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THE REACTION OF TOSYLHYDRAZONES WITH LITHIUM ALUMINIUM HYDRIDE

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Abstract—The reaction of tosylhydrazones of aromatic aldehydes and steroidal ketones has been studied. In the case of aromatic aldehydes, the aldehyde group be means of the tosylhydrazone is reduced to a methyl group. In the alicyclic series, the reaction seems to follow the same course, but some exceptions are reported.

TOSYLHYDRAZONES[1] of aldehydes and ketones are, generally, crystalline compounds easily purified and readily obtained.[2] Bamford and Stevens[3] have shown that tosylhydrazones react with bases at high temperature yielding *p*-toluensulphinic acid, nitrogen and olefines: thus from cyclohexanone it is possible to obtain cyclohexene in very high yields.

This reaction has found many applications, even in the steroid field[4] and the mechanism according to the type of solvent and to the experimental conditions has been the subject of many investigations[5].

The reaction of the tosylhydrazones of 3-indolaldehyde (Ia) and β-naphthaldehyde (IIa) with $LiAlH_4$ has been investigated. In boiling THF[6] the tosylhydrazone (Ib) produces a 40–50% yield of scatole (III) identified by mixed m.p. and comparison of the I.R. and U.V. spectra with an authentic sample; whilst the tosylhydrazone (IIb) produces a 60–70% yield of β-methylnaphthalene (IV), identified by gas-chromatography in various systems, U.V. spectrum and comparison of the trinitrobenzene adduct with the same product from authentic β-methylnaphthalene.

In both cases, the reaction follows the same course, resulting in the reduction of the aldehyde group—through the corresponding tosylhydrazone—to a methyl group.

As this reaction takes place readily under such mild conditions, it was extended to carbonyl compounds of the alicyclic series, and to steroids with a carbonyl group in position 3 (5α), 3 (5β), 7 (5α) and 12 (5α). The reaction of lithium aluminium hydride with the tosylhydrazones of 5α-cholestan-3one (Vb) (m.p. 173°–174°) and of coprostan-3-one (VIb) (m.p. 168°) yields in both cases[7] saturated products, namely cholestane (VII) m.p. 79° from methanol, $[\alpha]_D^{20°} = +27°$, 70% and coprostane (VIII) m.p. 70°, $[\alpha]_D^{20°} = +25°$, 60%). Similarly, the tosylhydrazone (IXb) of 3β-acetoxy-5α-cholestane-7-one (IXa) results in a good yield (65–75%) of the corresponding 3β-hydroxy-5α-cholestane (X); m.p. 142° from diluted methanol, $[\alpha]_D^{20°} = +14°$) and the tosylhydrazone (XIb) of hecogenin acetate (XIa) yields tigogenin (XII) in a lower yield (40–50%; m.p. 201–203° from dilute methanol, $[\alpha]_D^{20°} = -62°$; acetate: m.p. 206°). Fig. 1.

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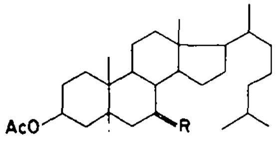
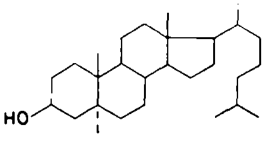
[1] Tosylhydrazones: for *p*.toluensulphonylhydrazones.
[2] For preparation of tosylhydrazine: *Org. Synth.* (**40**) 93 (1960).
[3] W. R. Bamford and T. S. Stevens, *J. Chem. Soc.* 4735 (1952).
[4] E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.* **78**, 6269 (1956); J. Elks, G. H. Phillips, D. A. H. Taylor and L. J. Wyman, *J. Chem. Soc.* 1793 (1954) etc.
[5] J. W. Powell and M. C. Whiting, *Tetrahedron* **12**, 168 (1961); L. Friedman and H. Shechter, *J. Amer. Chem. Soc.* **83**, 3159 (1961).
[6] THF: for dry, freshly distilled tetrahydrofurane.
[7] L. Caglioti. M. Magi. *Tetrahedron Letters* 1261 (1962).

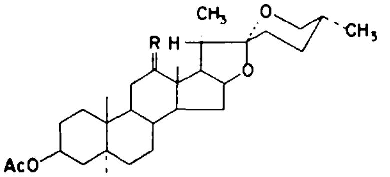
All these products were identified by comparison with authentic samples (m.p. mixed m.p., specific rotation and I.R. spectrum). But, the examination of the reduction products by thin layer chromatography on Kieselgel G Merck—$AgNO_3$ plates,[8] proved in the case of cholestane and coprostane, the presence of traces of unsaturated compounds.



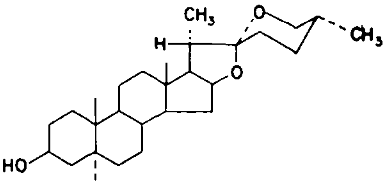
IXa R=O
IXb R=N-NH-SO_2-C_6H_4-p.CH_3



X



XIa R=O
XIb R=N-NH-SO_2-C_6H_4-p.CH_3



XII

Extension of the reaction to steroids with a carbonyl group in position 17[7] has given unexpected results; the tosylhydrazone (XIIIb) of the 17-keto-3β-acetoxy-5α-androstane (XIIIa) producing in 60–70% yield the Δ^{16}-5α-androsten-3β-ole (XIV, m.p. 123°, $[\alpha]_D^{20°} = +16°$). This product, identified by comparison with an authentic sample, was hydrogenated with platinum in acetic acid yielding after absorption of 1·0 mole hydrogen the 5α-androstan-3β-ole (XV; m.p. 148°, $[\alpha]_D^{20°} = -1°$); also identified by comparison with an authentic sample.

Similarly, the tosylhydrazone (XVIb) of estrone methyl ether (XVIa): resulted in a 60–70% yield of the corresponding product unsaturated at 16 (XVII; m.p. 63°, $[\alpha]_D = +113°$) which on hydrogenation, and after absorption of 1·1 moles hydrogen, yielded the corresponding saturated product (XVIII m.p. 75–76°, $[\alpha]_D^{20°} = +87°$), identified by comparison with an authentic sample of 3-methoxy-1,3,5(10) estratriene.

The reaction of XVII with osmium tetroxide in pyridine-ethyl ether, followed by treatment of the reaction mixture, after evaporation *in vacuo* of the solvents, with mannitol in 5% methanolic sodium hydroxide supplied the corresponding diol (XIX; m.p. 158–160°, $[\alpha]_D^{20°} = +48°$) in high yield. (Fig. 2).

The reaction of tosylhydrazones of 17-keto androstane yielding an unsaturated product is analogous to the reaction of Bamford-Stevens. It is however, important to note that the treatment of (XVIb) with sodium in ethylene glycol yields[9], by migration

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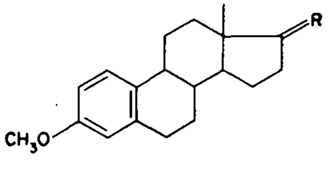
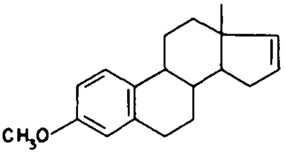
[8] C. B. Barret, M. S. J. Dallas, and F. B. Padley, *Chem. Ind.* 1050 (1962).
[9] W. F. Johns, *J. Org. Chem.* **26**, 4583 (1961).

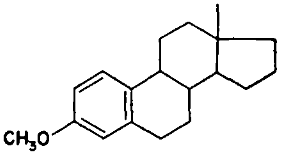
of the 18-methyl group, the 17β-methyl-3-methoxy-18 norestra-1,3,5(10), 13(14)-tetraene and other isomers.



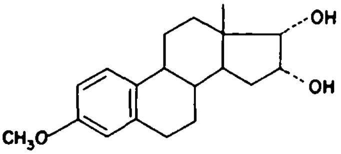
XVIa R=O
XVIb R=N-NH-SO$_2$-C$_6$H$_4$-p.CH$_3$



XVII



XVIII



XIX

The lithium aluminium hydride reduction of tosylhydrazones of $\alpha\beta$-unsaturated ketones, likewise produced interesting results. The tosylhydrazone of Δ^1,-3-keto-cholestene (XXb) resulted in a good yield of a mixture of Δ^1 and Δ^2 5α-cholestene,[10] with a high percentage of Δ^2 5α-cholestene, whilst the tosylhydrazone of Δ^4-3-keto-cholestene resulted in a mixture consisting of 30% Δ^{2-4} cholestadiene, and a mixture of cholestenes with only one double bond, probably Δ^3 and Δ^4 cholestene.

The experimental data available at present indicates that this reaction promises to be an efficient method for the reduction of carbonyls to CH$_2$ under relatively mild conditions.

The formation of the reduction product is combined (except in the case of aromatic aldehydes) with the formation of traces of unsaturated products.[11] The sole formation of unsaturated compounds only occurs in the case of tosylhydrazones of compounds possessing a carbonyl in position 17.

Work in this field is in progress, in order to ascertain the possible existence of other exceptions, and to determine the limits and the course of the reaction.

EXPERIMENTAL[12]

β-naphtaldehyde tosylhydrazone (IIb). β-Naphtaldehyde (5 g) was added to a dilution of 8·5 g tosylhydrazine in 200 cc methanol and the mixture boiled under reflux for 4 hr. On cooling, naphtaldehyde tosylhydrazone separated and recrystallized from methanol in needles, mp 174° (dec).

In a similar manner, derivatives were obtained of 5α-cholestan-3-one (Vb; from ether-heptane, mp 173°–174°); coprostan-3-one (VIb; from ether-methanol, mp 168°); 7-keto-3β-acetoxy-5α-cholestane (IXb; from ether-heptane, mp 233°); hecogenin acetate (XIb; from methanol, mp 266°); 3β-acetoxy-5α-androstane-17 one (XIIIb; from dil methanol, mp 175°); oestrone methyl ether XVIb; from methanol, mp 198°); Δ^4-cholesten-3 one (XXIb; from methanol, mp 142°); Δ^1-5α-cholesten-3 one (XXb; from methanol, mp 162°).

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[10] Tentatively identificated by thin-layer chromatography.

[11] The considerable formation of diene compounds in the case of the reduction of the tosylhydrazone of Δ^4-3-keto-cholestene (if compared with the absence of doubly unsaturated compounds in the case of the tosylhydrazone of Δ^1-3-keto-5α-cholestene) is probably ascribed to the same course.

[12] M.p's. are uncorrected, rotations were taken in chloroform, U.V. spectra in ethanolic solution and I.R. spectra in N.J. suspension.

Treatment of β-naphthaldehyde tosylhydrazone (IIb) *with* $LiAlH_4$. To a solution of IIb (2g) in 50 cc THF $LiAlH_4$ (3g) was added and the mixture refluxed overnight. After careful decomposition of excess hydride with moist ether and water, the ethereal solution was washed with dil. H_2SO_4 and water, dried and evaporated. The low melting residue (620 mg, 70%, λ_{max} 224, 265, 275, 286, 306 mμ) furnished a 1,3,5-trinitrobenzene derivative (mp 120–122°) identical with an authentical specimen obtained from β-methylnaphthalene.

Treatment of indole-3-aldehyde tosylhydrazone (Ib) *with* $LiAlH_4$. Indole-3-aldehyde (1 g) was added to a solution of tosylhydrazine (1·7 g) in 50 cc methanol, and the mixture boiled 4 hr under reflux. The solution was then evaporated *in vacuo*, extracted with ether, the ether washed with water, dried and evaporated. The residue was dissolved in 50 cc THF, 2 g $LiAlH_4$ added and the mixture refluxed overnight. The usual procedure produced 335 mg of crystalline residue (mp 95°, 35–40%, λ_{max} 223, 275, 282, 291 mu). Mixed m.p. with an authentical specimen of scatole showed no depression.

Treatment of 5α-cholestan-3-one tosylhydrazone (5b) *with* $LiAlH_4$. To a solution of 1g 5α-cholestan-3-one tosylhydrazone in 50 cc THF 1·5 g $LiAlH_4$ were added and the mixture refluxed overnight. The usual procedure yielded 455 mg of crystalline residue (mp 79°, from methanol, $[\alpha]_D^{20°} = +27°$; Found C, 87·15; H, 12·83. Calc. for $C_{27}H_{48}$: C, 87·02; H, 12·98%. Yield: 70%). Spot test with tetranitromethane was negative. The compound proved identical (mixed mp, I.R. spectrum) to an authentical sample of cholestane.

Treatment of coprostan-3-one tosylhydrazone with $LiAlH_4$. To a solution of 1 g coprostan-3-one tosylhydrazone in 30 cc THF 1·5 g $LiAlH_4$ was added, and the mixture refluxed overnight. The usual procedure yielded 425 mg of crystalline residue (mp 70°, from methanol, $[\alpha]_D^{20°} = +25°$; Found: C, 86·95; H, 12·79. Calc. for $C_{27}H_{48}$: C, 87·02; H, 12·98%. Yield: 60–70%). Spot test with tetranitromethane was negative. The compound proved identical to an authentic sample of coprostane.

Treatment of 3β-acetoxy-5α-cholestan-7-one tosylhydrazone (IXb) *with* $LiAlH_4$. To a solution of 1 g 3β-acetoxy-5α-cholestan-7-one tosylhydrazone in 40 cc THF g $LiAlH_4$ was added and the mixture refluxed overnight. The usual procedure yielded 460 mg of crystalline residue (mp 142° from dil methanol, $[\alpha]_D^{20°} = +26°$; Found: C, 83·51; H, 12·40. Calc. for $C_{27}H_{48}O$: C, 83·43; H, 12·45%. Yield: 65%). Acetate: mp 110° from methanol, $[\alpha]_D^{20°} = +14°$ (Found; C, 80·53; H, 11·61. Calc. for $C_{29}H_{50}O_2$: C, 80·87; H, 11·70%). Spot test with tetranitromethane was negative. The compound, and its acetate, proved identical with authentic samples of 3β-hydroxy and 3β-acetoxy-5α-cholestane.

Treatment of hecogenin acetate tosylhydrazone (XIb) *with* $LiAlH_4$. To a solution of 1 g hecogenin acetate tosylhydrazone in 40 cc THF 1·5 g $LiAlH_4$ was added, and the mixture refluxed overnight. The usual procedure yielded 360 mg of crystalline residue (mp 203° from dil methanol, $[\alpha]_D^{20°} = -62°$; Found: C, 78·07; H, 10·28. Calc. for $C_{27}H_{44}O_3$: C, 77·83; H, 10·65%; Yield: 40–50%). The acetate mp 206° was crystallized from methanol.) The compound, and its acetate, proved identical with authentic samples to tigogenin and tigogenin acetate.

Treatment of Δ^4*-3 keto-cholestene tosylhydrazone* (XXIb) *with* $LiAlH_4$. To a solution 1 g Δ^4-3 keto-cholestene tosylhydrazone in 30 cc THF 1·5 g $LiAlH_4$ was added and the mixture refluxed overnight. The usual procedure yielded 410 mg of a complex mixture of hydrocarbons. The U.V. spectrum of the mixture (λ_{max} 265, 275, 285 mu) indicated the presence of 30% of $\Delta^{2,4}$ cholestadiene. The remaining 70% is probably a mixture of Δ^4 and Δ^3 cholestenes (thin layer chromatography on Kieselgel G Merck-$AgNO_3$ plates).

Treatment of Δ^1*-3-keto 5α-cholestene tosylhydrazone* (XXb) *with* $LiAlH_4$. To a solution of 1 g Δ^1-3-keto-5α-cholestene tosylhydrazone in 30 THF 1·5 g $LiAlH_4$ was added and the mixture refluxed overnight. The usual procedure yielded 460 mg of a mixture of hydrocarbons (mp 67° from methanol, $[\alpha]_D^{20°} = +59°$, no adsorption in UV spectrum). Examination of the mixture with thin layer chromatography (Kieselgel G-$AgNO_3$) showed the presence of Δ^2 (more abundant) and of Δ^1-5α-cholestene.

Treatment of 3β-acetoxy-17-keto-5α-androstane tosylhydrazone (XIIIb) *with* $LiAlH_4$. To a solution of 1 g 3β-acetoxy-17-keto-5α-androstane tosylhydrazone in 30 cc THF 1·5 g $LiAlH_4$ was added,and the mixture refluxed overnight. The usual procedure yielded 390 mg of crystalline residue (mp 123°, $[\alpha]_D^{20°} = +16°$; Found: C, 83·22; H, 11·20. Calc. for $C_{19}H_{30}O$: C, 83·15; H, 11·02%. Yield: 60–70%). The compound proved identical with an authentic sample of Δ^{16}-3β-hydroxy-5α-androstene.

Reduction of Δ^{16}*-3β-hydroxy-5α-androstene with* Pt. 100 mg of Δ^{16}-3β-hydroxy-5α-androstene in 15 ml acetic acid were shaken with 50 mg prereduced PtO_2 in hydrogen atmosphere for 4 hr. After adsorption of 1·0 mole hydrogen the acetic solution was filtered, dried *in vacuo* and the crystalline residue (mp 148°, from dil methanol, $[\alpha]_D^{20°} = -1°$; Found: C, 82·79; H, 11·88; Calc. for $C_{19}H_{32}O$: C, 82·54; H, 11·65%) was identical with an authentic specimen of 3β-hydroxy-5α-androstene.

Treatment of oestrone methyl ether tosylhydrazone (XVIb) *with* $LiAlH_4$. To a solution of 1 g oestrone methyl ether tosylhydrazone in 30 cc THF 1·5 g $LiAlH_4$ was added, and the mixture refluxed overnight. The usual procedure yielded 415 mg of crystalline residue (mp 63°, from methanol,

$[\alpha]_D^{20°} = +113°$; Found: C, 84·93; H, 9·05. Calc. for $C_{19}H_{24}O$: C, 85·02; H, 9·01%. Yield: 70%). The compound was the 3-methoxy-1,3,5(10),16-estratetraene.

*Reduction of 3-methoxy-*1,3,5(10),16*-estratetraene with* Pd. 3-Methoxy-1,3,5(10),16-estratetraene (106 mg) in 20 cc ethanol were shaken with 50 mg prereduced 10% Pd charcoal in an hydrogen atmosphere. After adsorption of 1·1 mole H_2 the alcoholic solution was filtered, dried *in vacuo*: the crystalline residue (mp 75–76°, from methanol, $[\alpha]_D^{20°} = +87°$; Found: C, 84·34; H, 9·89. Calc. for $C_{19}H_{26}O$: C, 84·39; H, 9·69%) was identical with an authentic specimen of 3-methoxy-1,3,5(10)-estratriene.

3-Methoxy-1,3,5(10),16-estratetraene in 20 ml dry ether and two drops of pyridine were reacted during 48 hr at room temp with 250 mg of OsO_4. After evaporation *in vacuo* of the solvents, the reaction mixture was boiled 3 hr with 1 g mannite in 15 cc of methanolic NaOH (5%).

After working up with ether and evaporation of the solvent, 120 mg of crystalline residue were obtained (mp 158–160°, from acetone–heptane, $[\alpha]_D^{20°} = +48°$; Found: C, 72·52; H, 8·68. Calc. for $C_{19}H_{26}O_3$: C, 75·46; H, 8·67%). The compound was 16α-17α-dihydroxy-3-methoxy-1,3,5(10)-estratriene.

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