Reaction of Phenylhydrazine with α-Substituted Epoxides and Ketones. Intermediates in Osazone Formation in Steroids[1]

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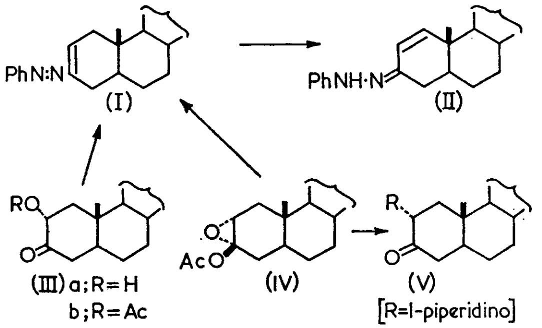
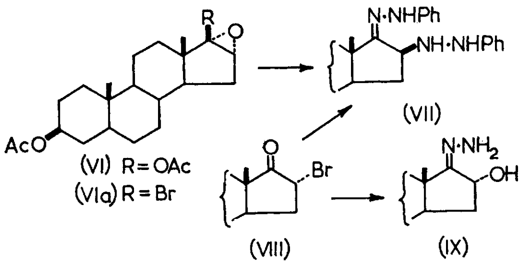
THE recent findings by Buckingham and Guthrie regarding intermediates in the formation of steroidal osazones[2] prompt us to report our results that shed additional light on this probelm. Little is known about the chemistry of negatively α-substituted epoxides.[3] In an effort to elucidate the stereochemistry of the reaction of such systems and in connection with our studies of the mechanism of osazone formation we investigated the chemistry of steroidal epoxides of type (IV), (VI) and (VIa).

Acetoxy-epoxide (IV), when exposed to phenylhydrazine–ethanol, yields the yellow 3-phenylazocholest-2-ene (I) m.p. 175—176°, azo-band at 1650 cm.$^{-1}$. This reaction, which presumably occurs by attack of phenylhydrazine on the acetate carbonyl, leading to ketol (III) as an intermediate in the formation of (I), is in marked contrast to the formation of 2-piperidinocholestan-3-one (V), m.p. 139—141°, from (IV) with piperidine (attack of piperidine at C-2). Compound (I) also results in 70% yield from the reaction of 2-bromocholestan-3-one with phenylhydrazine in alcohol at −5°.

Whereas compound (I), when purified, is stable to heat, acid, or base, as reported,[2] crude (I), prepared as above, isomerized to the colourless phenylhydrazone (II)[4] m.p. 171—173° (lit., m.p. 205°),[2] NH at 3370 cm.$^{-1}$, strong bands at 1605, 1570, 1260 cm.$^{-1}$ on recrystallization from acetone. The transformation of pure (I) into (II) can be carried out in the presence of phenylhydrazine hydrobromide but not with either phenylhydrazine or acetic acid alone, indicating the necessity for combined acid–base catalysis. Isomerization of (II) to (I) could not be achieved and only (I) [but not (II)] leads to an osazone on heating with phenylhydrazine in acetic acid.



The intermediacy of azo-olefin (I) in osazone formation can also be demonstrated by its isolation from the reaction of acetoxy-ketone (III) with phenylhydrazine. These results point to azo-olefins as intermediates in the osazone formation from steroidal α-hydroxy-, α-acetoxy-, and α-bromo-ketones with phenylhydrazine and extend recent findings in this field.[2,5,6]



On the other hand, acetoxy-epoxide (VI) with phenylhydrazine in ethanol leads in 45% yield to phenylhydrazino-phenylhydrazone (VII), m.p. 211—213°, which is also obtainable from 16α-bromo-17-oxoandrostan-3β-ol acetate (VIII) with phenylhydrazine in 70% yield and convertible into an osazone[6] with hot phenylhydrazine in acetic acid or pyridine. Compound (VII) probably results by phenylhydrazine addition to a phenylazo-intermediate similar to (I). Bromo-epoxide (VIa), m.p. 129—131°, also yields (VII). Epoxides (VI) and (VIa) can be obtained by peroxidation of the corresponding olefins.

The reaction of bromo-ketone (VIII) with hydrazine takes an entirely different course from the reaction with phenylhydrazine leading to the 16-hydroxy-17-ketohydrazone (IX), m.p. 209—211°. Here the reaction probably proceeds *via* a hydrazino-epoxide analogous to (VI).

This work was supported by a U.S. Public Health Service grant from the National Cancer Institute.

(*Received, December* 19*th*, 1966; *Com.* 1011.)

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[3] R. N. McDonald and T. E. Tabor, *Chem. Comm.*, 1966, 655; C. L. Stevens and Chung-Chang, *J. Org. Chem.*, 1962, **27**, 4392; A. Hassner and P. Catsoulacos, *ibid.*, 1966, **31**, 3149; 1967, **32**, in the press.

[4] Identical with the phenylhydrazone of cholest-1-en-3-one.

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