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CYCLODESAMINATION OF N-AZOLYLFORMAMIDINES. SYNTHESIS OF POLYAZAHETEROCYCLES WITH ISOQUINOLINE AND INDOLO[2,3-C]-PYRIDINE STRUCTURAL FRAGMENTS

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Treatment of 4-aryl-5-aminopyrazoles and 2-aryl-3-amino-maleimides with tris(morpholino)methane gives N-azolyl formamidines which are converted upon heating in trifluoroacetic acid to polycondensed heterocycles with isoquinoline and indolo[2,3-c]pyridine structural fragments.

Isoquinoline and indolo[2,3-c]pyridine (β-carboline) heterocyclic systems occur as structural components in many alkaloids. It is probably this fact which has stimulated interest in the class of compounds amongst which are found, and successfully used, many medicinal substances. Work on structure determination, synthesis of natural alkaloids and their synthetic analogs, and the search for novel, biologically active compounds based on isoquinoline and indolo[2,3-c]pyridine has had a significant effect on the progress of the chemistry of heterocyclic compounds and of organic chemistry as a whole.

It is remarkable that the overwhelming majority of isoquinolines, indolo[2,3-c]pyridines, and related polycondensed heterocycles have been prepared through the use of the Pomeranz-Fritsch [1, 2], Bischler-Napieralski [3] and Pictet-Spengler [4] reactions which are long established and thoroughly studied. Novel synthetic routes, formulated during the last 10-20 years do not have preparative potential with the exception of the recyclization reaction of benzo[c]- and indolo[2,3-c]-pyrilium salts [5, 6].

We have previously reported the cyclization of 4-aryl-5-aminopyrazoles and 3-aryl-4-amino-2,5(2H, 5H)-dioxopyrroles to 5-alkylpyrazolo[5,4-c]- [7] and 5-alkyl-1,3(1H, 3H)-dioxopyrrolo[2,3-c]isoquinolines [8] using the system carboxyanhydride-perchloric acid. By investigating other possible syntheses of polycondensed heterocycles with isoquinoline and indolo[2,3-c]pyridines structural components, we have discovered a novel, convenient method for preparing azoloisoquinolines and azoloindolopyridines. We recently reported the first examples of its use in a short communication [9].

It was found that heating N-(4-arylpyrazol-5-yl)formamidines II (obtained from the corresponding 4-aryl-5-aminopyrazoles I and tris(morpholino)methane) in trifluoroacetic acid leads to formation of pyrazolo[5,4-c]isoquinolines IIIa-c and indolo-[2,3-c: 4,5-e]pyrazolopyridine IV in 70-75% yields.

The IR spectra of formamidines IIa-d and heterocycles IIIa-c, IV do not have clearly marked, diagnostic signals. The structure of the compounds is clearly illustrated by their PMR spectra. The formamidines IIa-d show a characteristic formamidine C–H proton signal in the range 7.50-7.65 ppm and a group of signals for the protons of the morpholino fragment. A well resolved system of signals for the 3,4-dimethoxyphenyl substituent is seen in the spectra of IIa-c. The PMR spectra of the pyrazolo-[5,4-c]isoquinolines IIIa-c and the indolo[2,3-c: 4,5-e]-pyrazolopyridine IV do not contain the proton signals for the formamidine or morpholino substituents. A splitting of the protons signals 6-H and 9-H ($J = 1.8$ Hz) is observed in the spectrum of IIIa. Hence the one proton singlet signal at 6.94 ppm can be assigned to 5-H in the aromatic pyridine ring. In the spectra of IIIb,c an analogous proton interaction is not recorded but we propose that the singlets at 6.96 and 6.80 ppm in the

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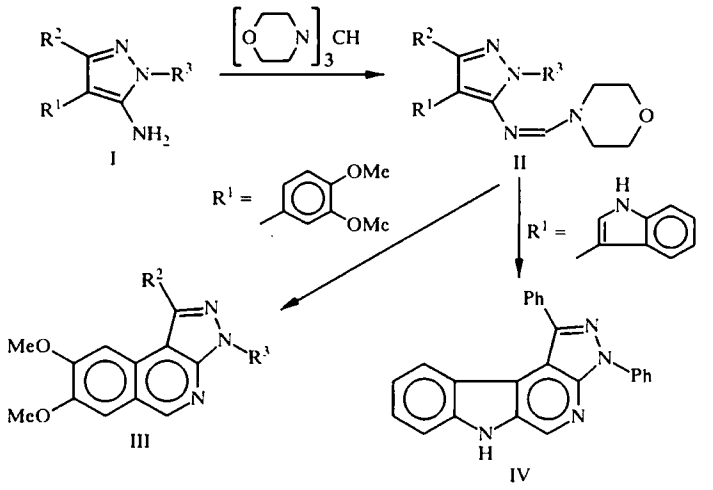
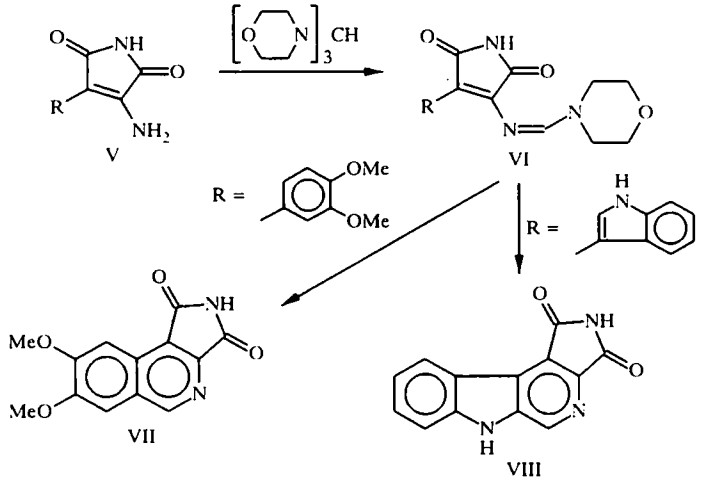


I—III a R^2 = Me, R^3 = Ph; b R^2 = R^3 = Ph; c R^2 = Ph, R^3 = CH_2Ph, d R^2 = Ph, R^3 = Ph

spectra of the pyrazoloisoquinolines IIIb and IIIc can also be assigned to the 5-H proton signal. The spectrum of IV, characterized by a greater degree of coupling, has the same identifying features as the spectra of IIIa-c.

Formamidines VIa, b, obtained from 2-amino-3-R-2,5-(2H,5H)-dioxopyrroles Va,b and tris(morpholino)methane, also undergo reaction to pyrrolo[3,4-c]isoquinoline VII and indolo-[2,3-c: 3,4-e]pyrrolopiperidine VIII in the conditions reported above.

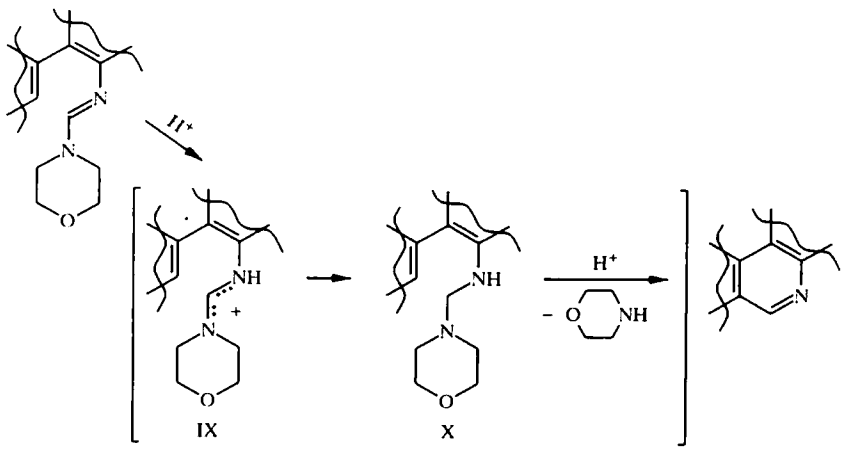


In the PMR spectra of VI-VIII, the aromatic proton signals are shifted to low field of those in the pyrazolo annelated heterocycles IIIa-c, IV and the signals for the protons on the formamidine carbon are found at 8.59 and 8.43 ppm in VIa and VIb respectively. This shift to the low field part of the spectrum for the aromatic protons and the formamidine proton is due, in our opinion, to the acceptor properties of the dioxopyrrole ring.

The method we have discovered for formation of the central aromatic pyridine ring in polyazaheterocycles through formation of the C–C bond can equally well be considered as a cyclodesamination reaction with a more specific formation of a carbon–heteroatom bond. Bearing in mind that amidines are principally protonated on the nitrogen atoms at the double bond [10], we propose a scheme of formation of the annelated pyridine ring as follows: 1) protonation of the amidine giving the cation IX, 2) formation of a 1,2-dihydropyridine intermediate X, and 3) aromatization of intermediate X via fission of a molecule of amine.

TABLE 1. Physicochemical Parameters for the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
IIa	$C_{23}H_{26}N_4O_3$	67,5 68,0	6,3 6,4	14,0 13,8	142...144	84
IIb	$C_{28}H_{28}N_4O_3$	71,6 71,8	5,9 6,0	12,1 12,0	160...162	87
IIc	$C_{29}H_{30}N_4O_3$	71,9 72,2	6,1 6,3	11,9 11,6	154...156	81
IId	$C_{28}H_{25}N_5O$	74,7 75,1	5,3 5,6	15,8 15,6	249...251	77
IIIa	$C_{19}H_{17}N_3O_2$	71,2 71,5	5,2 5,4	13,3 13,2	167...169	73
IIIb	$C_{22}H_{19}N_3O_2$	73,5 73,9	5,1 5,4	12,0 11,8	79...81	75
IIIc	$C_{23}H_{21}N_3O_2$	74,1 74,4	5,4 5,7	11,7 11,3	120...122	75
IV	$C_{24}H_{16}N_4$	79,8 80,0	4,4 4,5	15,7 15,5	226...228	78
VIa	$C_{17}H_{19}N_3O_5$	59,0 59,1	5,4 5,5	12,3 12,2	198...200	71
VIb	$C_{17}H_{16}N_4O_3$	62,8 63,0	4,8 5,0	17,4 17,3	235...237	79
VII	$C_{13}H_{10}N_2O_4$	60,1 60,5	3,7 3,9	11,1 10,8	251...253	68
VIII	$C_{13}H_7N_3O_2$	65,5 65,8	2,7 3,0	17,9 17,7	>350 (decomp.)	65



The proposed reaction scheme includes features both of the Pictet-Spengler reaction (the appearance of the carbocation IX) and of the Bischler-Napieralski reaction (the structure of the final cyclization product).

EXPERIMENTAL

PMR spectra were recorded on Tesla BS-467 (60 MHz for ^1H nuclei) and Gemini spectrometers (200 MHz for ^1H nuclei) in DMSO-D_6 solvent unless indicated otherwise. The internal standard was TMS. IR spectra were taken on a UR-20 instrument as suspensions in Vaseline oil. The synthesis of 5-aminopyrazoles Ia,b has been reported by us before [7] and the aminomaleimides in [8].

1-Benzyl-3-phenyl-4-(3,4-dimethoxyphenyl)-5-aminopyrazole (Ic). A mixture of α-benzoylhomoveratronitrile (7.5 g, 26.7 mmole), benzylhydrazine (3.6 ml, 29.4 mmole), and glacial acetic acid (3.6 ml) in 2-propanol (50 ml) was refluxed for 6 h. The reaction mixture was treated with water (40 ml) and left overnight. The precipitate was filtered, washed with water, and crystallized from 2-propanol to give the aminopyrazole Ic (8.53 g, 83%) with mp 167°C. IR spectrum: 3380, 3320 cm^{-1} (NH_2). PMR spectrum: 3.6 (3H, s, OCH_3); 3.67 (3H, s, OCH_3); 5.02 (2H, s, CH_2); 6.81 (10H, m, H_{arom}, NH_2); 7.32

TABLE 2. Spectroscopic Parameters for II-IV, VI-VIII

Compound	PMR spectrum, δ, ppm, J, Hz
IIa	2,15 (3H, s, CH_3); 3,12 (4H, m, H morpholine); 3,51 (4H, m, H morpholine); 3,67 (3H, s, OCH_3); 3,74 (3H, s, OCH_3); 6,65 (1H, dd, J_1 = 7,53, J_2 = 2); 6,77 (1H, d, J_2 = 2); 6,93 (1H, d, J_1 = 8); 7,24 (1H, t, J = 7,5); 7,43 (2H, t, J = 7,5); 7,54 (1H, s, C—H amidine); 7,76 (2H, d, J = 7,5)
IIb	3,12 (4H, m, H morpholine); 3,51 (4H, m, H morpholine); 3,62 (3H, s, OCH_3); 3,75 (3H, s, OCH_3); 6,74 (1H, dd, J_1 = 8,3, J_2 = 1,5); 6,81 (1H, d, J_2 = 1,5); 6,93 (1H, d, J_1 = 8,3); 7,25...7,32 (6H, m, H_{arom}.); 7,44 (2H, d, J = 8); 7,61 (1H, s, C—H amidine); 7,82 (2H, d, J = 8)
IIc	3,18...3,25 (4H, m, H morpholine); 3,50...3,57 (4H, m, H morpholine); 3,60 (3H, s, OCH_3); 3,73 (3H, s, OCH_3); 5,21 (2H, s, CH_2); 6,67 (1H, dd, J_1 = 8, J_2 = 2); 6,76 (1H, d, J_2 = 1,5); 6,89 (1H, d, J_1 = 8); 7,19...7,38 (10H, m, H_{arom}.); 7,54 (1H, s, C—H amidine)
IId	3,03...3,50 (8H, m, H morpholine); 6,97...8,17 s 16H, m, H_{arom}, C—H amidine); 11,3 (1H, s, N—H pyrrole nucleus)
IIIa	2,31 (3H, s, CH_3); 3,92 (6H, s, $2OCH_3$); 6,91 (1H, d, J = 1,8); 6,93 (1H, d, J = 1,8); 6,95 (1H, s, H_{arom}); 7,34 (1H, t, J = 7,5); 7,49 (2H, t, J = 7,5); 7,62 (2H, d, J = 7,5)
IIIb	3,76 (3H, s, OCH_3); 4,00 (3H, s, OCH_3); 6,96 (1H, s, H_{arom}); 7,17 (2H, s, H_{arom}.); 7,43...7,59 (6H, m, H_{arom}); 7,68...7,80 (4H, m, H_{arom})
IIIc	3,71 (3H, s, OCH_3); 3,88 (3H, s, OCH_3); 5,33 (2H, s, CH_2); 6,80 (1H, s, H_{arom}); 7,19...7,36 (12H, m, H_{arom}.)
IV	6,20...6,32 (4H, m, H_{arom}.); 6,97, 7,15 (1H, d, J = 8,2); 7,38 (1H, t, J = 8); 7,49 (1H, t, J = 8); 7,57 (1H, t, H_{arom}); 7,61...7,83 (4H, m, H_{arom}); 8,42 (2H, d, J = 8,6); 12,59 (1H, s, N—H pyrrole nucleus)
VIa	3,49...3,57 (4H, m, H morpholine); 3,60...3,67 (4H, m, H morpholine); 3,74 (3H, s, OCH_3); 3,77 (3H, s, OCH_3); 6,97 (1H, d, J = 8,6); 7,85 (1H, dd, J_1 = 8,6, J_2 = 1,8); 7,97 (1H, d, J_2 = 1,8); 8,59 (1H, s, (N)—H amidine); 10,53 (1H, s, N—H imide ring
VIb	3,03...3,44 (8H, m, H morpholine); 7,07...7,79 (5H, m, H_{arom}.); 8,43 (1H, s, N—H morpholine); 10,35 (1H, s, N—H imide ring); 11,30 (1H, s, NH pyrrole nucleus)
VII	3,77 (3H, s, OCH_3); 3,80 (3H, s, OCH_3); 7,02 (1H, s, H_{arom}); 7,13 (1H, s, H_{arom}.); 7,61 (1H, s, H_{arom}); 11,08 (1H, s, N—H imide ring)
VIII	7,63...8,01 (3H, m, H_{arom}); 8,47 (1H, s, H_{arom}); 9,10 (1H, d, J = 8); 9,53 (1H, s, N—H); 9,90 (1H, s, N—H)

(1H, t, J = 7.2 Hz); 7.50 (2H, t, J = 7.2 Hz); 7.64 ppm (2H, d, J = 7.2 Hz). Found, %: C 70.4, H 6.5, N 13.1. $C_{19}H_{21}N_3O_2$. Calculated, %: C 70.5, H 6.5, N 13.0.

1,3-Diphenyl-4-(indol-3-yl)-5-aminopyrazole (Id) was synthesized similarly to Ic from 1-cyano-1-(indol-3-yl)-acetophenone and phenylhydrazine to give Id (68%) with mp 215-217°C. IR spectrum: 3400, 3350 (NH_2), 3180 cm^{-1} (NH). PMR spectrum: 7.39 (17H, m, H_{arom}, NH_2); 9.45 ppm (1H, s, NH). Found, % C 77.7; H 5.2; N 15.9. $C_{23}H_{18}N_4$. Calculated, %: C 78.8; H 5.2; N 16.0.

Reaction of Aminopyrazoles Ia-d and Aminomaleimides Va,b with Tris(morpholino)methane. The amino-heterocycle (10 mmole) and tris(morpholino)methane (15 mmole) was heated in dry DMF (20 ml) for 4-6 h at 120-130°C, The cooled reaction mixture was poured into water, and the precipitated N-heterylformamidine was filtered, washed with water, and crystallized from ethanol or 2-propanol.

Cyclization of N-heterylformamidines IIa-d, VIa,b. The N-hetarylformamidine (5 mmole) was refluxed in trifluoroacetic acid for 8-12 h. The reaction mixture was evaporated *in vacuo*, and water (50 ml) and aqueous ammonia solution were added to pH 12. The product was filtered, washed with water, and dried.

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