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SYNTHESIS OF PYRROLO[1,2-a]QUINOXALINE DERIVATIVES BY THE REACTION OF 2-HYDROXY-1,5-DIKETONES WITH o-PHENYLENEDIAMINE

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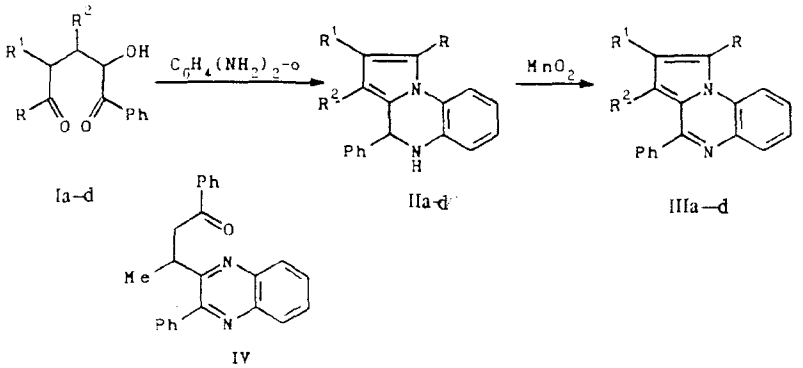
The reaction of 2-hydroxy-1,5-diketones with o-phenylenediamine leads to the formation of 4,5-dihydropyrrolo[1,2-a]quinoxaline derivatives, which are dehydrogenated by the action of MnO_2 to give the corresponding pyrrolo[1,2-a]quinoxaline derivatives.

Methods have been reported for the synthesis of derivatives of pyrrolo[1,2-a]quinoxaline from derivatives of pyrrole [1, 2] and quinoxaline [3, 4] and also by the reaction of o-phenylenediamine with several polyfunctional compounds, in particular, with α-ketoglutarate esters [5]. We have found a simple method for the synthesis of pyrrolo[1,2-a]quinoxalines by the reaction of relatively available 2-hydroxy-1,5-diketones (Ia)-(d) [6, 7] with o-phenylenediamine upon heating in 2:1 ethanol—acetic acid at reflux.



I — III a R = R_2 = Ph, b R = Ph, R^1 = H, R^2 = Me; c R = Ph, R^1 = R^2 = H; d R + R^1 = $(CH_2)_4$, R_2 = Ph

The initial products of the reaction are derivatives of 4,5-dihydropyrrolo[1,2-a]quinoxaline (IIa)-(IId) (see Table 1).

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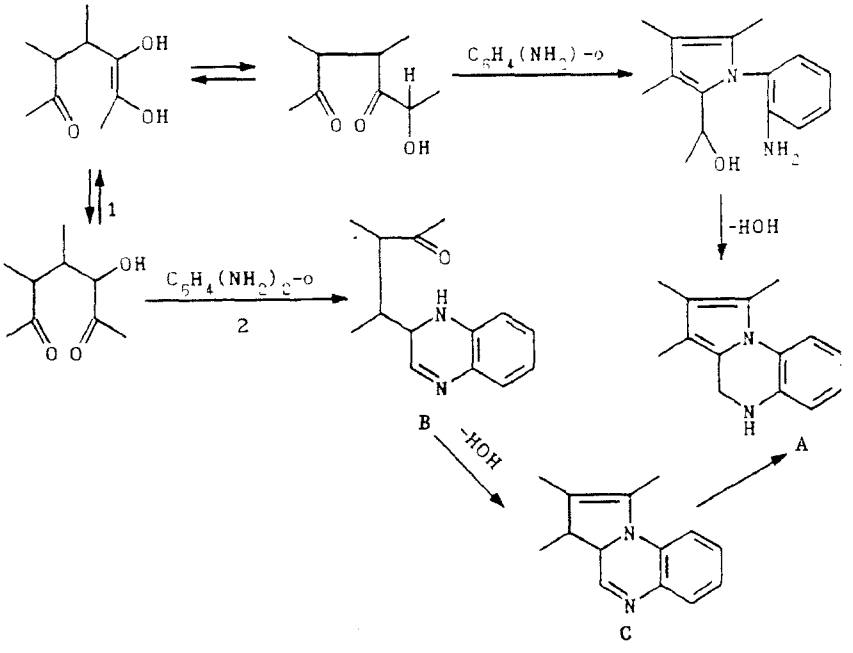
TABLE 1. Characteristics of Pyrrolo[1,2-a]quinoxaline Derivatives IIa, IId, and IIIa-IIId

Compound	Chemical formula	Mp, °C	PMR spectrum, δ, ppm (coupling constant, J, Hz)	Yield, %
IIa	$C_{29}H_{22}N_2$	98...100	4.27 (1H, br.s 5-H); 5.71 (1H, s, 4-H); 6.58 (1H, s, 2-H)	89
IId	$C_{27}H_{24}N_2$	133...135	1.70 (2H, m, CH_2); 2.05 (2H, m, CH_2); 2.60 (2H, m, CH_2); 3.05 (2H, m, CH_2); 4.28 (1H, br.s 5-H); 5.50 (1H, s, 4-H)	79
IIIa	$C_{29}H_{20}N_2$	167...158	6.90 (1H, s, 2-H); 8.05 (1H, d, 6-H, $J_{6,7}$=8)	75
IIIb	$C_{24}H_{18}N_2$	133...135	1.88 (3H, s, CH_3); 6.59 (1H, s, 2-H); 7.95 (1H, d.d, 6-H, $J_{6,7}$=8, $J_{6,8}$=2)	45
IIIc	$C_{23}H_{16}N_2$	111...112	6.88 (1H, d, 2-H, $J_{2,3}$=4); 7.02 (1H, d, 3-H, $J_{3,2}$=4); 8.00 (3-H, m, 6-H, 2'-H*, 6'-H*)	33
IIId	$C_{27}H_{22}N_2$	171...173	1.83 (2H, m, CH_2); 2.10 (2H, m, CH_2); 2.66 (2H, t, CH_2, J=6); 3.48 (2H, t, CH_2, J=6); 8.03 (1H, m, 6-H); 8.29 (1H, m, 9-H)	81

*Protons of the phenyl substituent at $C_{(4)}$.

Products IIa and IId were isolated as pure compounds. Upon treatment with γ-MnO_2, these compounds are readily dehydrogenated to give the corresponding pyrrolo[1,2-a]quinoxaline derivatives (IIIa) and (IIId). Products IIb and IIc are less stable and undergo partial dehydrogenation during their synthesis and were not isolated. Mixtures of the products of the reaction of hydroxydiketones IIb and IIc with o-phenylenediamine were oxidized by γ-MnO_2 and pyrrolo[1,2-a]quinoxaline derivatives IIIb and IIIc were isolated.



The IR spectra of 4,5-dihydro derivatives IIa and IId have NH group bands at 3360 cm^{-1}. These bands are lacking in the spectra of IIIa-IIId. The PMR spectra of IIa and IId have characteristic singlets for 4-H and broad singlets corresponding to the NH group proton. These signals are lacking in the spectra of IIIa-IIId. The spectrum of IIIc has doublets for 2-H and 3-H with characteristic coupling for the pyrrole ring (4 Hz). The spectra of IIa, IIIa, and IIIb have singlets for 2-H, while there are no signals for pyrrole ring protons in the spectra of IId and IIId. The spectra of IIIa-IIId have signals at 7.95-8.30 ppm. The spectrum of IIId has signals for two protons (6-H and 9-H) in this region, while the spectra of IIIa and IIIb have only one signal in this region (6-H). The signal for 9-H is shifted upfield and overlaps with the signals of the other aromatic protons.

This shift is a consequence of the shielding of this proton by the benzene ring at $C_{(1)}$, which is noncoplanar to the pyrroloquinoxaline system. Analogous shielding was noted in our previous work [8]. The spectrum of IIIc has a three-proton multiplet in the vicinity of 8 ppm assigned to 6-H and the protons of the benzene ring at $C_{(4)}$ in ortho position to this carbon atom. As a consequence of the lack of a substituent at $C_{(3)}$, this ring may be coplanar to the pyrroloquinoxaline system. The mass spectra of IIIa-IIId have strong molecular ion peaks, corresponding to the calculated molecular masses. Products IIIa and IIIb have weak peaks, corresponding to the loss of the substituent from $C_{(3)}$: $[M - C_6H_5]^+$ for IIIa and $[M - CH_3]^+$ for IIIb. The spectrum of IIId have a peak for $[M - C_2H_4]^+$, corresponding to fragmentation of the 1,2-tetramethylene substituent.

The formation of the pyrrolo[1,2-a]quinoxaline structure in this reaction may occur by one of two pathways: 1) isomerization of the 2-hydroxy-1,5-diketone to a 5-hydroxy-1,4-diketone [9] followed by formation of an o-aminophenylpyrrole derivative with subsequent ring closure to give the dihydroquinoxaline structure and 2) reaction of α-hydroxyketone fragment with o-phenylenediamine [10] followed by closure of the dihydropyrrole ring with subsequent isomerization of the 3,3a-dihydropyrrolo[1,2-a]quinoxaline species (C) to the more stable 4,5-dihydropyrrolo[1,2-a]quinoxaline structure (A).

Pathway 2 seems more likely since a 2:5 mixture of IIIb and quinoxaline derivative IV was isolated when the reaction of hydrodiketone Ib with o-phenylenediamine was carried out in 15:1 ethanol—acetic acid with subsequent oxidation of the reaction products. This mixture could not be separated due to the virtually identical chromatographic behavior and similar solubilities of IIIb and IV. The IR spectrum of this mixture has a band at 1682 cm^{-1} (C=O). The PMR spectrum of this mixture has a doublet for the methyl group at 1.25 ppm (J = 6.5 Hz), multiplet for C<u>H</u>—CH_3 at 4.14 ppm, and signals for the diastereotopic protons of the CH_2CO group at 3.20 (1H, d.d, J = −16 and 3.5 Hz) and 4.20 ppm (1H, d, J = −16 Hz) in addition to the signals for IIIb. The molecular ion peak with m/z 352 in the mass spectrum corresponds to the molecular mass of IV. Strong fragmentation peaks are found for ions with m/z 247 $[M - C_6H_5CO]^+$ and m/z 232 $[M - C_6H_5COCH_3]^+$. The peak with m/z 334 corresponds to the molecular mass of IIIb. We may assume that under these conditions with a lower acid concentration, the reaction partially stops at the first step in pathway 2 and the oxidation of species C leads to IV.

EXPERIMENTAL

The IR spectra were taken for chloroform solutions on a Specord IR-75 spectrometer. The NMR spectra were taken for solutions in $CDCl_3$ on a Bruker WM-250 spectrometer at 250 MHz with TMS as the internal standard. The mass spectra were taken on an LKB-9000 mass spectrometer at 70 eV with direct sample inlet. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol plates.

The elemental analysis data for II and III for C, H, and N corresponded to the calculated values.

1-R-2-R^1-3,4-Diphenyl-4,5-dihydropyrrolo[1,2-a]quinoxalines (IIa)-(IId). A mixture of 3 mmoles diketone Ia-Id and 3.5 mmoles o-phenylenediamine in 10 ml ethanol and 5 ml acetic acid was heated at reflux for 1.5-2 h. After cooling, 70 ml water was added and the precipitate was filtered with water and dried. Product IIa was recrystallized from 5:1 hexane—acetone, while IId was recrystallized from ethyl acetate.

1-R-2-R^1-3,4-Diphenylpyrrolo[1,2-a]quinoxalines (IIIa)-(IIId). A. A sample of 30 mmoles γ-MnO_2 was added with stirring to a solution of 2.5 mmoles IIa-IId in 40 ml acetone (for IIa) or benzene (for IId) and stirred for 1.5 h (for IIa) or 2.5 h (for IId). MnO_2 was filtered off and washed with acetone and then chloroform. The solvent was distilled off the combined filtrate and the residue was recrystallized from 10:1 ethanol—DMF.

B. A mixture of 2 mmoles diketone IIb or IIc and 2.5 mmoles o-phenylenediamine in 8 ml ethanol and 4 ml acetic acid was heated at reflux for 1.5 h. After cooling, 40 ml water was added and the mixture was extracted with ether. The ethereal extract was washed with water, aqueous Na_2CO_3, and again water and dried. The solvent was distilled off. The residue was dissolved in 20 ml acetone and 25 mmoles γ-MnO_2 was added. The mixture was stirred for 2 h (for Ic) or 4 h (for Ib). MnO_2 was filtered off and washed with acetone and chloroform. The solvent was distilled off the filtrate. The residue was subjected to chromatography on silica gel 100/250. Product IIIb was eluted with 5:1 hexane—ethyl acetate, while IIIc was eluted with 4:1 hexane—ethyl acetate.

Mixture of 3-Methyl-1,4-diphenylpyrrolo[1,2-a]quinoxaline (IIIb) and 1-Phenacyl-1-2-(3-phenylquinoxalyl)ethane (IV). A mixture of 0.76 g (2.6 mmoles) diketone Ib and 0.27 g (3 mmoles) o-phenylenediamine in 15 ml ethanol and 1 ml acetic acid was heated at reflux for 3 h and then treated analogously to the previous procedure (Method B using 1.5 g γ-MnO_2). The mixture of IIIb and IV were eluted with 2:1 hexane—ether. The yield was 0.45 g.

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MASS SPECTROMETRY OF NITROGEN HETEROCYCLES. 4.* MASS SPECTRAL BEHAVIOR OF TRIAZOLO[1,5-a]PYRIDO[2,3-d]PYRIMIDINES

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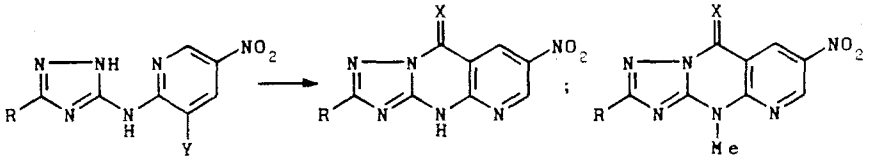
The electron impact mass spectra of substituted 9-imino- and 9-oxotriazolo[1,5-a]pyrido[2,3-d]pyrimidines were studied. The mass spectral data obtained permitted us to determine the order of the fusion of the triazole, pyrimidine, and pyridine rings as well as the position of the hydrogen atoms at the heteroatoms. Compounds labelled with ^{15}N and ^{13}C atoms were used to check the assignments made.

The thermal intramolecular cyclization of 2-triazolylamino-3-Y-5-nitropyridines I [1] and the closure of heteroaryl systems by the action of bases such as KOH [2] lead to the formation of triazolo[1,5-a]pyrido[2,3-a]pyrimidines (IIa)-(IIf). These processes are accompanied by the elimination of neutral molecules. Ethanol, ammonia, and hydrogen sulfide are lost when Y = $CO_2C_2H_5$, $CONH_2$, and $CSNH_2$, respectively.



I IIa-f III g-j

II, III a R=H, X=NH; b R=CH_3, c R-CF_3, X=NH; d R=H, X=O; e R=CH_3, X=O; f R=SCH_3, X=O; g R=H, X=NH; h R=CF_3, X=NH; i R=H, X=O; j R=CH_3, X=O; Y=$COOC_2H_5$, $CONH_2$, $CSNH_2$

*For Communication 3, see [1].

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