Communications to the Editor

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SYNTHESES OF VITAMIN D ANALOGUES I[1)]

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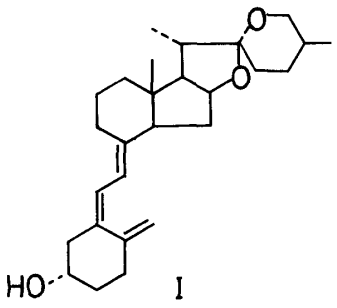
Two vitamin D analogues(I and II) were synthesized starting with diosgenin(III) and androst-5-en-3β-ol-17-one(IV), respectively.

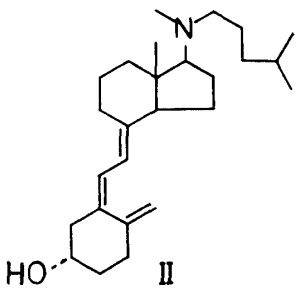
KEYWORDS ——— vitamin D; diosgenin; androst-5-en-3β-ol-17-one; 4-phenyl-1,2,4-triazoline-3,5-dione; Vycor filter

It is anticipated that vitamin D antagonists may be clinically useful for reducing the hypercalcemia of a variety of human disorders such as primary and tertiary hyperparathyroidism, vitamin D toxicity, idiopathic hypercalcemia of infancy, sarcoidosis, and hypercalcemia of malignancy. A few reports on vitamin D antagonists have appeared in the literature.[2)] Unfortunately none of them was adopted as a medicine. Therefore we tried to synthesize two hitherto unknown vitamin D analogues(I and II) as vitamin D antagonists starting with diosgenin(III) and androst-5-en-3β-ol-17-one(IV).

III-acetate(V) was brominated with N-bromosuccinimide(NBS, 1.1 mol eq) by refluxing in n-hexane for 15min[3)] to give 7-bromo-(25R)spirosta-5,7-dien-3β-ol acetate (VI) in a yield of 74.4%. mp 140-143°C $C_{29}H_{43}BrO_4$[4)] NMR($CDCl_3$)δ: 2.03(3H, s), 3.10(2H, d, J=4), 4.3-4.7(3H, m), 5.70(1H, d, J=4). Dehydrobromination of VI was carried out by refluxing in xylene for 90min in the presence of an excess of γ-collidine[5)] to give (25R)spirosta-5,7-dien-3β-ol acetate(VII). mp 157-160°C $C_{29}H_{42}O_4$.[4)] UV(MeOH), λ_{max}nm: 293, 282, 271. NMR($CDCl_3$)δ: 2.04(3H, s), 3.44(2H, d, J=4), 4.50(2H, br.s), 5.40 and 5.56(2H, s like). HPLC[6)](5% AcOEt in n-hexane): t_R 8.40 min. However an attempted dehydrobromination of VI by treatment with triethyl phosphite[3)] in xylene was unsuccessful. Then the crude VII was coupled with 4-phenyl-1,2,4-triazoline-3,5-dione(PTAD) in CH_2Cl_2 at room temperature[7)] to give the 1:1-adduct(VIII) after purification through SiO_2 column chromatography in a yield of 50.3% from VI. mp 170-172°C. $C_{37}H_{47}N_3O_6$[4)] UV(MeOH), λ_{max}nm(ε): 256(16000), 212(31200). NMR($CDCl_3$)δ: 2.03(3H, s), 3.40(2H, s like), 4.50(1H, br s), 5.47(1H, br s), 6.23 and 6.36(each 1H, d, J=8), 7.43(5H, s). The adduct, VIII, was reduced with $LiAlH_4$ in THF to give (25R)-spirosta-5,7-dien-3β-ol(IX) in a yield of 54.5%. mp 148-150°C. $C_{27}H_{40}O_3$[4)] UV(MeOH), λ_{max}nm(ε): 293(7100), 281(11800), 271(11600), λ_{min}nm(ε): 222(2700). NMR($CDCl_3$)δ: 1.85(3H, s), 3.3-3.5(2H, m), 3.64(1H, br s), 4.52(1H, q, J=4), 5.41 and 5.56(each 1H, s like). HPLC[6)](20% AcOEt in n-hexane): t_R 7.75min. To examine photochemical conditions needed to convert the dienol, IX, to previtamin D(X), which was transformed into vitamin D analogue(I) by refluxing for 1.5h in benzene, many experiments were carried out and the products were analyzed using HPLC and UV technique. It was revealed that the best conditions were irradiation of IX(100mg) in abs. Et_2O(250ml)



I



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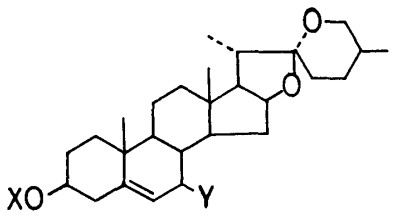
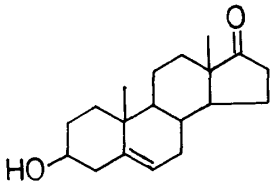
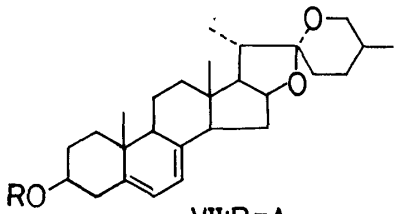


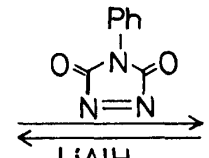
III: X = H, Y = H
V: X = Ac, Y = H
VI: X = Ac, Y = Br

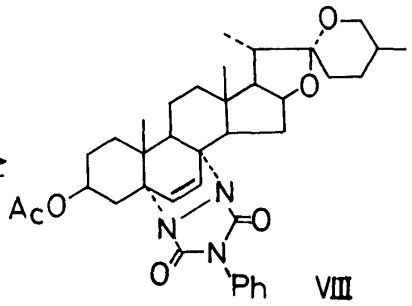


IV

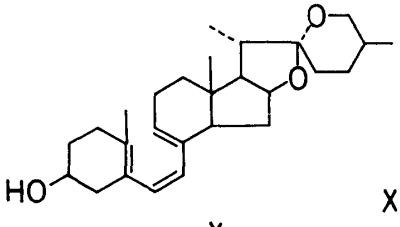


VII: R = Ac
IX: R = H

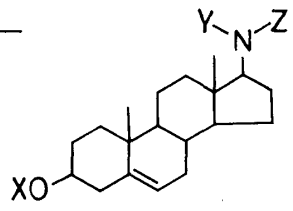




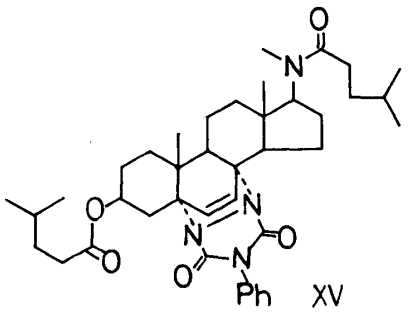
VIII



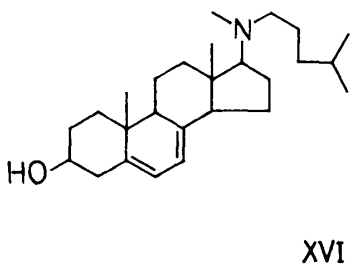
X



XI: X = Y = H
Z = -CH_2-CH_2-CH_2-$CH(CH_3)_2$
XII: X = H, Y = Me
Z = -CH_2-CH_2-CH_2-$CH(CH_3)_2$
XIII: X = Z = H, Y = Me
XIV: X = Z = -$\overset{O}{\overset{\|}{C}}$-$CH_2$-$CH_2$-$CH(CH_3)_2$
Y = Me



XV



XVI

for 10min using quartz vessel and high pressure mercury lamp(200W) filtered by Vycor glass under N_2 atmosphere maintaining the temperature below 18°C. The yield of I from IX via X was 28.1%. In the case of irradiation of IX in benzene for 10min using the same lamp without filter, the yield was only 8.4%. The product, I, was purified through SiO_2 column chromatography and eluted with 5% AcOEt in benzene. I: white amorph. softing at 90°C. HPLC[8] (5% H_2O in MeOH): t_R 5.46min. UV, λ_{max}nm: 262, λ_{min} nm: 227. NMR($CDCl_3$)δ: 3.50(3H, br s), 4.00(2H, br s), 4.50(1H, br s), 6.05 and 6.24 (each 1H, d, J=12). MS, m/e(%): 412(M^+, 30), 379(15), 138(80), 118(100). High resolution MS; Calcd for $C_{27}H_{40}O_3$: 412.2975. Found: 412.2964. $[\alpha]_D^{23}$ -32.4°(c=0.42, $CHCl_3$).

We have turned our attention to synthesis of II from IV. According to the manner reported in the literature,[9] IV-acetate was converted to 17β-(4-methylpentyl)amino-androst-5-en-3β-ol(XI) by treating it with 4-methylpentylamine in the presence of p-TsOH in benzene followed by reduction with $LiAlH_4$ in dioxane. Unfortunately conversion of XI into its N-methyl derivative(XII) under the reported conditions failed. Therefore, 17β-methylaminoandrost-5-en-3β-ol(XIII)[10], prepared from IV-acetate, N-methylformamide, and formic acid, was treated with isocaproyl chloride in the presence of Et_3N in benzene to give 17β-(N-isocaproyl-N-methyl)aminoandrost-5-en-3β-ol isocaproate(XIV) in a yield of 67.5%. XIV: mp 162-164°C $C_{32}H_{53}NO_3$[4] IR(KBr)cm^{-1}: $\nu_{C=O}$1730, 1640. NMR($CDCl_3$)δ: 0.68 and 0.75(2:1, 3H, each s), 2.86 and 2.91(1:2, 3H, each s), 4.60(2H, br s), 5.40(1H, s like). $[\alpha]_D^{23}$ -94.5°(c=0.53, $CHCl_3$). The signals at δ0.68, 0.75ppm and at δ2.86, 2.91ppm were due to C_{18}-methyl and N-methyl groups, respectively. This phenomenon could be attributed to two rotational isomers of the amide group. This consideration was supported by the NMR spectrum of XII, which was obtained by reduction of XIV with $LiAlH_4$ in a yield of 78.9%. That is, XII(mp 126.5-129°C) showed a singlet signal owing to C_{18}-methyl and N-methyl groups at δ0.81 and 2.22ppm, respectively. XIV was brominated with NBS in CCl_4 and dehydrobrominated with γ-collidine in xylene. The crude products was successively converted to its PTAD-adduct(XV) in CH_2Cl_2. The overall yield of XV from XIV was 31.5%. XV: mp 183-185°C. $C_{40}H_{56}N_4O_5$[4] IR(KBr)cm^{-1}: $\nu_{C=O}$1750, 1700, 1630. UV(MeOH) nm: λ_{max}256, λ_{min}nm: 244. NMR($CDCl_3$)δ: 2.94 and 3.00(1:3, 3H, each s, >N-Me), 5.49(1H, br s), 6.27 and 6.41(each 1H, d, J=8), 7.48(5H, s). XV was reduced to 17β-(N-methyl-N-4-methylpentyl)aminoandrosta-5,7-dien-3β-ol(XVI) by the ordinary method in a yield of 41.4%. XVI: yellow oil. IR($CHCl_3$) cm^{-1}: ν_{OH}3400, $\nu_{C=C}$1600. UV(MeOH) nm: λ_{max}292, 281, 271. λ_{min}nm: 236. NMR($CDCl_3$) δ: 0.77(6H, d, J=6), 0.93(6H, s), 2.30(3H, s), 3.56(1H, br s), 5.41 and 5.66(each 1H, d, J=6). MS, m/e(%): 385(M^+, 22), 154(100). Then the photochemical cleavage of XVI was examined. As XVI did not dissolve in Et_2O, the conditions used for IX could not be applied. The best condition to convert XVI into the corresponding previtamin D was irradiation by 200W mercury lamp in quartz vessel in benzene below 22°C under Ar atmosphere. Vitamin D analogue(II) was obtained by refluxing the resulting solution for 1.5h and purified through SiO_2 column chromatography eluted with 10% AcOEt in benzene. The overall yield of II from XVI was 36.1%. The formula was confirmed by high resolution MS spectrum. Calcd for $C_{26}H_{43}NO$: 385.3342. Found: 385.3289. UV(MeOH) nm: λ_{max} 261, λ_{min} 228. NMR($CDCl_3$)δ: 3.98(1H, br s), 4.92 and 5.04(each 1H, s like), 6.06 and 6.26(each 1H, d, J=12). HPLC[6] ($CHCl_3$): t_R 6.11min (cf; previtamin D: t_R 11.51min, XVI: t_R 7.61min). $[\alpha]_D^{23}$ +10.9°(c=0.29, $CHCl_3$).

The biological assay of these synthesized vitamin D analogues, I and II, is now being examined.

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REFERENCES AND NOTES

1) A part of this work was presented at the 58th Meeting of the Hokuriku Branch of the Pharmaceutical Society of Japan, Toyama, Nov. 1982.
2) R.L. Johnson, W.H. Okamura, and A.W. Norman, Biochem. Biophys. Res. Comm., 67, 797(1975); W.H. Okamura, M.L. Hammond, A. Rego, A.W. Norman, and R.M. Wing, J. Org. Chem., 42, 2284(1977); B.L. Onisko, H.K. Schnoes, and H.F. Deluca, J. Biol. Chem., 254, 3493(1979); H.E. Paaren, R.M. Moriarty, H.K.Schnoes, and H.F. Deluca, Biochemistry, 19, 5335(1980); S. Ishizuka, S. Ishimoto, and A.W. Norman, FEBS Letters, 139, 267(1982).
3) M. Morisaki, A. Saika, K. Bannai, S. Sawamura, J.R-Lightbourn, and N. Ikekawa, Chem. Pharm. Bull., 23, 3272(1975).
4) The formula was confirmed by its elemental analysis.
5) R.P. Esvelt, M.A. Fivizzani, H.E. Parren, H.K. Schnoes, and H.F. Deluca, J. Org. Chem., 46, 456(1981).
6) In this HPLC, Waters' radial pack B column (8m/m × 10cm) was used. The flow rate of solvent was 2ml/min.
7) K.Ochi, I. Matsunaga, H. Nagano, M. Fukushima, M. Shindo, C. Kaneko, M. Ishikawa, and H.F. Deluca, J Chem. Soc. Perkin Trans. I, 1979, 165.
8) In this HPLC, Waters' radial pack A column (8m/m × 10cm) was used. The flow rate was 2ml/min.
9) R.E. Counsell, P.D. Klimstra, L.N. Nysted, and R.E. Ranney, J. Med. Chem., 8, 45(1965).
10) R.E. Counsell, P.D. Klimstra, and R.E. Ranney, J. Med. Pharm. Chem., 5, 1224 (1962).

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