Das somit dargestellte *rac*-3-Hydroxy-19-norpregna-1,3,5(10)-trien-20-on (XIVa) und sein Methyläther (XVa) wurden einzeln mit den entsprechenden natürlichen Stoffen (XIVb) bzw. (XVb) verglichen, die in Anlehnung an die Angaben von Mills, *et al.*⁶⁾ und von Djerassi, *et al.*⁷⁾ aus Östron hergestellt wurden. Die IR-Spektren der beiden *rac*-Steroide in Lösung waren mit denjenigen der entsprechenden natürlichen Steroide in allen Einzelheiten identisch. Die UV-Spektren waren ebenfalls gleich. Ferner ergaben racemisches und natürliches 3-Hydroxy-19-norpregna-1,3,5(10)-trien-20-on (XIVa) bzw. (XIVb) auf Papier in einem Lösungsmittelsystem von Cyclohexan-Benzol-Methanol-Wasser (3:7:5:5) den gleichen Rf-Wert 0.865. ((XII): Schmp. 208~212°. Gef.: C, 77.22; H, 8.80. IR $\nu_{\max}^{\text{CHCl}_3}$ cm⁻¹: 3615, 1613, 1588, 1500. (XIII): Schmp. 112~113°. Gef.: C, 77.64; H, 9.09. IR $\nu_{\max}^{\text{CHCl}_3}$ cm⁻¹: 1611, 1578, 1500. (XIVa): Schmp. 227~229°. Gef.: C, 79.87; H, 8.67. UV $\lambda_{\max}^{\text{EtOH}}$ m μ (ϵ): 281 (2,070), 287 (1,850), IR $\nu_{\max}^{\text{CHCl}_3}$ cm⁻¹: 3610, 3360 (breit), 1699, 1611, 1587, 1502. (XIVb): Schmp. 246~248° (Lit.⁶⁾ 247~249°. UV $\lambda_{\max}^{\text{EtOH}}$ m μ (ϵ): 281 (2,060), 287 (1,880). IR $\nu_{\max}^{\text{CHCl}_3}$ cm⁻¹: 3610, 3360 (breit), 1697, 1610, 1585, 1500. (XVa): Schmp. 139~140°. Gef.: C, 80.66; H, 9.05. UV $\lambda_{\max}^{\text{EtOH}}$ m μ (ϵ): 279 (2,070), 287 (1,930). IR $\nu_{\max}$ cm⁻¹: 1700, 1611, 1578, 1501 (3.38 mg in 0.2 cc CH₂Cl₂). (XVb): Schmp. 134~136° (Lit.⁷⁾ 134~136°. UV $\lambda_{\max}^{\text{EtOH}}$ m μ (ϵ): 279 (2,050), 287 (1,920). IR $\nu_{\max}$ cm⁻¹: 1701, 1612, 1579, 1502 (3.57 mg in 0.2 cc CH₂Cl₂).

Da keine Epimerisierung während der Huang-Minlon'schen Reduktion möglich ist, besitzt die 18-Oxoverbindung (XI) offenbar die richtige räumliche Konfiguration des Steroides. Dies bedeutet daher, daß damit die erstmalige Synthese des biologisch interessanten 18-oxygenierten Steroides der Östrogen-Reihe⁸⁾ gelungen ist.

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Synthesis of Colchicine

Synthesis of *dl*-Demethoxydeoxy-hexahydrocolchicine

Boekelheide and others¹⁾ synthesized 9,10,11-trimethoxy-1,2,3,4,6,7-hexahydro-5*H*-di-benzo[*a,c*]cycloheptatrien-5-one (II) and the method he used was not applicable for the preparation of 1,2,3-trimethoxy-5,6,7,8,9,10,11,12-octahydrobenzo[*a*]heptalen-7-one (III). This compound (III) was prepared in this laboratory recently by modifying the reaction procedure.

Pechmann condensation of 1-O-methylpyrogallol and ethyl 2-oxocycloheptanecarboxylate afforded 3-methoxy-4-hydroxy-6,7,8,9,10,11-hexahydrobenzo[*b*]cyclohepta[*d*]pyran-6-one (IV), m.p. 176.5° (*Anal.* Calcd. for C₁₅H₁₆O₄: C, 69.21; H, 6.20. Found: C, 69.17; H, 6.21. UV $\lambda_{\max}^{\text{EtOH}}$ m μ (log ϵ): 258~264 (3.96), 320 (4.17). IR $\lambda_{\max}^{\text{Nujol}}$ μ : 3.00, 5.92). (IV) was allylated to the 4-allyloxy compound (V), m.p. 65° (*Anal.* Calcd. for C₁₈H₂₀O₄: C, 71.98; H, 6.71. Found: C, 71.69; H, 6.91) and its Claisen rearrangement gave 1-allyl-3-methoxy-4-hydroxy-6,7,8,9,10,11-hexahydrobenzo[*b*]cyclohepta[*d*]pyran-6-one (VI), m.p. 166° (*Anal.* Calcd. for C₁₈H₂₀O₄: C, 71.98; H, 6.71. Found: C, 71.91; H, 6.91). (VI) was isomerized to the

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1-propenyl compound (VII), m.p. 175° (*Anal.* Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.98; H, 6.85), which was submitted to ozone oxidation to form 1-formyl compound (VIII), m.p. 225° (*Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.72; H, 5.88). The Knoevenagel condensation of (VIII) with malonic acid converted it to the 1-(2,2-dicarboxyethylene) compound (IX), m.p. 248° (decomp.) (*Anal.* Calcd. for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85. Found: C, 60.86; H, 4.81) which was reduced to 1-(2,2-dicarboxyethyl) compound (X), m.p. 251° (*Anal.* Calcd. for $C_{19}H_{20}O_8$: C, 60.63; H, 5.36. Found: C, 60.56; H, 5.49) and decarboxylated to 1-(2-carboxyethyl) compound (XI), m.p. 248° (decomp.) (*Anal.* Calcd. for $C_{18}H_{20}O_8$: C, 65.05; H, 6.07. Found: C, 64.95; H, 6.00. UV $\lambda_{\max}^{EtOH}$ m μ (log ϵ): 264~267 (4.04), 328 (4.14). IR $\lambda_{\max}^{Nujol}$ μ : 2.95, 3.7~4.0, 5.76, 6.05). Cleavage of the coumarin ring in (XI) and subsequent methylation afforded 2-[2-(2-carboxyethyl)-4,5,6-trimethoxyphenyl]-1-cycloheptenecarboxylic acid (XII), m.p. 138° (*Anal.* Calcd. for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93. Found: C, 63.52; H, 7.00. UV: $\lambda_{\max}^{EtOH}$ 270 m μ (log ϵ 3.44). IR $\lambda_{\max}^{Nujol}$ μ : 2.98, 3.7~4.0, 5.73, 5.95) which was esterified to the methyl ester (XIII) as an oil (*Anal.* Calcd. for $C_{22}H_{28}O_7$: C, 65.01; H, 7.44. Found: C, 65.37; H, 7.67. UV: $\lambda_{\max}^{EtOH}$ 275 m μ (log ϵ 3.58). IR $\lambda_{\max}^{Liquid}$ μ : 5.74, 5.84) and its Dieckmann condensation, followed by alkali saponification, finally afforded (III), m.p. 107° (*Anal.* Calcd. for $C_{19}H_{24}O_4$: C, 72.12, H, 7.65. Found: C, 71.74; H, 8.05. UV $\lambda_{\max}^{EtOH}$ m μ (log ϵ): 240 (4.23), 302 (3.71). IR $\lambda_{\max}^{Nujol}$ μ : 6.02, 6.18). (III) formed an oxime (XIV)

Chart 1.

m.p. 151° (*Anal.* Calcd. for $C_{19}H_{25}O_4N$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.66; H, 7.34; N, 4.51. UV: $\lambda_{\max}^{EtOH}$ 267 m μ (log ϵ 3.98). IR $\lambda_{\max}^{Nujol}$ μ : 3.08, 6.06, 10.45) which was reduced to *dl*-7-amino compound (XV), m.p. 98° (*Anal.* Calcd. for $C_{17}H_{27}O_3N$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.69; H, 8.46; N, 4.63. UV $\lambda_{\max}^{EtOH}$ m μ (log ϵ): 218(4.35), 255(4.02). IR $\lambda_{\max}^{Nujol}$ μ : 2.91, 3.00). (XV) formed an acetyl compound (XVI), m.p. 155° (*Anal.* Calcd. for $C_{21}H_{24}O_4N$: C, 70.17; H, 8.13; N, 3.90. Found: C, 69.72; H, 7.73; N, 3.96. UV $\lambda_{\max}^{EtOH}$ m μ (log ϵ): 217(4.40), 253(4.05). IR $\lambda_{\max}^{CHCl_3}$ μ : 2.85, 2.96, 6.02, 6.65), whose double bond in the B/C ring juncture was submitted to rearrangement according to the method of Loewenthal, *et al.*²⁾ to form *dl*-demethoxydeoxy-hexahydrocolchicine (I), m.p. 185° (*Anal.* Calcd. for $C_{21}H_{29}O_4N$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.22; H, 7.82; N, 4.09. UV $\lambda_{\max}^{EtOH}$ m μ (log ϵ): 221(4.42), 255(4.14). IR $\lambda_{\max}^{CHCl_3}$ μ : 2.83, 2.94, 3.34, 3.43, 3.54, 6.02, 6.38, 6.40, 6.65, 6.73, 6.90, 7.12, 7.32, 7.42, 7.58, 7.72, 7.30, 7.90, 8.78, 9.05, 9.68, 9.92, 10.13, 10.35, 10.64, 10.88, 11.84). The ultraviolet and infrared spectra of (I) were in good agreement with those of *l*-demethoxydeoxy-hexahydrocolchicine obtained from colchicine by the method reported by Rapoport and others.³⁾ The structure of (I) was formulated as (XVI) by Rapoport and others but this was later corrected to (I) by Forbes.⁴⁾ The present series of work has synthetically proved the correctness of (I) formula.

Now that the synthesis of *dl*-demethoxydeoxy-hexahydrocolchicine (I) had been effected, it has become possible to carry out total synthesis of colchicine by the present method, together with the synthesis of colchicine from the levorotatory compound of (I) reported earlier,⁵⁾ a method entirely different from those used by Eschenmoser and others,⁶⁾ and by van Tamelen and others.⁷⁾

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