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Synthesis of Bridged Steroids. V.[1] Cholestane Derivatives having a Bridged 3-Azabicyclo[3.3.1]nonane Ring System

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Cholestane derivative (IIb) having a bridged 3-azabicyclo[3.3.1]nonane ring system was synthesized from 3-oxo-5α-cholestane-5-carbonitrile (III) by a six-step reaction sequence. The over-all yield was very high indicating high stereospecificity or uniformity of the reaction used. Reduction of 3α-formyl-3β-methyl-5α-cholestane-5-carbonitrile (VIII) to the amino alcohol (Xa) was effected by means of lithium aluminum hydride reduction in the presence of aluminum chloride.

The 3-azabicyclo[3.3.1]nonane ring system (I), in which one of the bridge heads is substituted by a tertiary methyl group and the other is located at an angular position, forms a common part of diterpene alkaloids such as atisine, garryine, and veatchine. Prior to initiating the total synthesis of these alkaloids,[3,4] some model experiments to construct this bridged ring system using steroid molecules were carried out. In the present paper we describe a successful transformation of 3-oxo-5α-cholestane-5-carbonitrile (III)[5,6] into 3β-methyl-3α,5-methanoiminomethano-5α-cholestane (II) involving the desired, azacyclo bridged ring.

The cyano ketone (III) was treated with methoxymethylenetriphenylphosphorane[7] giving a crystalline mixture of two geometrical isomers of IV. The mixture was separated by fractional crystallization and alumina chromatography into two isomers, A, mp 165—167°, and B, mp 140—142°, in 27 and 19% yields, respectively. Structural assignment for these isomers was not carried out. Two approaches starting from the methoxymethylene compound (IV) were investigated. The first one consists of reduction of IV followed by the internal Mannich condensation of the resulting methoxymethylene amine (V) giving 3β-formyl-3α,5-methanoiminomethano-5α-cholestane (VI). Compound (IV-B) was reduced with lithium aluminum hydride in a mixture of tetrahydrofuran and diglyme (ethylene glycol dimethyl ether) at 130° to the amorphous primary amine (V). An attempted condensation of V with formaldehyde in aqueous ethanol in the presence of hydrochloric acid failed most probably owing to difficulty of the reagent approach from the highly hindered α side. This route was therefore abandoned.

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6) *a*) W. Nagata, M. Yoshioka, and S. Hirai, *Tetrahedron Letters*, **1962**, 461; *b*) W. Nagata and M. Yoshioka, *ibid.*, **1966**, 1913; *c*) W. Nagata and M. Yoshioka, Proceedings of the 2nd International Congress on Hormonal Steroids, Milan, Italy, May 1966, Excerpta Medica Foundation, Amsterdam, 327 (1967).
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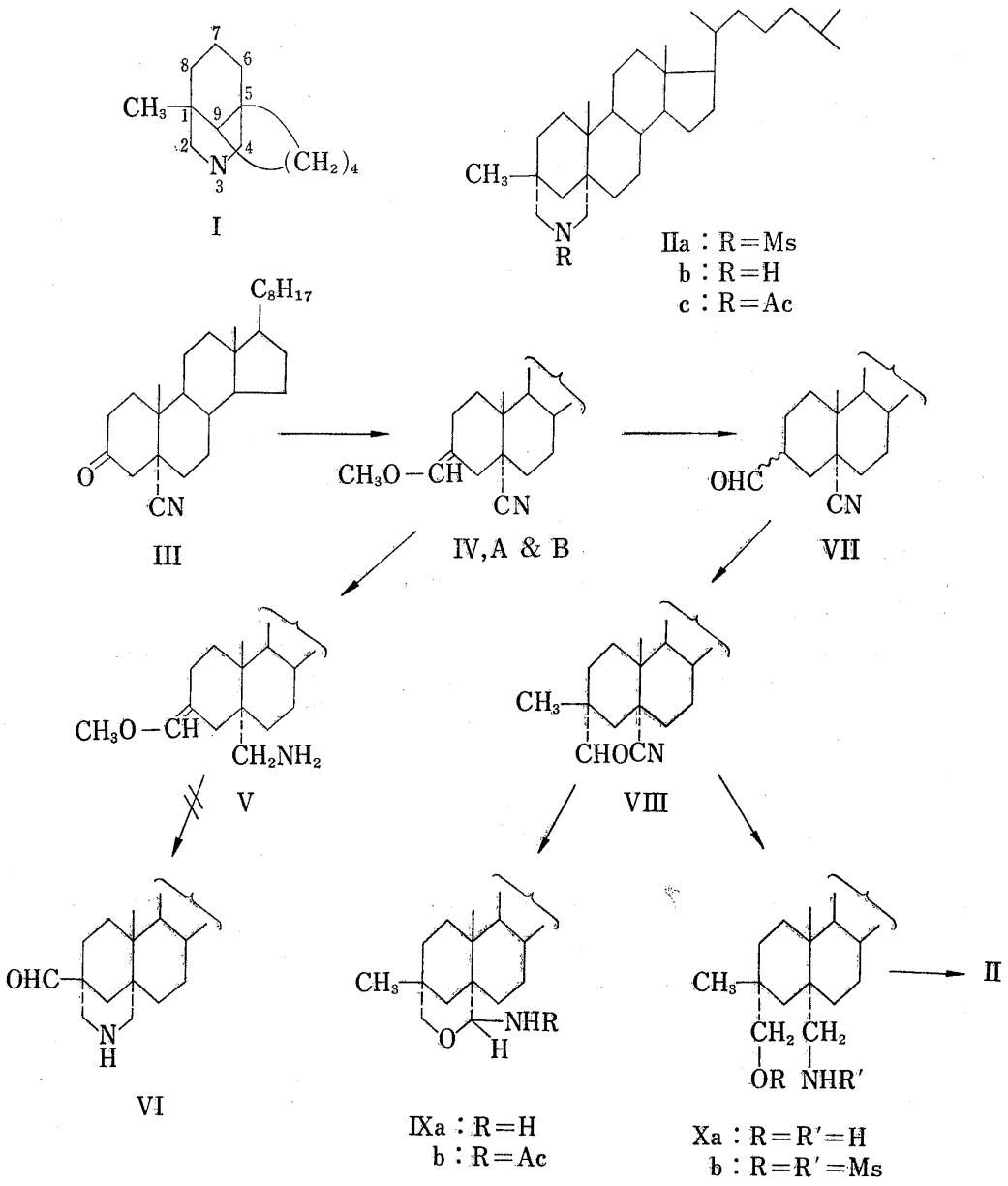

The second approach consisting of a reaction sequence illustrated in Chart (IV→VII→VIII→X→II) was then investigated. The methoxymethylenecarbonitrile (IV) on treatment with conc. hydrochloric acid in tetrahydrofuran yielded in good yield the crystalline aldehyde (VII). The product appeared to be composed of two stereoisomers differing in configuration of the formyl group at C_3 as evident from the wide range of the melting point. Several crystallizations gave, although in low yield, one isomer melting at 144—147° in a practically pure state. Configurational assignment of the formyl group was not carried out, since the subsequent methylation proceeding through an enolate anion must not be affected by the orientation of the formyl group. The crude aldehyde was treated with methyl iodide in *tert*–butanol in the presence of potassium *tert*–butoxide giving in 67% yield the methyl aldehyde (VIII) as the sole product. The infrared spectrum showed the presence of both the formyl and the cyano groups. The β configuration of the newly introduced methyl group was expected from the view that the reagent would approach from the less hindered β side avoiding hindrance of the 5α–cyano group. In fact, a successful transformation of this compound into the cyclic compounds (IX) and (II) supports this view and compound (VIII) was definitely assigned the structure depicted in the formula. The compound was then subjected to lithium

aluminum hydride reduction in boiling tetrahydrofuran giving an amorphous base. Acetylation of the base in the usual manner gave a crystalline acetamide melting at 233—236°. On the basis of elemental analysis and the infrared spectrum, this compound was assigned the structure (IXb) and consequently the preceding base the structure (IXa). These results clearly show that with lithium aluminum hydride alone, the reduction of the angular cyano group stops at the intermediate stage (the imide stage) by participation with the neighboring alkoxide anion formed initially. Lithium aluminum hydride reduction of VIII was therefore carried out in the presence of a half molar equivalent of aluminum chloride in the hope that an intermediate of the type (IXa) would be reductively cleaved giving the desired amino alcohol (Xa). As expected, the crystalline base obtained in good yield by this treatment showed the presence of both the hydroxyl and the primary amino groups in its infrared spectrum and therefore was assigned the structure (Xa). Compound (Xa) on treatment with mesyl chloride in pyridine in the presence of triethylamine was converted smoothly into the dimesyl derivative (Xb) which was then cyclized to IIa by treatment with potassium carbonate in dimethylformamide. Lithium–ammonia reduction of N–mesylpiperidinocholestane (IIa) gave finally the desired bridged azacyclic compound (IIb), mp 120—121°. The 60% over–all yield of this compound was attained from the 3–formyl–5–carbonitrile (VIII) through four steps by working without purification of the intermediates, indicating high uniformity and stereospecificity of the reactions used. Compound (IIb) was converted into its acetyl derivative (IIc) in the usual manner and characterized. It should be noted that the six–step reaction sequence used for the present synthesis was successfully applied to our total synthesis of atisine.[3]

Experimental

All melting points were measured on a Kofler hot–stage apparatus and are corrected. Unless otherwise stated, infrared spectra were taken in chloroform by use of a Koken OS–201B spectrophotometer and $[\alpha]_D$ in chloroform with Perkin–Elmer Polarimeter Type 141. Unless otherwise specified, the extracts were dried on anhyrous sodium sulfate and column chromatography was performed according to the method reported by Reichstein and Shoppee[8] using Woelm alumina (activity II).

3-Methoxymethylene-5α-cholestane-5-carbonitrile (IV) A and B——To a stirred suspension of methoxymethyltriphenylphosphonium chloride (11.92 g, 34 mmoles) in anhydrous ether (50 ml) was added dropwise 1.29 N ethereal solution of BuLi (26.3 ml, 34 mmoles) under ice–cooling and nitrogen, and the mixture was stirred vigrously for 1 min. To the resulting orange red ylid mixture was added dropwise a solution of III (7 g, 17 mmoles) in anhydrous tetrahydrofuran in 15 min, and the mixture was stirred for 3 hr at room temperature. The precipitate was filtered off by suction and washed with ether. The combined filtrate and the washings were poured into ice–water and extracted with ether—$CHCl_3$ (3:1). The organic layer was washed with H_2O, dried and evaporated. The residue was recrystallized twice from $CHCl_3$–CH_3OH to give IV A (2.060 g), mp 154—158°. The residue of the mother liquor was chromatographed on Al_2O_3 (75 g). Fractions (4.51 g) eluted with benzene (*ca.* 2 liter) was chromatographed again on Al_2O_3 (135 g). Fractions (1.467 g) eluted with petrol ether—benzene (4:1) was recrystallized from $CHCl_3$–CH_3OH to give IV B (1.265 g), mp 140—142° and a second crop of IV B (137 mg), mp 136—138°. The combined yield of IV A and IV B is 46%. From the later fractions (1.350 g) eluted with benzene, III (1.133 g) was recovered. Compound IV A of mp 154—158°, obtained from the direct recrystallization, was purified by chromatography on Al_2O_3 (600 mg). Fractions eluted with petrol ether—benzene (4:1) was recrystallized from $CHCl_3$–CH_3OH to give a pure sample of IV A (524 mg) mp 165—167°. IV A. *Anal.* Calcd. for $C_{30}H_{49}ON$: C, 81.94; H, 11.23; N, 3.19. Found: C, 82.09; H, 11.33; N, 3.75. IR ν_{max} cm^{-1}: 2235, 1671, 1123. $[\alpha]_D^{25}$ +24.2° (±2°) (c =0.995). IV B. *Anal.* Calcd. for $C_{30}H_{49}ON$: C, 81.94; H, 11.23; N, 3.19. Found: C, 81.74; H, 11.38; N, 3.11. IR ν_{max} cm^{-1}: 2235, 1670, 1124. $[\alpha]_D^{24}$ +28.6° (±2°) (c=1.001).

An Attempted Synthesis of VI *via* V from IV B——To a stirred suspension of $LiAlH_4$ (1 g) in anhydrous tetrahydrofuran (25 ml) was added dropwise a solution of IV B (1 g) in anhydrous tetrahydrofuran (25 ml) and the mixture was refluxed for 2.5 hr. To complete the reduction, tetrahydrofuran (*ca.* 40 ml) was replaced by the same volume of diglyme and the mixture was heated at 130° (an oil–bath temperature) for 2 hr. After cooling, the excess of the reagent was decomposed with H_2O (4 ml) and the precipitates were filtered off

8) *Disc. Trans. Farad. Soc.*, No. 7, 305 (1949).

and washed well with $CHCl_3$. The combined filtrate and the washings were washed with H_2O, dried and evaporated to give an amorphous residue (919 mg). IR ν_{max}^{film} cm^{-1}: 1680, 1120 (>C=CH–OCH_3). A mixture of 190 mg (0.43 mmoles) of the residue, paraformaldehyde (26 mg, 0.86 mmoles) and 2 drops of conc. HCl in 99% EtOH (4 ml) was heated under reflux under nitrogen for 4 hr. The solution was poured into ice–2 N NaOH and extracted with $CHCl_3$. The $CHCl_3$–layer was washed with H_2O, dried and evaporated to give an oily residue (175 mg). The IR spectra of this residue showed no strong carbonyl band around 1740—1690 cm^{-1} after and before the chromatographic purification.

Hydrolysis of IV A and B to VII——A solution of IV A (505 mg) in tetrahydrofuran (5 ml) was mixed with conc. HCl (0.2 ml) and allowed to stand at room temperature for 30 min. Ice was added, and the resulting mixture was extracted with $CHCl_3$. The $CHCl_3$–layer was washed with 2 N Na_2CO_3 and H_2O, dried, and evaporated to give an crystalline residue (485 mg). Two crystallization from AcOEt gave a pure sample of VII (30 mg), mp 144—147°. *Anal.* Calcd. for $C_{29}H_{47}ON$: C, 81.82; H, 11.13; N, 3.29. Found: C, 81.60; H, 11.17; N, 3.24. IR ν_{max} cm^{-1}: 2736, 1730 (–CHO), 2244 (CN). $[\alpha]_D^{24.5}$ −4.0° (±2°) (c=0.997). Hydrolysis of IV B was carried out in the same manner as that for IV A and its IR spectrum of the crude product was superimposable on that of VII obtained from IV A.

3α-Formyl-3β-methyl-5α-cholestane-5-carbonitrile (VIII)——The crude cyano aldehyde VII (4.962 g, 11.4 mmoles) was dissolved in anhydrous *t*–BuOH (150 ml) and mixed with CH_3I (9.7 g, 68.4 mmoles) under nitrogen. To the stirred mixture was added a solution of potassium *tert*–butoxide in *t*–BuOH prepared from 1.33 g (34.2 mmoles) of potassium and 150 ml of anhydrous *t*–BuOH, over a period of 30 min and stirred further 2 hr at room temperature. The solution was concentrated under reduced pressure and the resulting mixture was poured into ice–water and extracted with $CHCl_3$. The $CHCl_3$–layer was washed with H_2O, dried and evaporated. The crystalline residue (4.7 g) was recrystallized from acetone–ether–pentane to give VIII (2.544 g, mp 158—159°, 0.307 g, mp 155—157°). The residue of the mother liquor (1.813 g) was chromatographed on Al_2O_3 (30 g). Fractions eluted with petrol ether–benzene (9:1—1:1) were recrystallized from ether–pentane to give an additional crop of VIII (485 mg, mp 156—157°). The total yield from IV was 67%. *Anal.* Calcd. for $C_{30}H_{49}ON$: C, 81.94; H, 11.23; N, 3.19. Found: C, 81.84; H, 11.20; N, 3.60. IR ν_{max} cm^{-1}: 2733, 1728 (–CHO), 2247 (CN). $[\alpha]_D^{26}$ +42.2° (±2°) (c=0.956).

Reduction of VIII with $LiAlH_4$ to IXa and Its Acetylation to IXb——To a stirred suspension of $LiAlH_4$ (280 mg) in anhydrous tetrahydrofuran (7 ml) was added dropwise a solution of VIII (144 mg) in anhydrous tetrahydrofuran and the resulting mixture was refluxed for 6 hr. After the decomposition of the excess of the reagent the precipitate was filtered off by suction and washed well with $CHCl_3$. The combined filtrate and the washings were washed with H_2O, dried and evaporated. The oily residue (IXa) was mixed with Ac_2O (0.5 ml) and pyridine (3 ml) and allowed to stand at room temperature for 20 hr. The usual work–up gave a crystalline residue (147 mg), which was recrystallized from acetone to give IXb (64 mg, mp 225—230°). A pure sample melts at 233—236°. *Anal.* Calcd. for $C_{32}H_{55}O_2N$: C, 79.12; H, 11.41; N, 2.88. Found: C, 79.10; H, 11.53; N, 3.10. IR ν_{max} cm^{-1}: 3457, 1680, 1498 ($NHCOCH_3$), $[\alpha]_D^{26}$ +64.8° (±2°) (c =0.979).

Reduction of VIII with $LiAlH_4$ and $AlCl_3$ to Xa and Its Dimesylation to Xb——To a stirred suspension of $LiAlH_4$ (4.32 g, 114 mmoles) in anhydrous tetrahydrofuran (200 ml) was added dropwise a solution of $AlCl_3$ (7.6 g, 57 mmoles) in anhydrous tetrahydrofuran (80 ml) under ice–cooling. To this stirred mixture was added dropwise a solution of VIII (1 g, 2.28 mmoles) in anhydrous tetrahydrofuran in 20 min and the mixture was refluxed for 10 hr. After cooling, 2 N NaOH and ice were added and the resulting mixture was extracted with $CHCl_3$. The $CHCl_3$–layer was washed with H_2O, dried and evaporated to give a crystalline residue (crude Xa, 1.06 g). To a solution of the crude Xa in pyridine (50 ml) were added $(Et)_3N$ (575 mg, 5.7 mmoles) and methanesulfonyl chloride (MsCl) (1.305 g, 11.4 mmoles) and the solution was kept at room temperature overnight. Ice was added and after standing for 30 min at room temperature the mixture was extracted with $CHCl_3$. The $CHCl_3$–layer was washed with 2 N HCl, 2 N Na_2CO_3 and H_2O, dried, and evaporated to give a crystalline residue (1.43 g). A portion of this residue chromatographed on Al_2O_3 and fractions eluted with benzene and benzne—$CHCl_3$ (9:1) were recrystallized from CH_3OH to give pure Xb mp 140—142°. *Anal.* Calcd. for $C_{32}H_{59}O_5NS_2$: C, 63.85; H, 9.88; N, 2.33; S, 10.65. Found: C, 63.31; H, 9.83; N, 2.35; S, 10.53. IR ν_{max} cm^{-1}: 3365, 1331, 1148 (NH–SO_2), 1343, 1170 (OSO_2). $[\alpha]_D^{24.5}$ +0.4° (±4°) (c=0.536).

Cyclization of Xb to IIa——The crude Xb (1.43 g) dissolved in dimethylformamide (DMF) (90 ml) was heated under reflux with 15% K_2CO_3 (6.2 ml) and H_2O (18 ml) for 3 hr. The resulting solution was concentrated under reduced pressure, diluted with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried and evaporated to give an amorphous residue (1.235 g). A portion of this residue was purified by sublimation at 210—215°/0.015 mmHg. *Anal.* Calcd. for $C_{31}H_{55}O_2NS$: C, 73.60; H, 10.96; N, 2.77; S, 6.34. Found: C, 74.10; H, 10.98; N, 2.71; S, 6.17. IR ν_{max} cm^{-1}: 1330, 1148 (N–SO_2).

Reduction of IIa to IIb and Its Acetylaiton to IIc——A solution of the crude IIa (1.23 g) in anhydrous ether (50 ml) and anhydrous EtOH (10 ml) was added dropwise to a stirred solution of Li (2.2 g) in liq. NH_3 (200 ml) at −70° and the solution was stirred further at the same temperature for 30 min. Anhydrous EtOH was then added until the excess of Li was destroyed. The ammonia was distilled off and after dilution with H_2O, the residue was extracted with ether—$CHCl_3$. The organic layer was washed with H_2O, dried

and evaporated. A crystalline residue (1.013 g) was recrystallized from ether–acetone to give IIb (418mg, mp 117—120°). The residue of the mother liquor was chromatographed on Al_2O_3 (15 g). Fractions eluted with petrol ether–benzene (1:1) and benzene–$CHCl_3$ (2:1) were recrystallized from ether–acetone to give IIb (157 mg, mp 120—121°). The overall yield from VIII was 60%. *Anal.* Calcd. for $C_{30}H_{53}N$: C, 84.24; H, 12.49; N, 3.27. Found: C, 84.11; H, 12.37; N, 3.69. IR ν_{max} cm^{-1}: 3200—3500 (broad) (NH). $[\alpha]_D^{24.5}$ +13.9° (±4°) (c=0.518). Acetylation of IIb with Ac_2O and pyridine in the usual manner gave IIc. A pure sample melts at 110—111°. *Anal.* Calcd. for $C_{32}H_{55}ON$: C, 81.81; H, 11.80; N, 2.98. Found: C, 81.59; H, 11.89; N, 3.10. IR ν_{max} cm^{-1}: 1625 (N–Ac). $[\alpha]_D^{24.5}$ +19.5° (c=0.590).