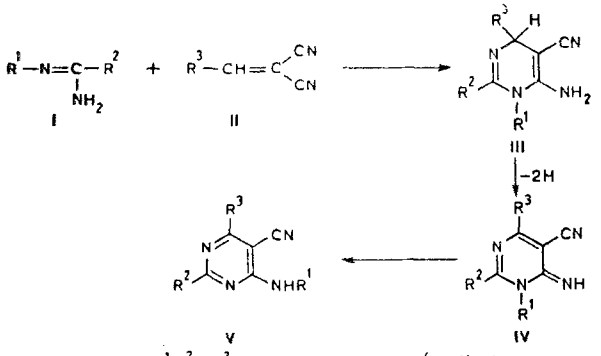
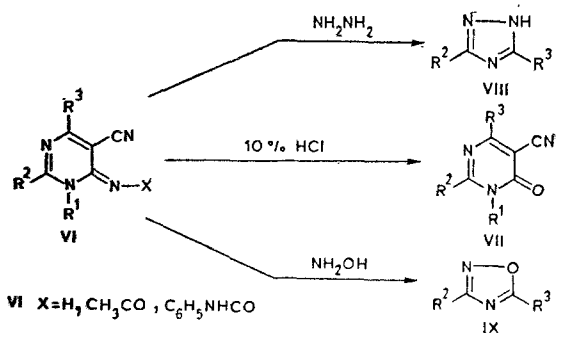
This review includes the results of research on the reaction of N-substituted amidines with ylidenemalononitriles conducted in the last several years.

In 1976 we established that N-monosubstituted amidines I readily react with ylidenemalononitriles II to give, through the intermediately formed 3,6-dihydro-4-amino-5-cyanopyrimidines III, the corresponding 4-imino-5-cyano-3,4-dihydropyrimidines IV, which subsequently, as a result of the Dimroth rearrangement, undergo almost quantitative conversion to the previously unknown 2,6-disubstituted 4-arylamino-5-cyanopyrimidines V [1-6]:



Here and subsequently, R^1,R^2 u R^3-aryl, heteroaryl; R^4- alkyl

It was found that the preparation of at least three other types of heterocyclic compounds in addition to pyrimidines of the V type is possible on the basis of 4-imino-5-cyano-3,4-dihydropyrimidines IV. If the imino group in IV is acetylated or anilinoformylated, the corresponding iminopyrimidines VI are converted by heating with 10% hydrochloric acid to the corresponding 2,3,6-trisubstituted 5-cyano-pyrimidin-4(3H)-ones (VII) in high yields (up to 90%) [7]:



When IV or VI is refluxed briefly with hydrazine hydrate in alcohol (at 20°C the reaction takes several hours), R^1 is split out in the form of an amine, and 2,5-disubstituted 1,2,4-triazoles (VIII) are obtained in up to 95% yields [1, 8]. If hydroxylamine is used, 2,5-disubstituted 1,2,4-oxadiazoles (IX) are obtained [7, 9]. In this case the reaction proceeds regiospecifically — the substituent in the 2 position of the pyrimidine ring (IV and VI) occupies the 3 position in 1,2,4-oxadiazoles IX, while the substituent in the 6 position in the pyrimidines occupies the 5 position in the oxadiazole ring of IX.

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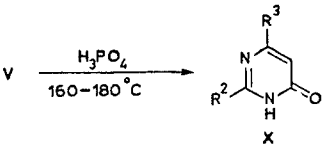
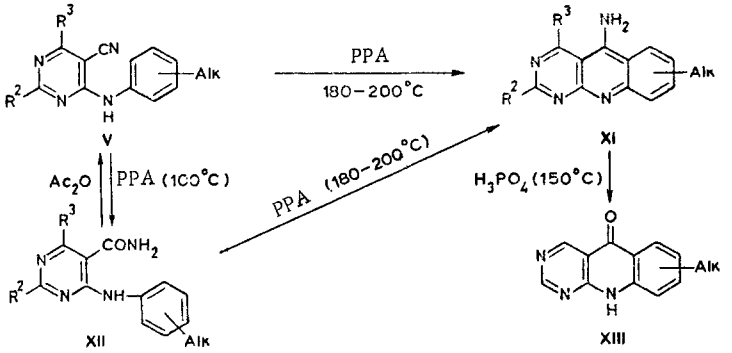
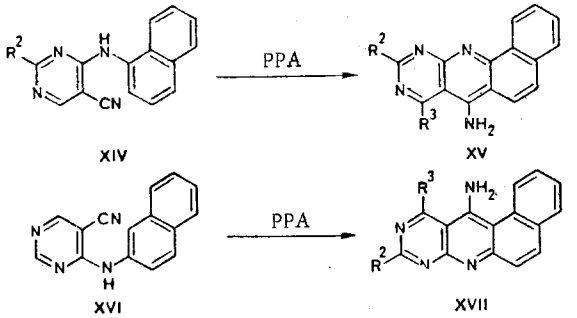
When 2,6-disubstituted pyrimidines V are heated with concentrated phosphoric acid, they give, after elimination of a cyano group and an arylamine, the corresponding previously known [10] 2,6-disubstituted pyrimidin-4(3H)-ones (X):



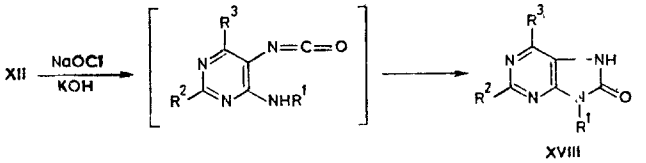
When polyphosphoric acid (PPA) is used, pyrimidines V are converted in high yields (up to 80%) to the corresponding 2,4-disubstituted 5-aminopyrimido[4,5-b]quinolines (XI):



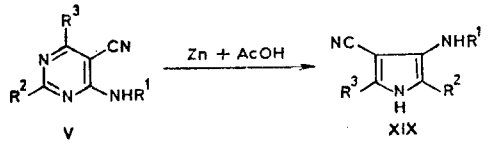
Some characteristics of these interrelationships are given in the scheme presented above [11, 12]. 8,10-Disubstituted 7-amino-9,11,12-triazabenz[a]anthracenes (XV) are obtained under similar conditions from 4-(1-naphthylamino)-5-cyanopyrimidines (XIV) by heating with PPA [13-15]. If 4-(2-naphthylamino)-5-cyanopyrimidines (XVI) are subjected to the reaction, 7,8,10-triazabenz[a]anthracene derivatives (XVII) are obtained [16].



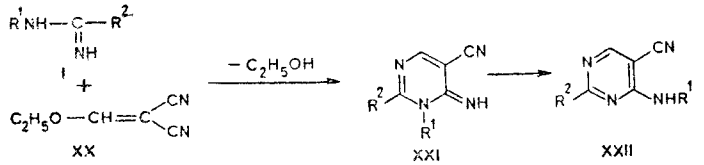
Our studies showed that amides XII can be converted through a Hofmann rearrangement, as modified by Dornow [17-19], to the corresponding heretofore unknown 2,6,9-triarylpurin-8(7H)-ones (XVIII) (in up to 90% yields), which are of definite biological interest [19].



When pyrimidines V are heated with zinc powder [20, 21] in acetic acid, they are converted to 2,5-disubstituted 3-arylamino-4-cyanopyrroles (XIX) (in up to 80% yields) via a scheme involving splitting out of ammonia (ammonium acetate) with ring contraction [22-24], i.e., the cyano group remains unaffected.

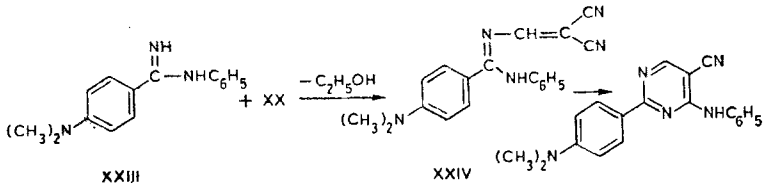


If ethoxymethylenemalononitrile (XX) rather than ylidenemalononitriles II are subjected to the reaction with N-monosubstituted amidines I, the reaction proceeds as follows [25]:



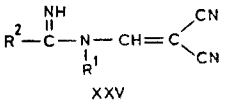
XX XXI XXII

The initial product is a 2,3-disubstituted 4-amino-5-cyano-3,4-dihydropyrimidine (XXI), which subsequently undergoes rearrangement in a basic medium to give a 2-substituted 4-arylamino-5-cyanopyrimidine (XXII). In the case of N-phenyl-4-dimethylaminobenzamidine (XXIII) the reaction with ethoxymethylenemalononitrile gave an isomer of XXI, which was identified as N'-(2,2-dicyanovinyl)-N-phenyl-4-dimethylaminobenzamidine (XXIV). Like XXI, the latter on refluxing in quinoline gives the corresponding pyrimidine XXII:



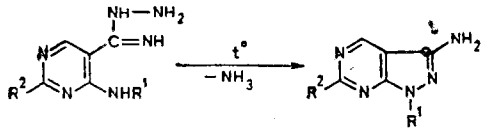
XXIII XXIV

Our experiments subsequently showed that stable amidines XXV, which are not subsequently converted to pyrimidines, are obtained in the reaction of amidines I with ethoxymethylenemalononitrile in acetic acid [25].



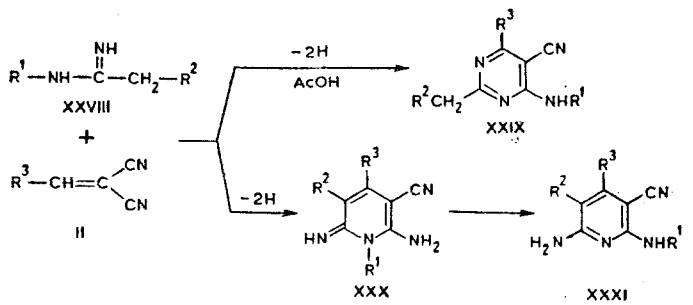
XXV

Evidently for steric reasons, the cyano group in pyrimidines V proved to be inert in our attempts to convert it to a hydrazidino group by reaction with hydrazine. However, the cyano group in pyrimidines XXII is not deactivated by the presence of a substituent in the 6 position and reacts quite readily with hydrazine. From pyrimidines XXII we obtained the corresponding hydrazidines of 2-substituted 4-arylaminopyrimidine-5-carboxylic acids (XXVI), which upon heating give (with splitting out of ammonia) 1,6-disubstituted 3-aminopyrazolo[3,4-d]pyrimidines (XXVII) [25]:



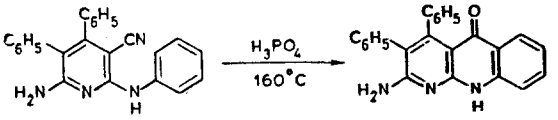
XXVI XXVII

The reactions of N-substituted arylacetamidines occupy a special place among the reactions of amidines with ylidenemalononitriles. Starting from N-monoaryl-substituted arylacetamidines of the XXVIII type we have shown [26] that when they are heated in a neutral or basic medium (in an acidic medium the reaction gives 2-arylmethylated pyrimidines XXIX), they react with ylidenemalononitriles II to give, respectively, 1,4,5-triaryl-substituted 2-amino-3-cyano-1,6-dihydro-6-iminopyridines (XXX), which could be subsequently converted by Dimroth rearrangement by heating with sodium n-propoxide in 1-propanol to 6-amino-2-arylamino-3-cyano-4,5-diarylpyridines (XXXI) [27]:



XXVIII II XXIX XXX XXXI

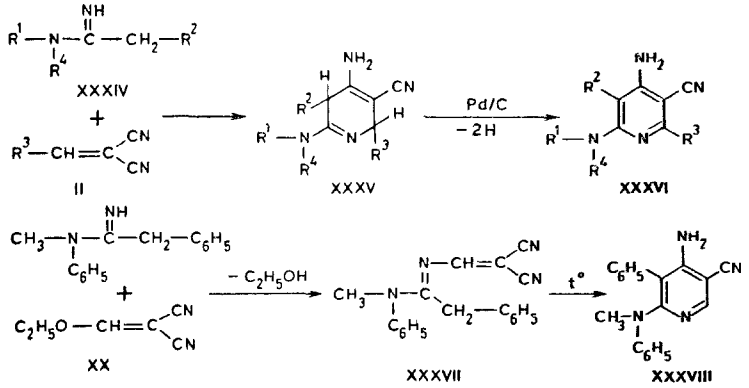
The migration of 1-aryl residue R^1 to the nitrogen atom in the 2 position (and not in the 6 position) was proved by our previously established [26] conversion of 6-amino-2-anilino-3-cyano-4,5-diphenylpyridine (XXXII) to 2-amino-3,4-diphenylbenzo[b][1,8]naphthyridin-5(10H)-one (XXXIII) by heating with concentrated phosphoric acid.



XXXII XXXIII

The behavior of N-aryl-N-alkylarylacetamidines XXXIV differs substantially from that of N-monoaryl-substituted arylacetamidines XXVIII in their reaction with ylidenemalononitriles II. The reaction is carried out in tetrahydrofuran (THF) and usually does not require any heating. In this case the addition of amidine XXXIV to the double bond of ylidenemalononitrile II begins with the NH group, and ring closure is subsequently realized by the addition of the active methylene group to CN (by the Thorpe reaction) to give the corresponding 6-(N-aryl-N-alkylamino)-3-cyano-2,5-diaryl-2,5-dihydropyridine (XXXV). The reaction makes it possible to readily synthesize (in up to 80% yields) 2,5-dihydropyridines [27], which, in contrast to the widely investigated 1,4-dihydropyridines, were almost unknown.

The structure of pyrimidines XXXV was proved by comparison of the IR and UV spectra of their dehydrogenation products (XXXVI) with the spectra of model compounds XXXVIII, which were obtained from amidines of the XXXIV type and ethoxymethylenemalononitrile (XX) through intermediate XXXVII:

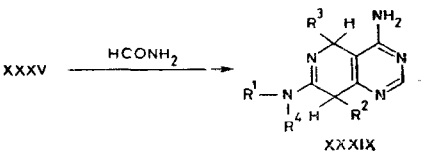


XXXIV II XXXV XXXVI

XX XXXVII XXXVIII

Polysubstituted 2,5-dihydropyridines of the XXXV type were obtained [27] in two forms, viz., cis-XXXV and trans-XXXV, which are readily separated by ordinary fractional crystallization. Both forms are stable during under ordinary conditions. When the cis isomers are heated briefly in a mixture of ethanol and acetic acid, they are converted to the trans isomers in high yields. In the investigated examples the ratios of the cis and trans isomers ranged from 1.5:1 to 1:1 (according to NMR spectroscopy) [27].

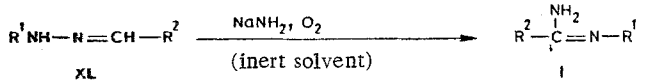
In analogy with many cyano enamines [28, 29], when cis and trans isomers XXXV are heated with formamide, they give pyrimidine derivatives, viz., 4-amino-7-(N-aryl-N-alkylamino)-5,8-diaryl-5,8-dihydropyrido[4,3-d]pyrimidines (XXXIX) in our case. In the investigated example ($R^1 = R^3 = C_6H_5$, $R^2 = p\text{-}ClC_6H_4$, $R^4 = C_2H_5$), of the two stereoisomers we obtained the same substance of the XXXIX type, which, according to the NMR data, is the trans form.



XXXIX

Some of the synthesized compounds, viz., V [1-3], XI [12], XV [13, 14], and XVIII [19], display antitumorigenic activity in mice (Crocker sarcoma-180). Compounds of the XXVII type are of definite biological interest as antimetabolites of purine bases [30-32], while some 6-(4-chlorophenyl)pyrimidines of the V type have bactericidal activity [33].

The syntheses of some groups of heterocyclic compounds described here are based chiefly on our discovery [34–36] of the rearrangement of aldehyde arylhydrazones (XL) to N-substituted amidines (I) [37]:



XL I

Several studies by Professor A. N. Kost and co-workers [40–42] have been devoted to the mechanism of this rearrangement [38, 39]. The present review is dedicated to the fond memory of Professor Kost.

LITERATURE CITED

1. S. K. Robev, Dokl. Bolg. Akad. Nauk, 30, 719 (1977).
2. S. K. Robev, Bulgarian Inventor's Certificate No. 34538; Byull. Izobret. NRB, No. 7, 19 (1977).
3. S. K. Robev, Bulgarian Inventor's Certificate No. 32754; Byull. Izobret. NRB, No. 7, 19 (1977).
4. S. K. Robev, Dokl. Bolg. Akad. Nauk, 32, 1235 (1979).
5. S. K. Robev, Dokl. Bolg. Akad. Nauk, 32, 309 (1979).
6. S. K. Robev, Dokl. Bolg. Akad. Nauk, 33, 791 (1980).
7. S. K. Robev, Dokl. Bolg. Akad. Nauk, 30, 1031 (1977).
8. S. K. Robev, Bulgarian Inventor's Certificate No. 34537; Byull. Izobret. NRB, No. 7, 19 (1977).
9. S. K. Robev, Bulgarian Inventor's Certificate No. 35550; Byull. Izobret. NRB, No. 4, 11 (1978).
10. A. Pinner Berichfe, 25, 1892 (1892).
11. S. K. Robev, Dokl. Bolg. Akad. Nauk, 31, 551 (1978).
12. S. K. Robev, Bulgarian Inventor's Certificate No. 38331; Byull. Izobret. NRB, No. 1, 18 (1979).
13. S. K. Robev, Bulgarian Inventor's Certificate No. 41695; Byull. Izobret. NRB, No. 12, 15 (1979).
14. S. K. Robev, Bulgarian Inventor's Certificate No. 41696; Byull. Izobret. NRB, No. 12, 15 (1979).
15. S. K. Robev, Dokl. Bolg. Akad. Nauk, 32, 903 (1979).
16. S. K. Robev, Dokl. Bolg. Akad. Nauk, 33, 929 (1980).
17. A. Dornow and E. Hinz, Chem. Ber., 91, 1835 (1958).
18. S. K. Robev, Dokl. Bolg. Akad. Nauk, 31, 1131 (1978).
19. S. K. Robev, Bulgarian Inventor's Certificate No. 39986; Byull. Izobret. NRB, No. 5, 12 (1979).
20. T. Thompson, Chem. Commun., No. 9, 532 (1968).
21. J. Longridge and T. Thompson, J. Chem. Soc., C, No. 12, 1658 (1970).
22. S. K. Robev, Dokl. Bolg. Akad. Nauk, 31, 197 (1978).
23. S. K. Robev, Bulgarian Inventor's Certificate No. 37462; Byull. Izobret. NRB, No. 1, 16 (1979).
24. S. K. Robev, Tetrahedron Lett., No. 13, 1163 (1978).
25. S. K. Robev, Dokl. Bolg. Akad. Nauk, 33, 635 (1980).
26. S. K. Robev, Heterocycles, 14, 461 (1980).
27. S. K. Robev, Tetrahedron Lett., No. 21, 2097 (1980).
28. D. M. Mulvey, S. G. Cottis, and H. Tieckelmann, J. Org. Chem., 29, 2903 (1964).
29. L. Fuentes, A. Lorente, and J. Soto, Ann. Quim., 73, 1359 (1977).
30. V. J. Ram, H. N. Panday, and L. Mishra, Arch. Pharm., 312, 586 (1979).
31. G. H. Hitchinds, Cancer Res., 23, 1218 (1963).
32. G. Elion, S. Callahan, H. Bieker, R. Rundles, and G. Hitchings, Biochem. Pharmacol., 12, 85 (1963).
33. M. Mincheva, Dokl. Bolg. Akad. Nauk, 33, 925 (1980).
34. S. K. Robev, Dokl. Akad. Nauk SSSR, 101, 277 (1955).
35. S. K. Robev, Chem. Ber., 91, 244 (1958).
36. S. K. Robev, Dokl. Bolg. Akad. Nauk, 21, 1181 (1968).
37. K. V. Vatsuro and G. L. Mishchenko, Name Reactions in Organic Chemistry [in Russian], Khimiya, Moscow (1976), p. 358.
38. Yu. P. Kitaev and B. I. Byzykin, Usp. Khim., 41, 1024 (1972).

39. M. F. Marshalkin and L. N. Yakhontov, Usp. Khim., 42, 1605 (1973).
40. I. I. Grandberg, Yu. N. Naumov, and A. N. Kost, Zh. Org. Khim., 1, 805 (1965).
41. I. I. Grandberg, Yu. N. Naumov, and A. N. Kost, Zh. Vses. Khim. Obshchestva, 9, 707 (1964).
42. I. I. Grandberg, Yu. N. Naumov, and A. N. Kost, Dokl. Bolg. Akad. Nauk, 17, 1025 (1964).

α,β-UNSATURATED KETONES IN SUBSTITUTIVE ADDITION WITH 2-ALKYLFURANS AND SOME TRANSFORMATIONS OF THE REACTION PRODUCTS

Sh. T. Akhmedov, N. S. Sadykhov, R. Sh. Akhmedova, and N. S. Zefirov

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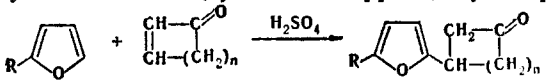
The substitutive addition of cyclic α,β-unsaturated ketones with 2-alkylfurans proceeds in the presence of catalytic amounts of sulfuric acid to give the corresponding furyl ketones. The latter were converted by Kishner reduction to cycloalkylfurans and were also converted to ethyleneketals, which form adducts with maleic anhydride.

The reaction of furan and its derivatives with unsaturated compounds usually proceeds either via the scheme of the diene synthesis [1-3] or via a scheme involving substitutive addition [1, 4, 5]. The direction of the reaction is determined chiefly by the nature of the olefin component [1]. Thus, for example, maleic acid derivatives react chiefly via the scheme of the diene synthesis, whereas α,β-unsaturated carbonyl compounds react chiefly via a substitutive addition scheme. The latter reaction has been investigated extensively in the case of aliphatic [1, 4] and aliphatic-aromatic [5] α,β-unsaturated ketones and is used for the synthesis of carbonyl derivatives of furan. The latter are used as intermediates in various syntheses (for example, see the synthesis of jasmone and its analogs [6], syntheses based on menthofuran [1], etc.).

However, the literature does not contain systematic data on the substitutive addition of cyclic α,β-unsaturated ketones with furans. Moreover, the data available in the literature indicate the possibility of the occurrence of this reaction via the scheme of the diene synthesis. Thus, in particular, the photochemical reactions of furan with cyclohexenone [7], cycloheptenone [8], and cis- and trans-cyclooctadienones [9] proceed as [4 + 2] cycloaddition. Bicyclo[3.3.1]non-1-en-3-one reacts with furan via the same scheme [10]. A systematic study of the reactions of monosubstituted furans with cycloalkenones under the conditions of substitutive addition is therefore of undoubted interest.

We have found that α,β-unsaturated cyclic ketones, viz., cyclopentenone and cyclohexenone, react with 2-alkylfurans in the presence of catalytic amounts of sulfuric acid via a substitutive addition scheme to give ketones I-VII. The optimum conditions were worked out for all of the reactions, and the products were obtained in 60-75% yields. The characteristics of the ketones obtained are given in Table 1. Absorption bands of a C=O group (1720 cm^{-1}) and of a furan ring (1615 and 1570 cm^{-1}) are present in the IR spectrum of ketone I. Signals at 1.72-2 (m, 6H, methylene groups), 2.1 (s, 3H, CH_3), 3.3 (t, 1H, proton attached to a tertiary carbon atom), and 5.8 ppm (2H, unsplit AB system of protons



I-VII

I R=CH_3, n=2; II R=CH_3, n=3; III R=i-C_3H_7, n=2; IV R=i-C_3H_7, n=3; V R=n-C_3H_7, n=3; VI R=n-C_4H_9, n=3; VII R=n-C_5H_{11}, n=3

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