Steroids and related products. XXVIII.[1] Cardiotonic steroids. III.[2] The synthesis of 3β-hydroxy steroids of the A/B-*cis* series[3]

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In the course of the synthesis of 3β-hydroxy-21,21-dimethoxy-5β-pregnan-20-one (**8**), a method was developed for the preferential reduction of steroid 3-ketones of the A/B-*cis* series to the axial 3β-alcohols, the stereochemistry in positions-3 and -5 of which corresponds to that of the truly active steroid cardiotonics. This method, which seems the best available to date, consists of a Meerwein–Ponndorf reduction carried out over a very short reaction period.

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It is well known that the highly active steroid cardiotonics show a *cis* fusion of rings A and B and that their 3-hydroxy substituent has a β-configuration which presents itself in the thermodynamically unfavorable axial conformation (1–3).[4] Because of this situation, the synthesis of such products presents certain difficulties, since for the majority of suitable starting materials, the 3-hydroxy function is equatorial, and since the chemical reduction and the catalytic reduction in neutral and alkaline media of suitable 3-ketones lead predominantly to equatorial alcohols (cf., *inter alia*, refs. 4, 5).

It is true that Butenandt and Müller (6) have reported the catalytic reduction of 5β-pregnane-3,20-dione in ether – acetic acid, in very good yield, to the axial 3β-alcohol (cf. also 4*a*) but, as already reported (7), in our hands, even in acidic media, such catalytic reductions gave rise predominantly to the equatorial 3α-alcohols. We also have already reported (7) that the use of aged Raney nickel (8) for the reduction of 3-ketones of the A/B-*cis* series to axial alcohols (compare also ref. 9) may be regarded as an improvement over catalytic reduction, but that it still does not represent a satisfactory solution to the problem.

We have now found that the best results for the production of 3β-hydroxy steroids of the A/B-*cis* series could be obtained by subjecting a 3-ketone to a Meerwein–Ponndorf reduction. The characteristic feature of the procedure consists of the limitation of the reaction time. This approach had seemed logical since the accepted mechanisms for the Meerwein–Ponndorf reduction (10–15) would be consistent with the assumption that an axial hydroxy derivative would be formed, if the reaction were to take place under kinetic control (compare refs. 11–13, 16), but that equilibration to the equatorial alcohol could and did occur under the actual reaction conditions.

We elaborated the procedure in the course of the synthesis of a steroid glyoxal derivative, 3β-hydroxy-21,21-dimethoxy-5β-pregnan-20-one(**8**), which we used in connection with synthetic work in the field of butadienolides.

In a first series of experiments we had synthesized this product from Reichstein's Compound S (**1**).[5] This readily available starting material[6] (18–21)[7] was transformed in the usual fashion (23, 24) to its bismethylenedioxy derivative **2** which was then reduced in high yield, with

[1]For paper XXVII of this series, see Ch. R. Engel and M. N. Roy Chowdhury. Tetrahedron Letters, 2107 (1968).

[2]For the preceding paper in this series, see G. Bach, J. Capitaine, and Ch. R. Engel, Can. J. Chem. **46**, 733 (1968).

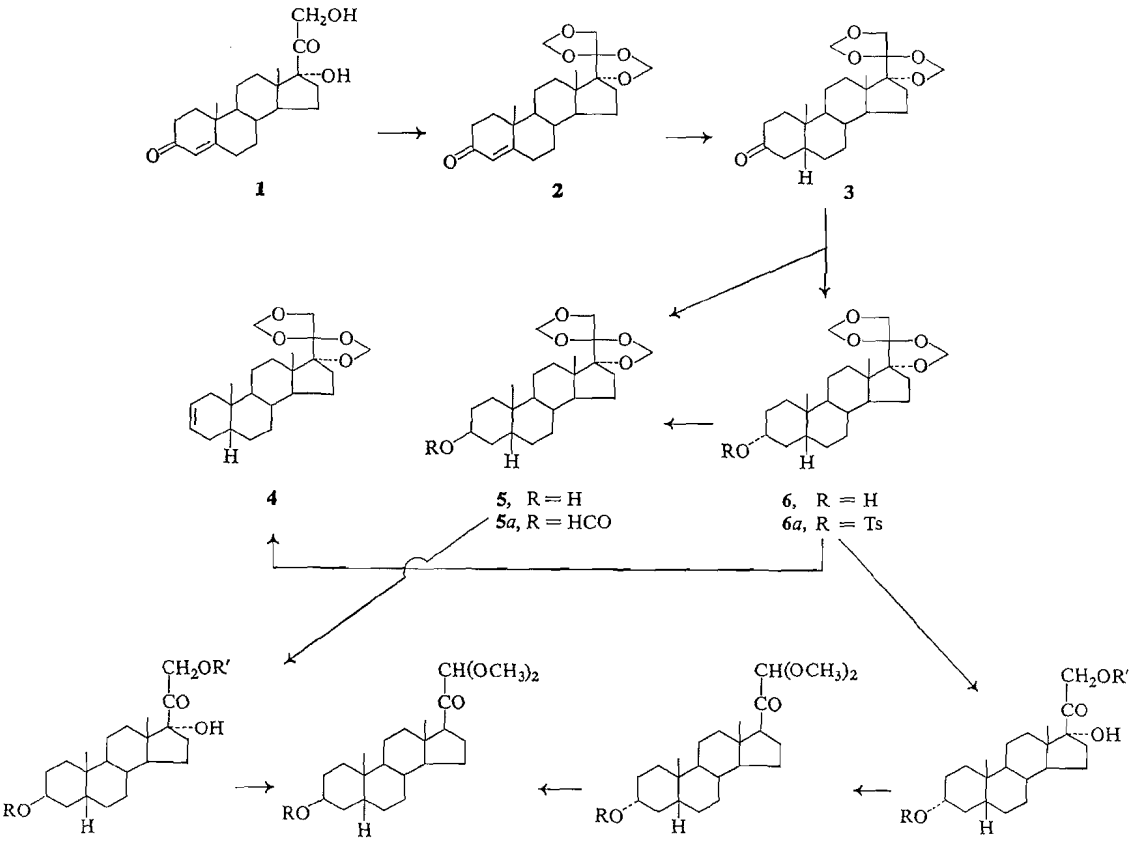
[3]Abbreviated from part of the D.Sc. Thesis of R. Bouchard, to be presented to the School of Graduate Studies, Laval University. The synthetic work described in this paper was first presented as part of an invited lecture on the synthesis of cardiotonics at the Steroid Symposium of the VIth Pan-American Congress of Pharmacy and Biochemistry, Mexico City, December 1963. The general method for the synthesis of 3β-hydroxy steroids of the A/B-*cis* series was reported in a communication to the 49th Annual Conference of the Chemical Institute of Canada, Saskatoon, June 1966.

[4]Only a selection of references is given.

[5]The synthesis of this product from another starting material, by an entirely different route, was reported by Ruzicka *et al.* (17).

[6]We express very sincere thanks to Dr. E. B. Hershberg from the Schering Corp., Bloomfield, New Jersey, for kindly providing us with this product.

[7]Only a small selection of references is given. Compare also with ref. 22.



palladium on calcium carbonate in the presence of potassium hydroxide, to the 5β-pregnanone **3**. This ketone was now reduced with lithium aluminium hydride, predominantly (in 88% yield) to the equatorial alcohol **6**, the axial alcohol **5** representing a minor side product. The equatorial alcohol **6** was converted via its tosylate **6***a* and the formate **5***a* to the axial alcohol **5**. In this sequence of reactions, some starting material, the tosylate **6***a*, was recovered and some 2,3-unsaturated material (**4**), arising from an elimination reaction, was isolated (in 22% yield). Even when taking into account the recovery of starting material the yield of the desired axial alcohol **5** amounted only to 47%.

For the completion of the synthesis the dihydroxyacetone side chain was liberated in the usual fashion (23, 24) by treatment with acetic acid and the resulting triol **7** was acetylated to the hydroxy diacetate **7***b*. This product was now subjected to the Mattox rearrangement (25) with methanolic hydrogen chloride which gave in 60% yield the desired glyoxal derivative **8**.

In a modified pathway, the equatorial 3α-hydroxy derivative **6** was transformed via the triol **10** to the hydroxy diacetate **10***b* and thence, by rearrangement with hydrochloric acid, to the 3α-hydroxy glyoxal derivative **9**. This product was then converted through its tosylate **9***a* and the formate **8***a* to the 3β-hydroxy derivative **8**. Again, the yield of the inversion of the equatorial to the axial alcohol was, for practical purposes, not satisfactory (24% from alcohol **9**).

Independently, Harnik (9) had isomerized in a similar fashion alcohol **10***a* to alcohols **7** and **7***a*, using the same method; also in this case, the yield of the inversion reaction had not been satisfactory.

TABLE I

Relationship between the reaction time and the yields of the axial and equatorial alcohols **5** and **6** in the Meerwein–Ponndorf reduction of ketone **3**

Reaction time (min)	Starting material **3** (g)	Yield of axial alcohol **5** (g)	(%)	Yield of equatorial alcohol **6** (g)	(%)	Yield of recovered starting material **3** (g)	(%)	Yield of reduction (%)
120	1	0.430	43	0.56	56	0	0	99
50	2	0.968	48.4	1.00	50	0	0	98.4
35	10	5.7	57	4.1	41	0	0	98
15	10.4	6.14	59	4.0	38.5	0	0	97.5
8	5.6	2.91	52 (56)*	2.24	40 (43)*	0.403	7.2	92

*The figures in parentheses correspond to the yields of the alcohols when the recovery of starting material is taken into account.

These not very encouraging results of a relatively lengthy and cumbersome procedure prompted us to investigate, as intimated, the Meerwein–Ponndorf reduction of ketone **3** and we were able to show that, according to our expectations, the yield of the axial alcohol increased with the diminution of the reaction period. Table I gives the relation between reaction time and the yields of the epimeric alcohols **5** and **6**. The reaction was carried out with *sec*-butyl alcohol and aluminium *t*-butylate in absolute benzene at reflux temperature.

The first observation of interest was that the Meerwein–Ponndorf reduction was practically complete in 15 min, a fact which becomes significant if one considers that usually Meerwein–Ponndorf reductions are carried out over prolonged periods. Furthermore, we could establish that the yield of the thermodynamically unfavored axial alcohol could indeed be raised to approximately 60% by reducing the reaction time to 15 min. In the previous paper in this series on cardiotonic steroids (7), we have shown that this method proved superior to any other known method for the preparation of an axial 3α-hydroxy steroid of the A/B-*cis* series from the corresponding 3-keto derivative.[8]

[8]It is evident that this method is particularly attractive if the equatorial alcohol formed along with the axial alcohol is reoxided in a simple and rapid manner, for instance with Jones' reagent (26), to the ketone which is then subjected to another Meerwein–Ponndorf reduction, carried out over a very short period (cf. ref. 7). Such a recyclization is, of course, not practical in the case of the inversion sequence involving the tosylate, since the reaction product contains, apart from the desired alcohol and starting material, a dehydrated product, and since, furthermore, the procedure would be lengthy.

Experimental[9]

17,20;20,21-Bismethylenedioxy-4-pregnen-3-one (2)

Following the procedure of Beyler *et al.* (23, cf. also 24), 980 mg of Reichstein's Compound S (17α,21-dihydroxy-4-pregnen-3,20-dione) (**1**) was transformed with 16 ml of a 37% aqueous formaldehyde solution and 16 ml of concentrated hydrochloric acid, at room temperature in 54 ml of dichloromethane, to its bismethylenedioxy derivative **2**. The crude reaction product (1.404 g) gave, by chromatography on aluminium oxide, 920 mg (83.6% yield) of pure 17,20;20,21-bismethylenedioxy-4-pregnen-3-one (**2**), m.p. 254–255°. A sample was recrystallized three times from dichloromethane–ether for analysis; shiny prisms, m.p. 254–255°, $[\alpha]_D^{25}$ −7.8° (*c*, 1.000 in $CHCl_3$); λ_{max}(EtOH) 235 mμ (log ε 4.27); ν_{max}(KBr) 1683 cm^{-1} (ketone), 1625 cm^{-1} (double bond), 1100 cm^{-1} (ether bonds).

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 71.11; H, 8.30. Found: C, 71.05; H, 8.48.

17,20;20,21-Bismethylenedioxy-5β-pregnan-3-one (3)

To a solution of 4.98 g of the above-described bismethylenedioxy derivative **2** of Reichstein's Compound S, m.p. 254–255°, in 250 ml of 95% ethanol, there were added 600 mg of potassium hydroxide in 50 ml of 95% ethanol and 1 g of a 4% palladium on calcium carbonate catalyst. The mixture was hydrogenated at room temperature. After 3 h, 270 ml of hydrogen had been taken up. The mixture was filtered through sodium sulfate and the filtrate was reduced to 200 ml and poured into 500 ml of cold water. The precipitate was extracted with ether, the ethereal solution was washed with water, dried over sodium sulfate, and the solvent was removed. The

[9]The melting points were taken in evacuated capillaries and the temperatures were corrected. If not otherwise stated, non-alkaline aluminium oxide Woelm, activity III, and Davison's silica gel No. 923 were used for chromatography. The infrared spectra were recorded on a Beckman IR-4 spectrophotometer and the ultraviolet spectra on a Beckman DK-1A spectrophotometer. The microanalyses were performed by Mr. A. Bernhardt, Mülheim (Ruhr), Germany, and Dr. C. Daesslé, Montreal, to whom we express our sincere appreciation.

crystalline residue (5.283 g) was recrystallized from ether–hexane to give 3.446 g of 17,20;20,21-bismethylenedioxy-5β-pregnan-3-one (**3**), m.p. 180–181°. The residue of the mother liquors (1.9 g) was chromatographed on 60 g of aluminium oxide. Elutions with petroleum ether – benzene (4:1 and 1:1) afforded another 1.15 g of the pure 5β-pregnane derivative **3**, m.p. 180–181° (total yield, 92%). A sample was recrystallized three times from ether–hexane for analysis; colorless needles, m.p. 180.5–181.5°; $[\alpha]_D^{25}$ −69° (*c*, 1.000 in $CHCl_3$); ν_{max}(KBr) 1718 cm^{-1} (ketone), 1100 cm^{-1} (ether bonds).

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.74; H, 8.78. Found: C, 70.68; H, 8.71.

3β-Hydroxy-17,20;20,21-bismethylenedioxy-5β-pregnane (5) and 3α-Hydroxy-17,20;20,21-bismethylenedioxy-5β-pregnane (6) by Lithium Aluminium Hydride Reduction of 17,20;20,21-Bismethylenedioxy-5β-pregnan-3-one (3)

To a slurry of 2.2 g of lithium aluminium hydride in 30 ml of absolute tetrahydrofuran were added, over a period of 50 min, dropwise and with stirring, 2 g of the above-described bismethylenedioxy derivative **3** of 17α,21-dihydroxy-5β-pregnane-3,20-dione, m.p. 180–181°, in 100 ml of absolute tetrahydrofuran. The mixture was refluxed for 1 h, with stirring, and was then left at room temperature for 16 h. Subsequently, there were added, at 0°, 10 ml of ethyl acetate and a small quantity of ice, followed by 25 ml of an aqueous ammonium chloride solution. The mixture was poured into 1.5 l of cold water, and the precipitate was extracted with ether. The ethereal layer was washed with a saturated ammonium chloride solution and with water and was dried over sodium sulfate. The evaporation of the solvent gave 2.04 g of white needles, melting between 160 and 170°. The product was chromatographed on 60 g of aluminium oxide. Elutions with petroleum ether – benzene (1:1) gave 150 mg (7.5%) of *3β-hydroxy-17,20;20,21-bismethylenedioxy-5β-pregnane (5)*, m.p. 151–158°. A sample was recrystallized three times from ether–hexane for analysis; colorless needles, m.p. 157.5–158.5°; $[\alpha]_D^{25}$ −99.5° (*c*, 1.000 in $CHCl_3$); ν_{max}(KBr) 3490 cm^{-1} (small band, hydrogen-bonded hydroxyl, absent in the 3α-isomer), 3250 cm^{-1} (hydroxyl), 1100 cm^{-1} (ether bonds).

Anal. Calcd. for $C_{23}H_{38}O_5$: C, 70.37; H, 9.24. Found: C, 70.32; H, 9.49.

Elutions in the above-described chromatogram with petroleum ether – benzene (1:4) gave 1.757 g (87.8%) of *3α-hydroxy-17,20;20,21-bismethylenedioxy-5β-pregnane* (*6a*), m.p. 177–178°. A sample was recrystallized three times from ether–hexane for analysis; colorless needles, m.p. 180.5°; $[\alpha]_D^{25}$ −80° (*c*, 1.000 in $CHCl_3$); ν_{max}(KBr) 3225 cm^{-1} (sharp hydroxyl band), 1310 cm^{-1} (characteristic band of the 3α-hydroxy isomer, absent in the 3β-hydroxy isomer), 1110 cm^{-1} (ether bonds).

Anal. Calcd. for $C_{23}H_{38}O_5$: C, 70.37; H, 9.24. Found: C, 70.37; H, 9.35.

3α-Tosyloxy-17,20;20,21-bismethylenedioxy-5β-pregnane (6a)

Following the experimental procedure of Fukushima and Daum (26), 11.3 g of the bismethylenedioxy derivative **6** of 3α,17α,21-trihydroxy-5β-pregnan-20-one, m.p. 177–178°, was transformed with 11.3 g of *p*-toluenesulfonyl chloride in 125 ml of pyridine into its tosylate *6a*. There was obtained 15.5 g (98% yield) of crystalline product, m.p. 140–144°. A sample was recrystallized three times from acetone–hexane for analysis; colorless needles, m.p. 151–152°; $[\alpha]_D^{25}$ −39° (*c*, 1.000 in $CHCl_3$); λ_{max}(EtOH) 225 mμ (log ε 4.04); ν_{max}(KBr) 1600, 1185, and 1175 cm^{-1} (tosylate), 1100 cm^{-1} (ether bonds).

Anal. Calcd. for $C_{30}H_{42}O_7S$: C, 65.91; H, 7.74; S, 5.86. Found: C, 65.96; H, 7.50; S, 5.73.

3β-Hydroxy-17,20;20,21-bismethylenedioxy-5β-pregnane (5) and17,20;20,21-Bismethylenedioxy-5β-pregn-2-ene (4) from 3α-Tosyloxy-17,20;20,21-bismethylenedioxy-5β-pregnane (6a)

A solution of 15.5 g of crude tosylate *6a*, m.p. 140–144°, in 130 ml of unpurified *N,N*-dimethylformamide was heated to 80–82° for 72 h, cooled, and poured into ice-water. The precipitate was extracted with ether, the ethereal layer was washed with water and was dried over sodium sulfate. The solvent was removed and the oily residue, containing crude *3β-formoxy-17,20;20,21-bismethylenedioxy-5β-pregnane (5a)*, was treated for 4 h at room temperature with 1.5 l of a 5% methanolic potassium hydroxide solution. The solution was reduced *in vacuo* and then extracted with ether. The ethereal layer was washed with water, dried over sodium sulfate, and taken to dryness. The residue (11.1 g) crystallized from hexane. The product was chromatographed on 340 g of aluminium oxide. Elutions with petroleum ether – benzene (9:1) gave 2.3 g (21.7%) of *17,20;20,21-bismethylenedioxy-5β-pregn-2-ene (4)*, m.p. 117–123°. A sample was recrystallized three times from methanol for analysis: colorless prisms, m.p. 129–130°; ν_{max}(KBr) 3025 cm^{-1} (double bond), 1100 cm^{-1} (BMD-protection).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.98; H, 9.07.

Elutions in the above-described chromatogram with petroleum ether – benzene (1:1) gave 3.3 g (25%) of starting material, *tosylate 6a*, m.p. 149–151°. Elutions with petroleum ether – benzene (1:4) and with pure benzene gave 4.1 g (36.8% yield) of *3β-hydroxy-17,20;20,21-bismethylenedioxy-5β-pregnane (5)*, m.p. 154–155°. The identity of the product with an authentic sample (compare above) was established by the comparison of the infrared spectra and by the determination of a mixture melting point. Considering the recovery of starting material, the yield of the 3β-hydroxy derivative **5** amounted to 47%, that of the dehydrated product **4** to 27.5%.

3β,17α,21-Trihydroxy-5β-pregnan-20-one (7) from 3β-Hydroxy-17,20;20,21-bismethylenedioxy-5β-pregnane (5)

Following the experimental procedure of the Merck group (23, 24), 486 mg of 3β-hydroxy-17,20;20,21-bismethylenedioxy-5β-pregnane (**5**), m.p. 154–155°, was hydrolyzed under nitrogen with 40 ml of acetic acid and 40 ml of water at 90° for 8 h. After having been left for another 16 h at room temperature, the mixture was neutralized with 35 g of sodium hydroxide in 75 ml of water and was worked up in the usual fashion. There were obtained 435 mg of colorless small crystals, m.p. 230–232° (yield 98.5%). A sample was recrystallized three times from acetone for analysis; m.p. 240–243°; $[\alpha]_D^{25}$ +53° (*c*, 1.000 in ethanol) [Lit. m.p. 224–226° (28), 232–234° (9);

$[\alpha]_D$ (ethanol) +54° (28), +50° (9)]; ν_{max}(KBr) 3450 and 3390 cm^{-1} (hydroxyls), 1715 cm^{-1} (20-ketone).

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.94; H, 9.87. Found: C, 71.82; H, 9.69.

Diacetate 7b

The diacetate was prepared in the usual way from 53 mg of the diol **7** with 0.5 ml of acetic anhydride in 1 ml of pyridine. The reaction product (65 mg), m.p. 143–148°, was recrystallized twice from ethyl acetate – ether for analysis; m.p. 152–154°; $[\alpha]_D^{25}$ +50.3° (*c*, 1.000 in $CHCl_3$) [Lit. m.p. 149–151° (29); 154–157° (30); 152–154° (9); $[\alpha]_D$ (ethanol) +51° (9, 30); $[\alpha]_D$ (dioxane) +49° (29)]; ν_{max}(KBr) 3475 cm^{-1} (17α-hydroxyl), 1745 and 1722 cm^{-1} (21-acetoxy-20-keto doublet) (the peak at 1745 cm^{-1} is enlarged by the 3-acetate band), 1250 cm^{-1} (acetates).

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.82. Found: C, 69.23; H, 8.93.

*3α,21-Diacetoxy-17α-hydroxy-5β-pregnan-20-one (**10b**)*

A quantity of 180 mg of 3α-hydroxy-17,20;20,21-bismethylenedioxy-5β-pregnane (**6**) was hydrolyzed as described for the 3β-hydroxy derivative **5**, to 160 mg of *3α,17α,21-trihydroxy-5β-pregnan-20-one (**10**)*, m.p. 222–230°; ν_{max}(KBr) 3450 cm^{-1} (large hydroxyl band), 1720 cm^{-1} (20-ketone). This product was acetylated without further purification with 1 ml of acetic anhydride in 2 ml of pyridine. The reaction product (200 mg), representing *3α,21-diacetoxy-17α-hydroxy-5β-pregnan-20-one (**10b**)*, melted at 186–192°. A sample was recrystallized three times from ether–hexane for analysis; colorless pellets, m.p. 199–201°; $[\alpha]_D^{25}$ +83°(*c*, 1.000 in ethanol) [Lit. m.p. 201–206° (28); 205° (Kofler block) (30); $[\alpha]_D$ (ethanol) +77° (28), +88° (30)]; ν_{max}(KBr) 3450 cm^{-1} (sharp 17α-hydroxyl band), 1740 and 1732 cm^{-1} (21-acetoxy-20-ketone doublet and 3-acetate), 1265 and 1245 cm^{-1} (acetates).

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.82. Found: C, 69.09; H, 8.72.

*3β-Hydroxy-21,21-dimethoxy-5β-pregnan-20-one(**8**)*

(a) From 3β,21-Diacetoxy-17α-hydroxy-5β-pregnan-20-one (7b)

Following the procedure of Mattox (25), 700 mg of the 3β,21-diacetate **7b** was treated with 40 ml of a dry 0.5 *N* methanolic hydrogen chloride solution and with 20 ml of chloroform at room temperature. After 3 h, the steroid was dissolved and the solution was allowed to stand for 48 h at 25°. After addition of 2.2 g of sodium acetate in 10 ml of water, the mixture was concentrated *in vacuo* and water was added. The precipitate was extracted with ether, the ethereal layer was washed with water, saturated sodium bicarbonate solution, and water, and was dried over sodium sulfate. The solvent was evaporated and the residue (660 mg of a yellow oil) was chromatographed on 25 g of aluminium oxide. Elutions with petroleum ether – benzene (1:4) gave 360 mg (59% yield) of the glyoxal derivative **8**, m.p. 102–104°. A sample was recrystallized once from ether–hexane for analysis; long needles, m.p. 104–106°; $[\alpha]_D^{26}$ +143° (*c*, 1.000 in $CHCl_3$) [Lit. (17): m.p. 126–129° (recrystallization from ligroin, followed by sublimation); $[\alpha]_D$ ($CHCl_3$) +132°(± 10°)]; ν_{max}(KBr) 3340 cm^{-1} (3β-hydroxyl), 1725 cm^{-1} (20-ketone), 1090 cm^{-1} (ketal).

Anal. Calcd. for $C_{23}H_{38}O_4$: C, 72.98; H, 10.12. Found: C, 73.20; H, 10.18.

*(b) From 3α,21-Diacetoxy-17α-hydroxy-5β-pregnan-20-one (**10b**)*

As described for the 3β-acetoxy epimer **7b**, 7.8 g of 3α,21-diacetoxy-17α-hydroxy-5β-pregnan-20-one (**10b**) m.p. 199–201°, was transformed in 220 ml of chloroform with 460 ml of a dry 0.5 *N* methanolic hydrogen chloride solution to 7.27 g of a product representing the crude glyoxal derivative **9**. Chromatography on 250 g of aluminium oxide gave 5.8 g (85.2% yield) of crystalline *3α-hydroxy-21,21-dimethoxy-5β-pregnan-20-one (**9**)*, m.p. 114–117°, eluted with petroleum ether – benzene (4:1 and 1:1). Recrystallization from ether–hexane raised the melting point to 121.5–122.5°; $[\alpha]_D^{25}$ +130° (*c*, 1.000 in $CHCl_3$); ν_{max}(KBr) 3390 cm^{-1} (strong band, 3α-hydroxyl), 1735 cm^{-1} (20-ketone), 1100, 1085, 1035 cm^{-1} (ether bands). The product was transformed without further purification into the tosylate **9a**, as described in the following paragraph.

A quantity of 7.5 g of the 3α-hydroxy-21,21-dimethoxypregnanone **9**, m.p. 120–122°, was converted, as above, with a solution of 7.5 g of *p*-toluenesulfonyl chloride in 120 ml of pyridine to crude *tosylate* **9a**. This product (8.8 g), which showed the ultraviolet (31) and infrared absorptions typical of a tosylate, was dissolved in 300 ml of *N,N*-dimethylformamide. The solution was heated for 72 h at 82° and was then poured into ice-water. The usual work-up gave a crude product, consisting mainly of *formate* **8a**, which was dissolved in 300 ml of a 5% methanolic potassium hydroxide solution. The mixture was kept for 4 h at room temperature and was worked up in the usual fashion (see above). Chromatography of the crude reaction product (5 g) on 150 g of aluminium oxide gave 1.6 g (21%) of pure *3β-hydroxy-21,21-dimethoxy-5β-pregnan-20-one(**8**)*, eluted with petroleum ether – benzene (1:1) and melting at 103–105°. The product proved to be identical with the product obtained by Mattox rearrangement of 3β,21-diacetoxy-17α-hydroxy-5β-pregnan-20-one (**7b**) (see above), as established by the determination of a mixture melting point and the comparison of the infrared spectra.

*Meerwein–Ponndorf Reductions of 17,20;20,21-Bismethylenedioxy-5β-pregnan-3-one(**3**)*

The various Meerwein–Ponndorf reductions summarized in Table I were carried out under identical conditions with the exception of a variation of the reaction period and the quantities of materials used.[10] Our experimental procedure was adopted from that described by Miescher and Fischer (32). We report here, as an example, the reduction carried out over a period of 2 h.

To a solution of 1 g of 17,20;20,21-bismethylenedioxy-5β-pregnan-3-one (**3**), m.p. 180–181°, in 5 ml of absolute benzene, 25 ml of *sec*-butyl alcohol and 1 g of aluminium *t*-butoxide were added. The mixture was refluxed for 2 h, diluted with 2 ml of benzene, and then poured into ice-water. The precipitate was extracted with a 1:3 mixture of dichloromethane and ether, the organic layer was washed with a saturated cold ammonium chloride solution and

[10]While the quantities varied, the proportions of reagents and solvent remained identical.

with water, and was dried over sodium sulfate. Evaporation of the solvent gave 1.116 g of an oil which crystallized upon trituration with ether. This product was chromatographed on 35 g of aluminium oxide. Elutions with petroleum ether – benzene (4:1) gave 432 mg (43%) of *3β-hydroxy-17,20;20,21-bismethylenedioxy-5β-pregnane (5)*, m.p. 150–152°. Elutions with petroleum ether – benzene (1:1 and 1:4) gave 560 mg (56% yield) of *3α-hydroxy-17,20;20,21-bismethylenedioxy-5β-pregnane (6)*, m.p. 175–177°.

The identity of the products with authentic samples (see above) was established by the determination of mixture melting points and the comparison of the infrared spectra.

As apparent from Table I, in the case of the experiment carried out over a reaction period of 8 min, 7.2% of starting material, *17,20;20,21-bismethylenedioxy-5β-pregnan-3-one (3)*, m.p. 180–181°, eluted from the chromatogram with petroleum ether – benzene (9:1), was isolated in addition to the isomeric alcohols **5** and **6**.

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