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HYDRATION OF SOME BICYCLIC ETHYNYL ALCOHOLS AND DERIVATIVES

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Abstract—The epimeric ethynyl alcohols II and III react with mercuric acetate to yield the same acetoxy dione VI, also obtained by hydration of the β-ethynyl-α-acetoxy ketone X. Inversion of configuration occurs, therefore, during the conversion of the α-ethynyl alcohol II to the acetoxy dione VI. If the above reaction is done in the presence of pyridine, the ethynyl alcohol II furnishes the epoxy intermediate XII which isomerizes readily to either the acetoxy dione VI or its epimer XI, obtained independently. The observed inversion of configuration has been interpreted to involve the epoxy intermediate XII.

EARLIER work[1] has shown that the product of condensation of lithium acetylide with 1,6-dioxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene (I) is the β-hydroxy-α-ethynyl alcohol II which can be epimerized to the α-hydroxy-β-ethynyl alcohol III by treatment with BF_3-etherate. The configuration of the ethynyl alcohol II is the reverse of the one assigned by other workers[2] and was preferred by us on the basis of NMR evidence. The conversion[3] of the α-ethynyl alcohol II to the bridged ketol IV whose structure has since been confirmed[4] by X-ray studies provides further support for our assignment.

Studies of hydration of the ethynyl alcohols II and III and their derivatives are now reported. These were undertaken primarily to ascertain if homoannulation of the type encountered[5] during attempted hydration of 17-ethynyl steroids and/or bridging reactions of the type involved in the formation of compound IV can be realized. As will be seen from the sequel, no evidence was obtained for the occurrence of such unusual reactions under a variety of conditions of hydration using mercury catalyst; however, some unexpected transformations and products were encountered and these are indicated in Chart I.

As already reported[3] the treatment of the epimeric ethynyl alcohols II and III with Nieuwland's catalyst leads respectively to the compounds IV and V. With the milder mercurated resin catalyst found[6] to be effective for similar hydrations, no hydration could be effected with both the ethynyl alcohols II and III; only the starting materials were recovered. With mercuric acetate in ethanol both the epimers furnished surprisingly the same acetoxy dione VI, having the expected UV, IR and NMR absorptions. This dione could also be obtained by hydrating similarly the crude mixture of the ethynyl alcohols II and III, usually obtained[1] in large amounts during the

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[1] M. S. Newman, S. Ramachandran, S. K. Sankarappa and S. Swaminathan, *J. Org. Chem.* 26, 727 (1961).

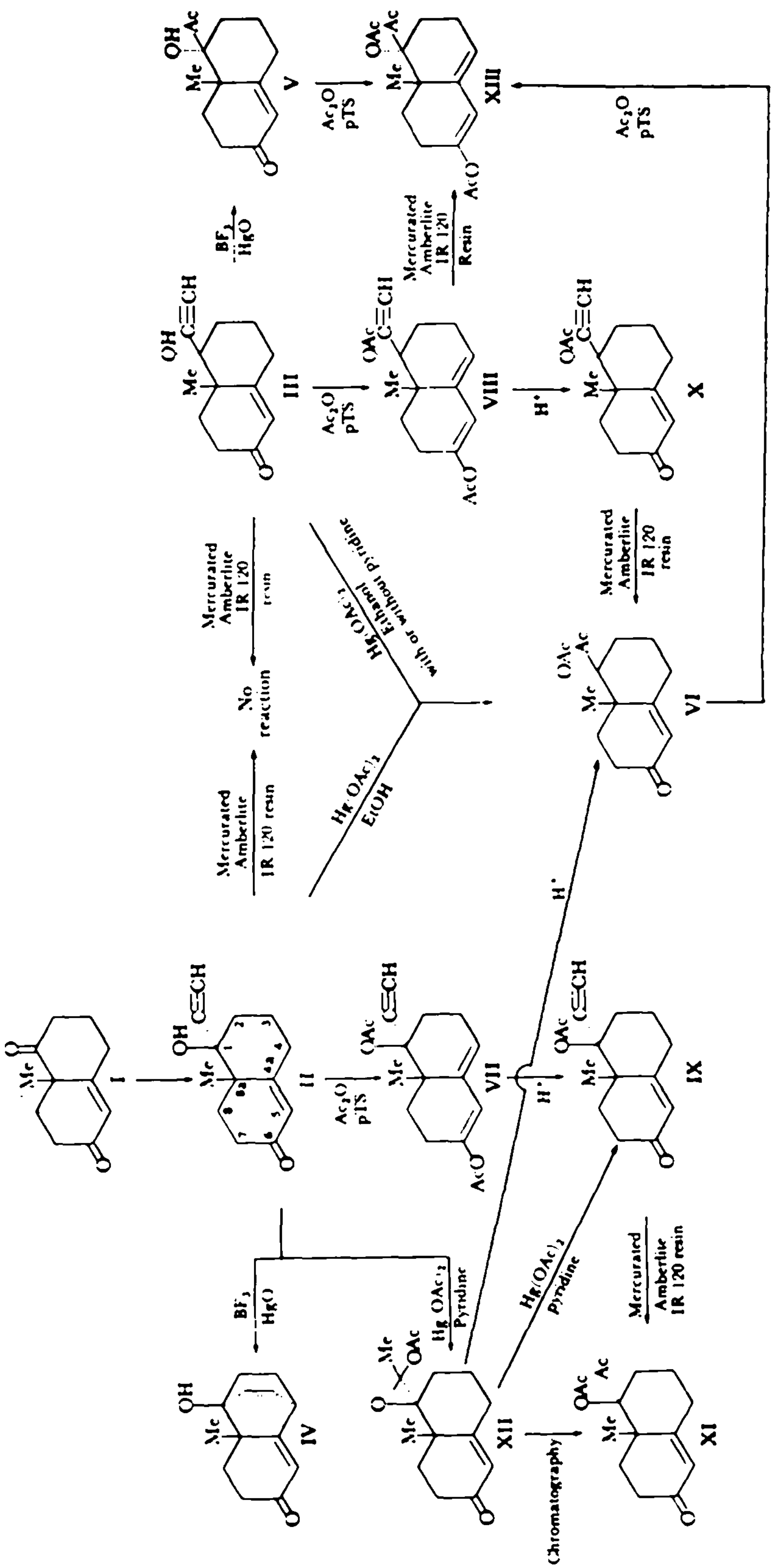
[2] I. N. Nazarov and I. A. Gurvich, *Zhur. Obsch. Khim.* 25, 956 (1955).

[3] S. Swaminathan, S. Ramachandran and S. K. Sankarappa, *Tetrahedron* 20, 1119 (1964).

[4] K. Venkatesan and E. Subramanian, *Z. Krist.* 123, 206 (1966).

[5] L. F. Fieser and M. Fieser, *Steroids* pp. 577–578. Reinhold, New York, N.Y. (1959).

[6] M. S. Newman, *J. Am. Chem. Soc.* 75, 4740 (1953).



I
II
III
IV
V
VI
VII
VIII
IX
X
XI
XII
XIII
Me
OH
C≡CH
OAc
Ac
AcO
1
2
3
4
4a
5
6
7
8
8a
Ac₂O
pTS
H⁺
BF₃
HgO
Hg(OAc)₂
Pyridine
Hg(OAc)₂
EtOH
Hg(OAc)₂
Ethanol
with or without pyridine
Mercurated
Amberlite
IR 120 resin
No
reaction
Chromatography

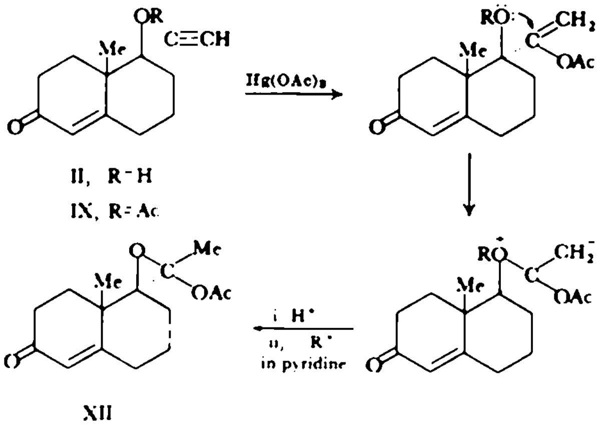
preparation of the β-epimer III. It was obvious that inversion of configuration had occurred and with a view to fix the configuration of the acetoxy dione VI, both the epimeric ethynyl diacetates VII and VIII previously[1] described were hydrolysed with dilute acid to furnish the epimeric ethynyl monoacetoxy ketones IX and X respectively and then hydrated. Unlike the parent ethynyl alcohols II and III, these acetoxy derivatives IX and X were found to undergo ready hydration in the presence of the resin catalyst to furnish the β-acetoxy dione XI and the epimer VI respectively, showing conclusively that the above inversion of configuration occurs during the transformation of the α-ethynyl alcohol II to the compound VI. An attempted hydration of the β-acetoxy-α-ethynyl ketone IX with Nieuwland's catalyst expected to furnish the acetate of the bridged ketol IV, also furnished the β-acetoxy dione XI instead but in poorer yield. It was also found that hydration of the β-ethynyl diacetate VIII and acetylation of either compound V or VI gave the same diacetoxy ketone XIII in excellent yields. This establishes that no inversion is involved in the hydration of the β-ethynyl alcohol III with Nieuwland's catalyst to the ketol V, previously reported.[3]

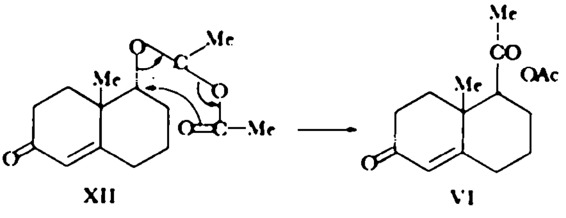
In attempts to gain a better understanding of the reactions leading to the inverted product VI from II, both the ethynyl alcohols II and III were treated with mercuric acetate in ethanol containing an excess of pyridine to neutralize the acetic acid formed. Whereas the β-ethynyl alcohol III gave the α-acetoxy dione VI, the α-ethynyl epimer II furnished a colourless crystalline material m.p. 97·4–98·6°, isomeric with the compounds VI and XI in 54·1 % yield. This product which also resulted by treatment of the β-acetoxy-α-ethynyl ketone IX under similar conditions, was soon found to undergo easy transformation to either compound XI or VI depending on experimental conditions. Thus, chromatography over basic alumina converted it to the β-acetoxy dione XI whereas treatment with dilute hydrochloric acid transformed it to the epimeric α-acetoxy dione VI. In fact, it was soon found that the conditions of preparation of the above solid itself were critical since often either epimer VI or XI resulted due to some unaccountable variations in the work-up. The product, unlike the epimers VI and XI which showed three carbonyl absorptions in the infra-red, showed only two such absorptions—one, an unconjugated C═O at 5·78 μ and another, a conjugated C═O at 5·98 μ. The former was undoubtedly an acetate carbonyl in view of the strong absorption at 8 μ, while the UV absorption at 243 mμ (ε, 4·08) confirmed the presence of the conjugated carbonyl. A comparison of the NMR spectrum of the material with those of compounds VI and XI revealed significant differences only in the region of absorptions of Ac and OAc. Whereas these showed up as separate singlets for compound VI at τ 7·82 and τ 7·92 and for the epimer XI at τ 7·85 and τ 7·9 respectively, in the case of the above solid these peaks merged to give a single absorption (ca. 8 protons) centered at τ 7·8. The above data seem best accounted for by the epoxide structure XII in terms of which the inversion of configuration and the unusual acetylation of a tertiary —OH involved in the conversion of the ethynyl alcohol II to the compound VI are best explained.

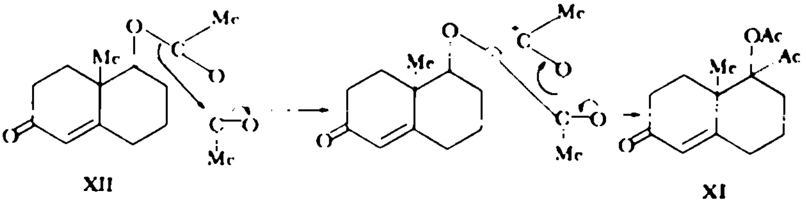
A priori, it seems likely that this conversion occurs via the sequence

$$\text{II} \rightarrow \text{III} \rightarrow \text{X} \rightarrow \text{VI} \qquad \text{(a)}$$

since the epimerization[1] of the α-ethynyl alcohol II to the β-ethynyl alcohol III and the hydration of the α-acetoxy ethynyl ketone X have both been experimentally realized.







Compound VI may also be pictured to arise by acetylation of the ketol V formed either by epimerization of the α-ethynyl alcohol II to the β-ethynyl alcohol III followed by hydration or by a reverse sequence. Either variation of this route is unsatisfactory since (i) compound II has resisted all our attempts at hydration to the corresponding ketol and (ii) the hydration of the β-ethynyl alcohol III to the ketol V proceeds only in poor yields. The epimerization of the ethynyl alcohol II involved in the above preferred sequence (a) may be pictured to arise by an initial cleavage of the C_1—C_{8a} bond and then reformation since there is evidence available that such a cleavage does take place in certain rearrangements[7,8] of the compound II and related δ-hydroxy-α,β-enones. There is however a serious drawback to the postulated sequence (a). Previous studies[1] have shown that the epimerization of the ethynyl alcohol II is only partial under the best of conditions—the equilibrium mixture containing roughly only 30% of the epimer III and 70% of unchanged alcohol II. Significant amounts of the β-acetoxy dione XI should also have been formed along with its epimer VI which was however the sole product obtained. An alternative explanation free from this drawback which provides an understanding at the same time of the unusual acetylation of a tertiary hydroxyl group with mercuric acetate is to invoke the epoxy intermediate XII which

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[7] S. Swaminathan, J. P. John and S. Ramachandran, *Tetrahedron Letters* 729 (1962).

[8] S. Swaminathan, R. K. Natarajan, S. Ramachandran and S. K. Sankarappa, *J. Org. Chem.* 31, 656 (1966).

as already mentioned has been isolated, though only from the α-ethynyl alcohol II. Its formation from the α-ethynyl alcohol II or its monoacetoxy derivative IX and conversion exclusively either to the α-acetoxy dione VI or the epimeric β-acetoxy dione XI may be rationalized as opposite.

The above explanation seems plausible in view of reports[9] that some steroidal enol acetate (Δ^{16} and Δ^{17}) epoxides with structures similar to XII undergo similar acetyl group migrations with or without inversion. It seems likely that epoxide compounds of type XII are intermediates in mercuric acetate catalyzed hydrations of other α-ethynyl alcohols.

EXPERIMENTAL

1α-*Acetoxy*-1β-*acetyl*-6-*oxo*-8a-*methyl*-1,2,3,4,6,7,8,8a-*octahydronaphthalene* (VI)

(a) *By treatment of* II *with mercuric acetate.*[10] A mixture of II (2·04 g), mercuric acetate (6·05 g) and abs EtOH was refluxed for 4 hr. The Hg formed was filtered off, the filtrate saturated with H_2S and the ppt of HgS removed. The filtrate was concentrated, extracted with ether and the extract washed with $NaHCO_3$aq. Removal of solvent furnished a solid (1·5 g) which after recrystallization from ether had m.p. 127–129°. Repeated crystalizations from ether afforded the analytical sample m.p. 131–132°. (Found: C, 68·1, 68·1; H, 7·6, 7·6. $C_{15}H_{20}O_4$ requires: C, 68·2; H, 7·6%.) IR spectrum (Chf): 5·78, 5·86, 6·02, 6·2 and 8·08 μ; UV (EtOH): 237 mμ, (ε, 4·25). NMR ($CDCl_3$): τ 4·17 (1H, d, $-\overset{O}{\overset{\|}{C}}-\underset{H}{\underset{|}{C}}=C-$), τ 7·82 (3H, s $-\overset{O}{\overset{\|}{C}}-CH_3$), τ 7·92 (3H, s $-O-\overset{O}{\overset{\|}{C}}-CH_3$) and τ 8·72 (3H, s, $-\overset{|}{\underset{|}{C}}-CH_3$).

(b) *By treatment of* III *with mercuric acetate.* Treatment of III (1 g) with mercuric acetate (3·5 g) in EtOH (30 ml) similarly furnished VI (0·6 g) m.p. and mixed m.p. 131–132° and having identical IR absorptions.

(c) *By hydration of* X. A mixture of X (1·3 g), mercurated amberilite IR 120 resin (1·3 g), MeOH (25 ml) and water (0·15 ml) was stirred for 3 hr at 60–70°. The resin was filtered off and washed with alcohol. The filtrate was evaporated and the residue taken up in ether, dried and concentrated to furnish VI m.p. and mixed m.p. with the sample obtained from (a): 130–131° (1·13 g, 81%). With a reaction period of 1 hr, the hydration of X was incomplete.

1β-*Ethynyl*-1α-*acetoxy*-6-*oxo*-8a-*methyl*-1,2,3,4,6,7,8,8a-*octahydronaphthalene* (X)

The diacetate VIII (2·9 g) was treated with 4N HCl (5 ml) in EtOH (50 ml) and left overnight at room temp. The solvent was removed *in vacuo* and the residue taken up in ether, washed with water and brine and dried over $MgSO_4$. Concentration of the ether solution gave X, m.p. 115–117° (1·95 g, 78·72%). Repeated crystallizations from pet. ether (60–80°) afforded the analytical sample m.p. 119·5–120·5°. (Found : C, 72·8; H, 7·5; $C_{15}H_{18}O_3$ requires: C, 73·2; H, 7·3%.) IR spectrum (Chf): 3·0, 5·725, 6·0 and 6·15 μ; UV (EtOH): 238 mμ (ε, 4·24). NMR ($CDCl_3$): τ 4·13 (1H, d, $-\overset{O}{\overset{\|}{C}}-\underset{H}{\underset{|}{C}}=C-$), τ 7·33 (1H, s, $-C\equiv C-H$), τ 7·97 (3H, s, $-O-\overset{O}{\overset{\|}{C}}-CH_3$) and τ 8·57 (3H, s, $-\overset{|}{\underset{|}{C}}-CH_3$).

1α-*Ethynyl*-1β-*acetoxy*-6-*oxo*-8a-*methyl*-1,2,3,4,6,7,8,8a-*octahydronaphthalene* (IX)

The above procedure was followed with VII (22·4 g), 4N, HCl (40 ml) and EtOH (200 ml) when IX, m.p. 102–104° (15·5 g, 81·02%) was obtained. A sample recrystallized from pet. ether, m.p.

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[9] N. S. Leeds, D. K. Fukushima and T. F. Gallagher, *J. Am. Chem. Soc.* **76**, 2941, 2943 (1954).

[10] This experiment was first carried out by Dr. S. K. Sankarappa to whom our thanks are due.

106–107°. (Found: C, 72·8; H, 7·5. $C_{15}H_{18}O_3$ requires: C, 73·2; H, 7·3%.) IR spectrum (Chf): 3·02, 5·75, 6·02 and 6·175 μ; UV (EtOH): 234 mμ (ε, 4·14). NMR ($CDCl_3$): τ 4·12 (1H, d, $-\overset{\overset{O}{\|}}{C}-\underset{\underset{H}{|}}{C}=C-$), τ 7·27 (1H, s, $-C\equiv C-H$), τ 7·92 (3H, s, $-O-\overset{\overset{O}{\|}}{C}-CH_3$) and τ 8·6 (3H, s, $-\underset{|}{\overset{|}{C}}-CH_3$)

1α-Acetyl-1β-acetoxy-6-oxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene (XI)

(a) *By hydration of* IX *with mercurated resin.* Compound IX (1·0 g) was treated with mercurated amberlite IR 120 resin (1·0 g) as in the hydration of X. The reaction mixture was stirred for 1 hr. The product XI obtained was crystallized from ether, m.p. 106–108° (0·85 g, 79·2%). The analytical sample obtained after several recrystallizations from ether had m.p. 110–111°. (Found: C, 68·1; H, 7·6. $C_{15}H_{20}O_4$ requires: C, 68·2; H, 7·6%.) IR spectrum (Chf): 5·76, 5·85, 6·01 and 6·18 μ; UV (EtOH): 241 mμ (ε, 4·09). NMR ($CDCl_3$): τ 4·26 (1H, d, $-\overset{\overset{O}{\|}}{C}-\underset{\underset{H}{|}}{C}=\underset{|}{C}-$), τ 7·85 (3H, s, $-\overset{\overset{O}{\|}}{C}-CH_3$), τ 7·90 (3H, s, $-O-\overset{\overset{O}{\|}}{C}-CH_3$) and τ 8·62 (3H, s, $-\underset{|}{\overset{|}{C}}-CH_3$).

(b) *By hydration of* IX *with Nieuwland's catalyst.* A soln of IX (2·0 g) in MeOH (30 ml) was stirred at 70° for 4 hr with Nieuwland's catalyst (prepared from red HgO, 0·5 g, BF_3-etherate, 1·0 ml and MeOH, 2 ml) and left overnight. The mixture was cooled, treated with anhyd K_2CO_3 (1·0 g) and decanted from the sludge of Hg and undissolved matter. The MeOH was removed and the residue extracted with ether. The ether extract was washed with water and brine, dried ($MgSO_4$) and concentrated. Trituration with ether furnished XI (0·35 g), m.p. and mixed m.p. with authentic sample XI, 110–111°.

The organic extract remaining after separation of XI furnished a liquid product of uncertain structure.

Treatment of II *with mercuric acetate in the presence of pyridine*

To a hot soln of mercuric acetate (3·2 g) in a mixture of abs EtOH (15 ml) and pyridine (20 ml), II (2·1 g) was added and heated at gentle reflux for 4 hr. The reaction mixture was filtered from the pptd Hg and filtrate saturated with H_2S. The pptd HgS was removed and the filtrate concentrated. The residue was taken up in ether, washed successively with water, 5% HCl, water, dil $NaHCO_3$aq, water and brine and dried over $MgSO_4$. On concentration a residue (2·1 g) was obtained which on trituration with ether and cooling gave a solid (XII; 1·43 g) m.p. 92–95°. For purification it was chromatographed over neutral alumina and eluted with ether. The analytical sample was obtained after 3 crystallizations from ether; m.p. 97·4–98·6°. (Found: C, 68·3, 68·3; H, 7·7, 7·4; $C_{15}H_{20}O_4$ requires: C, 68·2; H, 7·6%.) IR spectrum (KBr): 5·78, 5·98 and 6·14 μ, UV (EtOH): 243 mμ (ε, 4·08). NMR ($CDCl_3$): τ 4·16 (1H, s, $-\overset{\overset{O}{\|}}{C}-\underset{\underset{H}{|}}{C}=\underset{|}{C}-$), τ 7·8 (s for ca. 8 protons attributed to $-O-CO-CH_3$, epoxide CH_2 plus 2 other protons) and τ 8·55 (3H, s, $-\underset{|}{\overset{|}{C}}-CH_3$).

The monoacetate IX on similar treatment with mercuric acetate and pyridine gave XII m.p. 95–96° having no depression in m.p. with the sample obtained from II.

Treatment of III *with mercuric acetate in the presence of pyridine*

A mixture of III (1·5 g), mercuric acetate (3·0 g), pyridine (20 ml) and abs EtOH (15 ml) was refluxed for 4 hr and the pptd Hg was filtered off. The dissolved Hg salt was removed as HgS by passing H_2S. The clear filtrate was concentrated and extracted with ether; the ether extract, after washing with dil HCl and water, on concentration gave VI (630 mg); mixed m.p. with an authentic sample, 130–131°. The mother liquor on passing through alumina gave an additional amount (250 mg) of VI (Net yield: 45%). The same product was obtained by omitting the acid wash in the above work up.

Isomerization of XII

Compound XII on passing through a column of basic alumina and elution with ether gave quantitatively XI, m.p. and mixed m.p. 110–111° and with superimposable IR absorptions. XII could also be converted to VI by treatment with alcoholic HCl at room temp. In fact, in some attempted preparations of XII, epimer VI resulted as the sole product due apparently to some variations in the work up which have not been understood yet.

1α,6-*Diacetoxy*-1β-*acetyl*-8a-*methyl*-1,2,3,7,8,8a-*hexahydronaphthalene* (XIII)

(a) *By acetylation of* VI. Compound VI (750 mg) was treated with a mixture of Ac_2O (6 ml) and *p*-toluenesulphonic acid (~10 mg) and the mixture left overnight. The reaction mixture was poured into ice water when solid separated. It was filtered off, dissolved in ether dried and solvent removed. The residue (550 mg) was recrystallized from ether to furnish XIII, m.p. 108–110°. The analytical sample obtained after 4 recrystallizations from pet. ether (60–80°) had m.p. 113–115°. (Found: C, 66·9; H, 7·5; $C_{17}H_{22}O_5$ requires: C, 66·7; H, 7·2%.) IR spectrum (Chf): 5·78, 5·825, 5·9, 6·035 and 6·13 μ; UV (EtOH): 232 mμ (ε, 4·15). NMR ($CDCl_3$): τ 4·23 (d, C_5 proton), τ 4·53 (m, C_4 proton), τ 7·8 (s, $-\overset{\overset{O}{\|}}{C}-CH_3$), τ 7·88 and τ 7·94 (ss, two $-O-\overset{\overset{O}{\|}}{C}-CH_3$) and τ 8·91 (s, $-\overset{|}{\underset{|}{C}}-CH_3$).

(b) *By acetylation of* V. Compound V (300 mg) was similarly acetylated with Ac_2O (6 ml) and *p*-toluenesulphonic acid (~10 mg) and the product obtained (125 mg) was twice recrystallized from pet. ether (60–80°), m.p. and mixed m.p. 113–115° with material obtained in the previous experiment.

(c) *By hydration of* VIII. The diacetate VIII (1·0 g) was stirred with mercurated IR 120 resin (1·0 g) in MeOH for 3 hr at 60–70°. The product obtained (550 mg) after usual work up was crystallized from pet. ether (60–80°) and found to be XIII by IR and mixed m.p. determination.

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