REARRANGEMENTS OF STEROIDS, IX

Schmidt Reactions and Beckmann Rearrangements of Bile Acid Ketones and Ketoximes*

By

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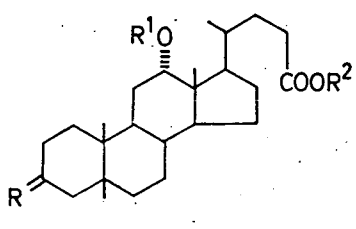
Various O-acetyl-protected 3-keto, 6-keto, 7-keto- and 12-keto-cholanic acid methyl esters were subjected to Schmidt rearrangement, and the resulting homo-lactams were compared with the homo-lactams isolated in the Beckmann rearrangement of the corresponding ketoximes. In addition, the structures of the homo-lactams formed were confirmed by Hofmann degradation from the side of the amine formed after hydrolysis of the homo-lactam, by pyrolysis and in several cases by subsequent Oppenauer oxidation, *via* the structures of the substances isolated.

Comparatively few publications deal with the rearrangements of bile acid ketones and ketoximes [1—3]. We have primarily regarded the bile acid ketones and ketoximes as the simplest and most easily accessible coprostane skeleton model for the comparative study of the mechanisms of the Schmidt reaction and Beckmann rearrangement [4, 5].

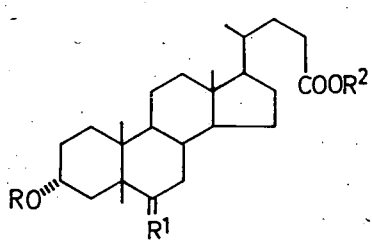
Bile acid derivatives were dealt with earlier in another respect [6—8], and thus their investigation, preparation and isolation did not cause any particular difficulty.

The following bile acid ketones and ketoximes (**I—VIII**) were prepared and subjected to rearrangement.



I: R=O; R^1=Ac; R^2=CH_3

II: R=NOH; R^1=Ac; R^2=CH_3



III: R=Ac; R^1=O; R^2=CH_3

IV: R=Ac; R^1=NOH; R^2=CH_3

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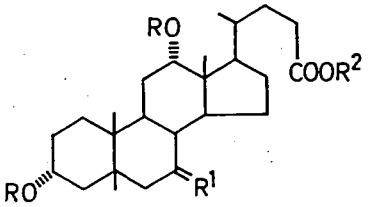
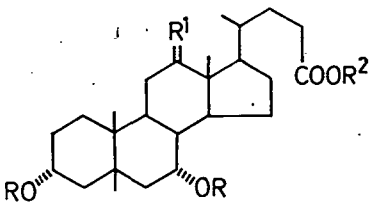


V : R=Ac ; R^1=O; R =CH_3

VI: R=Ac; R^1=NOH; R^2=CH_3



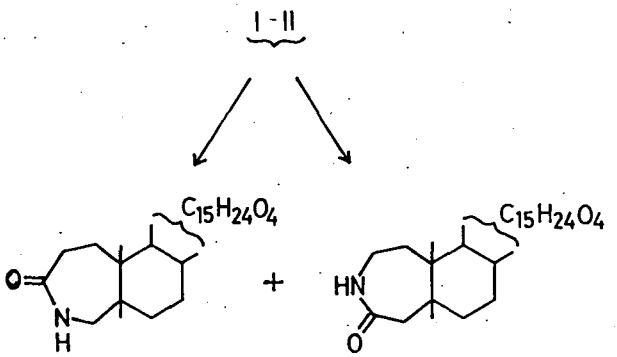
VII : R=Ac ; R^1=O; R^2=CH_3

VIII : R=Ac; R^1=NOH; R^2=CH_3

The rearrangements of **I** and **II** lead to two A-homo-lactams with different structures, which are formed side by side. It was necessary to determine the structures of these products (**IX—X**).

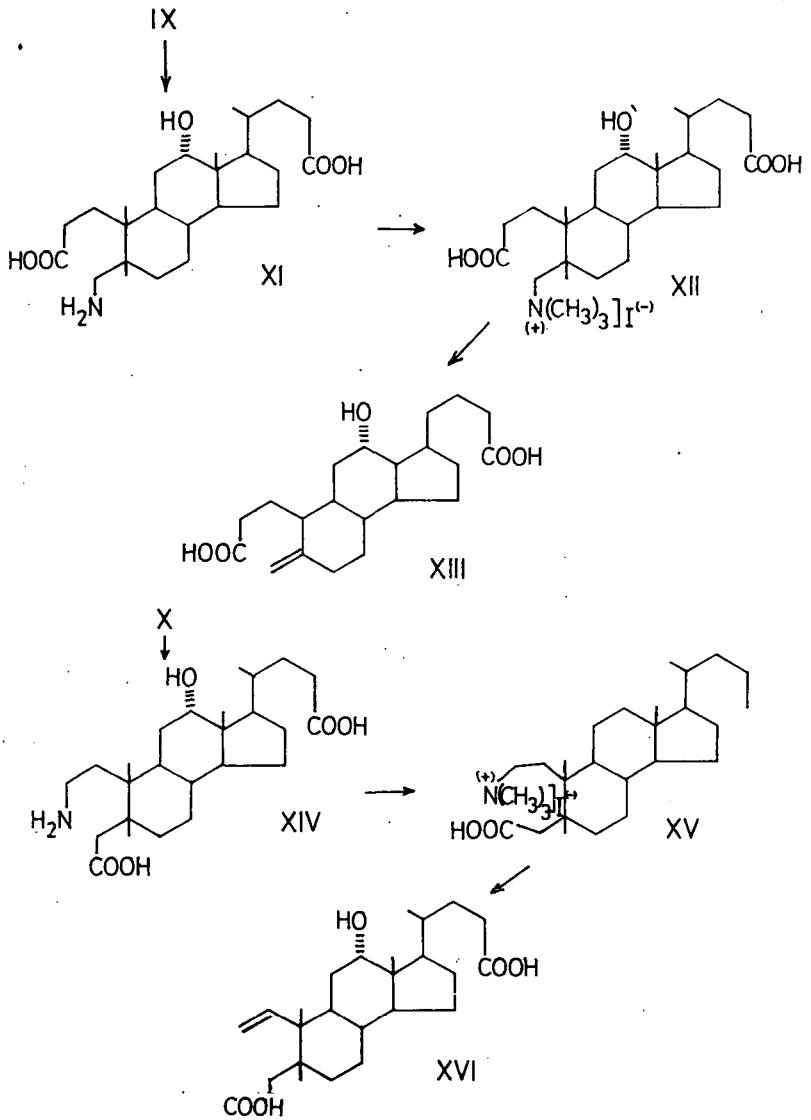
HARA [3] carried out the Schmidt reactions of 3-keto-A-nor-methylcholanate and 3-keto-methylcholanate in chloroform in the presence of sulphuric acid, and the Beckmann rearrangements of the oximes, and isolated both lactams and homo-lactams formed in the rearrangements. Thus, in our case, too, the formation of both homo-lactams was to be expected in both rearrangements. Infact, in the Schmidt reaction of 3-keto-methylcholanate a third homo-lactam was found; as regards its physical constants, this differed from the other homo-lactams, and we assume it to be a derivative containing a free carboxyl group. HARA observed that one lactam and homo-lactam are produced only in low amounts, whereas the yield of the main product is much more significant.

In the rearrangements of 12α-acetoxy-3-keto-methylcholanate (**I**) and its oxime (**II**) we similarly expected, and did isolate two homo-lactams (**IX, X**). Interestingly, however, the rearrangements of **I** and **II** led to the lactams **IX** and **X**, respectively, in almost pure states. The structures of the homo-lactams were established by



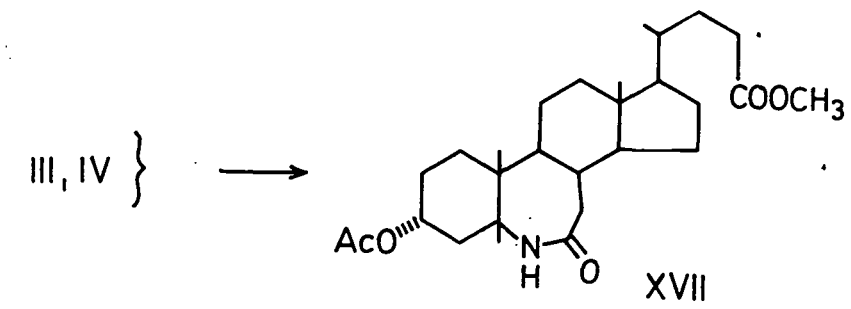
IX X

Hofmann exhaustive methylation following hydrolysis, and by study of the infrared spectra, of various physical constants, and other properties of the products of various structures (**XI—XVI**) produced on pyrolysis.

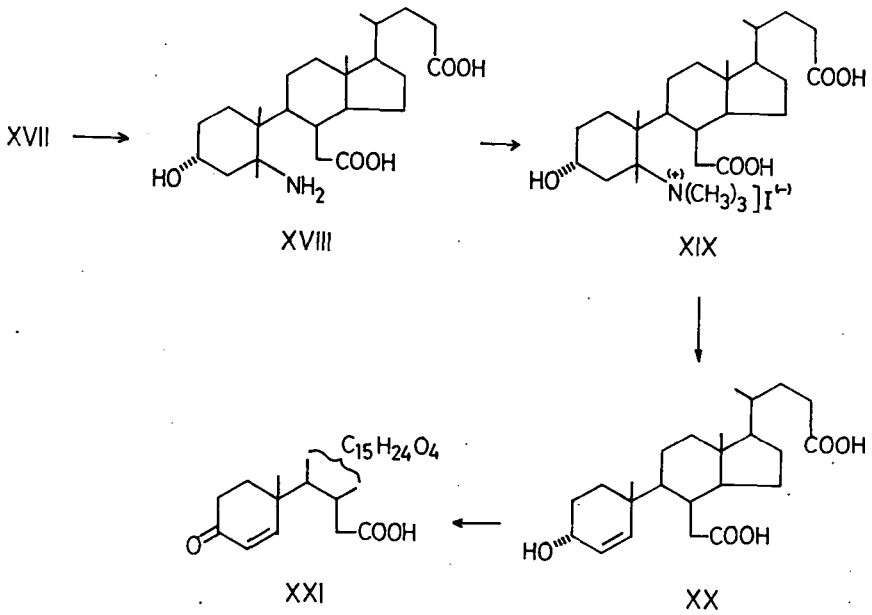


Compound **XIII** displays a methylene vibration in the infrared spectrum, while **XVI** is found to contain an isolated double-bond.

Rearrangement of 3α-acetoxy-6-keto-methylcholanate (**III**) and its oxime (**IV**) gave the homo-lactam **XVII**:

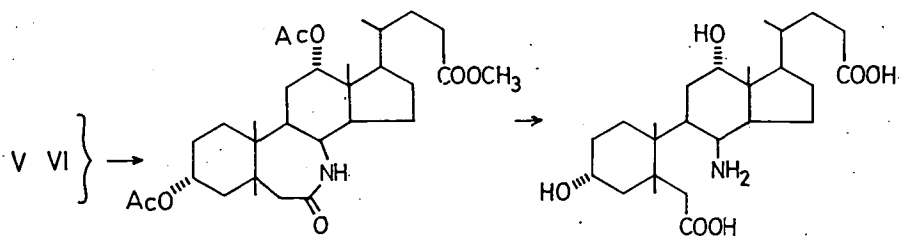


This was hydrolysed, and then pyrolysed after quaternary salt formation under alkaline conditions. The pyrolysis here was followed by Oppenauer oxidation [10]: (**XVIII—XXI**)



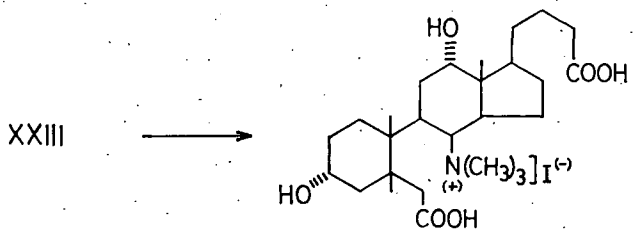
The end-product of the Oppenauer oxidation was compound **XXI**; the characteristic infrared spectrum of this is due to the conjugated ketone structure of ring A.

Under the normal conditions of the Schmidt reactions [11] and Beckmann rearrangements, the same homo-lactam (**XXII**) was isolated from 3α,12α-diacetoxy--7-ketomethylcholanate (**V**) and its oxime (**VI**):

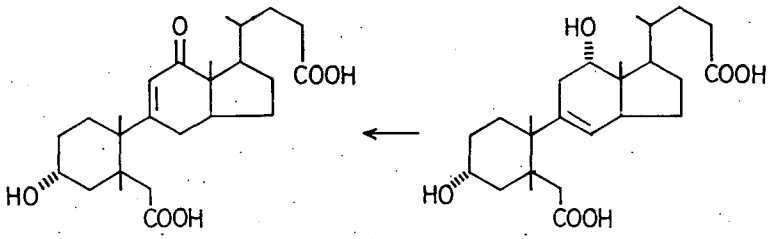


XXII XXIII

This was subsequently hydrolyzed, and the structure of the product was established by Oppenauer oxidation, similarly as for the homo-lactam isolated in the rearrangement of 6-ketone (**XXIV—XXVI**):



XXIV



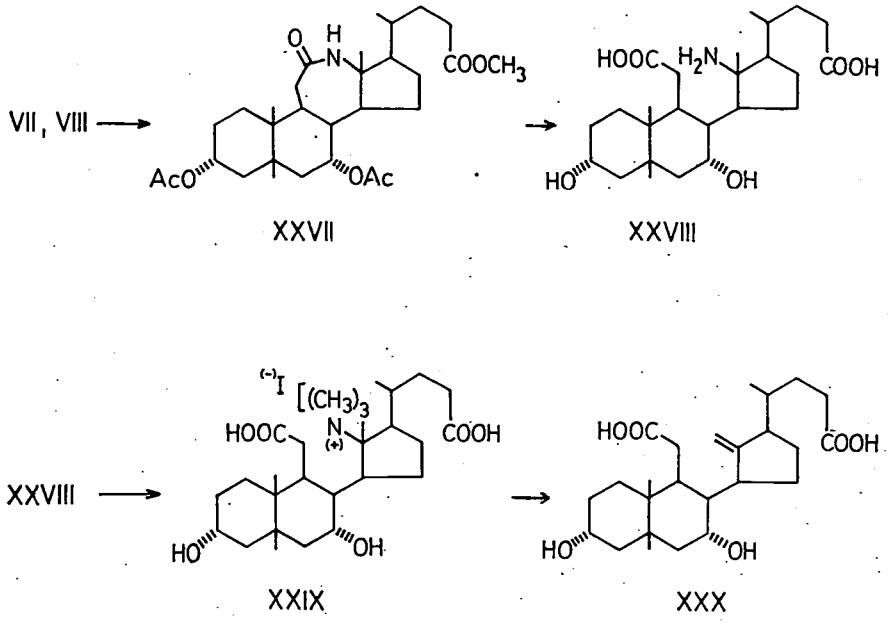
XXVI XXV

Thus, a conjugated ketone structure developed in ring C of the seco-steroid skeleton on Oppenauer oxidation. This made it easier to follow the events.

After hydrolysis of the homo-lactam the presence of the two carboxylic acid groups was proved by microtitration [7].

Finally, 3α,7α-diacetoxy-12-keto-methylcholanate (**VII**) and its oxime (**VIII**) were subjected to the Schmidt reaction and the Beckmann rearrangement, and again one homo-lactam was obtained. The structure of this was determined as before, with hydrolysis, quaternary salt formation and pyrolysis, resulting in a methylene group at C_{18}.

The characteristics of the methylene structure, and of the compounds produced in general (**XXVII—XXX**), are described in the experimental part.



Experimental

Details of the experimental conditions were published earlier [7, 11—13], while details on the TLC are to be found in [6] and [14].

3α,12α-Dihydroxycholanic acid (deoxycholic acid)

This was a gift of the Gedeon Richter Pharmaceutical Works (Budapest). After repeated recrystallization, m.p.: 176—177 °C (literature m.p.: 176—177 °C [15]). This was used to prepare 3α,12α-dihydroxy-methylcholanate with conc. hydrochloric acid in methanol. M.p.: 79—81 °C (lit. m.p.: 80—81 °C [15]).

The methyl compound was acetylated with acetic anhydride in pyridine to give 3α,12α-diacetoxy-methylcholanate. Partial hydrolysis of the 3α-acetoxy group at room temperature with methanolic hydrochloric acid led to 3α-hydroxy-12α-acetoxy-methylcholanate. Repeated attempts were made to recrystallize this from aqueous methanol, without success. The same partial deacetylation was carried out with K_2CO_3 in aqueous methanol, but this did not give a crystalline end-product either [16]. The material was subsequently treated with diazomethane in ether for the methyl ester to be taken further quantitatively.

3-Keto-12α-acetoxy-methylcholanate (**I**) [15]

Prepared from 3α-hydroxy-12α-acetoxy-methylcholanate by CrO_3 oxidation in glacial acetic acid at room temperature. The product was recrystallized several times from ether. M.p.: 121—122 °C; $[\alpha]_D = +83 \pm 2°$ (c=2.15; acetone) [16].

$C_{27}H_{42}O_5$ (446.64). Calcd.: $C_{27}H_{42}O_5$ C 72.61; H 9.43. Found: C 72.64; H 9.48%. ν_{max}^{KBr} 1730, 1700 (C=O), 1260 (C—O acetate) cm^{-1}.

12α-Acetoxy-3-ketoxime-methylcholanate (**II**)

Prepared from **I** in pyridine with hydroxylamine hydrochloride. Recrystallized repeatedly from methanol. M.p.: 74—75 °C; $[\alpha]_D = +99 \pm 2°$ (c=1.0; $CHCl_3$);

$C_{27}H_{42}O_5$=(461.65). Anal.: Calcd.: $C_{27}H_{43}O_5N$ C 70.25; H 9.39; N 3.03. Found: C 70.29; H 9.42; N 3.18%. ν_{max}^{KBr} 3450 (OH), 1720 (C=O), 1650 (C=N), 1250 (C—O acetate) cm^{-1}.

12α-Acetoxy-3-ketoxime-methylcholanate: Beckmann rearrangement

The Beckmann rearrangement of **II** was carried out in pyridine in the presence of *p*-acetylamino-benzenesulfonic acid chloride (PAABSCl) at room temperature, or in dioxane with thionyl chloride at 10 °C. The material obtained by ether extraction was chromatographed on a neutral alumina/activity grade II (n. Al_2O_3/II) column after evaporation of the solvent. The lactam could be eluted from the column only with chloroform. The isolated lactam, the structure of which is given on the basis of the reconstruction of further structural examinations, is 3-keto-3a-aza-12α-acetoxy-A-homo-methylcholanate (**IX**), M.p.: 60—62 °C; $[\alpha]_D = +63 \pm 2°$ (c=1.0; $CHCl_3$);

$C_{27}H_{42}O_5$ (446.64). Calcd: for M.w., molecular formula and calculated values, of C, H and N see **II**). Found: C 70.24; H 9.24; N 3.25%.
ν_{max}^{KBr} 3350, 3300 (NH), 1730, 1670 (C=O), 1250 (C—O ester) cm^{-1}. (Similar rearrangement of **II** is described in [2] and [17].)

3-Keto-12α-acetoxy-methylcholanate: Schmidt reaction

The Schmidt reaction was carried out in polyphosphoric acid (PP) [12], and thus the homo-lactam **X** was obtained in addition to the lactam **IX**.

3-Aza-3a-keto-12α-acetoxy-A-homo-methylcholanate

M.p.: 91—92 °C; $[\alpha]_D = +31 \pm 2°$ (c=1.0; $CHCl_3$);

$C_{27}H_{42}O_5$ (446.64). Cald: for M.w., *etc.* see **II**). Found: C 70.26; H 9.38; N 3.10%. ν_{max}^{KBr} 3350, 3200, 3100 (NH), 1720, 1670 (C=O), 1250 (C—O acetate) cm^{-1}.

3α-Acetoxy-6-keto-methylcholanate (**III**)

Prepared from 3α-acetoxy-6α-hydroxy-methylcholanate. First the methyl ester was prepared from 3α,6α-dihydroxycholanic acid with diazomethane, and this was used to prepare 3α-acetoxy-6α-hydroxy-methylcholanate [7, 18], which was oxidized to **III** with CrO_3 by the method of HOEHN *et al.* [19]; the product was repeatedly

recrystallized from aqueous methanol. M.p.: 156—157 °C; $[\alpha]_D = -19 \pm 2°$ (c=1.0; dioxane); M.w.: 446.63. (Lit. M.p.: 155—157 °C; $[\alpha]_D^{23} = -18.8 \pm 3°$ (dioxane) [19].)

$C_{27}H_{42}O_5$ (446.64). Calcd.: $C_{27}H_{42}O_5$ C 72.61; H 9.48. Found: C 72.65; H 9.52%. ν_{max}^{KBr} 1720, 1700 (C=O), 1250 (C—O acetate) cm^{-1}.

3α-Hydroxy-6-keto-cholanic acid [19]

The method of HOEHN *et al.* [19] can also be used to prepare the deacetylated bile acid 6-ketone. It was recrystallized from aqueous methanol. M.p.: 138—140 °C; $[\alpha]_D = -42 \pm 2°$ (c=1.0; $CHCl_3$); M.w.: 374.57. (Lit. m.p.: 138—140 °C; $[\alpha]_D^{27} = -41.5 \pm 3°$ (dioxane) [19].)

$C_{27}H_{42}O_5$ (446.64). Calcd.: $C_{24}H_{38}O_4$ C 73.81; H 9.80. Found: C 73.94; H 9.86%. ν_{max}^{KBr} 3500 (OH), 1710, 1690 (C=O) cm^{-1}.

3α-Acetoxy-6-ketoxime-methylcholanate (**IV**) [19]

Prepared from **III** in pyridine with hydroxylamine hydrochloride as before. Repeatedly recrystallized from aqueous methanol. M.p.: 161—163 °C; $[\alpha]_D = -18 \pm 2°$ (c=1.0; $CHCl_3$); M.w.: 461.55 (Lit. m.p.: 162—163 °C; $[\alpha]_D^{25} = -17.6 \pm 3°$ (benzene));

$C_{27}H_{42}O_5$ (446.64). Calcd.: $C_{27}H_{43}O_5N$; C 70.25; H 9.39; N 3.04. Found: C 70.26; H 9.41; N 3.10%. ν_{max}^{KBr} 3360 (OH), 1720, 1690 (C=O), 1640 (C=N), 1240 (C—O acetate) cm^{-1}.

3α-Hydroxy-6-ketoxime-cholanic acid

Similarly prepared in pyridine with hydroxylamine hydrochloride. The isolated material was repeatedly recrystallized from aqueous methanol. M.p.: 110—112 °C; $[\alpha]_D = +15 \pm 2°$ (c=1.0; $CHCl_3$); M.w.: 405.58.

$C_{27}H_{42}O_5$ (446.64). Calcd.: $C_{24}H_{39}O_4N$; C 71.08; H 9.69; N 3.45. Found: C 71.12; H 9.73; N 3.43%. ν_{max}^{KBr} 3450 (OH), 1700 (C=O), 1630 (C=N) cm^{-1}.

3α-Acetoxy-6-ketoxime-methylcholanate: Beckmann rearrangement

A solution of 4.61 g of **IV** in 150 ml anhydrous dioxane was added dropwise at room temperature to 8 ml thionyl chloride. The solution was allowed to stand at room temperature for an hour, and then poured onto ice. The product formed was extracted with ether, the extract was washed with distilled water, 5% $NaHCO_3$ solution, and distilled water. The extract was dried and evaporated to dryness. leaving a residue of 3.95 g. The residue consisted of 3.95 g brown crystalline material. The crude product was chromatographed on a silica gel column. Data of 3α-acetoxy-6-aza-6a-keto-B-homo-methylcholanate (**XVII**): m.p.: 82—84 °C; $[\alpha]_D = +72 \pm 2°$ (c=1.0; methanol); M.w.: 461.55.

$C_{27}H_{42}O_5$ (446.64). Calcd: For molecular formula and calculated C, H and N values see **IV**.) Found: C 70.22; H 9.43 N 3.15%. ν_{max}^{KBr} 3420 (NH), 1730, 1660 (O=C.NH), 1350 (C—O acetate) cm^{-1}.

3α-Acetoxy-6-keto-methylcholanate: Schmidt reaction

The Schmidt reaction was carried out by two methods:

a) 4.46 g (0.01 mole) **III** was dissolved in 100 ml dry benzene, and 8.3 ml conc. sulphuric acid was layered under it. 0.62 g (0.015 mole) hydrazoic acid in benzene was added dropwise at room temperature. After stirring for an hour, the mixture was poured onto ice. The benzene phase was separated, washed with 2*N* NaOH and dried. This phase contained 1.02 g material. When the aqueous fraction was extracted with ethyl acetate, a further 2.53 g material was isolated. The two portions of solid were combined, and 1.88 g pure **XVII** was obtained by column chromatography. The calculated physical data for the material are the same as described earlier. Found: C 70.20; H 9.35; N 3.20%.

b) Under the Schmidt reaction conditions employed with **I**, besides the starting substance and **XVII** the lactam of the deacetylated free acid was obtained. See also: 3α-hydroxy-6-ketoximecholanic acid and its Beckmann rearrangement.

3α-Hydroxy-6-ketoxime-cholanic acid: Beckmann rearrangement

When the Beckmann rearrangement of the above oxime was carried out in the manner described, with thionyl chloride and the reaction mixture was poured onto ice, the deacetylated form of the homo-lactam **XVII** was isolated. Physical constants: m.p.: 88—90 °C; $[\alpha]_D = +54 \pm 2°$ (c=1.0; $CHCl_3$).

$C_{27}H_{42}O_5$ (446.64). Calcd: M.w.: 389.58. (For the calculated data, see the oxime.) Found. C 74.03; H 10.12; N 3.75%. ν_{max}^{KBr} 3400 (OH), 1730, 1650 (O=C.NH) cm^{-1}.

3α,12α-Diacetoxy-7-keto-methylcholanate (**V**)

Prepared from the methyl ester of cholic acid by the method of COREY [20]. This is first oxidized with N-bromosuccinimide to 3α,12α-dihydroxy-7-keto-methylcholanate, which is transformed to 3α,12α-diacetoxy-7-keto-methylcholanate with a mixture of acetic acid and acetic anhydride. Physical characteristics: m.p.: 117—118 °C; $[\alpha]_D = +48 \pm 2°$ (c=1.0; $CHCl_3$). M.w.: 504.67.

$C_{27}H_{42}O_5$ (446.64). Calcd.: $C_{29}H_{44}O_7$ C 69.02; H 8.78. Found: C 69.51; H 8.96%. ν_{max}^{KBr} 1725 (C=O), 1250, 1030 (C—O acetate) cm^{-1}.

3α,12α-Diacetoxy-7-ketoxime-methylcholanate (**VI**)

Formed on reaction of **V** with hydroxylamine hydrochloride in ethanol in the presence of anhydrous sodium acetate. The product was repeatedly recrystallized from aqueous methanol. Physical data: m.p.: 99—100 °C; $[\alpha]_D = +8 \pm 2°$ (c=1.0; $CHCl_3$); M.w.: 519.69.

$C_{27}H_{24}O_5$ (446.64). Calcd.: $C_{29}H_{45}O_7N$ C 67.02; H 8.73; N 2.70. Found: C 67.07; H 8.76; N 2.82%. ν_{max}^{KBr} 3500 (OH), 1720 (C=O), 1650 (C=N), 1240 (C—O acetate) cm^{-1}.

3α,12α-Diacetoxy-7-ketoxime-methylcholanate: Beckmann rearrangement

2.48 g (0.005 mole) **VI** was dissolved in pyridine and subjected to rearrangement in the presence of PAABSCl at room temperature. The lactam isolated after chromatography on Al_2O_3/II was 3α,12α-diacetoxy-7-keto-7a-aza-B-homo-methylcholanate (**XXII**). M.p.: 88—90 °C; $[\alpha]_D = +55 \pm 2°$ (c=1.0; $CHCl_3$).

$C_{27}H_{42}O_5$ (446.64). For calcd. m.w., *etc.*, see **VI**). Found: C 67.04; H 8.75; N 2.85%. ν_{max}^{KBr} 3450 (NH), 1720, 1660 (O=C.NH), 1250 (C—O acetate) cm^{-1}.

3α,12α-Diacetoxy-7-keto-methylcholanate: Schmidt reaction

The Schmidt reaction was carried out on **V** in PP. The chloroform extract obtained after neutralization was evaporated to give a yellow-brown oil; this was chromatographed and the lactam **XXII** was isolated. Its physical data were the same as those of the lactam obtained in the Beckmann rearrangement. M.p.: 89—91 °C. Found: C 67.04; H 8.70; N 2.79%. (The IR spectrum, too, coincided with the earlier one.)

3α,7α-Diacetoxy-12-keto-methylcholanate (**VII**) [21, 22]

VII was prepared from 3α,7α,12α-trihydroxycholanic acid methyl ester. 3α,7α-Diacetoxy-12α-hydroxy-methylcholanate was oxidized with Kiliani solution. The isolated material was repeatedly recrystallized from methanol. M.p.: 179—180 °C; $[\alpha]_D = +71 \pm 2°$ (c=1.0; $CHCl_3$); (for M.w. and calcd. values, see **V**). (lit. m.p.: 178—179 °C; $[\alpha]_D^{20} = +73.5°$ (dioxane) [21].)

$C_{27}H_{42}O_5$ (446.64). Found: C 68.78; H 8.81%. ν_{max}^{KBr} 1720, 1690 (C=O), 1250, 1030 (C—O acetate) cm^{-1}.

3α,7α-Diacetoxy-12-ketoxime-methylcholanate (**VIII**)

The oxime was prepared from **VII** in ethanol with hydroxylamine hydrochloride in the presence of anhydrous sodium acetate. The isolated material was repeatedly recrystallized from methanol. M.p.: 99—100 °C; $[\alpha]_D = +160 \pm 2°$ (c=1.0; $CHCl_3$).

$C_{27}H_{42}O_5$ (446.64). (for M.w., *etc.*, see **VI**). Found: C 66.97; H 8.69%. ν_{max}^{KBr} 3450 (OH), 1720 (C=O), 1630 (C=N), 1250, 1030 (C—O acetate) cm^{-1}.

3α,7α-Diacetoxy-12-ketoxime-methylcholanate: Beckmann rearrangement

Rearrangement of 0.005 mole **VIII** was carried out at room temperature in pyridine in the presence of PAABSCl; after evaporation of the extract to dryness 2.2 g crude product was obtained. Column chromatography finally led to a substance with m.p. 93—95 °C; $[\alpha]_D = +37 \pm 2°$ (c=1.0; $CHCl_3$); (for M.w. *etc.*, see **VII**). The lactam is 3α,7α-diacetoxy-12-keto-12a-aza-C-homo-methylcholanate (**XXVII**).

$C_{27}H_{42}O_5$ (446.64). Found: C 67.05; H 8.71; N 2.75%. ν_{max}^{KBr} 3450 (NH), 1720, 1650 (O=C.NH), 1250 (C—O acetate) cm^{-1}.

3α,7α-Diacetoxy-12-keto-methylcholanate: Schmidt reaction

2.87 g (0.005 mole) **VII** was dissolved in 20 ml dry benzene, and 2.5 ml conc. sulphuric acid was layered under it, as described earlier. The calculated amount of hydrazoic acid was added in benzene solution, with constanst stirring, and stirring was continued for further 1 hr at room temperature. The mixture was then poured onto ice, and the product was isolated in the usual manner; a yellow-brown oil was obtained. This was chromatographed, and yielded a lactam with the same physical properties as the homo-lactam **XXVII**. M.p.: 93—95 °C. Found: C 67.04; H 8.78; N 2.88%. (The IR spectrum was the same as that of the C-homo-lactam isolated in the Beckmann rearrangement.)

3,3a-Seco-3a-amino-12α-hydroxycholane-dicarboxylic acid (**XI**)

IX was refluxed for 5 hrs with 5% methanolic KOH and yielded the seco-amino-dicarboxylic acid **XI**. The presence of the primary amine was confirmed by the positive iodine-azide test, and that of the dicarboxylic acid by the microtitration used in the study of the bile acids [7]. (Both methods were used later, for structural determinations, too, and in the following will be mentioned only of their positive or negative nature.) The product was repeatedly recrystallized from methanol. M.p.: 240—244 °C; $[\alpha]_D = +40 \pm 2°$ (c=0.5; methanol);

Calcd.: $C_{24}H_{41}O_5N$ (423,6). C 68.05; H 9.75; N 3.30. Found: C 68.08; H 9.72; N 3.40%. ν_{max}^{KBr} 3500 (OH, NH_2), 1700, 1670 (C=O) cm^{-1}.

3,3a-Seco-3a-amino-12α-hydroxy-dimethylcholanate

XI was dissolved in a few ml methanol. Ether was then added, the mixture was cooled, and an excess of diazomethane was added. The mixture was allowed to stand at room temperature for several hours, filtered and evaporated to dryness in vacuum. The residue was a yellow mastic, which was used to prepare the quaternary compound without further purification.

3,3a-Seco-12α-hydroxy-dimethylcholanate-3a-trimethylammonium iodide (**XII**)

XII was prepared from the former seco-dimethylcholanate by the method of HEUSSER *et al.* [9, 10]. M.p.: 136-138 °C; $[\alpha]_D = -107 \pm 2°$ (c=0.75; methanol);

M.w.: 621.65. Calcd.: $C_{29}H_{52}O_5NI$ C 56.03; H 8.43; N 2.25; I^- 20.41. Found: C 56.05; H 8.17; N 2.31; I^- 20.64%. ν_{max}^{KBr} 3420 (OH), 1720 (C=O), 1440 (C—O-alkyl) cm^{-1}.

Hofmann decomposition of **XII**

Hofmann decomposition is described in the articles of HEUSSER *et al.* [9, 10], in aqueous ethylene glycol in the presence of a base. In the isolation, the reaction mixture was acidified after reaction. The material separating out from the neutral aqueous solution was filtered off and crystallized from methanol. The physical

constants of compound **XIII**: m.p.: 186—188 °C; $[\alpha]_D = +42 \pm 2°$ (c=0.25; $CHCl_3$); M.w.: 406.56. Calc.: $C_{24}H_{38}O_5$ C 70.91; H 9.42. Found: C 71.05; H 9.39%. ν_{max}^{KBr} 3350 (OH), 1730 (C=O), 1620 (C=C) cm^{-1}.

3,3a-Seco-3-amino-12α-hydroxycholane-dicarboxylic acid[3,24] (**XIV**)

X was hydrolyzed, similarly to **IX**, in methanolic KOH, and the end-product was isolated. The hydrolysis was followed by neutralization, and the precipitate was filtered off and recrystallized from methanol. M.p.: 268—270 °C; $[\alpha]_D = +50 \pm 2°$ (c=1.0; $CHCl_3$); (for M.w.: and other calcd. data, see **XI**). Found C 68.10; H 9.72; N 3.22%. ν_{max}^{KBr} 3350, 3250 (OH, HN_2), 1620 (C=O) cm^{-1}.

3,3a-Seco-3-amino-12α-hydroxy-dimethylcholanate

Similarly as above, with an excess of diazomethane in ether, and used after evaporation of the solvent.

3,3a-Seco-12α-hydroxy-dimethylcholanate-3-trimethylammonium iodide (**XV**)

It was prepared by the method of HEUSSER *et al.* [9, 10]. M.p.: 123—125 °C; $[\alpha]_D = -23 \pm 2°$ (c=0.7; methanol); (for M.w. and calculated C, H, N and I^- data see **XII**). Found: C 55.98; H 8.25; N 2.31; I^- 20.64%. ν_{max}^{KBr} 3400 (OH), 1710 (C=O), 1440 (C—O-alkyl) cm^{-1}.

Hofmann decomposition of **XV**

The Hofmann decomposition of **XV** was carried out by the method described above, and **XVI** was isolated. M.p.: 160—162 °C; $[\alpha]_D = 55.5 \pm 2°$ (c=0.25; methanol); M.w.: 406.56 (for the other calcd. data, see **XIII**). Found: C 70.86; H 9.55%. ν_{max}^{KBr} 3420 (OH), 1700 (C=O), 1630 (C=C) cm^{-1}.

6,6a-Seco-5-amino-3α-hydroxycholanedicarboxylic acid[6,24] (**XVIII**)

The lactam **XVII** was hydrolyzed to **XVIII** by refluxing it with 5% methanolic KOH. The substance gives a positive iodine-azide test, and the new carboxylic acid group can be demonstrated by microtitration. M.p.: 168—170 °C; $[\alpha]_D = +6.5 \pm 2°$ (c=1.0; methanol); (M.w. and calculated data: as for **XIV**); Found: C 68.02; H 9.70; N 3.35%. ν_{max}^{KBr} 3300, 3220 (OH, NH_2), 1680, 1630 (C=O) cm^{-1}.

6,6a-Seco-5-amino-3α-hydroxy-dimethylcholanate

was prepared from **XVIII** with diazomethane in ethanol, and used without preliminary identification for preparation of the quaternary salt.

6,6a-Seco-3α-hydroxy-dimethylcholanate-5-trimethylammonium iodide (**XIX**)

Prepared from the former substance by the method of HEUSSER *et al.* [9, 10]. M.p.: 145—148 °C; $[\alpha]_D = +67 \pm 2°$ (c=0.28; methanol). (for M.w., *etc.*, see **XII**). Found: C 55.96; H 8.48; N 2.30; I^- 20.60%. ν_{max}^{KBr} 3350 (OH), 1700, 1630 (C=O), 1460 (C—O-methyl) cm^{-1}.

Hofmann decomposition of **XIX**

The Hofmann decomposition was carried out as above, and **XX** was isolated. M.p.: 204—206 °C; $[\alpha]_D + 36 \pm 2°$ (c=0.01; $CHCl_3$); M.w.: 406.57. Calcd.: $C_{24}H_{38}O_5$ C 70.91; H 9.42. Found: C 71.06; H 9.45%. ν_{max}^{KBr} 3440 (OH), 1720 (C=O), 1640 (C=C) cm^{-1}.

5,6a-Seco-3-ketochol-4-ene-dicarboxylic acid (**XXI**)

The Oppenauer oxidation of **XX** was carried out by the method of ANLIKER *et al.* [10]. In our case the ether extraction was preceded by acidification with 1:1 hydrochloric acid. The substance was recrystallized from acetone. M.p.: 183—185 °C; $[\alpha]_D = +85 \pm 2°$ (c=0.01; methanol); M.w.: 404.55. Calcd.: $C_{24}H_{36}O_5$ C 71.26; H 8.97. Found: C 71.45; H 9.01%. ν_{max}^{KBr} 3400 (OH), 1700, 1650 (C=CH=C=O) cm^{-1}.

7,7a-Seco-8-amino-3α,12α-dihydroxycholane-dicarboxylic acid[7,24] (**XXIII**)

Alkaline hydrolysis of **XXII** led to **XXIII**. M.p.: >350 °C; $[\alpha]_D = +50 \pm 2°$ (c=1.0; methanol); M.w.: 439.60. Calcd.: $C_{24}H_{41}O_6N$ C 65.57; H 9.40; N 3.18. Found: C 65.61; H 9.44; N 3.26%. ν_{max}^{KBr} 3400, 3280 (OH, HN_2), 1700, 1650, 1620 (C=O) cm^{-1}.

7,7a-Seco-8-amino-3α,12α-dihydroxy-dimethylcholanate

Prepared from **XXIII** with diazomethane in ether, and used without purification

7,7a-Seco-3α,12α-dihydroxy-dimethylcholanate-8-trimethylammonium iodide (**XXIV**)

Prepared by the earlier method. M.p.: 208 °C; $[\alpha]_D = +200 \pm 2°$ (c=0.2; $CHCl_3$); M.w.: 637.65 Calcd.: $C_{29}H_{52}O_6NI$ C 54.62; H 8.22; N 2.19; I^- 19.43. Found: C 54.73; H 8.45; N 2.22; I^- 19.38.% ν_{max}^{KBr} 3450 (OH), 1735, 1650 (C=O), 1480 (C—O -methyl) cm^{-1}.

Hofmann decomposition of **XXIV**

The Hofmann decomposition was carried out as above and led to isolation of an unsaturated-seco-dicarboxylic acid (**XXV**). M.p.: 106—108 °C; $[\alpha]_D = +57 \pm 2°$ (c=0.07; methanol); M.w.: 422.57. Calcd.: $C_{24}H_{38}O_6$ C 68.22; H 9.06. Found: C 68.32; H 9.42%. ν_{max}^{KBr} 3450. (OH), 1710) C=O), 1640 (CH_2=CH) cm^{-1}.

7,8-Seco-3α-hydroxy-12-ketochol-9(11)-ene-dicarboxylic acid (**XXVI**)

Prepared from **XXV** by Oppenauer oxidation as previously. M.p.: 142—144 °C; $[\alpha]_D = +92 \pm 2°$ (c=0.25; $CHCl_3$); M.w.: 420.55. Calcd.: $C_{24}H_{36}O_6$ C 68.55; H 8.62. Found: C 68.64; H 8.60%. ν_{max}^{KBr} 3420 (OH), 1710, 1680 (C=CH−C=O) cm^{-1}.

12,12a-Seco-13-amino-3α,7α-dihydroxycholane-dicarboxylic acid[12,24] (**XXVIII**)

Prepared by hydrolysis of **XXVII** with methanolic KOH. The substance gave a positive iodine-azide test, and the two carboxylic acid groups were detected by microtitration. M.p.: 260—263 °C; $[\alpha]_D = -39 \pm 2°$ (c=1.0; $CHCl_3$); (for M.w., *etc.*, see **XXIII**). Found: C 65.68; H 9.43; N 3.45%. ν_{max}^{KBr} 3400, 3300 (OH, HN_2), 1690, 1600 (C=O) cm^{-1}.

12,12a-seco-13-amino-3α,7α-dihydroxy-dimethylcholanate

Prepared from **XXVIII** with diazomethane in ether, and used in the following step.

12,12a-Seco-3α,7α-dihydroxy-dimethylcholanate-13-trimethylammonium iodide (**XXIX**)

Prepared as previously. M.p.: 145—150 °C; $[\alpha]_D = +12 \pm 2°$ (c=0.7; $CHCl_3$); (for M.w. and other calcd. data, see **XXIV**). Found: C 54.66; H 8.26; N 2.35; I^- 20.20%. ν_{max}^{KBr} 3450 (OH), 1730, 1640 (C=O), 1470 (C—O-methyl) cm^{-1}.

Hofmann decomposition of **XXIX**

The Hofmann decomposition was carried out as earlier, and resulted in **XXX**. M.p.: 168—170 °C; $[\alpha]_D = +71 \pm 2°$ (c=0.07; methanol); M.w.: 422.57. Calcd.: $C_{24}H_{38}O_6$ C 68.22; H 9.06. Found: C 68.34; H 9.42%. ν_{max}^{KBr} 3450, 3350 (OH), 1710 (C=O), 1620, 1520 (CH_2=CH), 770 (CH_2=CH) cm^{-1}.

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ПЕРЕГРУППИРОВКИ СТЕРОИДОВ, IX

Перегруппировки Шмидта и Бекмана кетонов и кетоксимов желчной кислоты

Б. Маткович, Дь. Балаж, Л. Балашпири

Различные метиловые эфиры 3-кето, 6-кето, 7-кето и 12-кето-желчной кислоты, защищенные О-ацетильной группой подвергались перегруппировке Шмидта и образовавшиеся гомолактамы были сравнены с образующимися из соответствующих кетоксимов Бекмановской перегруппировкой гомо-лактамами. Структуру полученных гомо-лактамов, кроме вышеуказанного сравнения, доказывали деструкцией Гофмана, проведенной со стороны образовавшегося амина, пиролизом и, в некоторых случаях, структурой соединений, которые могли быть выделены из последующей реакции окисления Опенауэра.