205. Transformations of 9α, 10α-Epoxy-Hexahydrocannabinol Acetate

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(3. V. 76)

Summary. 9α,10α-Epoxy-hexahydrocannabinol acetate **1** in presence of boron trifluoride etherate rearranged to a fluoro compound **6** and to a ketone **5**, and in perchloric acid to compound **11**. The fluoro compound **6** had been considered erroneously in earlier literature as **4**. Compounds **6** and **11** were produced by the initial opening of the epoxide followed by the acetyl transfer from the neighbouring phenolic group.

Tetrahydrocannabinol acetates **2** and **3**, on oxymercuration-demercuration followed by reduction gave the known 9α-hydroxy-hexahydrocannabinol (**13**).

In an earlier communication [1], we described the synthesis of (–)-11-hydroxy-Δ^8-6a,10a-*trans*-THC (THC = tetrahydrocannabinol). In the present paper we report some transformations of epoxy acetate **1** and the results of oxymercuration-demercuration experiments on Δ^8- and Δ^9-6a,10a-*trans*-THC acetates **2** and **3** respectively.

The rearrangement of 9α,10α-epoxy-HHC acetate **1** (HHC = hexahydrocannabinol) with boron trifluoride etherate was reported earlier by *Mechoulam et al.* [2]. A fluorine containing compound and a ketone were isolated from this reaction and were assigned structures **4** and **5** respectively. Being interested in examining the biological activity of fluorine containing cannabinoids, we selected the above reaction with the intention of obtaining compound **7** by the deacetylation of compound **4**.

A reinvestigation including the NMR. data (*i.e.*, the hydroxy proton chemical shift at 6.82 and the aromatic protons chemical shifts[1]) at 6.24 and 6.30) of the fluoro compound led us to believe that the fluoro compound may have structure **6**, the formation of which involves migration of acetyl from the neighbouring phenolic group to the hydroxyl at C(10). This assumption was supported by the fact that the above fluoro compound can be recovered unchanged from i) methanolic sodium hydroxide solution at room temperature and ii) from refluxing aqueous methanol containing sodium hydrogencarbonate; conditions that were known for the deacetylation of cannabinoid derivatives with an acetyl group on the phenolic function [3] [4].

The fluoro compound on acetylation with acetic anhydride and pyridine yielded an acetyl derivative **8** which showed the two aromatic protons at 6.34 and 6.54, as expected a downfield shift[1]) compared to the similar proton chemical shift values in the parent compound. The acetyl derivative **8** could be selectively deacetylated to

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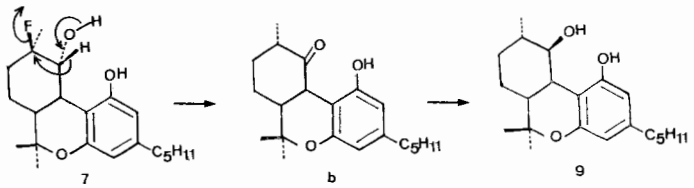
[1]) A correlation of aromatic proton chemical shift values of known cannabinoid derivatives showed that the two aromatic protons appear in the range 6.00–6.30 ppm in cannabinols and at 6.34–6.56 ppm in cannabinoid acetates [1].

the parent compound **6** by refluxing in aqueous methanol with sodium hydrogen carbonate, thus adding conclusive evidence in favour of structure **6** for the fluoro compound. The UV. absorption data (see exper. part) also supports the above formulation.

Reduction of compound **6** with lithium aluminium hydride at 0° gave 9β-fluoro-10α-hydroxy-HHC **7** and at 40° gave a defluorinated compound *i.e.*, 10β-hydroxy-HHC (C(9α)-methyl) **9** which could also be obtained from **7**. The inversion of hydroxy group at C(10) in going to compound **9** from **6** or **7** was evident from comparison of coupling constants[2]) for protons at C(10β) and C(10a) in compounds **9** and **10** with those of C(10α) and C(10a) in compounds **6**–**9** (see exper. part). Finally the structure of compound **9** was established by an independent synthesis from compound **5** which in turn establishes the configuration at C(9)[3]).

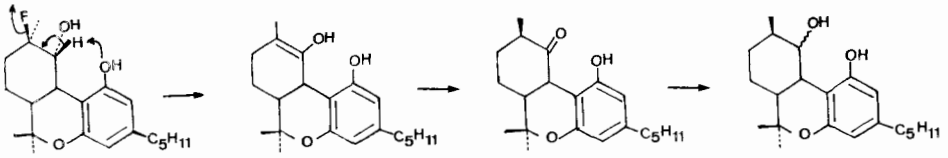
The transformation of compound **6** to **9** through compound **7** could be explained by visualising the intermediate formation of the 10-oxo-intermediate **b**, as shown in *scheme 1*, by a hydride shift[4]).

Scheme 1



An alternative mechanism, *scheme 2*, with the participation of a phenolic group is not favoured as it involves an enolic intermediate which then should lead to the thermodynamically more stable C(9β)-methyl compound[5]), which is not the case with compound **9**.

Scheme 2



[2]) The C(10α)-proton appears relatively downfield in compound **9** (4.90) and **10** (5.71) compared to the C(10β)-proton in compound **7** (3.57) and compound **8** (4.85) or compound **6** (4.98) respectively. This was in good agreement with the earlier observation [5] that the C(10α)-proton appears downfield compared to the C(10β)-proton in the cannabinoid derivatives.

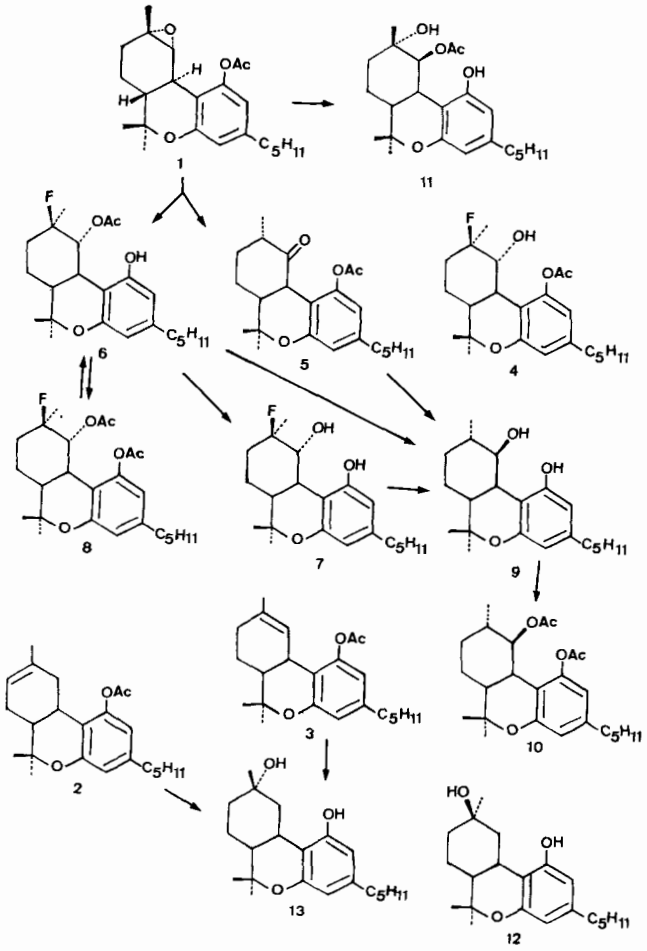
[3]) As the conditions were those used in the reduction of ketones [7] having a centre of asymmetry at the α-position, and which are known to proceed without racemisation, we did not consider epimerisation as a possibility.

[4]) This rearrangement would be analogous to the known rearrangement of fluorohydrins to the corresponding oxo compounds under boron trifluoride etherate [6].

[5]) *Mechoulam et al.* have shown earlier [2] that the 10-oxo-HHC (C(9α)-methyl) is the kinetic product and the 10-oxo-HHC (C(9β)-methyl) is the thermodynamically more stable product by epimerisation experiments.

Perchloric acid treatment of epoxide **1** yielded 9α-hydroxy-10β-acetoxy-HHC (**11**), in which there was also a migration of the acetyl group from phenolic group to the hydroxyl at C(10). The two exchangeable hydrogens at 6.88 and 2.92 accounting for the phenolic and hydroxyl protons respectively, and the aromatic protons at 6.08 and 6.20 support structure **11**.

In addition to the above transformations involving the epoxide **1**, we have also studied the oxymercuration-demercuration of Δ^8- and Δ^9-6a,10a-*trans*-THC acetates **2** and **3** with the intention of isolating the optically active form of 9β-hydroxy-6a,10a-*trans*-HHC **12**, which to our knowledge is not known in literature. However, only the 9α-hydroxy isomer **13** is obtained by the epoxidation followed by the reduction of either Δ^8- or Δ^9-THC acetates **2** and **3** respectively. Δ^8-6a,10a-*trans*-THC acetate **2** on epoxidation [1] gives both 8,9-α-epoxy and 8,9-β-epoxy isomers in the ratio of 10:3. The lithium aluminium hydride reduction of α-isomer results in the formation of 9α-hydroxy-HHC (**13**), whereas the β-isomer gives 8β-hydroxy-HHC. Because of the known selectivity for the tertiary hydration in the oxymercuration-



demercuration procedure of *Brown et al.* [8], we felt it interesting to study this reaction on the acetates **2** and **3**.

The acetate **2**, on treatment with mercuric acetate followed by reduction with sodium borohydride and lithium aluminium hydride, yielded only the known 9α-hydroxy-6a,10a-*trans*-HHC (**13**). The reaction was found to be very slow and the yield depended on the reaction time. Similarly the acetate **3** yielded the same α-hydroxy isomer **13**. These results were in accordance with the conclusion drawn by earlier workers [8] regarding the hydration of the double bond from the less hindered side.

Experimental Part

Melting points were taken on a *Tottoli* apparatus and are uncorrected. IR. spectra (bands in cm^{-1}) were determined in chloroform on a *Perkin Elmer* 125. Mass spectra were taken with a *Hitachi* RMU 6A, operating with an ionization energy of 70 eV, the temperature of the ion source was about 200°. NMR. spectra were taken in deuteriochloroform on a *Varian* 4 A 100 using TMS as internal reference. Chemical shifts are given in δ (ppm) and the coupling constants in Hz. The UV. spectra were recorded on a *Perkin Elmer* 137 in ethanol.

Reaction of 9α,10α-Epoxy-hexahydrocannabinol acetate (**1**) *with Boron trifluoride etherate.* 372 mg (1 mmol) of **1** [1] were dissolved in 10 ml of dry benzene, the solution was cooled to 10° and 0.14 ml of boron trifluoride etherate was added drop by drop. After the addition, the reaction mixture was stirred for 10 min at room temp. and the reaction was quenched by washing with water. The organic phase was separated, dried and evaporated. The residue thus obtained, on passing over a column of silica gel using light petroleum/ether 9:1 as eluent gave compound **6**, 156 mg (40%), oil, $[\alpha]_D^{25} = -85°$ ($CHCl_3$). – UV. (λ_{max} (ε)): 283 (1810); + drop of alkali: 288 (2790), 300 sh (1675). – IR.: 3500, 1760, 1625, 1570. – NMR.: 6.82 (*s*, 1H, D_2O exchangeable); 6.30 (*d*, $J = 1.8$, 1H); 6.24 (*d*, $J = 1.8$, 1H); 4.98 (*q*, $J_{HH} = 10$, $J_{HF} = 24$, 1H); 3.28 (*t*, $J_{HH} = 10$, $J_{HH} = 10$, 1H); 2.55–0.80 (28H); 2.46 (*t*, $J = 7$, 2H); 2.24 (*s*, 3H); 1.45 (*s*, 3H); 1.34 (*d*, $J_{CH3,F} = 23$, 3H); 1,02 (*s*, 3H); 0.88 (*t*, $J = 7$, 3H)). – MS. (*m/e* (%)): 392 (18, M^+), 377 (3), 350 (7), 333 (16), 332 (68), 317 (14), 312 (13), 297 (16), 295 (8), 294 (10), 289 (6), 276 (10), 256 (15), 231 (6), 196 (6), 105 (7), 91 (10), 87 (10), 85 (74), 83 (100).

$C_{23}H_{33}FO_4$ (392.517) Calc. C 70.39 H 8.48% Found C 70.26 H 8.52%

Polar fractions gave compound **5**, 141 mg (38%), m.p. 94–95° (lit [2] 93–95°), $[\alpha]_D^{25} = -138°$ ($CHCl_3$). – UV. (λ_{max} (ε)): 275sh (2250), 283 (2650). – IR. (CCl_4): 1765, 1730, 1630 and 1575. – NMR.: 6.54 (br., 2H); 3.76–0.88 (30 H); 3.76 (*d*, $J = 12$, 1H); 2.66 (*m*, 1H); 2.52 (*t*, $J = 7$, 2H); 2.15 (*s*, 3H); 1.41 (*s*, 3H); 1.35 (*d*, $J = 7$, 3H); 1.18 (*s*, 3H); 0.88 (*t*, $J = 7$, 3H). – MS. (*m/e* (%)): 373 (7), 372 (26, M^+), 357 (4), 331 (23), 330 (100), 315 (12), 312 (5), 302 (7), 288 (7), 287 (15), 275 (5), 274 (26), 260 (5), 259 (21), 247 (5), 246 (17), 245 (5), 231 (9), 217 (5), 193 (9), 174 (5).

$C_{23}H_{32}O_4$ (372.49) Calc. C 74.16 H 8.66% Found C 73.98 H 8.60%

1,10-Dihydroxy-9β-fluoro-3-(n-*pentyl*)*-6,6,9α-trimethyl-6a,10a-*trans*-*6a,7,8,9,10,10a-hexahydrodibenzo*[b,d]*pyran* (**7**). 392 mg (1 mmol) of compound **6** were dissolved in 10 ml of dry ether and the reaction mixture was cooled with ice. After 10 min 38 mg (1 mmol) of lithium aluminium hydride were added and the reaction mixture was stirred for 20 min. Then 0.2 ml of saturated sodium sulfate solution was added dropwise, followed by 4 ml of 2N hydrochloric acid and 50 ml of ether. The organic phase was dried with sodium sulfate and evaporated. The residue was purified by passing on a column of silica gel and methylene chloride as eluent: 313 mg (89%) of **7**, oil, $[\alpha]_D^{25} = -59°$ ($CHCl_3$). – UV. (λ_{max} (ε)): 282 (1790); + drop of NaOH: 286sh (2720), 294 (3140). – IR.: 3520, 3180, 1630, 1570. – NMR.: 6.30 (*d*, $J = 1.8$, 1H); 6.23 (*d*, $J = 1.8$, 1H); 3.57 (*q*, $J_{HH} = 10$, $J_{HF} = 22$, 1H); 2.97 (*t*, $J_{HH} = 10$, $J_{HH} = 10$, 1H); 2.60–0.80 (26H); 2.44 (*t*, $J = 7$, 2H); 1.53 (*d*, $J = 23$, 3H); 1.38 (*s*, 3H); 1.04 (*s*, 3H); 0.88 (*t*, $J = 7$, 3H). – MS. (*m/e* (%)): 350 (70, M^+), 336 (4), 335 (16), 334 (4), 332 (16), 331 (8), 330 (32), 317 (7), 316 (4), 315 (19),

313 (4), 312 (8), 309 (4), 308 (23), 307 (9), 297 (17), 295 (23), 294 (100), 276 (9), 275 (11), 274 (48), 272 (7), 271 (15), 247 (9), 246 (25), 245 (9), 233 (6), 232 (6), 231 (30), 217 (11), 194 (6), 193 (17).

$C_{21}H_{31}FO_3$ (350.479) Calc. C 71.97 H 8.92% Found C 71.81 H 8.83%

1,10α-Diacetoxy-9β-fluoro-3-(n-*pentyl*)*-6,6,9α-trimethyl-6a,10a-*trans*-6a,7,8,9,10,10a-hexahydrodibenzo*[b,d]*pyran* (**8**). 392 mg (1 mmol) of **6** were treated with 3 ml of pyridine and 3 ml of acetic anhydride and the reaction mixture was kept overnight at room temperature. The volatiles were removed i.V., and the residue was dissolved in methylene chloride and washed with sodium hydrogen carbonate solution. The organic phase was dried and evaporated. The residue, by passing over a column of silica gel, using benzene as an eluent gave 431 mg (99%) of **8**, oil, $[\alpha]_D^{25} = -135°$ ($CHCl_3$). – UV. (λ_{max} (ε)): 284 (2000); + drop of NaOH: 284 (2060). – IR.: 1740 br., 1630, 1570. – NMR.: 6.54 (*d*, $J = 1.8$, 1H); 6.34 (*d*, $J = 1.8$, 1H); 4.85 (*q*, $J_{HH} = 10$, $J_{HF} = 25$, 1H); 3.04 (*t*, $J_{HH} = 10$, $J_{HH} = 10$, 1H); 2.60–0.80 (30H); 2.50 (*t*, $J = 7$, 2H); 2.32 (*s*, 3H); 2.20 (*s*, 3H); 1.43 (*s*, 3H); 1.30 (*d*, $J_{CH_3F} = 23$, 3H); 1.06 (*s*, 3H); 0.90 (*t*, $J = 7$, 3H). – MS. (*m/e* (%)): 434 (7, M^+), 375 (19), 374 (69), 333 (26), 332 (100), 317 (14), 313 (9), 312 (33), 297 (21), 295 (9), 289 (7), 276 (9), 257 (9), 256 (28), 231 (7), 193 (9), 69 (12), 55 (9), 43 (52).

$C_{25}H_{35}FO_5$ (434.55) Calc. C 69.10 H 8.12% Found C 69.29 H 8.17%

1,10β-Dihydroxy-3-(n-*pentyl*)*-6,6,9α-trimethyl-6a,10a-*trans*-6a,7,8,9,10,10a-hexahydrodibenzo*[b,d]*pyran* (**9**). *From* **6**: 76 mg (2 mmol) of lithium aluminium hydride were taken in 10 ml of dry ether followed by the addition of 392 mg (1 mmol) of **6** in 10 ml of dry ether. The reaction mixture was refluxed at 40° for 1 h and 0.4 ml of saturated sodium sulfate solution were added dropwise followed by the addition of 4 ml of 1 N hydrochloric acid. After separation of the organic phase the aqueous phase was extracted twice with ethyl acetate and the combined organic phases were dried and evaporated. The residue thus obtained on recrystallisation from ether gave 233 mg (70%) of **9**, m.p. 218°, $[\alpha]_D^{25} = -66°$ ($CHCl_3$). – UV.: λ_{max} (ε) 277 (1340), 284 (1340); + drop of NaOH: 288 sh (2430), 295 (2685). – IR. (KBr): 3420, 3270, 1620, 1580. – NMR. (DMSO-d_6): 8.94 (*s*, 1H, D_2O exchangeable); 6.10 (*d*, $J = 1.8$, 1H); 5.97 (*d*, $J = 1.8$, 1H); 4.90 (br., 1H); 3.98 (*d*, $J = 5$, 1H, D_2O exchangeable); 2.70–0.70 (27H); 1.27 (*s*, 3H); 1.02 (*d*, $J = 7$, 3H); 0.96 (*s*, 3H); 0.87 (*t*, $J = 7$, 3H). – MS. (*m/e* (%)): 333 (14), 332 (61, M^+), 318 (10), 317 (36), 315 (17), 314 (66), 300 (22), 299 (100), 297 (10), 276 (10), 272 (14), 271 (46), 259 (14), 258 (44), 257 (10), 247 (4), 246 (6), 245 (12), 244 (10), 243 (19), 232 (14), 231 (46), 217 (10), 193 (46), 149 (19).

$C_{21}H_{32}O_3$ (332.47) Calc. C 75.86 H 9.70% Found C 75.80 H 9.65%

From **7**: 350 mg (1 mmol) of **7** on reduction as above gave 250 mg (75%) of **9**, identical in all respects with compound prepared from **6**.

From **5**: 372 mg (1 mmol) of **5** on reduction as above gave 298 mg (90%) of **9**, identical in all respects with the compound isolated in earlier experiments.

1,10β-Diacetoxy-3-(n-*pentyl*)*-6,6,9α-trimethyl-6a,10a-*trans*-6a,7,8,9,10,10a-hexahydrodibenzo*[b,d]*pyran* (**10**). 332 mg (1 mmol) of **9** were treated with 3 ml of pyridine and 3 ml of acetic anhydride and the reaction mixture was allowed to stand overnight at room temperature. The excess acetic anhydride and pyridine was removed i.V. and the residue was dissolved in 20 ml of methylene chloride and washed with sodium hydrogen carbonate solution. The organic phase was dried and evaporated. The residue on passing over a column of silica gel using methylene chloride as eluent gave 333 mg (80%) of **10**, oil, $[\alpha]_D^{25} = -136°$ ($CHCl_3$). – IR.: 1760, 1730, 1630 and 1575. – NMR.: 6.50 (*d*, $J = 1.8$, 1H); 6.38 (*d*, $J = 1.8$, 1H); 5.71 (br., 1H); 3.00–0.70 (33H), and specially: 2.82 (*d* × *d*, $J = 12$, $J = 2$, 1H); 2.50 (*t*, $J = 7$, 2H); 2.31 (*s*, 3H); 1.94 (*s*, 3H); 1.41 (*s*, 3H); 1.11 (*d*, $J = 7$, 3H); 1.09 (*s*, 3H) and 0.83 (*t*, $J = 7$, 3H). – MS. (*m/e* (%)): 417 (7), 416 (19, M^+), 375 (10), 374 (40), 315 (25), 314 (100), 300 (10), 299 (46), 297 (7), 271 (16), 258 (16), 243 (12), 231 (16), 183 (12), 149 (7).

$C_{25}H_{36}O_5$ (416.54) Calc. C 72.08 H 8.71% Found C 71.95 H 8.68%

10β-Acetoxy-1,9α-dihydroxy-3-(n-*pentyl*)*-6,6,9β-trimethyl-6a,10a-*trans*-6a,7,8,9,10,10a-hexahydrodibenzo*[b,d]*pyran* (**11**). 372 mg (1 mmol) of **1**, 2 ml of 30% perchloric acid and 5 ml of acetone

were stirred for 2 h. The acetone was removed i.V. and the residue was partitioned between sodium hydrogen carbonate solution and methylene chloride. The organic phase was dried, evaporated and the residue on chromatography over silicagel with chloroform as eluent gave 234 mg (60%) of **11**, oil, $[\alpha]_D^{25} = -65°$ ($CHCl_3$). – UV. (λ_{max} (ε)): 277 (1795), 283 (1795); + drop of NaOH: 286sh (2940), 294 (3120). – IR.: 3600, 3420, 1725, 1625 and 1575. – NMR.: 6.88 (*s*, 1H, D_2O exchangeable); 6.34 (*d*, *J* = 2, 1H); 6.20 (*d*, *J* = 1.8, 1H); 6.08 (*d*, *J* = 1.8, 1H); 3.34 (*d* × *d*, *J* = 11, *J* = 2, 1H); 2.92–0.77 (29H), and specially: 2.92 (br., 1H, D_2O exchangeable); 2.40 (*t*, *J* = 7, 2H); 1.86 (*s*, 3H); 1.41 (*s*, 3H); 1.20 (*s*, 3H); 1.08 (*s*, 3H); 0.87 (*t*, *J* = 7, 3H). – MS. (*m/e* (%)): 391 (26), 390 (91, M^+), 375 (6), 334 (13), 330 (43), 329 (6), 316 (22), 315 (90), 314 (13), 313 (54), 312 (72), 297 (33), 288 (13), 287 (30), 275 (9), 274 (39), 273 (9), 271 (16), 270 (9), 269 (13), 260 (17), 259 (30), 257 (30), 256 (100), 247 (13), 246 (26), 245 (73), 231 (26), 217 (13), 193 (35), 149 (17).

$C_{23}H_{34}O_5$ (390.50) Calc. C 70.74 H 8.78% Found C 70.68 H 8.75%

1,9α-Dihydroxy-3-(n-*pentyl*)*-6,6,9β-trimethyl-6a,10a-*trans*-6a,7,8,9,10,10a-hexahydrodibenzo*[b,d]*pyran* (**13**). 356 mg (1 mmol) of **2** [1] were dissolved in 10 ml of 5% aqueous acetonitrile, and 319 mg (1 mmol) of mercuric acetate dissolved in 5 ml of 5% acetonitrile were added to the reaction mixture at room temperature. The reaction mixture was stirred for 5 h and then reduced with 38 mg (1 mmol) of sodium borohydride. The mercury thus formed was allowed to settle. After the reaction mixture was saturated with sodium chloride, the organic phase was separated and evaporated to dryness. The residue was dissolved in dry ether and reduced with 76 mg (2 mmol) of lithium aluminium hydride, followed by the addition of 2 ml of saturated sodium sulfate solution and 3 ml of 2N hydrochloric acid. The organic phase was dried, and evaporated. The residue was chromatographed with ethyl acetate over silicagel and gave 166 mg (50%) of **13**, m.p. 74–76°, $[\alpha]_D^{25} = -80°$. Except for m.p. identical in all respects with the compound reported in [1].

Compound **3**, on treatment with mercuric acetate followed by reduction as above, gave **13** in 60% yield.

One of us (*K. K. Prasad*) gratefully acknowledges support of this work by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung*.

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