*Tetrahedron* Vol 24, pp 2789 to 2794 Pergamon Press 1968 Printed in Great Britain

# STUDIES ON C-NOR-D-HOMOSTEROIDS—VIII[1]

## C-NOR-D-HOMO-REARRANGEMENT OF CHOLANIC ACID AND ITS DERIVATIVES

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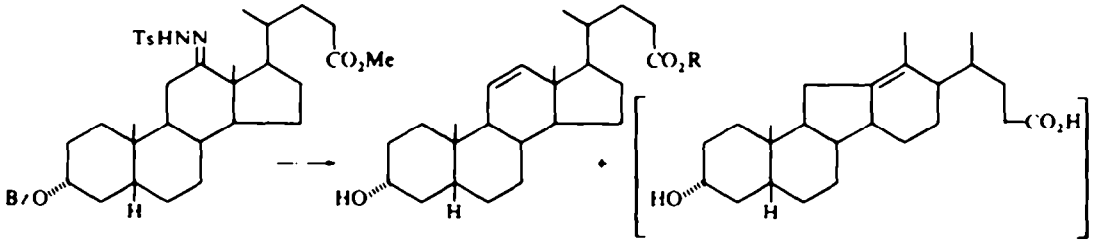
(*Received in Japan* 26 *July* 1967; *accepted for publication* 10 *October* 1967)

**Abstract**– Solvolysis of 12β-tosyl derivatives of A/B-*cis*-steroids was shown to give C-nor-D-homo-rearranged products. The previous report on the Bamford-Stevens reaction of desoxycholic acid derivatives has been revised.

PREVIOUSLY, Mitsuhashi and Harada reported that the Bamford–Stevens reaction of methyl 3α-benzoyloxy-5β-cholanate-12-tosylhydrazone (**1**) affords $\Delta^{11}$-3α-hydroxycholanic acid (**2a**) and a non-crystalline substance, to which a C-nor-D-homo-structure (**3**) was given.[2]

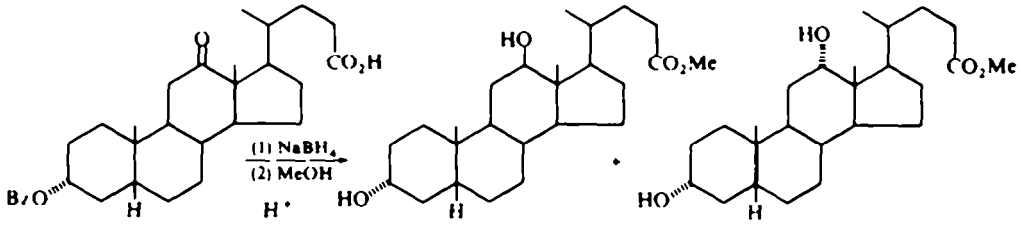


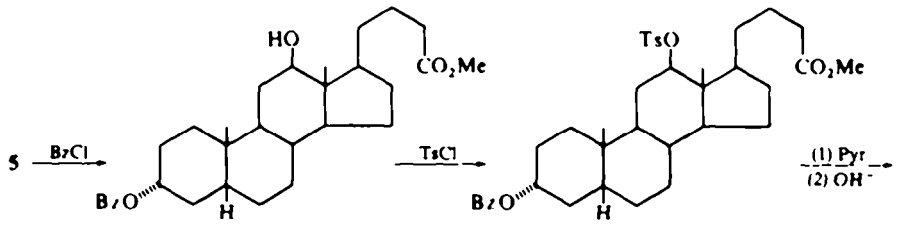

In a further study of the C-nor-D-homo-rearrangement of A/B-*cis*-steroids, we reached a somewhat different result, and we wish to revise the previous work and report some new data in the A/B-*cis*-series.

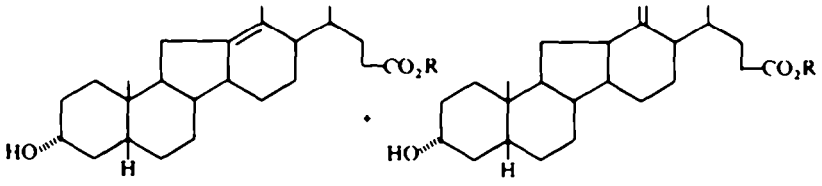
Methyl 3α-benzoyloxycholanate-12-one (**4**)[3] was reduced with sodium borohydride. After hydrolysis and methylation, the product was separated on an alumina column into methyl desoxycholate (**6**) and methyl 3α,12β-dihydroxycholanate (**5**). Benzoylation of **5** under a regulated condition gave the 3-monobenzoate (**7**), which was tosylated to unstable methyl 3α-benzoyloxy-12β-tosyloxycholanate (**8**), in a good yield. Solvolysis of **8** in pyridine gave an oily product, which resisted to crystallization. Alkaline hydrolysis of the product gave a crystalline acid, **9**, $C_{25}H_{40}O_3$, m.p. 168–171° in 40% yield. The compound **9** shows a signal for the vinylic 18-methyl group at τ 8·38 besides other signals at τ 9·14 (singlet, 19-Me) and 8·98 (doublet, $J$ = 6 c/s, 21-Me).

The methylation of the mother liquor and separation on a silver nitrate-impregnated TLC afforded another compound **11** besides the methyl ester of **9** (**10**). Although the compound **11** was obtained only as an oily substance, it gave a clear NMR

spectrum, which lacks the 18-methyl, but possesses typical terminal methylene signals (τ 4·72, 4·86). This result is entirely analogous to all the similar reactions in the A/B-*trans* series.[4] Thus, **9** should be designated as **3**, and the compound **11** should be the double bond isomer of an exomethylene type.




As the compound **3**, which should correspond to **9**, was not crystalline in the previous report, Bamford–Stevens reaction of **1** was repeated. A careful study of the NMR spectrum of the resulting mixture shows that it consists of various products, among which **9** is a rather minor component; a relatively small peak can be seen at τ 9·14. After methylation, the mixture was separated by preparative TLC using silver nitrate-impregnated silica gel into four fractions: **10** + **12**, **13**, **14** and **2b** (in the order of mobility). The compound **2b** was easily crystallized and identified as methyl $\Delta^{11}$-3α-hydroxycholenate. The fraction **10** + **12** is not separable by TLC, but the NMR measurement proved it is the composite of two compounds, **10** and **12**. Compounds **13** and **14** were also not crystalline, but seems to be pure by NMR. The methyl signals listed in the Table, suggest compounds **12**, **13** and **14** could be corresponding to one of the double bond isomers of the methyl migrated products (**A**) and C-nor-D-homo-compound (**B**).*

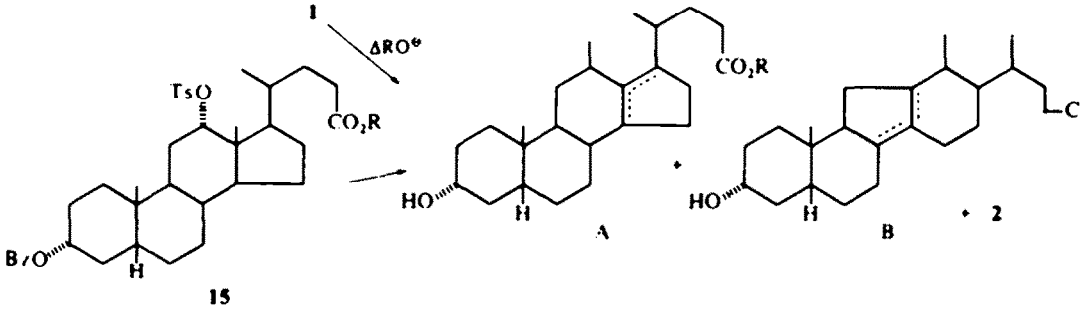
This speculation was supported by the finding that those products were also

* These structures were speculated only on the ground of the reaction mechanism, and at present, we do not have enough data to assign the compounds to the corresponding structures. The $\Delta^{8(14)}$-isomer of either A or B cannot be excluded, but under a basic condition, such a double migration is little known.

formed by the solvolysis of the 12α-tosylate, **15**. The NMR spectrum of the crude product formed by solvolysis of **15** has essentially the same pattern as that from **1**, though the ratio of the components varies a little. Furthermore, the mixture was separated in the same manner to **10** + **12**, **13**, **14** and **2b**, which were spectrographically identified with the corresponding products from **1**.

TABLE 1

| Compounds | Signals (τ in $CDCl_3$) |
|---|---|
| **12** | 9·09 (19-Me), 9·04 (21-Me, d, $J$ = 5 c/s), 8·74 (18-Me, d, $J$ = 6 c/s) |
| **13** | 9·03 (19-Me), 9·01 (21-Me, d, $J$ = 6 c/s), 8·91 (18-Me, d, $J$ = 6 c/s) |
| **14** | 9·05 (19-Me), 8·94 (21-Me, d, $J$ = 6 c/s), 8·68 (18-Me, d, $J$ = 6 c/s) |




In pregnane and spirostane series, the Bamford–Stevens reaction products of 12-tosylhydrazones are mainly C-nor-D-homosteroids, which can be also obtained by the solvolysis of 12β-tosylates or mesylates, and the solvolysis of 12α-tosylates are known to afford $\Delta^{11}$-compounds and the 18-Me migrated products.[5] This is quite different from the results we obtained in the cholanic acid derivatives.

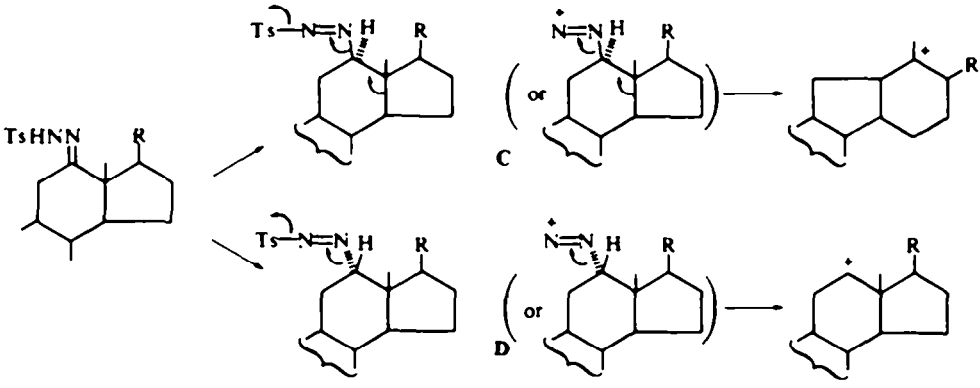
Huffmann *et al.* studied the reduction of various 12-keto-steroids and concluded, only in cholanic acid series, because of the steric hindrance by the side-chain, the 12α-(axial) configuration is more thermodynamically stable form.[6] Thus the reduction of 12-keto and 12-oxime gave 12α-orientated product predominantly. This speculation can also explain our results very reasonably.

If we could assume the rearrangement go through the diazo-intermediates,* either type **C** or **D**, the more stable form in pregnane or spirostane compounds is β-orientated and has the same fate as the 12β-tosylate. In cholanic acid, however, the stable form is the α-isomer, which is expected to behave like the 12α-tosylate. This is quite compatible with the facts.

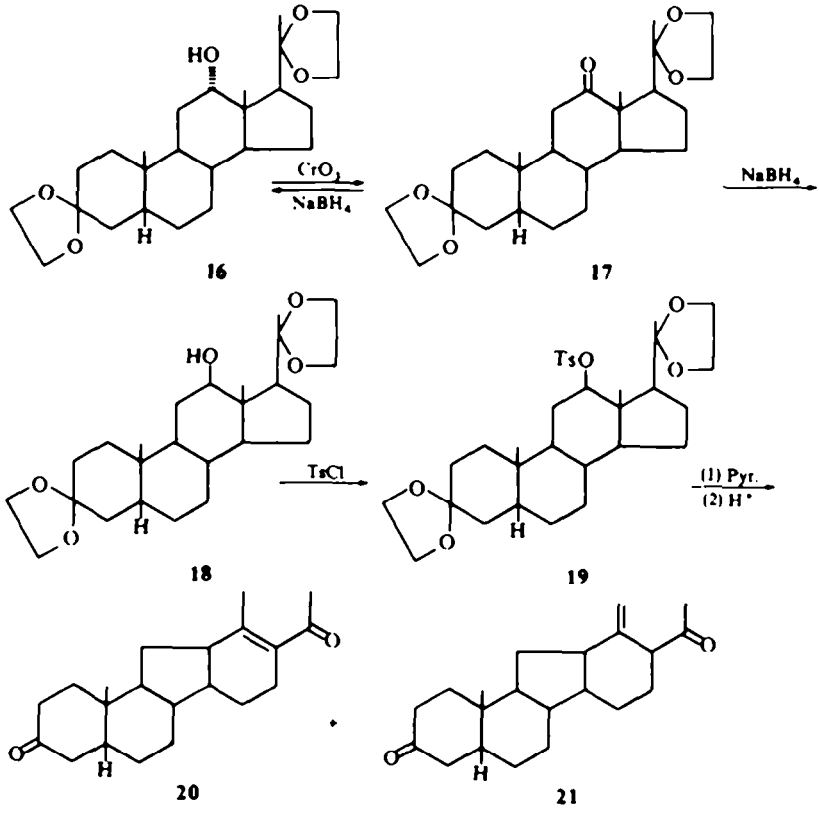
In an attempt to obtain C-nor-D-homopregnanes having A/B-*cis*-juncture, the following experiment was done. The known bis-ketal (**16**)[7] was oxidized with Jones reagent to **17**, which was reduced with sodium borohydride to **16** and its 12β-isomer **18**. Compound **18** was tosylated and tosylate **19** was solvolyzed in pyridine.

The product was an oily substance, which, after deketalization in acetic acid, were separated into two substances, **20** and **21**. The compound **20** is a conjugated ketone

* Other mechanisms, such as *via* carbene intermediates, cannot be excluded.



($\lambda_{max}$ 250 mμ) and has a vinylic Me signal at τ 8·01 besides 19-Me and 21-Me signals at τ 8·95 and τ 7·75, respectively. The compound **21** has vinylic protons at τ 4·78 and 5·00, suggesting the structure of the exomethylene isomer of **20**. This rearrangement pattern also well-coincides with those of other 12β-tosylates.



## EXPERIMENTAL

All m.ps were measured on a Kofler block. For homogenity tests and identification, TLC using silica gel $HF_{254}$ and alumina G were used. The NMR spectra were taken on either Nihon Denshi JNMC-60 or Hitachi H-60 instrument working at 60MC. The IR spectra were taken in a Shimadzu IR Spectrometor-Type IR. The UV spectra were measured in EtOH on a Shimadzu RS-27.

*Sodium borohydride reduction of methyl 3α-benzoyloxy-12-oxo-cholanate* (4). To a soln of 4 (5 g) in MeOH (20 ml), was added a soln of $NaBH_4$ (5 g) and KOH (10 g) in 250 ml 80% MeOH. The mixture was heated at reflux for 4·5 hr. After addition of water, MeOH was removed *in vacuo* and the mixture was extracted with $CH_2Cl_2$. The organic layer was washed with water and dried ($Na_2SO_4$). After removal of the solvent, the residue was crystallized from acetone (4·5 g). After methylation with 1% HCl in MeOH (30 ml), the resulting ester mixture (4·34 g) was chromatographed on alumina (120 g). Elution with benzene–ether (8:2) gave **15** (1·78 g) which was directly treated with benzoyl chloride and pyridine in abs benzene at 20° for 2 hr to afford 1·56 g of non-crystalline **7**, τ 9·24 (singlet, 18-Me), 8·95 (doublet, $J$ = 6 c/s, 21-Me), 9·00 (singlet, 19-Me), 6·48 (doublet, $J$ = 10 c/s, 12α-H), 6·32 (singlet, ester Me). (Found: C, 75·13; H, 9·11. $C_{32}H_{46}O_5$ requires: C, 75·26; H, 9·08%).

Elution with benzene–ether (8:3) and ether gave a sample identical with **6**.

*Rearrangement of the tosylate* (8). To a solution of **7** (1 g) in pyridine (20 ml), was added tosyl chloride (1 g) under ice-cooling. The mixture was allowed to stand at room temp for 24 hr.

Introduction of ice water deposited crystals of **8**, m.p. 127° (dec), $\nu_{max}^{Nujol}$ 1600, 1170 $cm^{-1}$, which were very unstable and used for the solvolysis without purification.

A soln of **8** (1 g) in pyridine (20 ml), was refluxed for 6 hr. After cooling, the mixture was poured into ice water. Extraction with ether followed by the usual treatment afforded an oily substance (600 mg), which shows an almost single spot on TLC and was hydrolyzed with methanolic KOH for 4 hr. After acidification, the acidic substance was extracted with ether. The ether extract was processed by the usual method to afford a residue, which was crystallized from MeOH–water. Recrystallization from acetone, gave **9**, m.p. 168 171°; $\nu_{max}^{Nujol}$ 3520, 1710 $cm^{-1}$ τ 9·14 (singlet, 19-Me), 9·02 (doublet, $J$ = 6 c/s, 21-Me), 8·38 (singlet, 18-Me), 6·32 (multiplet, 3α-H). (Found: C, 76·82; H, 10·15. $C_{24}H_{38}O_3$ requires: C, 76·96; H, 10·23%).

The mother liquor was esterified under the above conditions and the product was isolated with preparative TLC (silica gel G, containing 5% $AgNO_3$) to give an oily substance, **10**, (87 mg), τ 9·14 (singlet, 18-Me), 6·33 (Me ester), and **11** (56 mg), τ 9·07 (singlet, 19-Me), 9·05 (doublet, $J$ = 6 c/s, 21-Me), 6·30 (singlet, ester Me), 5·28, 5·32 (vinylic protones).

*Bamford–Stevens reaction of the tosylhydrazone* (1). Tosylhydrazone **1** (2·3 g) was suspended in a soln of Na (1·5 g) in ethylene glycol (67 ml) and heated gradually under a $N_2$ atmosphere. The evolution of $N_2$ started at ca. 135°. The soln was kept at 170° for 1 hr. Addition of water to the cooled mixture followed by acidification with dil HCl and extraction with ether gave a mixture of acids, which was esterified with MeOH with 1% HCl to the methyl ester mixture (1·45 g). Before and after the esterification, the mixture was tested by NMR (*vide supra*). The mixture was separated by TLC using silica gel G with 5% $AgNO_3$ (solvent: $CH_2Cl_2$) to **13** (78 mg), **14** (285 mg), **10** + **12** (563 mg), **2b** (95 mg), m.p. 102–105°, τ 9·23 (singlet, 18-Me), 9·08 (singlet, 19-Me), 8·99 (doublet, $J$ = 6 c/s, 12-H), 6·07 (doublet, $J$ = 10 c/s, $J$ = 2 c/s). (Found: C, 77·12; H, 10·23. $C_{25}H_{40}O_3$ requires: C, 77·27; H, 10·38%).

*The solvolysis of the 12α-tosylate* (15). To a soln of methyl 3α-benzoyloxy-12α-hydroxycholanate (630 mg) in pyridine (15 ml), tosyl chloride (1 g) was added under ice-cooling. The mixture was allowed to stand for 4 days at 60° and then refluxed for 3 hr. After dilution with water, the mixture was extracted with ether. The ethereal layer was washed with dil HCl, water, and dried. Evaporation of ether gave an oily substance, which was hydrolyzed with 5% methanolic KOH and re-esterified with 1% HCl in MeOH. The methyl ester (360 mg) was separated by TLC ($AgNO_3$ impregnated silica gel G, $CH_2Cl_2$) to **13** (33 mg), **14** (56 mg), **10** + **12** (39 mg) and **2b** (70 mg). The NMR spectrum and IR spectrum for each compound were identical with those from **1**.

3,20-*Bisethylenedioxy-5β-pregnan-12-one* (17). To a heterogenous mixture of $CrO_3$ (2 g) in pyridine (20 ml), was added a soln of **16** (1 g)[9] in 8 ml pyridine under ice cooling. The mixture was allowed to stand at room temp for 16 hr. After addition of water, the soln was extracted with ether. The organic layer was washed with water. Evaporation of ether followed by removal of pyridine by co-distillation with EtOH under a reduced press gave a crystalline residue, which was recrystallized from MeOH to give **17** (0·8 g), m.p. 143–146°, $\nu_{max}^{Nujol}$ 1705 $cm^{-1}$. (Found: C, 71·81; H, 9·20. $C_{25}H_{38}O_5$ requires: C, 71·74; H, 9·15%).

3,20-*Bisethylendioxy-12β-hydroxy-5β-pregnane* (18). Compound **17** (5 g) was dissolved in dioxan (75 ml) and a soln of $NaBH_4$ (2 g) in 50% dioxan (20 ml) containing a trace of NaOH added. After standing for 24 hr the excess reagent was destroyed with acetone and the mixture was poured into ice–water to afford crystals (4·9 g), which were crystallized fractionally from ether–hexane to the 12β-ol **18**, (700 mg) and **16** (3 g). The rest remained as a mixture of both compounds. Compound **18**, m.p. 110–112°, $\nu_{max}^{Nujol}$ 3400, 1030, 1060 $cm^{-1}$. (Found: C, 71·19; H, 9·78. $C_{25}H_{40}O_5$ requires: C, 71·39; H, 9·59%).

*Rearrangement of* **18** *via* **19**. To a soln of **18** (1 g) in pyridine (20 ml), was added tosyl choloride (1·68 g) under ice-cooling. After standing at 38° for 7 days or refluxing for 1 hr, the mixture was poured into ice-water and extracted with ether. The ethereal extract was washed with water and evaporated to dryness under a reduced press. The residue (632 mg) was oily, and deketalyzed directly by heating at 100° in 90% AcOH for 1 hr. Dilution with water and extraction with ether gave an oily residue. TLC (silica gel $HF_{254}$, benzene:ethyl acetate = 9:1) showed two spots, which were separated preparatively using the same system as for **20** (55 mg), m.p. 107–110° (from MeOH), $\lambda_{max}$ 250 mμ ($\varepsilon$ = 11,000), $\nu_{max}^{Nujol}$ 1715, 1680, 1630 $cm^{-1}$; τ ($CDCl_3$) 9·05 (singlet, 19-Me), 8·09 (singlet, 18-Me), 7·75 (singlet, 21-Me). (Found: C, 78·20; H, 9·25. $C_{21}H_{30}O_2 \cdot \frac{1}{2}H_2O$ requires: C, 77·97; H, 9·66%) and **21**, non-crystalline, $\nu_{max}^{CH_2Cl_2}$ 1700 $cm^{-1}$, τ (in $CDCl_3$) 9·00 (singlet, 19-Me), 7·77 (doublet, $J$ = 2 c/s, 21-Me), 4·78, 5·00 (vinylic protons).

*Acknowledgements*—The authors wish to thank Dr. K. Takeda, Director of Shionogi Laboratory, for the starting material, Mr. S. Shimokawa and Miss Y. Kishio for measurements of NMR spectra. They are also indebted to Mrs. T. Toma and Miss A. Maeda for elemental analysis.

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