THE TOTAL SYNTHESIS OF DIACETYLOXODENUDATINE

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Abstract -- The total synthesis of racemic diacetyloxodenudatine (2) is described. Treatment of this material with $LiAlH_4$ in dioxane at reflux caused the reduction of not only the lactam but also the exocyclic double bond and yielded racemic dihydrodenudatine (23).

Ten years ago we have conjectured on the basis of a few degradation reactions and some biogenetic considerations, the structure (1) (configuration not implied) as one of two basic possibilities for the alkaloid denudatine.[1] A short time later, the structural problem was solved rigorously when two independent crystallographic investigations have shown denudatine to be represented by the formula (1).[2,3] As the sole member of the ring B bridged atisine group of alkaloids, denudatine has considerable biogenetic importance.[4] In our synthetic studies on hexacyclic aconitum alkaloids we have described previously total syntheses of polysubstituted denudatine type intermediates.[5,6] Nevertheless, we felt that it was worthwhile to synthesize also denudatine itself, since it presented special problems which required the development of novel synthetic devices. We wish to disclose in the present Communication the total synthesis of racemic diacetyloxodenudatine (2).

The most convenient starting material for the synthesis of denudatine by the masked o-quinone method would be the aromatic intermediate (3) (cf. ref. 6). However, we have had in our laboratory 650 mg of compound (4) (mp 237-8°C) prepared by cleavage of the methoxyl in (5). This last product was in turn obtained by a routine application of our "aziridine synthesis" and removal of the substituents.[7] We have decided to base a direct synthesis of denudatine on this material and to introduce the second aromatic substituent. The phenol

(4) was quantitatively converted to the oily allyl ether (6) with allyl bromide in dry acetone in the presence of K_2CO_3 and 18-Crown-6 ether.† The solution of compound (6) in N,N-dimethylaniline was heated to 200°C for 48 h. The Claisen rearrangement product (7) (mp 168-170°C) was obtained in a yield of 80% after crystallization from CH_2Cl_2. [Infrared spectrum (I.R.) ($CHCl_3$): 3600-3700 (-OH), 1630 cm^{-1} (C=O); proton magnetic resonance spectrum (N.M.R.) ($CDCl_3$): τ = 3.1 (AB_q, J = 8 Hz, $\Delta\nu$ = 15.6 Hz, 2H, aromatic H), 3.94 (m, 1H, -CH=), 4.67-4.90 (m, 2H, $=CH_2$)]. The phenol (7) was alkylated with methyl bromoacetate using exactly the same conditions as in the alkylation of (4). The oily ester (8) was obtained quantitatively. [I.R. ($CHCl_3$): 1765 ($-COOCH_3$), 1665 cm^{-1} (-CON)]. The ester (8) was now isomerized in refluxing benzene with bis-(benzonitrile)-$PdCl_2$.[8] The product (9) was isolated by preparative thin layer chromatography (tlc) in a yield of 84% as an oil which was a mixture of the cis and trans olefins. [I.R. ($CHCl_3$): 1765 ($-COOCH_3$), 1665 cm^{-1} (-CON); N.M.R. ($CDCl_3$): τ = 3.6 (m, 2H, -CH=CH-, cis and trans)]. The olefins (9) were oxidized in aqueous dioxane with OsO_4 and $NaIO_4$. The oily aldehyde (10) was isolated by preparative tlc in a yield of 80%. [I.R. ($CHCl_3$): 1765 ($-COOCH_3$), 1685 (-CH=O), 1630 cm^{-1} (-CON); N.M.R. ($CDCl_3$): τ = -0.46 (-CH=O)].

The synthesis of the formyl derivative (10) required several steps but it was quite efficient. We believe that our process might be occasionally useful since it worked well in a situation in which all other methods recorded in the literature for the preparation of o-formylphenols have failed.

The aldehyde (10) was now subjected to a Baeyer-Villiger oxidation with m-chloroperbenzoic acid in CH_2Cl_2. The unstable formate (11) was obtained in a quantitative yield and it was used immediately for the next step. [I.R. ($CHCl_3$): 1775 (-O-CH=O); N.M.R. ($CDCl_3$): τ = 1.73 (s, 1H, -O-CH=O)]. The formate (11) was reduced with $LiBH_4$ in tetrahydrofuran (t.h.f.). The crystalline phenol-alcohol (12) (mp 173.5-175°C) was obtained in a yield of 96%. [I.R. ($CHCl_3$): 3100-3600 (OH), 1625 cm^{-1} (-CON); N.M.R. ($CDCl_3$): τ = 6.0 (m, 4H, $O-CH_2-CH_2-O$)]. The phenol (12) was now dissolved in dry t.h.f. and oxidized in the presence of $CaCO_3$ with $Tl(NO_3)_3$[9] at 0°C for 15 min. The

† All products gave a correct m/e value in mass spectrometry. All crystalline products gave a satisfactory C/H and N analysis.

reaction mixture was poured into aqueous $NaHCO_3$ and extracted with $CHCl_3$. The crude o-quinone acetal (13)[††] obtained by drying and evaporation of the extract was dissolved in CH_2Cl_2 and treated with an excess of ethyl vinyl thioether for 20 h at 40°C. The adduct (14) was isolated by preparative tlc and crystallization from ether (mp 139-140°C) in an overall yield of 80% from the phenol (12). [I.R. ($CHCl_3$): 1740 (C=O), 1625 cm^{-1} (-CON); N.M.R. ($CDCl_3$): τ = 4.22 (d, J = 6 Hz, 1H, =CH-), 5.82 (m, 4H, O-CH_2-CH_2-O)]. The adduct (14) was reduced quantitatively with $NaBH_4$ to the corresponding alcohol (15) (mp 180-2°C) and this material was desulfurized with Ra-Ni for 2 h in alcohol at reflux. The hydroxy acetal (16) (mp 204-6°C) was obtained also in quantitative yield. [I.R. ($CHCl_3$): 3520 (OH), 1625 cm^{-1} (-CON); N.M.R. ($CDCl_3$): τ = 4.17 (d, J = 6 Hz, 1H, =CH-), 6.05 (m, 4H, O-CH_2-CH_2-O), 8.83 (t + s, 6H, CH_3, -CH_2-CH_3)].

Reoxidation of the alcohol (16) with CrO_3/Py in CH_2Cl_2 yielded 97% of the keto-acetal (17) (mp 150-2°C). [I.R. ($CHCl_3$): 1740 (CO), 1625 cm^{-1} (-CON); N.M.R. ($CDCl_3$): τ = 4.16 (d, J = 6 Hz, 1H, =CH-), 5.77 (m, 4H, O-CH_2-CH_2-O), 8.83 (s + t, 6H, $-CH_3$, -CH_2-CH_3)].

Treatment of the ketoacetal (17) with an excess of $(CH_3)_3SiCH_2MgCl$ (cf. ref. 10) in t.h.f. at 80°C for 12 h gave the tertiary alcohol (18) (mp 172-3°C) in a yield of 80% after crystallization from Et_2O-$CHCl_3$. [I.R. ($CHCl_3$): 3540 (OH), 1625 cm^{-1} (-CON); N.M.R. ($CDCl_3$): τ = 4.2 (d, J = 6 Hz, 1H, =CH-), 6.03 (s, 4H, O-CH_2-CH_2-O), 8.85 (s + t, $-CH_3$, -CH_2-CH_3), 9.12 (s, 2H, -CH_2-Si), 9.92 (s, 9H, -$Si(CH_3)_3$)].

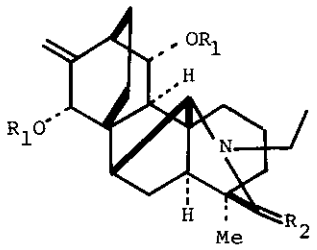
Compound (18) was converted quantitatively to the dienone (19) by treatment with $HClO_4$ in t.h.f. first at r.t. and then for 2 h at 60°C. [I.R. ($CHCl_3$): 1710 (CO), 1625 cm^{-1} (-CON + >C=CH_2); N.M.R. ($CDCl_3$): τ = 3.93 (d, J = 6 Hz, 1H, =CH-), 4.25, 4.88 (2d, J = 2 Hz, 2H, =CH_2), 8.83 (s + t, 6H, $-CH_3$, -CH_2-CH_3)].

[††]Crystallization of (13) from $CHCl_3$ gave the pure material (mp 205-7°C). [I.R. ($CHCl_3$): 1665 (CO), 1635 (-CON), 1600 cm^{-1} (C=C); N.M.R. ($CDCl_3$): τ = 3.5, 4.05 (2d, J = 10 Hz, 2H, CH=CH), 5.82 (m, 4H, O-CH_2-CH_2-O)]. In our denudatine model study[10] we have used the "Deslongchamps spirolactone" method for the preparation of a masked o-quinone intermediate corresponding to (13). This turned out to be useless in the synthesis proper since it led to more than 50% aromatic bromination. Unlike in our delphinine type alkaloid synthesis (cf. ref. 6), the removal of the bromine was impractical in the denudatine case. Intermediates of the type (13) are expected to have several advantages over the corresponding spirolactone and studies along these lines are in progress.

At this point we still had 150 mg of the dienone (19) in our hands and thus its conversion to denudatine appeared quite feasible. The dienone (19) was treated with CH_3-SH and Na_3BO_3 in aqueous t.h.f. at r.t. for 1 h. The pure oily thioether (20) was isolated by preparative tlc in a yield of 92%. [I.R. ($CHCl_3$): 1622 cm^{-1} (-CON); N.M.R. ($CDCl_3$): τ = 3.87 (d, J = 7 Hz, 1H, =CH-), 7.9 (s, 3H, -S-CH_3)]. The hydroboration of the thioether (20) was performed exactly as in our model study[10] in t.h.f. with an excess of B_2H_6 for four days, followed by H_2O_2 oxidation. As in the case of the model compound, the hydroboration of the double bond was stereospecific and the reduction of the keto group gave two epimers in approximately equal amount. Unfortunately, the yield was much lower with compound (20) than with the model system and only about 25% of each of the epimers was obtained. The epimers are, in principle, interconvertible and both of them may thus yield the denudatine system. However, since the only way in which we could rigorously assign configuration to the correct epimer (21) was a conversion to a denudatine derivative, we were unable (in view of the small amount of substance available) to utilize this possibility. The pure diol (21) was isolated as an oil by preparative tlc and acetylated with Ac_2O/Py. The acetate (22) was crystallized from Et_2O-$CHCl_3$ and melted at 194-5°C. [I.R. ($CHCl_3$): 1739 (COO), 1625 cm^{-1} (-CON); N.M.R. ($CDCl_3$): τ = 4.78 (t, J = 6 Hz, 1H, C<u>H</u>-OAc), 5.36 (d, J = 7 Hz, 1H, C<u>H</u>-OAc), 7.87 (s, 3H, -$COCH_3$), 7.91 (2s, 6H, -$COCH_3$, -SCH_3)].

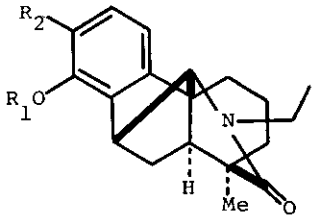
The diacetate (22) was treated with $NaIO_4$ in aqueous t.h.f. at r.t. for 30 min and the resulting sulfoxide was pyrolyzed in refluxing o-xylene under N_2 for 24 h. The synthetic racemic diacetyloxodenudatine (2) was isolated by preparative tlc in a yield of 50% as an oil. [I.R. ($CHCl_3$): 1735 (COO), 1625 cm^{-1} (-CON + C=C); N.M.R. ($CDCl_3$): τ = 4.50, 4.60 (2 broad s, 1H each, C=CH_2), 4.97, 5.09 (2 broad s, 1H each, C<u>H</u>OAc), 7.87, 7.97 (2s, 3H each, $COCH_3$)].

The racemate (2) was identical in its spectral (mass, I.R. and N.M.R.) and tlc properties with the optically active material of the same structure prepared from denudatine by acetylation and oxidation with CrO_3/Py (cf. ref. 1). We expected with confidence that reduction of (2) with $LiAlH_4$ would yield denudatine (1). However, reflux of (2) with this reagent in dioxane yielded synthetic racemic dihydro denudatine (23) (mp 89-91°C) which crystallized



(1) [R_1 = H, R_2 = H_2]

(2) [R_1 = Ac, R_2 = O]



(3) [R_1 = H, R_2 = CH_3-OCH_2-O-]

(4) [R_1 = H, R_2 = H]

(5) [R_1 = OCH_3, R_2 = H]

(6) [R_1 = -CH_2-CH=CH_2, R_2 = H]

(7) [R_1 = H, R_2 = -CH_2-CH=CH_2]

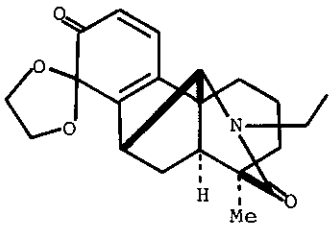
(8) [R_1 = -CH_2-$COOCH_3$, R_2 = -CH_2-CH=CH_2]

(9) [R_1 = -CH_2-$COOCH_3$, R_2 = -CH=CH〰CH_3]

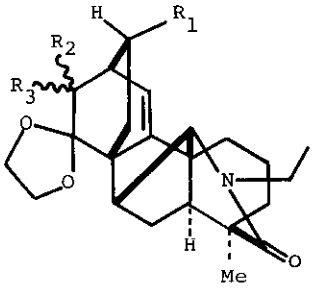
(10) [R_1 = -CH_2-$COOCH_3$, R_2 = CH=O]

(11) [R_1 = -CH_2-$COOCH_3$, R_2 = -O-CH=O]

(12) R_1 = -CH_2-CH_2-OH, R_2 = -OH]



(13)



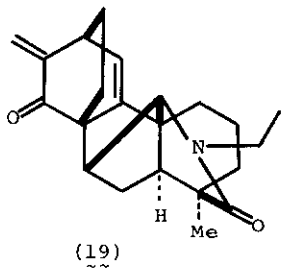
(14) [R_1 = -SEt, R_2R_3 = =O]

(15) [R_1 = -SEt, R_2R_3 = H,-OH]

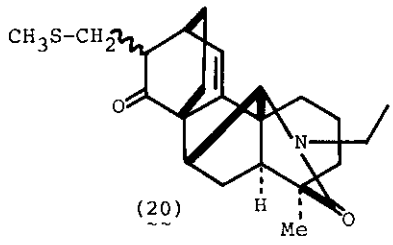
(16) [R_1 = H, R_2R_3 = H,-OH]

(17) [R_1 = H, R_2R_3 = =O]

(18) [R_1 = H, R_2R_3 = -OH,-CH_2-$Si(CH_3)_3$]



(19)



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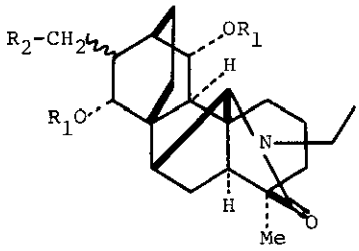
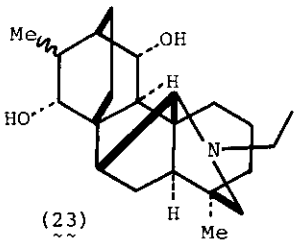


(21) [R_1 = H, R_2 = -S-CH_3]

(22) [R_1 = Ac, R_2 = -S-CH_3]



(23)

from Et_2O-hexane. [I.R. ($CHCl_3$): 3605, 3440 cm^{-1} (OH); N.M.R. ($CDCl_3$): τ = 8.82 (d, J = 8 Hz, 3H, $-CH_3$), 8.88 (t, J = 7 Hz, 3H, $-CH_2-CH_3$), 9.28 (s, 3H, $-CH_3$). This unexpected outcome could have been avoided had we tried also this seemingly obvious reduction with our tricyclic model compound. A simple reversal of the order of steps [$LiAlH_4$ reduction of 21] might have yielded denudatine as final product. We shall not repeat the synthesis but we hope to acquire natural denudatine and prepare compound (21) from it.

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