MeOH yielded 100 mg. of yellow prisms which melted at 241~243°. IR cm^{-1}: $\nu_{C=O}$ 1780 (Nujol). *Anal.* Calcd. for $C_{17}H_{28}O_2N^+ \cdot C_6H_2O_7N_3^-$: C, 54.53; H, 5.97; N, 11.06. Found: C, 54.43; H, 5.91; N, 10.94. By comparison of IR spectra and mixed melting point determination this picrate was identified with a sample of dendrobine methopicrate derived from dendrobine.

Dendrobine Methopicrate from Dendrobine——To a solution of dendrobine (200 mg.) in MeOH was added CH_3I (10 ml.) and the reaction mixture was heated on a water bath for 2 hr. The solvent and excess CH_3I were evaporated off and trituration with Et_2O gave crystals. Recrystallization from Me_2CO–MeOH afforded 286 mg. of prisms, m.p. 253°. A solution of dendrobine methiodide in MeOH was shaken vigorously with freshly precipitated AgCl. After separation of the precipitate of AgI by filtration, the filtrate was evaporated under reduced pressure at room temperature and an aqueous solution of sodium picrate was added. The precipitated crystals were collected by filtration and recrystallization from MeOH gave 302 mg. of dendrobine methopicrate which melted at 240~242°. *Anal.* Calcd. for $C_{17}H_{28}O_2N^+ \cdot C_6H_2O_7N_3^-$: C, 54.53; H, 5.97; N, 11.06. Found: C, 54.82; H, 5.90; N, 11.08.

The authors wish to express their deepest thanks to Messers K. Takebe and Y. Nagai of Mikuni & Co., Dosho-machi, Osaka, for their kindness in supplying the drugs. We are also grateful to Dr. F. Kusuda of Nippon Shinyaku Co., Kyoto, for his help in extraction of the drugs. Thanks are also due to Mr. T. Shingu, Faculty of Pharmaceutical Sciences, Kyoto University, for measuring NMR spectra.

Summary

From the Chinese drug "Chin-Shin-Hu" imported from Hong Kong, two tertiary bases were isolated. One is dendrobine, first isolated by H. Suzuki, *et al.*[2] and the second is a new base which has not previously been reported in the literature, for which the name dendramine is proposed. The water soluble alkaloid was also examined and it was concluded that the quaternary alkaloid found in this drug is the N-methyl dendrobium salt.

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163. Shunsaku Noguchi, Fujiko Nakayama, and Katsura Morita :

Aldol Condensation of Corticoids with Formaldehyde. II.[*1] 21-Hydroxymethylation of Reichstein's Substance S, Dexamethasone and Deoxycorticosterone.

(*Research Laboratories, Takeda Chemical Industries, Ltd.*[*2])

In continuation of our previous paper,[1] in which we reported the base catalyzed aldol condensation of hydrocortisone and prednisolone with formaldehyde, we now wish to report the condensation of other corticoids, such as Reichstein's substance S, dexamethasone and deoxycorticosterone, with formaldehyde.

When Reichstein's substance S (I) and dexamethasone (II) were treated with aqueous formaldehyde in the presence of sodium acetate as catalyst, the corresponding 21-hydroxymethylated compounds, *i.e.* 21-hydroxymethyl-Reichstein's substance S (III) and 21-hydroxymethyldexamethasone (IV), were obtained. Similarly, treatment of deoxycorticosterone

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[*1] This paper constitutes Part XXXI of Takeda Laboratories' series entitled "Steroids"; Part XXX: This Bulletin, **11**, 1235 (1963).

[*2] Juso-nishino-cho, Higashiyodogawa-ku, Osaka (野口俊作, 中山富士子, 森田 桂).

[1] S. Noguchi, K. Morita: This Bulletin, **11**, 1235 (1963).

(V), which has no hydroxyl group at C-17, with aqueous formaldehyde in the presence of the same catalyst resulted in a mixture of 21-hydroxymethyldeoxycorticosterone (VI) and 21,21-bis(hydroxymethyl)deoxycorticosterone (VII). These hydroxymethylated corticoids, III, IV, VI, and VII, were isolated as amorphous hydrated crystals by ordinary recrystallization, however, anhydrous specimens could be obtained by azeotropic distillation of water followed by recrystallization.[1,2]

As already reported in the previous paper,[1] 21-hydroxymethylprednisolone 21,22-diacetate readily rearranged to give 21-methyl-11β,17α-dihydroxypregna-1,4-diene-3,20,21-trione acetate on passing through an alumina column as shown in a) of Chart 2.

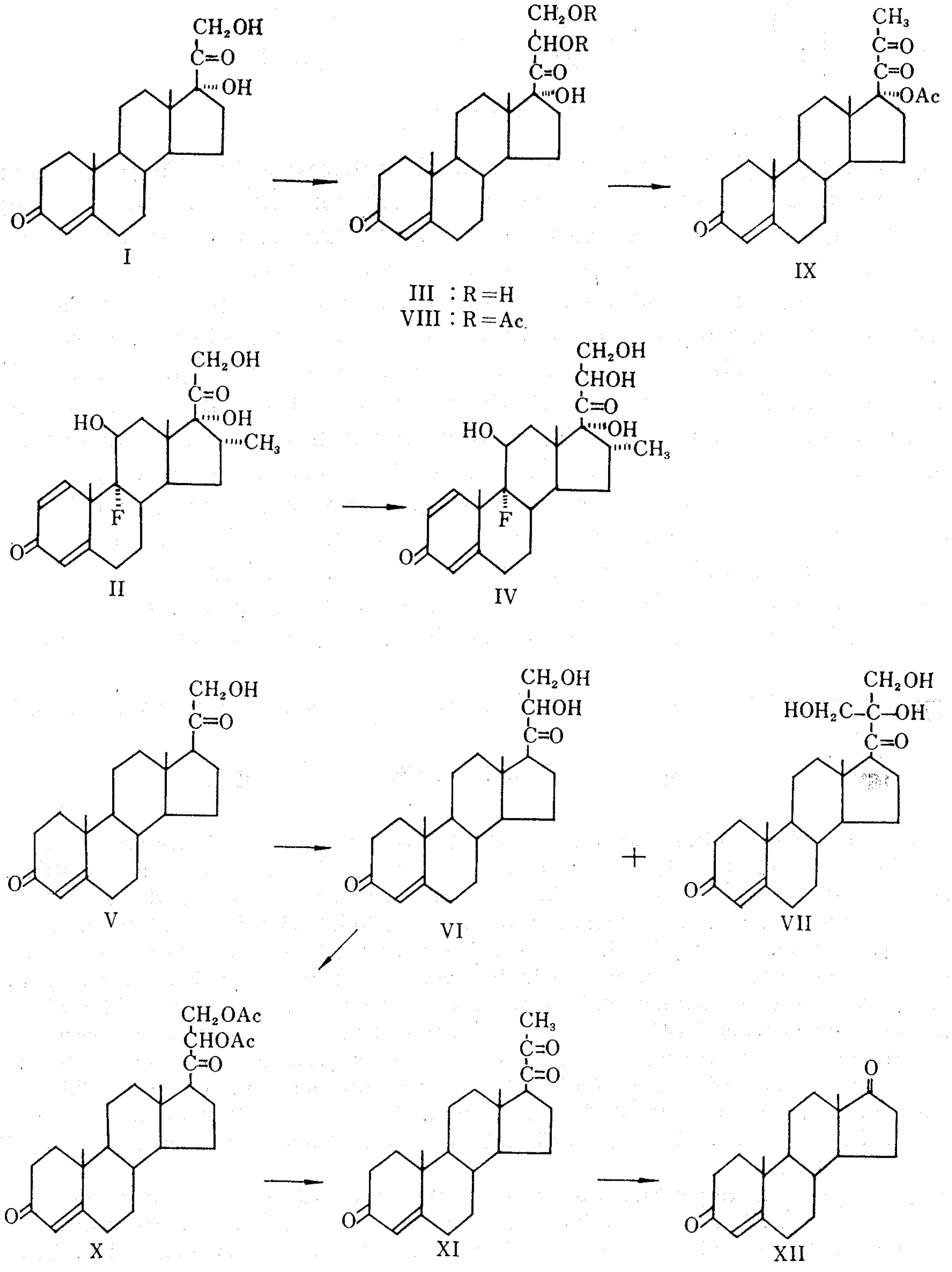

Chart 1.

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[2] T. Miki, K. Morita, S. Noguchi, T. Kishi, K. Hiraga, H. Nawa: This Bulletin, **11**, 95 (1963).

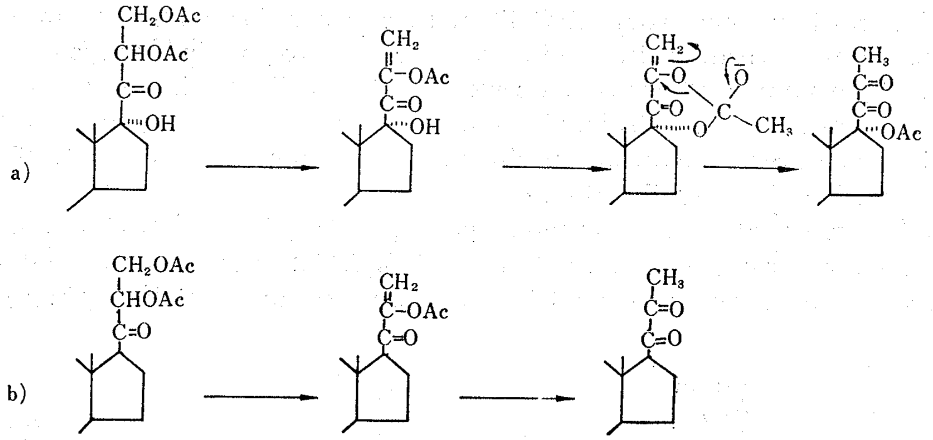

Chart 2.

Similarly, we observed that when a solution of 21-hydroxymethyl-Reichstein's substance S 21,22-diacetate (VIII) in benzene was passed through an alumina column, a light yellow product, 21-methyl-17α-hydroxypregn-4-ene-3,20,21-trione acetate (IX) had resulted. While alumina treatment of 21-hydroxymethyldeoxycorticosterone 21,22-diacetate (X), which has no hydroxyl group at C-17, afforded a single amorphous product.

The structure of this amorphous compound was assigned 21-methylpregn-4-ene-3,20,21-trione (XI) on the basis of the nuclear magnetic resonance spectrum, which showed a singlet at 2.35 p.p.m.[*3] associated with the C-22 methyl group. It is pertinent, therefore, to assume that XI was formed by simple elimination of the 22-acetoxyl group followed by deacetylation at C-21 as shown in b) of Chart 2. It was a surprise to note that when XI was allowed to stand in the air at room temperature for several days, most of XI had decomposed to give androst-4-ene-3,17-dione (XII). The identity of XII with an authentic sample was established by direct comparison of infrared- and nuclear magnetic resonance-spectra and also by their thin-layer chromatographic behaviors. That androst-4-ene-3,17-dione (XII) has been formed from the 20,21-diketone (XI) is undoubtedly a new reaction.

Further aspects of this novel reaction are under investigation in these laboratories.

Experimental[*4]

21-Hydroxymethyl-Reichstein's Substance S (21-Hydroxymethyl-17α,21-dihydroxypregn-4-ene-3,20-dione) (III)——To a solution of 10.0 g. of Reichstein's substance S (I) in 100 ml. of MeOH and 300 ml. of 37% aq. formaldehyde was added 30.0 g. of AcONa and the mixture was heated under reflux on a steam bath for 1.5 hr. After cooling, the reaction mixture was diluted with H_2O and extracted with AcOEt. The extracts were combined, washed with H_2O, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was dissolved in benzene and chromatographed on a column of 600 g. of Florisil, which was washed in advance with benzene containing 0.1% of AcOH. The column was eluted with benzene and then benzene-Et_2O (1:1). The benzene-Et_2O (1:1) eluate was dissolved in a small volume of MeOH, diluted with AcOEt and the solution was evaporated slowly on a steam bath at an atmospheric pressure to distil off water of crystals under azeotropic conditions.[1,2] This procedure was repeated to obtain anhydrous crystals of III, 3.6 g., m.p. 160°, $[\alpha]_D^{20}$ +102° (c=1.1, EtOH), UV: λ_{max}^{EtOH} 241 mμ (ε 17,400), IR λ_{max}^{KBr} μ: 2.91, 3.00, 5.86, 6.01. *Anal.* Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.22; H, 8.54.

21-Hydroxymethyl-Reichstein's Substance S 21,22-Diacetate (VIII)——A solution of 1.0 g. of III in 10 ml. of pyridine and 10 ml. of Ac_2O was allowed to stand overnight at room temperature. The reaction mixture was poured onto ice and the resulting oil was extracted with benzene. The benzene extract

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[*3] NMR spectrum was obtained with a Varian A-60 NMR spectrometer at 60 Mc. in $CHCl_3$ solution containing tetramethylsilane as an internal reference (δ-value).

[*4] All melting points are uncorrected.

was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was treated with hexane and then AcOEt to obtain crystals of Ⅷ, 0.8 g., m.p. 170~200°, UV: λ_{max}^{EtOH} 241 μ (ε 17,600), IR λ_{max}^{Nujol} μ: 2.94, 5.71, 5.80, 6.03, 6.18. *Anal.* Calcd. for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.84; H, 7.86.

21-Hydroxymethyldexamethasone (IV)——To a solution of 1.5 g. of dexamethasone (Ⅱ) in 20 ml. of MeOH and 10 ml. of 37% aq. formaldehyde was added 3.0 g. of AcONa and the mixture was heated under reflux on a steam bath for 6 hr. After cooling, the reaction mixture was diluted with H_2O and extracted with AcOEt. The extracts were combined, washed with H_2O, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was crystallized from MeOH-AcOEt under azeotropic conditions to give anhydrous crystals of Ⅳ, 1.0 g., m.p. 220~225°, $[\alpha]_D^{23}$ +87° (c=1.0, pyridine), UV: λ_{max}^{EtOH} 239 mμ (ε 15,500), IR λ_{max}^{KBr} μ: 2.88, 2.94, 5.87, 6.01, 6.28. *Anal.* Calcd. for $C_{23}H_{31}O_6F$: C, 65.38; H, 7.40; F, 4.50. Found: C, 65.28; H, 7.65; F, 4.60.

21-Hydroxymethyldeoxycorticosterone (VI) and 21,21-Bis(hydroxymethyl)deoxycorticosterone (VII)——To a solution of 10 g. of deoxycorticosterone (Ⅴ) in 100 ml. of MeOH and 300 ml. of 37% aq. formaldehyde was added 40 g. of AcONa and the mixture was heated under reflux on a steam bath for 6 hr. After cooling, the reaction mixture was diluted with H_2O and extracted with AcOEt. The extracts were combined, washed with H_2O, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The noncrystalline residue, 12.5 g., was dissolved in $CHCl_3$-Me_2CO-EtOH (80:20:3) and chromatographed on a column of 300 g. of silica gel, which was impregnated with 30% (w/w) of H_2O. Elution with the same solvent gave firstly 2.8 g. of Ⅵ, which was recrystallized from MeOH-Et_2O, m.p. 132~134°, $[\alpha]_D^{22}$ +196° (c=0.53, EtOH), UV: λ_{max}^{EtOH} 240 mμ (ε 17,000). *Anal.* Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.28; H, 8.60.

Continued elution with the same solvent gave 2.2 g. of Ⅶ, which was recrystallized from MeOH-benzene, m.p. 185~190°, $[\alpha]_D^{22}$ +133° (c=0.35, EtOH), UV: λ_{max}^{EtOH} 242 mμ (ε 16,000). *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 71.39; H, 8.58.

21-Hydroxymethyldeoxycorticosterone 21,22-Diacetate (X)——A solution of 200 mg. of Ⅵ in 1.5 ml. of pyridine and 1.5 ml. of Ac_2O was allowed to stand overnight at room temperature. The reaction solution was poured onto ice and the resulting crystals were filtered and washed with H_2O to give 240 mg. of Ⅹ (hydrate), m.p. 100~200°.

21-Methyl-17-hydroxypregn-4-ene-3,20,21-trione Acetate (IX)——A solution of 500 mg. of Ⅷ in benzene was passed through a column of 25 g. of alumina. The column was eluted with benzene and benzene-Et_2O (4:1) to give light yellow crystals of Ⅸ, 200 mg., m.p. 149~155°, $[\alpha]_D^{20}$ +34° (c=1.3, $CHCl_3$), UV: λ_{max}^{EtOH} 240 mμ (ε 17,800), IR λ_{max}^{Nujol} μ: 5.83, 5.88, 6.02, 6.21, NMR[*3],[*5]: δ (p.p.m.) ^{DCl_3} 0.61/s (3), 1.21/s (3), 2.07/s (3), 2.32/s (3), 5.75/bs (1). *Anal.* Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.83; H, 8.10.

21-Methylpregn-4-ene-3,20,21-trione (XI)——A solution of 200 mg. of Ⅹ in benzene was passed through a column of 20 g. of alumina. The column was eluted with benzene, benzene-Et_2O (1:1) and MeOH to give a light yellow noncrystalline product, Ⅺ, 100 mg., which was dissolved in benzene-AcOEt (5:1) and further purified by chromatography on a column of silica gel with the same solvent system. Ⅺ thus purified still failed to crystallize. UV: λ_{max}^{EtOH} 241 mμ (ε 14,700), IR λ_{max}^{liquid} μ: 5.87, 6.00, 6.19, NMR[*3],[*5]: δ (p.p.m.) ^{DCl_3} 0.65/s (3), 1.18/s (3), 2.35/s (3), 5.74/bs (1).

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Summary

21-Hydroxymethyl-Reichstein's substance S (Ⅲ), 21-hydroxymethyldexamethasone (Ⅳ), 21-hydroxymethyldeoxycorticosterone (Ⅵ) and 21,21-bis(hydroxymethyl)deoxycorticosterone (Ⅶ) were synthesized by the aldol condensation of the parent steroids with formaldehyde in the presence of sodium acetate. When 21-hydroxymethyl-Reichstein's substance S diacetate (Ⅷ) and 21-hydroxymethyldeoxycorticosterone diacetate (Ⅹ) were passed through a column of alumina, 21-methyl-17α-hydroxypregn-4-ene-3,20,21-trione acetate (Ⅸ) and 21-methylpregn-4-ene-3,20,21-trione (Ⅺ) were obtained. The diketone (Ⅺ) underwent further decomposition in the air to give androst-4-ene-3,17-dione.

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[*5] s: singlet, bs: broad singlet, numerals in parentheses: the number of protons.