Reaction of Phenylhydrazine with $\alpha,\beta$-Unsaturated Steroidal Ketones: Synthesis of Steroidal Pyrazoles

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The reaction of $\alpha,\beta$-unsaturated ketones with phenylhydrazine has been used to synthesize steroidal pyrazoles. This method is particularly useful in the preparation of steroidal pyrazoles, which have been synthesized by other methods and screened for their biological activity. This paper describes an attempt to obtain some of the steroidal pyrazoles from the corresponding $\alpha,\beta$-unsaturated ketones and phenylhydrazine.

Pyrazoles can be conveniently obtained by the reaction of appropriate $\alpha,\beta$-unsaturated ketones with phenylhydrazine and subsequent oxidation of the resultant pyrazolines. This method often finds its application in the synthesis of steroidal pyrazoles which have been synthesized by other methods and screened for their biological activity.

Reaction of 4-cholesten-6-one (I) with phenylhydrazine in the presence of acetic acid gives 2-phenyl-4-cholesteno[4,6-c]pyrazole (V) whereas 6-oxo-4-cholesten-3-yl acetate (II) and 4-cholestone-3,6-dione (III) afford the same pyrazole, 3-oxo-2-phenyl-4-cholesten-3-one (IV) gives besides the pyrazole VI, 2-phenyl-4-cholestenol[4,6-c]pyrazol-3-one phenylhydrazone (VII) which is also obtained by treating VI with phenylhydrazine. The structures are supported mainly by their spectral behavior and chemical properties. Probable pathways for their formation have also been suggested.

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Scheme 1

Scheme 2

signals at δ 6.9 (br w, C6-H3), 4.2 (br m, C4-H), 2.7 (d, J=12 Hz, C7-H2), 1.1, 0.9, 0.8 and 0.63 An unresolved doublet but not accounting for one full proton was observed at δ 3.3 which could be assigned to C5-2H. These spectral data supported the structure VIII. Pyrazoline VIII when left at room temperature started changing into V within a couple of hours and autooxidized completely within 24 hr. The lead tetraacetate oxidation of VIII into V was found to be complete within 20 min.

Interestingly, the reaction of phenylhydrazine with ketones (II-IV) gave 3-oxo-2'-phenyl-4-cholesten-4,6,7,8-pyrazole (VI) as one of the products in each case. The identification of VI was made on the basis of elemental analysis and spectral data. The IR bands for VI were observed at 1680 s, 1640 w, 1600 m, 1550 w, 1495 s, 750 s and 690 m cm⁻¹ and the PMR signals appeared at δ 7.5 (br m, 5H, C6-H3), 2.8 (br m, 2H, C7-H2), 2.3 (m, 2H, C2-H2), 1.2, 1.1, 0.8, 0.72 and 0.66 (methyls). Its UV spectrum showed absorption maxima at 310, 258 and 226 nm. Its mass spectrum gave the molecular ion peak at m/z 486 (C33H46N2O). These spectral data fairly supported the structure VI. The formation of the pyrazole VI from different starting materials must have occurred through different pathways (Schemes 1 and 2).

In order to obtain the precursor of VI from the three sources, the ketones II, III and IV were treated with phenylhydrazine under nitrogen atmosphere. The ketone II gave, after usual work-up and column chromatography, a fraction (petroleum-ether only) as an oil for which IR bands were obtained at 3040 w, 1620 s, 1590 m, 1480 m, 1420 m, 765 s and 690 s cm⁻¹. The PMR spectrum displayed signals at δ 7.5 (br m, 5H, C6-H3), 5.8 (br m, 1H, C5-H), 2.7 (br m, 2H, C7-H2), 1.2, 1.1, 0.9, 0.8 and 0.7 (methyls). The strong
band in its IR spectrum at 1620 cm$^{-1}$ and the PMR signal at $\delta$ 5.8 for C$_2$-vinyllic proton clearly indicate a C=C to be formed by the elimination of acetic acid giving rise to XII. With a view to obtaining the pyrazole V, the compound XII was treated with sodium methoxide which resulted in its C=C double bond isomerization to give V. However, with p-toluenesulphonic acid we failed to convert XII into V.

Further elution with light petroleum-ether (55:1) afforded an unstable oily material for which only IR spectrum could be obtained as it was changing to VI as revealed by TLC. The IR bands were observed at 3060 w, 1705 m, 1500 s, 750 s and 690 cm$^{-1}$. These data are compatible with the pyrazoline structure XI. The LTA oxidation of XI converted it into VI. It is to be noted that neither the acetoxy-(IX) nor hydroxypyrazoline (X) could be isolated.

The reaction mixture was refluxed for 3 hr. Benzene was removed under reduced pressure and the residue extracted with ether. The ethereal layer was washed with water, aq. sodium bicarbonate solution (5%) and again with water. dried (Na$_2$SO$_4$) and solvent removed. Column chromatography of the residue afforded an oily compound (VIII, 800 mg) which was oxidized to V with lead tetraacetate (vide infra).

**Reaction of I with phenylhydrazine in air**

To a solution of I (1.0 g) in benzene (30 ml) were added phenylhydrazine (2 ml) and acetic acid (2 ml). The reaction mixture was refluxed for 3 hr. Benzene was removed under reduced pressure and the residue extracted with ether. The ethereal layer was washed with water, aq. sodium bicarbonate solution (5%) and again with water. dried (Na$_2$SO$_4$) and solvent removed to give a semi-solid material which was chromatographed over silica gel (30 g). Elution with light petroleum-ether (35:1) gave 2'-phenyl-4-cholesteno[4,6-cd]pyrazole (V) which crystallized from methanol, yield 400 mg, m.p. 152° (Found: C, 83.6; H, 9.9; N, 5.2. C$_{33}$H$_{48}$N$_2$ requires C, 83.9; H, 10.2; N, 5.9%).

**Oxidation of VIII with lead tetraacetate**

The oily material (VIII; 800 mg) was dissolved in 25 ml benzene and a few crystals of freshly prepared lead tetraacetate were added to it. The reaction mixture was heated on a water-bath for 20 min and benzene removed under reduced pressure. Usual work-up and removal of the solvent gave a semi-solid which after crystallization from methanol afforded the pyrazole V (250 mg), m.p. and m.m.p. 152°.
**Reaction of IV**

The bromoketone IV $^{16}$ (2.0 g) was dissolved in benzene (30 ml) and to this solution were added phenylhydrazine (2.5 ml) and acetic acid (2 ml). The mixture was refluxed for 4-6 hr. The solvent was removed under reduced pressure and the residue extracted with ether and worked-up in the usual manner. Removal of the solvent provided an oily material which was chromatographed over silica gel (60 g). Elution with light petroleum-ether (50:1) gave VII which crystallized from methanol, yield 400 mg, m.p. 195° (Found: C, 81.2; H, 9.2; N, 9.4. C$_{39}$H$_{52}$N$_{4}$ requires C, 81.3; H, 9.0; N, 9.7%).

Further elution with the same solvent system (40:1) afforded the pyrazole VI which recrystallized from methanol, yield 300 mg, m.p. 226°.

**Isomerization of XII to V**

The oily compound XII (100 mg), obtained from the reaction of II under nitrogen, was dissolved in benzene (15 ml) and to this solution was added sodium methoxide solution (20 ml). The reaction mixture was heated under reflux for 1 hr. Removal of the solvent and usual work-up gave the pyrazole V which crystallized from methanol, yield 65 mg, m.p. and m.m.p. 152°.

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