MeOH yielded 100 mg. of yellow prisms which melted at 241–243°. IR cm⁻¹: ν_C=O 1780 (Nujol). Anal. Caled. for C₁₂H₁₆O₃N⁺·C₆H₅O₂N⁻: 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 CH₃I (10 ml.) and the reaction mixture was heated on a water bath for 2 hr. The solvent and excess CH₃I were evaporated off and triturated with Et₂O gave crystals. Recrystallization from Me₂CO-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. Caled. for C₁₂H₁₆O₃N⁺·C₆H₅O₂N⁻: C, 54.53; H, 5.97; N, 11.06. Found: C, 54.82; H, 5.90; N, 11.08.

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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. 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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In continuation of our previous paper, 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-hydroxyxymethylated compounds, i.e. 21-hydroxyethyl–Reichstein’s substance S (III) and 21-hydroxyxymethyldexamethasone (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，中山義一，森田 信).

(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-hydroxymethyldeoxy corticosterone (VI) and 21,21-bis(hydroxymethyl)deoxy corticosterone (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,\(^1,2\) 21-hydroxymethyl prednisolone 21,22-diacetate readily rearranged to give 21-methyl-11β,17α-dihydroxy pregn-1,4-diene-3,20,21-trione acetate on passing through an alumina column as shown in a) of Chart 2.

\[\text{Chart 1.}\]

Similarly, we observed that when a solution of 21-hydroxymethyl-Reichstein's substance S 21,22-diacetate (III) in benzene was passed through an alumina column, a light yellow product, 21-methyl-17α-hydroxyprog-4-ene-3,20,21-trione acetate (X) had resulted. While alumina treatment of 21-hydroxy methyldeoxy corticosterone 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 (X) on the basis of the nuclear magnetic resonance spectrum, which showed a singlet at 2.35 p.p.m. associated with the C-22 methyl group. It is pertinent, therefore, to assume that X 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 X was allowed to stand in the air at room temperature for several days, most of X 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 (X) is undoubtedly a new reaction.

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

**Experimental**

21-Hydroxymethyl-Reichstein's Substance S (21-Hydroxymethyl-17α,21-dihydroxyprog-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 H₂O and extracted with AcOEt. The extracts were combined, washed with H₂O, dried over Na₂SO₄, 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-Et₂O (1:1). The benzene-Et₂O (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 distill off water of crystals under azeotropic conditions. This procedure was repeated to obtain anhydrous crystals of III, 3.6 g., m.p. 180°, [α]D +102° (c=1.1, EtOH), UV: λ max 241 μ (ε 17,400), IR: ν max : 2.91, 3.00, 5.86, 6.01. Anal. Calcd. for C₂₃H₃₈O₄: 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 Ac₂O 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 was evaporated to leave a yellow oil which solidified after standing for 12 hours at room temperature (X).
was washed with H₂O, dried over Na₂SO₄ and evaporated to dryness under reduced pressure. The residue was treated with hexane and then AcOEt to obtain crystals of VII, 0.8 g., m.p. 170–200°. UV: λ max (η) 241 μ (ε 17,600), IR ν max μ: 2.94, 5.71, 5.80, 6.03, 6.18. Anal. Calcd. for C₂₅H₃₃O₅: C, 67.80; H, 7.88. Found: C, 67.84; H, 7.86.

21-Hydroxymethyldeoxycorticosterone (IV) — To a solution of 1.5 g. of deoxymethasone (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 H₂O and extracted with AcOEt. The extracts were combined, washed with H₂O, dried over Na₂SO₄ and evaporated to dryness under reduced pressure. The residue was crystallized from MeOH–AcOEt under azotropic conditions to give anhydrous crystals of N, 1.0 g., m.p. 220–225°, [α] D +87° (c=1.0, pyridine), UV: λ max (η) 299 μ (ε 15,500), IR ν max μ: 2.88, 2.94, 5.87, 6.01, 6.28. Anal. Calcd. for C₂₅H₃₃O₅F: 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 H₂O and extracted with AcOEt. The extracts were combined, washed with H₂O, dried over Na₂SO₄ and evaporated to dryness under reduced pressure. The noncrystalline residue, 12.5 g., was dissolved in CHCl₃–Me₂CO–EtOH (80:20:3) and chromatographed on a column of 300 g. of silica gel, which was impregnated with 30% (w/w) of H₂O. Elution with the same solvent gave firstly 2.8 g. of VII, which was recrystallized from MeOH–Et₂O, m.p. 132–134°, [α] D +196° (c=0.53, EtOH), UV: λ max (η) 240 μ (ε 17,000). Anal. Calcd. for C₃₃H₄₁O₈: 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°, [α] D +133° (c=0.35, EtOH), UV: λ max (η) 242 μ (ε 16,000). Anal. Calcd. for C₃₃H₄₁O₈: 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 VII in 1.5 ml. of pyridine and 1.5 ml. of Ac₂O was allowed to stand overnight at room temperature. The reaction solution was poured onto ice and the resulting crystals were filtered and washed with H₂O to give 240 mg. of X (hydrate), m.p. 100–200°.

21-Methyl-17-hydroxyprog-4-ene-3,20,21-trione Acetate (IX) — A solution of 500 mg. of VII in benzene was passed through a column of 25 g. of alumina. The column was eluted with benzene and benzene–Et₂O (4:1) to give light yellow crystals of IX, 200 mg., m.p. 149–155°, [α] D +34° (c=1.3, CHCl₃), UV: λ max (η) 240 μ (ε 17,800), IR ν max μ: 5.83, 5.88, 6.02, 6.21, NMR***,**: δ (p.p.m.) D₂O 0.61/s (3), 1.21/s (3), 2.07/s (3), 2.32/s (3), 5.75/b (s) (1). Anal. Calcd. for C₂₉H₃₇O₄: 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–Et₂O (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 (η) 241 μ (ε 14,700), IR ν max μ: 5.87, 6.00, 6.19, NMR***,**: δ (p.p.m.) D₂O 0.65/s (3), 1.18/s (3), 2.35/s (3), 5.74/b (s) (1).

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Summary

21-Hydroxymethyl-Reichstein's substance S (III), 21-hydroxymethyldeoxymethasone (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-hydroxyprog-4-ene-3,20,21-trione acetate (K) and 21-methylpregn-4-ene-3,20,21-trione (X) were obtained. The diketone (X) underwent further decomposition in the air to give androst-4-ene-3,17-dione.

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