Z(OMe)-Typ-OH dicyclohexylamine salt (VIII) was prepared in the usual manner[10], 71%, mp 151–152°, $[\alpha]_D$ +11.5°. The condensation reaction of VIII with H-D-Phe-OBzl by the DCC method gave Z(OMe)-Trp-D-Phe-OBzl (IX), 82%, mp 137–139°, $[\alpha]_D$ +3.6°, which was saponified to Z(OMe)-Trp-D-Phe-OH (XI), 80%, mp 84–86°, $[\alpha]_D$ −25.0°. XI (1.2 equiv.) in ethyl acetate was treated with HOSu (1.4 equiv.) and then DCC (1.1. equiv.) at 0 °C for 3 h. The filtrate from dicyclohexylurea was added to a solution of the octapeptide (VII) (1 equiv.) and triethylamine (1 equiv.) in DMF, the stirring being continued at 0° for 5 h. This treatment[11–14] gave Z(OMe)-Trp-D-Phe-Asn-Gln-Tyr-Val-Orn(δ-Z)-Leu-D-Phe-Pro-OH (XII), 70%, mp 215–216° dec, $[\alpha]_D$ −33.1° (DMF). (Anal. calcd. for $C_{85}H_{104}O_{19}N_{14}\cdot 2H_2O$: C, 61.42; H, 6.55; N, 11.80. Found: C, 61.26; H, 6.42; N, 11.85.)

Treatment of XII with 10 equiv. of di-*p*-nitrophenyl sulfite gave amorphous acyldecapeptide *p*-nitrophenyl ester (XIII) and the *p*-nitrophenyl ester content of XIII was estimated to be 105% by means of the method described by SCHWYZER and SIEBER[15]. The decapeptide *p*-nitrophenyl ester trifluoroacetate, obtained from XIII by the action of trifluoroacetic acid, was treated with a large amount of hot pyridine (55–60°) for the cyclization reaction. Purification of the crude product by passing its aqueous dioxane-methanol solution through columns of Amberlite IRC-50 (H^+ form) and Amberlite IR-45 (OH^- form) gave cyclo-Trp-D-Phe-Asn-Gln-Tyr-Val-Orn(δ-Z)-Leu-D-Phe-Pro (XIV), 43% (from XII), mp 198–200°, $[\alpha]_D$ −86.9°. (Anal. calcd. for $C_{76}H_{94}O_{15}N_{14}\cdot 2H_2O$: C, 61.68; H, 6.68; N, 13.25; mol. wt., 1479. Found: C, 61.79; H, 6.58; N, 13.05; mol. wt., 1440.) Removal of the benzyloxycarbonyl group from XIV was achieved by catalytic hydrogenation in the presence of an equivalent of hydrogen chloride in methanol to provide the crystalline cyclo-Trp-D-Phe-Asn-Gln-Tyr-Val-Orn-Leu-D-Phe-Pro·HCl·$5H_2O$ (II·HCl·$5H_2O$) as a desiccator (with $CaCl_2$)-dried product; 62%, mp 236–237° dec, $[\alpha]_D$ −93.0° (c 0.5, MeOH). (Anal. calcd. for $C_{68}H_{88}O_{13}N_{14}\cdot HCl\cdot 5H_2O$: C, 56.87; H, 6.95; N, 13.66. Found: C, 56.71; H, 6.82; N, 13.62.) Its homogeneity was also ascertained by thin-layer and paper chromatographies, paper electrophoresis and carboxymethylcellulose column chromatography. Quantitative amino acid determination gave the following molar ratio: Trp 1.06, Phe 1.86, Asp 1.01, Glu 1.02, Tyr 1.07, Val 0.97, Leu 0.97, Pro 0.96, Orn 1.00, NH_3 2.20[16].

The antibacterial activity toward several microorganisms was examined[17]. It was found that levels of the activity of the synthetic peptide (II·HCl) was the same as that of the synthetic tyrocidine A[5] for the Gram positive microorganisms (*Staph. aureus* and *B. subtilis*) except a microorganism, *Candida albicans*; minimum concentrations of growth-inhibition for *Candida albicans* were found to be 12.5 µg/ml with the TA and 100 µg/ml with II. Work on syntheses of the cyclic decapeptide corresponding to the proposed structures for tyrocidine C[18] and D[19] is in progress in this laboratory.

Zusammenfassung. Die Synthese von Tyrocidin B durch Zyklisierung des aktiven Esters des linearen Dekapeptids wird beschrieben.

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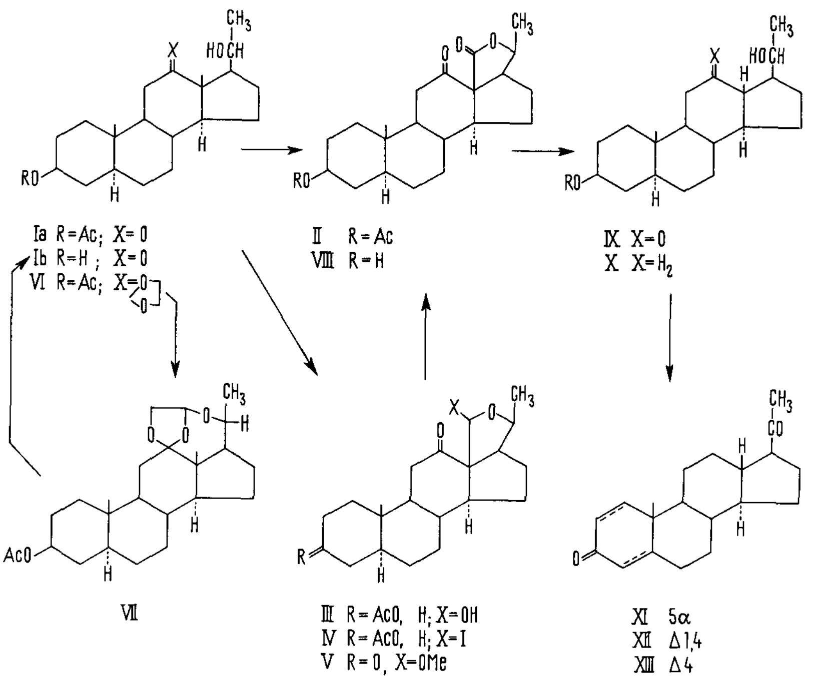
A Novel, Practical Synthesis of 18-Norsteroids

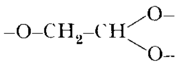
The syntheses of 18-norsteroids of potential medicinal importance have been reported by several groups[1]. The procedures are by either total synthesis or partial synthesis which involve multiple steps.

The author wishes to report a new, practical preparation of 18-norsteroids from an abundant steroid, hecogenin, by a simple sequence, which consists of the decarboxylation of a 12-keto-18-oic acid, a mechanism postulated to the biogenesis of fukujusonorone, the first naturally occuring 18-norsteroid isolated from *Adonis amurensis* by the author and co-workers[2].

3β-Acetoxy-20β-hydroxy-5α-pregnan-12-one (I), which is readily accessible from hecogenin[3], was treated with lead tetraacetate and iodine in cyclohexane expecting the hemiacetal (III), or iodine compound (IV)[4]. However, the main product directly obtained in 50% yield was the γ-lactone (II)[5], mp 209–211°, ν_{max}^{Nujol} 1760 (γ-lactone), 1730 (acetate), 1705 (12CO) cm^{-1}; τ (in $CDCl_3$): 8.93 (3H, s, 19-Me), 7.90 (3H, s, acetate), 5.54 (1H, q, J = 6.5 Hz, 20-H), 5.25 (1H, m, 3-H). The reason of this direct lactone formation may be attributed to activation of 18-methyl group by the 12-carbonyl function, though it is apart by one carbon unit. However, there are evidences of the formation of the hemiacetal (III) or the iodine derivative (IV), in small amounts. Thus, the solvolysis of the mother liquor in aqueous acetic acid followed by chromic acid oxidation gave an additional amount of the lactone (II) in 10% yield, and also treatment of the mother liquor with methanolic sodium hydroxide followed by chromic acid oxidation afforded a methoxyl compound (V), mp 209–210°, ν_{max}^{Nujol} 1710, 1700 cm^{-1}; τ (in $CDCl_3$): 8.89 (3H, s, 19-CH_3), 8.70 (3H, d, J = 7 Hz, 21-CH_3), 6.60 (3H, s, OCH_3), 5.89 (1H, q, J = 7 Hz, 20-H), 5.05 (1H, s, 18-H).



In view of the unexpected results, the ethylenedioxy derivative (VI), mp 116–117° was prepared, and submitted to the same oxidation. The product isolated in 60% yield was a hydroxyl-free compound, VII, mp 130–133°, ν_{max}^{Nujol} 1725 cm^{-1}, and analyzed as $C_{25}H_{38}O_5$. Treatment of VII with dilute sulphuric acid restored the deacetylated starting material (Ib), indicating the oxidation did not take place on the steroid moiety. The NMR-spectrum of VII [τ (in $CDCl_3$): 9.07 (6H, s, 18- and 19-CH_3), 8.77 (3H, d, J = 7 Hz, 21-CH_3), 7.90 (3H, s, CH_3CO), 6.5 (1H, m, 20-H), 6.0 (2H, m, -CH_2–O–), 5.26 (1H, m, 3-H), 4.23 (1H, q, O–CH–O)] suggests the presence of the intact steroid residue and the partial structure of



$$-O-CH_2-CH\begin{matrix} O- \\ O- \end{matrix}$$

From these data, it was speculated that the oxidation occured on the ethylenedioxy moiety, and a bicyclic acetalketal was formed. Although the newly formed acetal ring is 7-membered, the molecular model shows that the methylene moiety of the ketal is located very close to the 20-hydroxyl group.

Attempts to decarboxylate the 18-carbonyl group of II in acidic media were unsuccessful, but afforded the deacetylated lactone (VIII), mp 198–195°, ν_{max}^{Nujol}: 3450, 1750, 1680 cm^{-1}. However, treatment of II with dilute sodium hydroxide in aqueous methanol gave an 18-nor-derivative, IX, mp 144–145°, ν_{max}^{Nujol}: 3450, 1750, 1580 cm^{-1}; τ (in $CDCl_3$): 9.10 (3H, s, 19-CH_3), 8.82 (3H, d, J = 6 Hz, 21-CH_3), ca. 6.5 (2H, m, 3- and 20-H) as a sole product, showing either *cis* or *trans* C/D ring juncture is exclusively favored. Huang-Minlon reduction of IX provided again a single product, X, mp 162–165°, ν_{max}^{Nujol}: 3400 cm^{-1}. The *trans* ring juncture of IX and X was established by the following correlation.

The diol was oxidized with Jones' reagent to 5α-18-norpregnane-3, 20-dione (XI), mp 126–129°, ν_{max}^{Nujol}: 1700 cm^{-1}, which was dehydrogenated with dichlorodicyanobenzoquinone to $\Delta^{1,4}$-18-norpregnadiene-3, 20-dione (XII), mp 150°, λ_{max} 242 nm, ν_{max}^{Nujol}: 1690, 1658, 1618, 1600 cm^{-1}. Partial hydrogenation of XII with chlorotristriphenylphosphine rhodium gave an 18-norprogestrone, XIII, mp 113–114°, $[\alpha]_D$ + 135° (C = 1, $CHCl_3$), ν_{max}^{Nujol}: 1708, 1670, 1618 cm^{-1}, λ_{max} 242 nm (14,000). ANLIKER et al.[1] reported the synthesis of 18-norprogesterone, mp 110–111°, $[\alpha]_D$ + 134°, whose ring juncture was assigned as 13β, 14α-*trans* from mechanistic grounds. Identity of XIII and ANLIKER's sample was established by the IR-spectra comparison[6].

The 18-nor-17-keto-steroid was reported to form an equilibrium mixture in a ratio of 13β/13α = 7/3. Preferential formation of the 13β-epimers at the decarboxylation and Huang-Minlon reduction steps might be attributed to the possible increase of the steric hindrance between the 17β-oriented sidechain and the C-ring in C/D-*cis* configuration.

Zusammenfassung. Eine einfache Synthese von 18-Nor-Pregnan-Derivaten durch die Decarboxylierung eines 12-Keto-18-Säure-Lactons (→20) wird beschrieben.

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