Mononuclear Heterocyclic Rearrangements. Part 12 (1). Rearrangement of 1,2,4-Oxadiazoles into Indazoles

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The first example of a mononuclear heterocyclic rearrangement involving an XYZ = CCN side-chain sequence is reported. The 3-(*o*-aminophenyl)-, and 3-(*o*-methylaminophenyl)-5-methyl-1,2,4-oxadiazoles (**3a,b**) gave a thermally induced rearrangement into 3-acylaminoindazoles (**4a,b**). On the other hand, the 3-(*o*-acetylaminophenyl)-5-methyl-1,2,4-oxadiazole (**3c**) produced a base induced rearrangement into 3-acetylaminoindazole (**4a**).

In connection with our interest in mononuclear heterocyclic rearrangements (*m.h.r*) of the type **1** → **2** (2), and with the aim of studying the influence of the nature of the side-chain on the reactivity of **1**, we have considered the XYZ = CCN sequence. Although various XYZ side-chains in **1** have already been considered (1,2) in *m.h.r.*, the literature does not report any example involving the CCN one (3).

In this paper we report studies on the behaviour of the 1,2,4-oxadiazole derivatives (**3**) containing a CCN side-chain, where the CC atoms are part of a phenyl ring. From such a type of sequence, it would be expected a rearrangement into 3-acylaminoindazoles (**4**) (4).

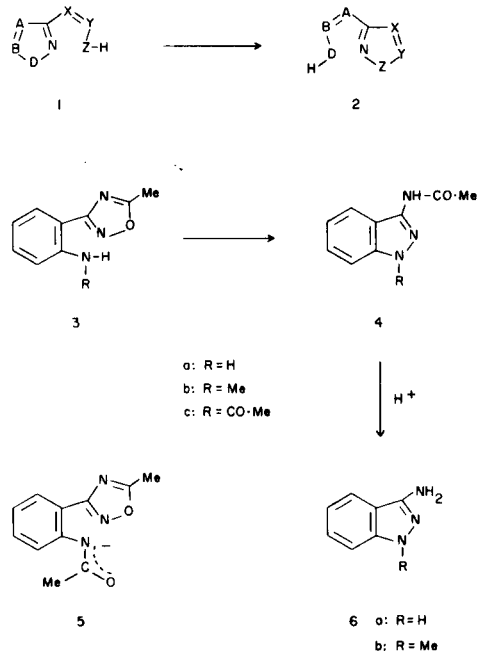
Compounds **3a** and **3c** have been prepared by the methods described in literature (5). Methylation of **3a** with dimethyl sulphate in aqueous sodium hydroxide gave the methylamino derivative **3b** in 35-40% yield.

We have observed that compounds **3a** and **3b** were practically unrearranged when refluxed with aqueous potassium hydroxide or sodium ethoxide in ethanol and only small amounts of rearrangement products were present. However, rearrangement of **3a** and **3b** into 3-acetylaminoindazoles (**4a**) and (**4b**) occurred in almost quantitative yield, by heating it at 160-180° (without solvent), *i.e.*, at a temperature much higher than their melting points. Compound **3b** was found to be more reactive than **3a**. In fact, after 4 hours at 160°, the rearrangement process was almost complete in the case of **3b**, whereas, in the case of **3a**, only small amounts (tlc) of the rearrangement product were present. The completeness of the process was achieved only after heating 8-10 hours at 180°.

Considering the high tendency of the 1,2,4-oxadiazole nucleus to undergo *m.h.r.* (1,6), the forced experimental conditions required in the rearrangement reaction can be ascribed to the low nucleophilic character of nitrogen atom of the amino or methylamino group in **3**. Moreover, the different reactivity of **3a** and **3b**, may be ascribed to the electronic and steric features of the methylamino group. The unsuccessful rearrangement in the presence of bases is due to the fact that amino group can not be converted into a salt under the experimental conditions used.

According to this view, the acetylamino derivative (**3c**), where the amide hydrogen atom is more acidic and then it is possible the formation of anionic center **5** with delocalized charge, reacts in the presence of bases. In fact, we have observed that **3c** easily rearranges into **4a**, through the unisolated **4c**, by gently refluxing it with aqueous potassium hydroxide in methanol. Obviously, compound **3c** does not rearrange by heating at 180° for 10 hours, owing to the still lower actual nucleophilicity of amide nitrogen atom in comparison with amino or methylamino group of **3a** and **3b**.

Acidic hydrolysis of 3-acetylamino derivatives (**4a,b**), gave 3-aminoindazole (**6a**) and 3-amino-1-methylindazole (**6b**).



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EXPERIMENTAL

Melting points were determined by using a Kofler hot-stage apparatus and are uncorrected. Ir spectra (Nujol mull) were determined on a Perkin-Elmer Infracord 137 instrument. Nmr spectra (60 MHz) were determined on a Jeol C-60H spectrometer with TMS as the internal standard.

3-(*o*-Methylaminophenyl)-5-methyl-1,2,4-oxadiazole (**3b**).

To a solution of **3a** (5) (5.5 g.) in 2*N* sodium hydroxide (26 ml.), dimethylsulphate (5.5 ml.) was added and the mixture was heated under reflux for 4-5 hours. After cooling, the mixture was extracted first with ether, and then, after neutralization, with chloroform. The two residues from ethereal and chloroform extracts were combined and chromatographed on a dry-column of silica-gel deactivated with water (15%). Elution with cyclohexane-ethyl acetate (5:1) gave first the 3-(*o*-methylaminophenyl)-5-methyl-1,2,4-oxadiazole (**3b**) (2 g.), m.p. 56° (light petroleum); ir: 3350 cm^{-1} (NH); nmr (DMSO): δ 2.68 (s, 3H, CH_3), 2.96 (d, 3H, NH-CH_3), 6.50-8.20 (m, 5H, NH, Ar-H).

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.55; H, 5.80; N, 22.50.

Further elution gave the starting amino compound (**3a**) (0.6 g.). Elution with ethyl acetate gave the rearrangement product (**4b**) (0.2 g.) (see Following).

Thermally Induced Rearrangement of **3a**.

A sample of **3a**, m.p. 79-80° (5) (0.5 g.) was heated in an oil-bath at 180° for 10-12 hours. After cooling, crystallization of the dark residue with water (charcoal) gave 3-acetylaminoindazole (**4a**) (0.4 g.), m.p. 204° (water); ir: 3280 cm^{-1} (NH), 1670 cm^{-1} (C=O); nmr (DMSO): δ 2.18 (s, 3H, CH_3), 6.90-8.0 (m, 4H, Ar-H), 10.35, 12.65 (2s, 2H, NH).

Anal. Calcd. for $C_9H_9N_3O$: C, 61.77; H, 5.18; N, 24.01. Found: C, 62.00; H, 5.12; N, 24.02.

Thermally Induced Rearrangement of **3b**.

A sample of **3b** (0.5 g.) was heated in an oil-bath at 160° for 4 hours. Crystallization with water gave 1-methyl-3-acetylaminoindazole (**4b**) (0.4 g.), m.p. 142° (water); ir: 3205 cm^{-1} (NH), 1660 cm^{-1} (C=O); nmr (DMSO): δ 2.15 (s, 3H, $COCH_3$), 4.0 (s, 3H, NCH_3), 6.90-8.0 (m, 4H, Ar-H), 10.32 (s, 1H, NH).

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.80; H, 5.70; N, 22.30.

Attempts of Base Induced Rearrangement of **3a** and **3b**.

A solution of **3a** or **3b** (6 mmoles) in ethanol (30 ml.) containing sodium ethoxide (6 mmoles), was refluxed for 5 hours. After cooling, the solvent was removed at reduced pressure and the residue was taken up with water and extracted with ether from which starting material (80-90%) was recovered. Neutralization of the aqueous solution with acetic acid and extraction with chloroform, gave small amounts of the rearrangement products. Similar results were found after refluxing (5 hours) in 10% aqueous sodium hydroxide

The Base Induced Rearrangement of **3c**.

A methanolic solution (15 ml.) of **3c** (5) (1.5 g.) and 20% aqueous potassium hydroxide (4 ml.), were refluxed for 10 minutes. Removal of the solvent, addition of water and neutralization with acetic acid gave the 3-acetylaminoindazole (**4a**), m.p. 204° (water), in almost quantitative yield. Similar treatment on the amino compound (**3a**), after refluxing for 2 hours, left it unchanged, only small amounts (tlc) of the rearrangement product (**4a**) being present.

Acidic Hydrolysis of 3-Acetylaminoindazoles (**4a**) and (**4b**).

An ethanolic solution (20 ml.) of **4a** or **4b** (1 g.) and concentrated hydrochloric acid (3 ml.) was refluxed for 4 hours. After removing the solvent at reduced pressure, the residue was taken up with water and the solution basified with 10% aqueous sodium hydroxide. In the case of **4a**, extraction with benzene and subsequent removal of the solvent, gave a residue which was crystallized from benzene, affording 3-aminoindazole (**6a**) (60%), m.p. 154-156°, identical in every respect to an authentic sample (7). In the case of **4b**, extraction with ether and subsequent removal of the solvent gave a residue which was chromatographed on a dry-column of deactivated silica-gel. First elution with cyclohexane-ethyl acetate (4:1) removed small amounts of by products, and then, elution with cyclohexane-ethyl acetate (2:1) gave 1-methyl-3-aminoindazole (**6b**) (60%), m.p. 96° (benzene-light petroleum) (lit. (8), m.p. 97-98°); ir: 3400, 3280, 3190 cm^{-1} (NH_2); nmr (DMSO): δ 3.88 (s, 3H, NCH_3), 5.45 (s, 2H, NH_2), 6.80-7.90 (m, 4H, Ar-H).

Anal. Calcd. for $C_8H_9N_3$: C, 65.28; H, 6.16; N, 28.55. Found: C, 65.50; H, 6.27; N, 28.66.

REFERENCES AND NOTES

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(3) The reported transformation of a 1,2,4-oxadiazole derivative containing an XYZ = CH_2-CH_2-NRR_1 sequence into a dihydropyrazole (9) cannot be classified in this series. In fact, as suggested by A. J. Boulton (2b), the *continuous π-electron system joining the reacting centers*, characteristic of *m.h.r.*, is lacking in the starting compounds.

(4) Indazole derivatives have been obtained through rerrangements in the benzo-fused series, *e.g.*, from benzofurazane oxides (10).

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