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STUDIES OF PYRAZOLES: XLVI. SYNTHESIS OF PYRAZOLOPYRIDONES

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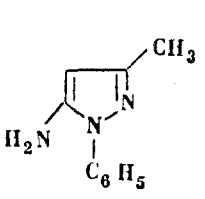
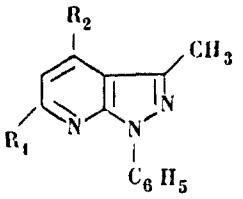
Cyclizations of acetoacetamidopyrazoles and of appropriate aminopyrazole crotonates to pyrazolopyridines with a hydroxy group in the pyridine ring are effected. In the case of an amino group at position 5 in the pyrazole ring cyclization takes place with acetylacetone. It is shown that the structure of pyrazolopyridone put forward by Bülow is incorrect.

Heating 1-phenyl-3-methyl-5-aminopyrazole (I) with β-dicarbonyl compounds has been found to give a series of pyrazolopyridines, which have been assigned structures II and III [2].

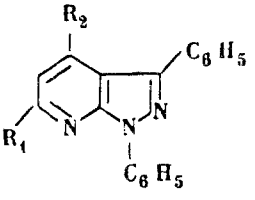


I



II R_1 and R_2 = alkyl or aryl

III $R_1 = CH_3$; $R_2 = OH$

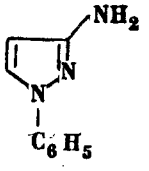


IV $R_1 = CH_3$, $R_2 = OH$;

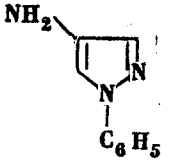
V $R_1 = OH$, $R_2 = CH_3$

Recently 1,3-diphenyl-5-aminopyrazole and acetoacetic ester at 150° have been found to give a compound for which formula IV or V has been suggested [3], since it was found impossible to maintain a priori (as in [2]) that the OH group is at position 4 or 6 in the pyridine ring.

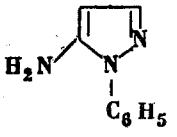
Products of condensation of aminopyrazoles with acetoacetic ester at the carbonyl or carboxyl group have already been synthesized [1], and now an attempt has been made to decide in which way condensation occurs. The behaviors of 1-phenyl-3-amino- (VI), 1-phenyl-4-amino- (VII), 1-phenyl-5-aminopyrazole (VIII), and the previously studied [2] compound I, when treated with acetoacetic ester and acetylacetone, were investigated.



VI

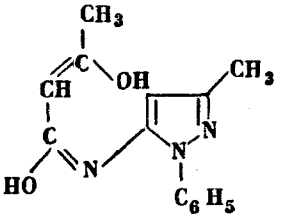


VII

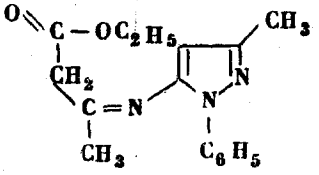


VIII

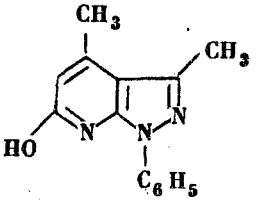
Under the conditions described in [2], only the amines I and VIII gave condensation products, while VI and VII were converted into acetyl derivatives with splitting off of a β-dicarbonyl compound. To elucidate the structure of the condensation product of I with acetoacetic ester, intermediate compounds IX and X were synthesized [1].



IX



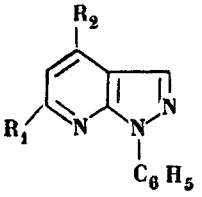
X

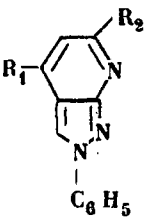


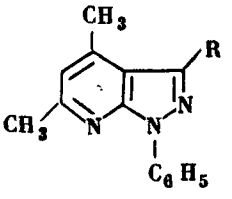
XI

Heating X at 130° for 40 min without a solvent, or at 210° in Dowtherm, gave a pyrazolopyridone m.p. 214°, to which structure III can be readily assigned. Cyclization of IX gave an isomer previously synthesized [2], but obviously having structure XI. The acetoacetamide structure IX is unaffected by the hydrolytic action of acetic acid, but at 120° cyclization sets in, giving XI. The actual crotonate X is partly transformed to amide IX [4] on heating in acetic acid,

and this latter also cyclizes to the pyrazolopyridine* XI. The acetoacetamides from amines VI and VII are hydrolyzed on boiling with acetic acid to give acylated amines. Condensation of crotonates of amines VI, VII, and VIII in Dowtherm gave the corresponding pyrazolopyridones XIIa, XIII, and XIV.

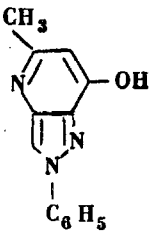


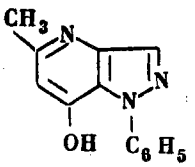




XIV $R_1=CH_3$, $R_2=OH$; XII $R_1=CH_3$, $R_2=OH$; XV $R=H$

XIVa $R_1=OH$, $R_2=CH_3$; XIIa $R_1=OH$, $R_2=CH_3$; XVa $R=CH_3$

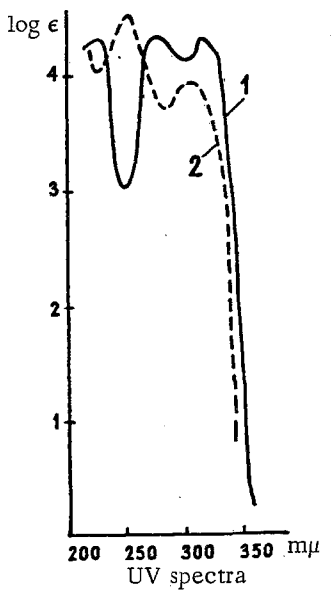




XIII a XIII

The acetoacetamide obtained from the aminopyrazole VI by condensation under the action of sulfuric acid [5] was converted into the pyrazolopyridone XIIa. The acetoacetamide obtained from amine VII could not be cyclized, evidently because a hydrogen atom at position 5, the least susceptible to electrophilic substitution, must participate.

It is known [6, 7] that the UV spectra of pyrazolo[4, 3-b]pyridines and pyrazolo[5, 4-b]pyridines differ markedly. Similarly, in the case of the present structures (see figure) the UV spectra of the systems condensed through positions 4 and 5 of the pyrazole ring have two maxima in the regions 245-255 mμ and 295-305 mμ, while when condensation involves positions 3 and 4 of the pyrazole, the maxima are displaced toward longer wavelengths (275-285 and 315-320 mμ). In particular, the condensation product derived from the crotonate of amine VII has maxima in the regions 239 mμ and 309 mμ, and over its entire length the spectral curve coincides with that for pyrazolopyridines, condensed at the 4 and 5 positions. Hence it should be assigned structure XIII and not XIIIa.



UV spectra

1. 1-phenyl-4-methyl-6-hydroxy-3-azaindazole (XII);
2. 1-phenyl-3, 6-dimethyl-4-hydroxy-7-azaindazole (III) (SF-4, solvent methanol).

None of the pyrazolohydroxypyridines with a hydroxyl at position 6 in the pyridone ring (XIVa type) give picrates. The pyrazolohydroxypyridines with a hydroxyl at position 4 readily give picrates (obviously because of their greater basicity). Once again this is evidence of the structure of the compounds formed.

Using acetylacetone it was possible to effect cyclization to structures XV and XVa only in the case of the aminopyrazoles I and VIII with the amino group in position 5. In all other cases cyclization with sulfuric acid fails to take place. Attempts to effect cyclization in alkaline media (by analogy with [8]) were unsuccessful, and what was isolated was the starting aminopyrazole and a small amount of acetoacetamide.

EXPERIMENTAL

Condensation in acetic acid. 0.1 mole aminopyrazole, 0.15 mole acetoacetic ester, and 60 ml glacial acetic acid were refluxed for 5 hr, 30 ml water added, and the substance which crystallized out was separated and recrystallized from 60% methanol. In this way compounds XI and XIVa were prepared, while XV and XVIa (table) were similarly prepared by condensation with acetylacetone.

Condensation in sulfuric acid. 0.01 mole aceto acetoamidopyrazole [1] was slowly poured into 3 ml concentrated H_2SO_4 at 80°, the mixture kept at 80° on a waterbath for 15 min and then diluted with 50 ml water. The reaction mixture was neutralized with sodium bicarbonate to pH 5, and the precipitate filtered off with suc-

*The full names of the compounds prepared are given in the table: 1-phenyl-3, 4-dimethyl-6-hydroxy-7-azaindazole may also be called 1-phenyl-3, 4-dimethyl-6-hydroxypyrazolo[5, 4-b] pyridine.

Compound no.	Compound	M.p., °C	Yield, %	Found, %		UV spectra*		Picrate m.p., °C
				C	H	mμ	log E	
XI	1-Phenyl-3, 4-dimethyl-6-hydroxy-7-azaindazole	189—190	70	70.50, 70.35	5.68, 5.64[b]	257, 296	4.41, 4.11	No picrate
III	1-Phenyl-3, 6-dimethyl-4-hydroxy-7-azaindazole	214	90	69.78, 69.84	5.73, 5.71[b]	248, 296	4.39, 4.04	183
XIV	1-Phenyl-6-methyl-4-hydroxy-7-azaindazole	178	30	68.97, 68.91	5.23, 5.07[c]	244, 294	4.37, 4.13	—
XIVa	1-Phenyl-4-methyl-6-hydroxy-7-azaindazole	180	71		N 18.66, 18.85[c]	253, 310	4.41, 4.30	No picrate
XIII	1-Phenyl-5-methyl-7-hydroxy-4-azaindazole	303	84	69.61, 69.39	5.24, 5.14[c]	239, 309	4.42, 4.30	232
XII	1-Phenyl-4-methyl-6-hydroxy-3-azaindazole	315	96		N 18.55, 18.61[c]	228, 285, 321	4.34, 4.34, 4.30	223
XIIa	1-Phenyl-4-hydroxy-6-methyl-3-azaindazole	240	20	69.21, 69.03	5.04, 4.89[c]	273, 314	4.13, 4.15	No picrate
XV	1-Phenyl-4, 6-dimethyl-7-azaindazole	65	70	75.20, 75.08	5.96, 5.87[d]	252, 304	4.46, 3.94	108
XVa	1-Phenyl-3, 4, 6-trimethyl-7-azaindazole	128	72	76.33, 76.33	6.46, 6.35[e]	255, 310	4.52, 3.95	No picrate

*SF-4, solvent methanol

b $C_{14}H_{13}N_3O$. Calculated: C 70.27, H 5.48%.

c $C_{13}H_{11}N_3O$. Calculated: C 69.31, H 4.92, N 18.65%.

d $C_{14}H_{13}N_3$. Calculated: C 75.37, H 5.86%.

e $C_{15}H_{15}N_3$. Calculated: C 75.92, H 6.37%.

tion. Then it was recrystallized from 60% methanol. In this way compound XII was prepared.

Condensation in Dowtherm. 0.01 mole of the appropriate crotonate [1] was slowly poured into 20 g boiling Dowtherm (1:1 mixture of diphenyl oxide-diphenyl), and boiling continued for 20 min more with stirring. After cooling the reaction mixture was diluted with 100 ml petroleum ether and the precipitate filtered off with suction. It was recrystallized from 60% methanol. Compounds III, XIIa, XIII, and XIV were prepared in this way.

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