ARYL-SUBSTITUTED 6,7-DIHYDROPYRAZOLO[1,5-a]PYRIMIDINE

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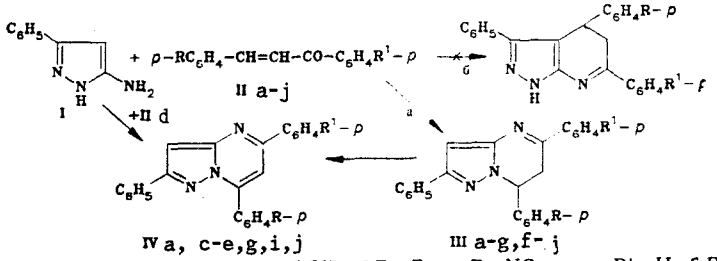
We have studied the reaction of 5-amino-3-phenylpyrazole with chalcones which takes place with the formation of arylsubstituted forms of dihydropyrazolo[1,5-a]pyrimidine and have discussed a possible mechanism for the reaction. Dehydrogenation of the compounds prepared has been effected using N-bromosuccinimide.

Continuing the study of the reactions of aminoderivatives of pyrazoles with aromatic α,β-unsaturated ketones [1], we have studied the reaction of 5-amino-3-phenylpyrazole (I) with chalcones (II). Interest in aminopyrazoles unsaturated at the ring nitrogen arises from their dual reactivity: in reactions with carbonyl compounds they form derivatives of pyrazolo[4,5-b]pyridine [2] or of pyrazolo[1,5-a]pyrimidine [3] or mixtures of these compounds [4].



IV a, c-e,g,i,j III a-g,f-j

II—IV a,f—j R=H, b R=CH_3, c R=OCH_3, d R=Br, e R=NO_2; a—e R^1=H, f R^1=CH_3, g R^1=OCH_3, h R^1=Cl, i R^1=Br, j R^1=NO_2

TABLE 1. Characteristics of 2,5,7-Triaryl-6,7-dihydropyrazolo-[1,5-a]pyrimidines (III)

Compound	mp, °C	UV spectrum, λ max, nm (ε ·10⁻³)	Proton NMR spec- δ, ppm*			Found N, %	Empirical formula	Calculated N, %	Yield, %
			CH_2	CH	=CH				
IIIa	170—171	309 (16,2), 255 (25,7)	3,45	5,68	6,81	12,3	$C_{24}H_{19}N_3$	12,0	54
IIIb	121—122	309 (15,5), 256 (24,3)	3,51	5,68	6,84	11,6	$C_{25}H_{21}N_3$	11,6	60
IIIc	159—160	315 (16,9), 260 (29,9), 227 (24,9)	3,44	5,61	6,80	11,2	$C_{25}H_{21}N_3O$	11,1	63
IIId	161—162	307 (16,1), 255 (23,0)	3,40	5,60	6,79	9,9	$C_{24}H_{18}BrN_3$	9,8	50
IIIf	201—202	308 (19,3), 257 (24,2)	—	—	—	11,6	$C_{25}H_{21}N_3$	11,6	60
IIIg	174—176	329 (22,0), 257 (19,8), 243 (21,3)	3,43	5,68	6,75	11,2	$C_{25}H_{21}N_3O$	11,1	65
IIIh	164—165	309 (17,6), 256 (27,9)	—	—	—	11,1	$C_{24}H_{18}ClN_3$	11,0	65
IIIi	208	313 (17,5), 258 (23,4)	—	—	—	9,9	$C_{24}H_{18}BrN_3$	9,8	65
IIIj	190	346 (8,7), 295 пл., 255 (19,9)	3,44	5,71	6,86	14,4	$C_{24}H_{18}N_4O_2$	14,2	68

*In the proton NMR spectra of compounds IIIb, c, g, proton signals from the CH_3 and OCH_3 groups were observed at 2.26, 3.66, and 3.79 ppm respectively.

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TABLE 2. Characteristics of 2,5,7-Triarylpyrazolo[1,5-a]-pyrimidines (IV)

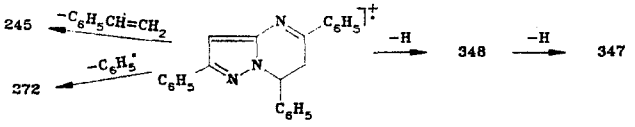
Compound	mp, °C	UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	Found N, %	Empirical formula	Calculated N, %	Yield, %
IVa	154	344 (11,6), 288 Sh., 279 (55,8)	12,3	$C_{24}H_{17}N_3$	12,1	70
IVc	172—174	340 (10,9), 288 (54,1), 237 Sh.	11,0	$C_{25}H_{19}N_3O$	11,1	70
IVd	199—200	342 (11,7), 287 (52,5), 235 (25,8)	9,8	$C_{24}H_{16}BrN_3$	9,9	75
IVe	260	353 (9,43), 276 (54,9)	14,3	$C_{24}H_{16}N_4O_2$	14,3	5
IVg	178—180	343 (10,3), 294 Sh., 279 (49,8)	11,2	$C_{25}H_{19}N_3O$	11,1	75
IVi	172	341 (11,9), 292 Sh., 284 (42,0)	9,8	$C_{24}H_{16}BrN_3$	9,4	75
IVj	235—236	345 Sh., 314 Sh., 281 (50,3), 237 (26,5)	14,5	$C_{24}H_{16}N_4O_2$	14,3	80

We have isolated compounds III from the reaction product obtained on boiling together equimolar quantities of the starting materials I and II in DMF and identified them as 6,7-dihydropyrazolo[1,5-a]pyrimidines (Table 1). The reaction is accompanied by the formation of small quantities of dehydrogenation products IV. The reaction of the amine I with 4-nitrochalcone IIe is an exception insofar as only compound IVe is obtained.

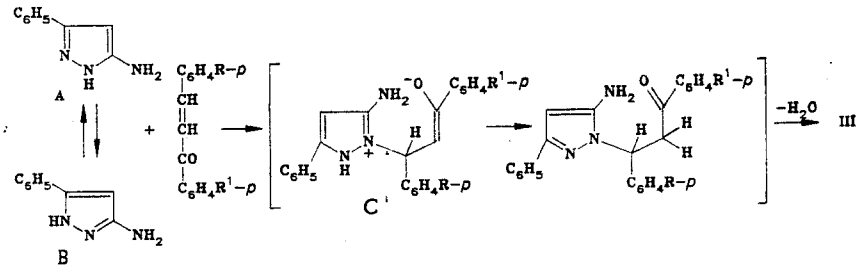
In the infrared spectra of the compounds III azomethine $\nu_{C=N}$ bands are observed (~1600 cm^{-1}) and N—H stretching vibration bands are absent. In the UV spectra the longest-wave absorption bands are quite intense and lie in the 306-346 nm region. Their λ_{max} values show evidence of the electronic influence of the R' substituent but are practically unchanged when the radical R is changed; this supports the presence of the former on the aromatic nucleus which occupies position 5 of the bicycle and is included in the conjugated azomethine system.

In the proton NMR spectra of compounds III (Table 1) there are distinct doublets from the methylene and triplets from the methine groups together with signals in the 6.75-6.86 ppm region assigned to the protons in position 3 of the bicycle. As a result of the electron-acceptor effect of the nodal nitrogen atom, signals from the CH_2CH fragment are shifted downfield (by 0.3-1.5 ppm) in comparison with the analogous values of aryl substituted forms of pyrazolo[4,5-b]pyridine [1] in which this effect is absent. The influence of the nodal nitrogen is significant enough to become apparent in a paramagnetic shift of the values of δ for the protons of methoxy groups introduced into the aryl substituent of the pyrimidine ring (compounds IIIc, IIIg). Thus, the proton spectra are fully in agreement with the proposed structure for compounds III and one can exclude the formation of the alternative pyrazolo[4,5-b]pyridine structure (route 'b').

Further support for a dihydropyrazolopyrimidine structure is provided by the mass spectrum of compound IIIa. The peak of maximum intensity is that of the molecular ion (m/z 349). The basic primary fragmentation processes are represented by the scheme:



It has been shown [5] that in the reaction of 2-aminoindole with chalcones, cyclization to pyridine but not to pyrimidine rings takes place. This result led the author of a review [6] to formulate this direction of the reaction as a general rule for the condensation of unsaturated ketones with aminoazoles. The structure of compounds III which we have established, however, shows a change in the direction of the condensation on passing from 2-aminoindole [5] to the amine I. This can be explained by the ability of the pyrazoles to be alkylated at the ring nitrogen [7]. On the other hand, indoles react with alkylating agents preferentially at the $C_{(3)}$ carbon since the indole nitrogen is comparatively inert to alkylation [7]. For 5-amino-3-phenylpyrazole I an equilibrium of the two tautomeric forms A and B is characteristic; from the results of [8], the fraction of tautomer B amounts to 53%. Tautomer B apparently also participates in a reaction the direction of which is determined by electrophilic attack by an α,β-unsaturated ketone at the most nucleophilic center of the amine I — the pyridine nitrogen — with the formation of the intermediate C and its subsequent cyclization.



Compounds III are readily dehydrogenated by N-bromosuccinimide to compounds IV (Table 2). Aromatization is accelerated as the electron-acceptor properties of the substituent R become greater. This serves to explain the observation noted above that compound IVe is formed directly from the amine I and 4-nitrochalcone IIe. Compound IVa is also obtained by the condensation of 5-amino-3-phenylpyrazole (I) with α,β-dibromochalcone in DMF and with dibenzoylmethane in acetic acid.

Conversion into compounds IV leads to a change in the UV spectra. In particular, the influence of the substituent R on the wavelength of the absorption band levels out and a marked shift of the spectrum towards the red region is observed. The pyrazolopyrimidines IV have a pronounced fluorescence in alcohols, aromatic hydrocarbons, and in the solid phase.

EXPERIMENTAL

The IR spectra of the compounds III and IVwere obtained, using KBr disks and CCl_4 solutions, on a Specord IR-75 spectrophotometer, the UV spectra of compounds III in methanol and compounds IV in ethanol on a Specord UV-vis instrument, and proton NMR spectra on a Tesla BS-2487-B (80 MHz) with TMS internal standard. Mass spectra were obtained on a Varian MAT-311A instrument under standard working conditions with an ionizing potential of 70 eV. Individual compounds were monitored by TLC using Silufol UV-254 plates and chloroform eluent.

2,5,7-Triphenyl-6,7-dihydropyrazolo[1,5-a]pyrimidine (IIIa). A solution of 0.3 g (1.9 mmole) amine I and 0.4 g (1.9 mmole) chalcone IIa in 1 ml DMF was heated at bp for 45 min, cooled, the precipitate filtered off and chromatographed on an Al_2O_3 column (column diameter 1 cm, filled height 10 ml, eluent chloroform), collecting the second, non-luminescent fraction which contained compound IIIa. The first fraction was compound IVa (0.1 g, 15%). Distilling off the solvent and crystallizing the residue from methanol yielded 0.35 g compound IIIa with mp 170-171°C (from methanol). Mass spectrum, m/z (%): 349 (100), 348 (88), 347 (22), 272 (42), 245 (15), 114 (25), 105 (31), 103 (39), 77 (51).

Compounds IIIb-d, f-j were prepared in a similar manner. Under these conditions compounds I and IIe yielded only compound IVe.

2,5,7-Triphenylpyrazolo[1,5-a]pyrimidine (IVa). A. To a boiling solution of 0.5 g (1.4 mmole) compound IIIa in 15 ml methanol was added, in two stages, 0.5 g (2.8 mmole) N-bromosuccinimide and boiling continued for 1 h. After cooling, the precipitate was filtered off and chromatographed on an Al_2O_3 column (column diameter 1 cm, filled height 10 ml, eluent chloroform). The first, luminescent fraction (R_f 0.69) contained compound IVa (0.35 g) with mp 154°C (from methanol).

Compounds IV d, g, i, j were prepared in a similar manner.

B. A solution of 0.27 g (1.7 mmole) amine I and 0.38 g (1.7 mmole) dibenzoylmethane in 5 ml acetic acid was heated at bp for 1 h. It was then diluted with 5 ml water, the precipitate separated and chromatographed as described for method A to yield 0.32 g (55%) compound IVa.

C. A solution of 0.27 g (1.7 mmole) amine I and 0.63 g (1.7 mmole) 2,3-dibromo-1,3-diphenyl-1-propanone in 3 ml DMF was heated at bp for 1 h. Subsequent treatment was carried out as described for method A to yield 0.4 g (68%) compound IVa.

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