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SYNTHESIS OF 3-R^2-4-R^1-ACETYL-(ETHOXYCARBONYL)-6-HYDROXY-6-METHYLINDAZOLES

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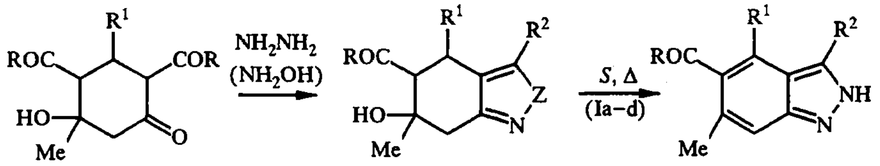
It was discovered that functionally substituted tetrahydroindazoles can be aromatized by the action of sulfur. Previously unknown 3-R^2-4-R^1-5-acetyl(ethoxycarbonyl)-6-methylindazoles were obtained. The products from aromatization cannot be obtained if a nitro group is introduced or one heteroatom in the substrate is replaced by oxygen.

Pyrazoles and isoxazoles have a wide spectrum of biological activity [1]. Condensed pyrazoles and isoxazoles and particularly the polysubstituted compounds have been investigated less in this respect [2]. We have presented the results [3] of investigations into the synthesis and biological activity of cyclohexa(*b*)pyrazoles and cyclohexa(*b*)isoxazoles.

The aim of the present work was to synthesize benzannelated pyrazoles and isoxazoles by the aromatization of 3-R^2-4-R^1-5-acetyl(ethoxycarbonyl)-6-hydroxy-6-methyl-2H-4,5,6,7-tetrahydroindazoles Ia-e and their O-hetero analogs IIa,b. Here it seemed of interest to determine the effect of the nature of the substituting groups and of the heteroatom in the substrate on the course of the reaction.

The initial tetrahydroindazoles Ia-e and condensed isoxazoles IIa,b were obtained with high yields by our previously developed methods [3] from hydrazine or the readily obtainable hydroxylamine and β-cycloketols IIIa-e, i.e., the products from the condensation of acetylacetone (acetoacetic ester) with aldehydes. All the compounds I and II except Ic had been obtained and characterized before [3, 4].

Compounds Ia-e were aromatized by the action of sulfur at 200°C until the release of hydrogen sulfide had stopped, which required ~60 min. Under the selected conditions these tetrahydroindazoles underwent dehydration and dehydrogenation with the formation of previously unknown 3-R^2-4-R^1-5-acetyl(ethoxycarbonyl)-6-methylindazoles IVa-d.



IIIa–e Ia–e, IIa,b IVa–d

I, IV Z = NH, II Z = O; I–IV a R = R^1 = R^2 = Me; b R = R^2 = Me, R^1 = Ph;
c R = R^2 = Me, R^1 = C_6H_4OH-*p*; d R = OEt, R^1 = Ph, R^2 = OH; e R = R^2 = Me, R^1 = $C_6H_4NO_2$-*m*

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TABLE 1. The Characteristics of the Obtained Compounds

Compound	Empirical formula	Found, % Calculated, %			mp, °C	Yield, %
		C	H	N		
Ic	$C_{17}H_{20}N_2O_3$	68.21 67.98	7.21 6.71	8.97 9.33	156-157	61
IVa	$C_{12}H_{14}N_2O$	70.52 71.26	6.94 6.98	13.60 13.85	210-212	76
IVb	$C_{17}H_{16}N_2O$	77.10 77.25	6.72 6.10	10.19 10.60	199-200	71
IVc	$C_{17}H_{16}N_2O_2$	71.43 72.84	6.19 5.75	9.47 9.99	225-226	62
IVd	$C_{17}H_{16}N_2O_3$	69.71 68.91	5.94 5.44	9.19 9.45	145-146	47

The characteristics of the new compounds Ic and IVa-d are given in Table 1. In the IR spectra of the indazoles IVa-d compared with their hydrogenated precursors Ia-d there are no bands for the stretching vibrations of the OH group, but there are bands for the NH group (3350-3280 cm^{-1}); the absorption bands of the C=O bonds are shifted bathochromically on account of the conjugation with the aromatic ring and are found in the region of 1665-1645 cm^{-1}. The PMR spectra contain singlets for the aromatic proton (~7.44 ppm), the NH group (~7.25 ppm), and the methyl substituents (2.80-2.75, 2.15 ppm).

The presence of a methyl, phenyl, or *p*-hydroxyphenyl group at position 4 of the tetrahydroindazoles Ia-c does not have a significant effect on the course of the reaction; the yields of the aromatization products IVa-c are 62-76%. If the acetyl group is replaced by an ethoxycarbonyl group, as in the case of compound Id, the yield of the corresponding indazole IVd is reduced to 47%.

The presence of a nitro group in the benzene ring of the tetrahydroindazole prevents isolation of the aromatization products. Thus, when 5-acetyl-6-hydroxy-2,6-dimethyl-4-(*m*-nitrophenyl)-2H-4,5,6,7-tetrahydroindazole Ie was heated with sulfur it was not possible to isolate any individual product due to carbonization of the reaction mixture. Similar observations were made in [4], where the dehydrogenation of (nitrophenyl)-substituted pyrazolines by sulfur was studied. It can be supposed that the nitro group acts as oxidizing agent at high temperature (200°C), which leads to intense degradation of the molecule.

Our attempts at the aromatization of the O-hetero analogs of tetrahydroindazoles 4-R^1-5-acetyl-6-hydroxy-3,6-trimethyl-4,5,6,7-tetrahydro-2,1-benzoxazoles IIa,b were also unsuccessful on account, probably, of the thermal instability of the isoxazole fragment.

Thus, we have demonstrated the fundamental possibility of the aromatization of polysubstituted tetrahydroindazoles by the action of sulfur. The introduction of a nitrophenyl substituent into the substrate molecule or substitution of one nitrogen atom by oxygen in the heterocycle leads to degradation.

EXPERIMENTAL

The composition of the products was monitored by TLC on Silufol UV-254 plates with a 2:2:1 mixture of hexane, ether, and chloroform as eluant. The IR spectra were recorded on a Specord M80 spectrometer for suspensions in Vaseline oil and hexachlorobutadiene. The PMR spectra were obtained on a Varian FT-80A instrument at 80 MHz with tetramethylsilane as internal standard.

The initial compounds Ia,b,d,e, IIa,b were obtained by the known method [3].

5-Acetyl-6-hydroxy-4-(*p*-hydroxyphenyl)-3,6-dimethyl-2H-4,5,6,7-tetrahydroindazole (Ic). To 2.28 g (0.0075 mol) of the ketol IIIc in 20 ml of ethanol we added dropwise 0.75 ml (0.015 mol) of hydrazine hydrate. The reaction mixture was kept on a boiling water bath for 30 min. Crystals of the product Ic separated on cooling.

5-Ethoxycarbonyl-3-hydroxy-6-methyl-4-phenylindazole (IVd). In a flask fitted with a thermometer and a gas outlet tube we placed 0.74 g (0.0025 mol) of the tetrahydroindazole Id and 0.08 g (0.0025 mol) of sulfur. The mixture was kept at 200°C for 30 min. When the release of hydrogen sulfide had stopped the reaction mixture was kept at the same temperature for a further 20 min and cooled, and 30 ml of ether was added. The crystals of the product IVd that separated were filtered off and recrystallized from alcohol. Compounds IVa-c were obtained similarly.

REFERENCES

1. M. A. Metwally and M. Khalil Abdel-Galil, *J. Indian Chem. Soc.*, **65**, No. 11, 766 (1988).
2. S. Niwas, S. Kumar, and A. P. Bhaduri, *Indian J. Chem.*, B, **24**, No. 7, 747 (1985).
3. N. S. Smirnova, O. P. Plotnikov, N. A. Vinogradova, V. V. Sorokin, and A. P. Kriven'ko, *Khim.-Farm. Zh.*, No. 1, 44 (1995).
4. I. I. Grandberg, Wey Ny Din, and A. N. Kost, *Zh. Org. Khim.*, **30**, 1373 (1960).