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INTERCONVERSION OF HETIDINE- AND ATISINE-TYPE DITERPENOID ALKALOIDS: FACILE CLEAVAGE AND REGENERATION OF THE C(14)-C(20) BOND

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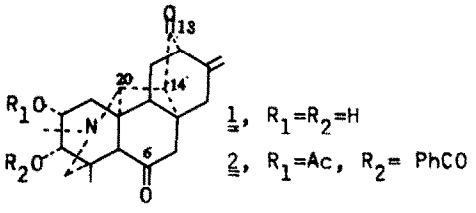
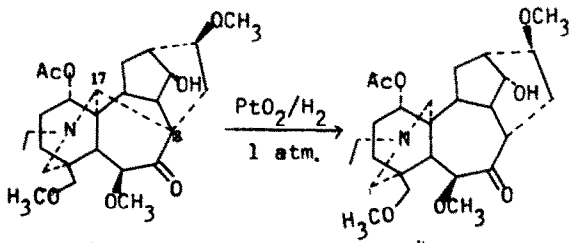
Abstract- The simultaneous presence of 2α-hydroxy and 13-keto groups in hetidine (1) gives rise to a facile conversion to a structure (24) of the atisine-type simply by heating in alkaline media, the transient formation of the intermediate (23) as the result of C(14)-C(20) cleavage being captured intramolecularly by the 2α-hydroxy group. Reversion of 24 to 1 can be simply effected by treatment with acid. Included herewith are also some miscarried prior probings leading to the formation of other products.

Hetidine (1) belongs to one of the most rigidly fused polycyclic systems of the C_{20}-diterpenoid alkaloids. One of the pivotal problems toward the total synthesis (yet to be accomplished) is the construction of the C(14)-C(20) bond[2]. This



1, $R_1=R_2=H$
2, $R_1=Ac$, $R_2=PhCO$



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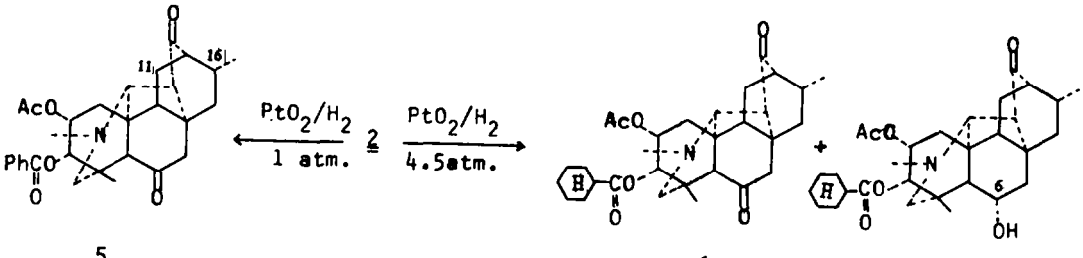
paper is concerned with a number of chemical transformations of our recently isolated episcopalidine (2)[3], an esterified form of hetidine available to us in gram quantities, and the main theme is centered upon the cleavage and regeneration of the C(14)-C(20) bond. To this end, four different lines of attack have been undertaken as follows.

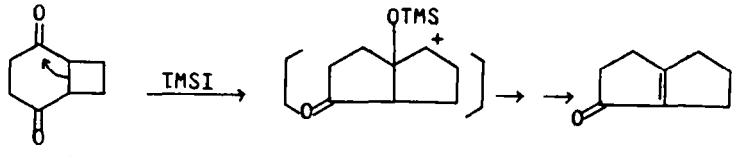
1. Catalytic Hydrogenolysis: Literature precedent[4] can be found in the case of 3, where the facile cleavage of the C(8)-C(17) bond was ascribed to the presence of the β-amino ketone functionalities also embodied in 2. But the correspondent C(14)-C(20) bond in 2 proved to be recalcitrant and hydrogenation gave compounds 5, 6 and 7 instead. The α-hydroxy group on C-6 of 7 and the C_{16}-α-methyl in 5 - 7 are



5 6 7

assigned on steric grounds. α-Configuration of the C_{16}-methyl was also supported by the absence of γ-effect on the δ-values of C-11 in the ^{13}C NMR spectra[5] of 5 and 6.

2. Trimethylsilyl iodide (TMSI) method: TMSI[6] was found to initiate, e.g., the cleavage of the α,β-bond of the keto group in 8. However, similar treatment(Me_3SiCl-NaI/MeCN) of 2 gave only 9, 10 and 11, the latter two possessing the isomerized



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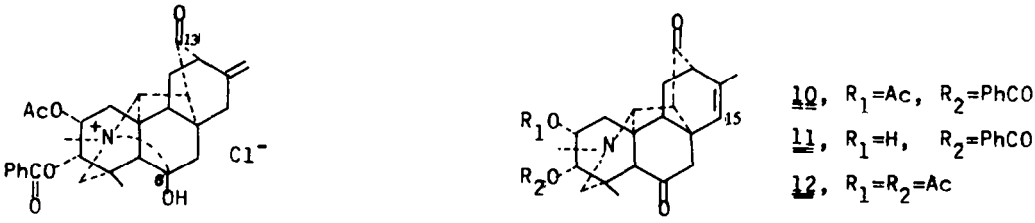
endocyclic unsaturation. This exo to endo isomerization was found to be a facile process, exemplified by the formation of 10 upon treatment of 9 with BF_3/HOAc/glycol or $NaBH_4$/DMF at room temperature. Similarly, acetylation of hetidine (1) with

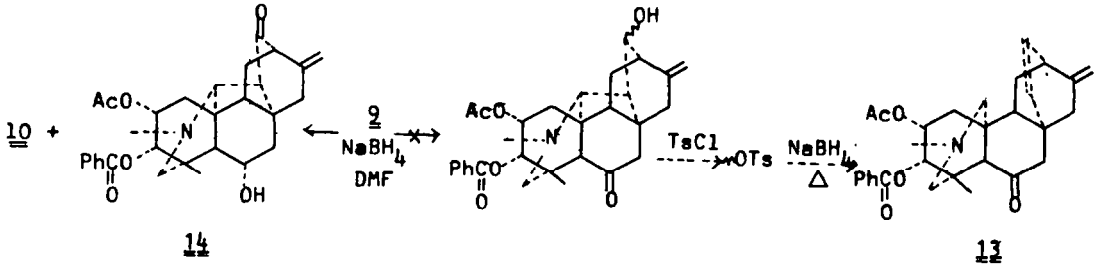


9

10, R_1=Ac, R_2=PhCO
11, R_1=H, R_2=PhCO
12, R_1=R_2=Ac

p-toluenesulfonic acid as catalyst gave some 12 as the by-product.

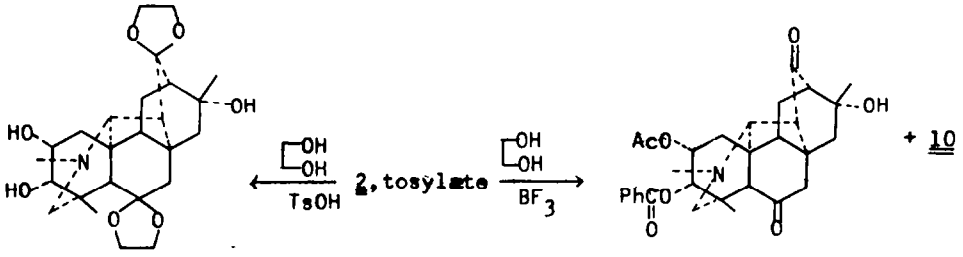
3. Fragmentation of γ-amino tosylate[7]: The miscarried selective reduction of the C-13 keto group of 9 was intended to be followed by tosylation and reductive



14 13

thermolysis to give 13. Apparently the hemiketal of C-6 in 9 was not an adequate form of protection and rapid consumption of the protective acid (HCl) by $NaBH_4$ very soon laid bare the C-6 keto group which is more vulnerable to reduction than the relatively hindered C-13 keto group. As a consequence, 14 was obtained along with some 10.

Ketalization of 2 with glycol was only cursorily exploited and under the strongly acidic conditions used 10, 15 and 16 were formed. Here hydration led to the

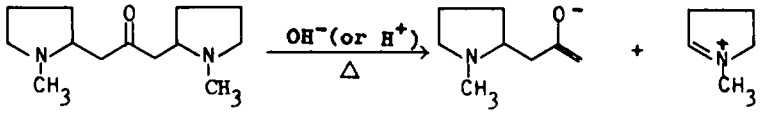


15 16

formation of the C-16 hydroxy groups in 15 and 16 which were assigned α-configurations according to the work of Pelletier et al.[8]

The IR absorption of the C-6 keto group occurs at about 1690 cm^{-1} which can be readily differentiated from the C-13 keto group at about 1720 cm^{-1}. The low frequency shown by the former is a consequence of the transannular interaction with the electron pair on the amino nitrogen. Quaternization by MeI brings the C-6 ketonic absorption to a normal value of 1724 cm^{-1}.

4. Acid or base catalysis: This approach was fashioned after the successful fragmentation of cuscohygrine (17) with aqueous alcoholic base under reflux[9] or with acid under much more drastic conditions[10]. Evidently the β-amino ketonic functionalities per se have already set the stage for bond rupture which, however,

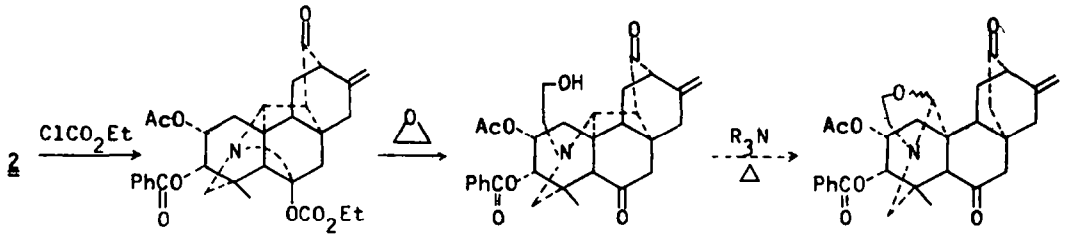


17 18 19

would tend to be thwarted by a geometrically favored intramolecular recombination in the case of hetidine and its analogs. In order to trap the bond rupture at its onset, some appropriate trapping agent is needed either to react with the enolate (like 18) or preferably with the more reactive immonium (like 19) moiety. At first we explored three reductive methods on episcopalidine (2): (i), Zn/HOAc, (ii), Zn/NaOH, and (iii), HCO_2H/Ac_2O[11]. All three methods turned out to be ineffective and the last-mentioned method gave rise to the isomerised compound 10.

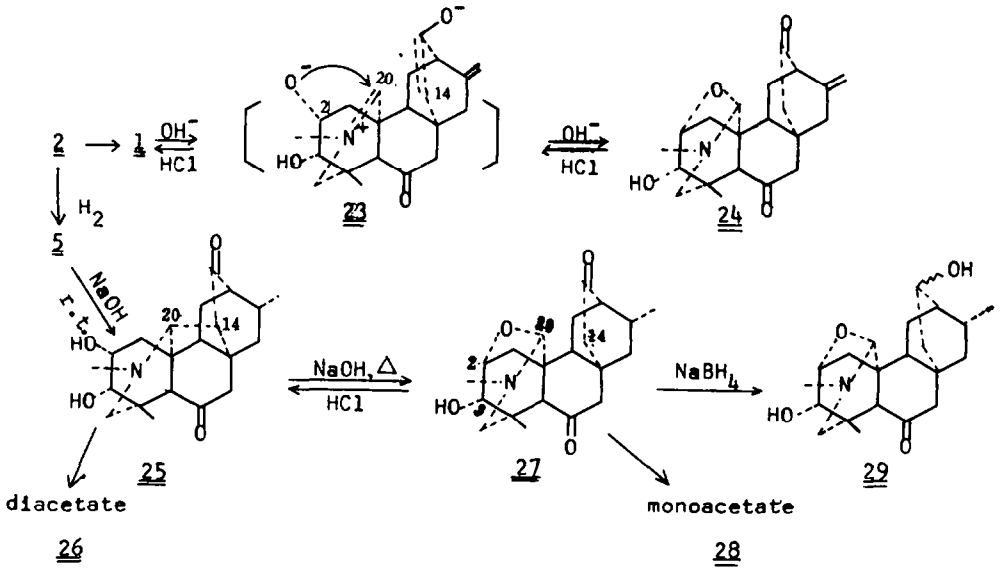
Trapping of the immonium by oxasolidine formation was then attempted. For this purpose, the N-methyl group has to be replaced by a hydroxyethyl group. Mercuric acetate[12] in aqueous acetic acid failed to bring about N-demethylation. The demethylation was accomplished by treatment of 2 with ethyl chloroformate[13] in the presence of large amounts of anhydrous potassium carbonate under rigorously anhydrous conditions. The demethylation product (20) has IR absorption at 1725 and 1750 cm^{-1}, the latter to be expected of a carbonate carbonyl[14]; an alternative structure with a simple replacement of the N-Me in 2 with $N-CO_2Et$ can be safely excluded by its ease of hydrolysis and the absence of the 1690 cm^{-1} band of the C-6 carbonyl. The yield of 20 was low and was not noticeably improved by the addition of NaI and

triethylbenzylammonium chloride(phase-transfer catalyst). Inadequate quantities of



20 and much less of 21 therefrom led to a halt of our endeavor toward the obtainment of 22, further prompted by the success of a much simpler approach to be described below.

It occurred to us that the C-2 axial hydroxy group of hetidine (1) itself is a built-in trap for the immonium ion. This was actually foreshadowed by the fact that saponification of 2 even at room temperature would give alongside of the expected 1 an additional faint spot with higher Rf value. This spot was later shown to be 24, whose dihydro counterpart (27) was more fully characterised.



Thus refluxing of 25 with 10% methanolic NaOH led to a partial conversion to 27. In the ^{1}H NMR spectrum of 27, a doublet at δ3.95 (J=5.7 Hz) and a singlet at δ3.22 are ascribed to the C-2 and C-3 protons, respectively, to be compared with the corresponding protons of 25 at δ3.94 (m) and 3.36(d, J=4.5). The change of splitting patterns is in accord with the conformational differences. Acetylation gave a diacetate (26) from 25 and a monoacetate (28) from 27, and the latter acetate displayed the expected downfield shift for the C-3 proton (to δ4.50).

The ^{13}C NMR data for 27 and 28 are shown in Table 1. As expected, there are only minor differences mainly restricted to the vicinity of the C-3 function.

Conspicuous and definitive differences in the ^{13}C NMR data between 25 and 27 are concerned with C-14 and C-20. For 25 we have the respective values of 57.8 (d) and 45.6 (d)[5] and for 27, 53.2 (t) and 93.7 (d). Thus there is a change of multiplicity for C-14 and a marked change of shift for C-20.

The ^{13}C NMR spectra of 1, 2, 5, 6, 9, 10, 20, 25 and a few other hetidine-type

compounds incident to this research will be reported elsewhere[5].

Table 1. ^{13}C NMR data of 27 and 28 (in $CDCl_3$)

carbon	1	2	3	4	5	6	7	8	9	10	11	12
27[a]	44.9	76.5	78.8	38.9	57.4	204.5	52.4	40.7	44.7	43.5	26.6	49.9
28[b]	40.9	74.5	80.4	39.4	57.4	203.9	52.7	40.0	44.9	43.7	27.1	50.3

carbon	13	14	15	16	17	18	19	20	NCH_3	$CO—CH_3$	
27	214.7	53.2	29.7	30.4	22.6	22.9	48.9	93.7	42.0		
28	214.8	53.6	30.2	30.8	21.6	23.1	45.4	93.9	42.4	171.3	21.6

[a]At 22.63 MHz(FX-90Q). [b]At 25.1 MHz(FX-100).

Treatment of 27 with $NaBH_4$ gave 29. The C-13 ketonic carbonyl now became less hindered and hence vulnerable to reduction in contrast to the case of 14. The ^1H NMR data revealed that the C-16 methyl and the C-20 proton of 29 were shifted down-field by 0.28 and 0.2 ppm, respectively, as compared with 27, indicative of the shielding effect of the implicated C-13 ketonic carbonyl and thus correborating further the α-configuration of the C-16 methyl group.

Treatment of 24 and 27 (atisine-type) with hydrochloric acid causes facile conversion to 1 and 25 (hetidine-type), respectively.

The cleavage and regeneration of the C(14)-C(20) bond might have some significance in connection with the biogenesis of diterpenoid alkaloids as well[15].

Finally, the successful participation of the 2α-hydroxy group to trap the immonium ion involves a 5-exo-trigonal process favored by the Baldwin rule of ring closure[16]. The disfavored 5-endo-trigonal process of 21 → 22 is thus worthy of further examination. It should be noted, however, that the "disfavored" oxazolidine ring closure is a commonplace process in diterpenoid alkaloids, presumably because of the less stringent requirement of the immonium ion to ring closure and the absence of other competitive reactions (for example, conversion of 21 to 22 might well be defeated by a preponderant recombination of the enolate with the immonium).

EXPERIMENTAL

Mps were taken on a Kofler hot stage, uncorrected. IR spectra were recorded on a Perkin-Elmer 399B instrument. MS were taken with VG ZAB-2F spectrometer. NMR spectra were measured in $CDCl_3$ with TMS internal standard on JEOL FX-90Q and FX-100 instruments. Tlc silica G and preparative tlc silica GF 254 were manually plated using water or 0.5% aq. NaOH. The solvent systems used were s-1 ($CHCl_3$/MeOH 9:1) and s-2 ($CHCl_3$/MeOH 95:5), with iodine or modified Dragendorff's reagent for spot allocation.

Hydrogenation of episcopalidine (2). To a suspension of PtO_2 (10 mg) in HOAc(2 ml), presaturated with hydrogen, was added 2(10 mg) in HOAc(3 ml). Hydrogenation was performed for 2.5 h. Evaporation of the filtered soln gave a residue which was taken to dryness again after addition of water. Treatment with aq. ammonia and evaporation gave a white solid showing one spot (solvent system s-1) on tlc. HRMS m/z 505.2477 ($C_{30}H_{35}NO_6$ reqs 505.2464) and other spectral data showed the product to be 5.

Hydrogenation under 4.5 atm of H_2 was performed on 2(145 mg) in HOAc(30 ml) with PtO_2 (100 mg) for 29 h. Evaporation of the filtrate gave a colorless residue(280 mg) showing two main spots on tlc (s-1). Preparative tlc (s-1) gave 6(80 mg) and 7 (8 mg).

Recrystallisation of 6 from EtOH gave colorless needles, m.p. 229-231°C. ^1H NMR (90 MHz), 0.96(3H, d, J=7, 16-CH_3), 1.50(3H, s, 4-CH_3), 2.10(3H, s, OAc), 2.50(3H, s, N-CH_3), 2.82(1H, s, 20-H), 2.56, 3.22(2H, ABq, J=12, 19-H_2), 4.62(1H, d, J=4.3, 3-H), 5.42(1H, dt, J=4.3 & 2, 2-H). HRMS m/z 511.2883($C_{30}H_{41}NO_6$ reqs 511.2934).

Compound 7, IR 3400(OH), 1744(C=O) cm^{-1}. ^1H NMR(90 MHz), 0.95(3H, d, J=7, 16-CH_3), 1.50(3H, s, 4-CH_3), 1.95(3H, s, OAc), 2.12(3H, s, N-CH_3), 2.98(1H, s, 20-H), 3.20 (1H, d, J=12, 19-H), 4.43(1H, m, 6-H), 4.80(1H, d, J=4.5, 3-H), 5.40(1H, m, 2-H). MS m/z 513(5%), 496(10), 386(100), 326(12), 286(2), 258(1).

Hydrogenation in EtOH at 3 atm. gave 5 as the main product.

Iodoperization. To a soln of 2(10 mg) in MeCN(3 ml) were added Me_3SiCl(1 ml) and 1.5 g of dry NaI, and the whole stirred at r.t. for 4 h. Evaporation gave a residue which

was partitioned between aq. ammonia and $CHCl_3$. The organic layer was washed twice with saturated Na_2CO_3 and dried over anhyd. K_2CO_3. Stripping of solvent gave a light yellow solid which was separated by preparative tlc(s-1) into three compounds. The middle one was identified as 9, i.e., the HCl salt of 2.

The upper one was identified as 10, ^1H NMR(90 MHz), 1.61(3H, s, 4-CH_3), 1.82(3H, d, J=1.2, 16-CH_3), 2.05(3H, s, OAc), 2.75(3H, s, N-CH_3), 3.18(1H, s, 20-H), 3.32, 3.72(2H, ABq, J=12, 19-H_2), 4.93(1H, d, J=4.5, 3-H), 5.55(1H, dt, J=4.5 & 2, 2-H), 5.38(1H, s, 15-H), 7.50, 7.55; 7.97(5H, m, ArH). HRMS m/z 503.2308($C_{30}H_{33}NO_6$ reqs 503.2308).

The lower one was identified as 11, ^1H NMR(90 MHz), 1.40(3H, s, 4-CH_3), 2.80(3H, s, N-CH_3), 4.36(1H, m, 2-H), 4.90(1H, d, J=5, 3-H), 5.65(1H, s, 15=CH-), 7.58, 7.62, 8.10(5H, m, ArH). MS m/z 461(M^+, 2), 340(M-C_6H_5COO, 5), 282(2), 279(7), 254(2), 185 (25), 112(21).

Hetidine(1), 30 mg, was mixed with TsOH(50 mg)and Ac_2O(2 ml) and heated on the steam bath for 1 h. The cooled reaction mixture was treated with ice-water, basified with ammonia and extracted with $CHCl_3$(3×20 ml). The $CHCl_3$ extracts after washing and drying furnished ca. 80 mg of residue which was processed with preparative tlc. The lower band was hetidine diacetate[5], and the upper band was 12, HRMS m/z 441.2192 ($C_{26}H_{31}NO_4$ reqs 441.2151). ^1H NMR(90 MHz), 1.54(3H, s, 4-CH_3), 1.86(3H, d, J=1.2, 16-CH_3), 2.03, 2.10(3H each, s, OAc), 2.54(3H, s, N-CH_3), 3.14(1H, d, J=12, 19-H), 4.68(1H, d, J=4.5, 3-H), 5.42(1H, dt, J=4-5 & 2.2, 2-H), 5.58(1H, s, 15-H).

Sodium borohydride reduction of 2. The HCl salt of 2(78 mg) was prepared by passing HCl gas into a soln of 2 in Et_2O. To this solid was added $NaBH_4$(145 mg) and DMF (2 ml) and the whole stirred for 5 h at r.t. After storage overnight in a refrigerator, the reaction mixture was neutralised with 6 N HCl and aspirated to dryness. Basification and extraction with $CHCl_3$ gave 70 mg of white solid. Preparative tlc (s-2) gave two products, 10(20 mg) and 14(17 mg).

Compound 10 was characterised by MS(M^+ 503) and comparison of tlc and IR with a specimen obtained above.

Compound 14. IR 3400(OH), 1750, 1729(C=O) cm^{-1}. ^1H NMR(90 MHz), 1.59(3H, s, 4-CH_3), 2.23(3H, s, OAc), 4.21(1H, br s, 6-H), 4.95(2H, br s, 17-CH_2), 5.07(1H, d, J=4.5, 3-H), 5.63(1H, m, 2-H). MS m/z 505(5), 384(100), 324(38), 284(2), 256(2), 105(47).

Ketalization of 2. A mixture of 2(120 mg) and TsOH(100 mg) in benzene(30 ml) was heated under reflux for 5.5 h, using a Dean-Stark water-separator. Treatment with saturated aq. $NaHCO_3$ and extraction with $CHCl_3$ gave 130 mg of residue. Preparative tlc(s-1) gave 15(ca. 20 mg) and A(80 mg) B(trace). A had MS mol. wt. 323 and B 365, yet to be characterized.

Compound 15, ^1H NMR(90 MHz), 1.38(3H, s, 4-CH_3), 1.66(3H, s, 16-CH_3), 2.32(3H, s, N-CH_3), 3.34(1H, d, J=4.5, 3-H), 4.16(1H, m, 2-H). HRMS m/z 463.2532 ($C_{25}H_{37}NO_7$ reqs 463.2570).

Compound 9(110 mg) was dissolved in glycol(0.2 ml) and glacial HOAc(4 ml). BF_3-Et_2O(0.2 ml) was then added under ice-cooling, and the mixture left at r.t. for 15 min. The mixture was cooled again and basified, and extracted with $CHCl_3$ to give 152 mg of colorless solid. Preparative tlc gave 10(40 mg), 2(ca. 50 mg) and a few mg of 16 with MS m/z 521(M^+, 4) 464(5), 400(M-C_6H_5COO, 38), 382(4), 340(12). The structure of 16 was only tentative.

N-Demethylation of 2. A soln of 2(150 mg) in anhyd. benzene(6 ml) was mixed with anhyd. K_2CO_3 (214 mg), freshly dist. ethyl chloroformate(3 ml) and a few drops of $CHCl_3$. The whole was refluxed for 5 h. The usual work-up and preparative tlc (s-2) furnished recovered 2(ca. 100 mg), isomerization product 10(ca. 20 mg) and 20(35 mg). The recovered 2 was originally present in the reaction mixture as the quaternary methochloride of 20, which was very susceptible to hydrolysis[5].

Compound 20, IR, 1750, 1725(C=O); 1600, 1470, 710(C_6H_5COO); 1270, 915(=CH_2) cm^{-1}. ^1H NMR(90 MHz), 1.18(3H, s, 4-CH_3), 1.20(3H, t, J=7.2, OCH_2CH_3), 1.98(3H, s, OAc), 3.40(1H, d, J=6, 20-H), 3.02, 3.52(2H, ABq, J=12, 19-H_2), 4.12(2H, q, J=7.2, OCH_2CH_3), 4.78, 4.92(1H each, br s, =CH_2), 5.04(1H, d, J=5.4, 3-H), 5.52(1H, m, 2-H), 7.58-8.04(5H, m, ArH). HRMS m/z 561.2374($C_{32}H_{35}NO_8$ reqs 561.2362).

N-Hydroxyethylation. Compound 20(ca. 30 mg) was dissolved in EtOH(3 ml) containing 30-35% ethylene oxide, and allowed to stand overnight at r.t. The usual work-up gave a yellowish solid which agreed with structure 21 by its MS behavior, m/z 533 (M^+, 2), 502(90), 482(55), 460(18), 440(19), 412(3), 382(4), 356(63), 105(100).

Interconversion of 1 and 24. A soln of 1(20 mg) in DMF(4 ml) was heated in an oil bath at 140°C for 4 h, cooled, 20 mg of NaH added, and heated again for 80 min. Preparative tlc(s-1) gave ca. mg of 24, MS m/z 358(M+1, 60), 357(M^+, 72), 340(12), 328 (22), 322(3), 313(5), 300(4), 254(5), 208(31). In comparison, 1 has normal M+1 intensity, among other conspicuous differences.

Reflux in 10% methanolic NaOH also caused the formation of 24 from 1.

Compound 24, when dissolved in a small amount of acetone, acidified to pH 1-2 with conc. HCl and allowed to stand for several h, underwent almost complete reversion to 1 as shown by tlc(s-1).

Preparation of 25 and its conversion to 27. Compound 5(385 mg) was dissolved in 60 ml of 1o% methanolic NaOH and allowed to stand for 90 min. Tlc(s-1) showed complete transformation to 25 along with trace amounts of 27. The soln was then refluxed for 2h, aspirated to near dryness and extracted with $CHCl_3$ to give 236 mg of white foam

which was separated by preparative tlc(s-1). There were thus obtained 25(187 mg) and 27(47 mg).

Compound 25, colorless prisms from acetone-methanol, m.p. 202-210°C. HRMS m/z 359.2108($C_{21}H_{29}NO_4$ reqs 359.2096). MS m/z 359(10), 342(38), 330(10), 324(20), 316(1), 314(6), 284(2), 276(11), 256(3), 208(12), 182(11). IR(film), 3457-3359(OH), 1715(C=O) cm⁻¹. ^{1}H NMR(100 MHz), 0.94(3H, d, J=7, 16-CH_3), 1.22(3H, s, 4-CH_3), 2.54(3H, s, N-CH_3), 2.92(1H, d, J=12, 19-H), 3.36(1H, d, J=4.5, 3-H), 3.94(1H, m, 2-H).

Compound 27, colorless powder, tlc showing one spot. HRMS m/z 359.2119($C_{21}H_{29}NO_4$ reqs 359.2096). MS m/z 359(82), 342(8), 330(38), 316(10), 315(11), 300(6), 284(4), 272(5), 256(4), 208(18), 112(55), 96(100). ^{1}H NMR(90 MHz), 0.94(3H, d, J=7, 16-CH_3), 1.40(3H, s, 4-CH_3), 2.32(3H, s, N-CH_3), 2.52, 2.80(2H, ABq, J=11, 19-H_2), 3.20(1H, s, 3-H), 3.95(1H, d, J=5.7, 2-H), 4.30(1H, s, 20-H).

Diacetate 26. Compound 25(ca. 100 mg) was allowed to stand overnight in Ac_2O(2 ml) and pyridine(2 ml). Preparative tlc(s-2) gave 26(ca. 10 mg), MS m/z 443(M^+, 11) 384(100), 359(6), 342(11), 324(38), 296(6), 284(5), 256(3). ^{1}H NMR(100 MHz), 0.92(3H, d, J=7, 16-CH_3), 1.48(3H, s, 4-CH_3), 2.00, 2.09(3H each, s, OAc), 2.50(3H, s, N-CH_3), 3.22(1H, d, J=12, 19-H), 4.60(1H, d, J=5, 3-H), 5.34(1H, m, 2-H).

Monoacetate 28. Compound 27(60 mg) was allowed to stand overnight in Ac_2O(2 ml) and pyridine(1.5 ml). Preparative tlc(s-2) gave 28(34 mg), HRMS m/z 401.2196($C_{23}H_{31}NO_5$ reqs 401.2202). MS m/z 401(48), 372(27), 358(10), 342(22), 341(12), 312(12), 284(8), 256(6), 250(10), 134(14), 96(66), 43(100). ^{1}H NMR(100 MHz), 0.94(3H, d, J=7, 16-CH_3) 1.28(3H, s, 4-CH_3), 2.12(3H, s, OAc), 2.32(3H, s, N-CH_3), 2.80(2H, br s, 19-H_2), 3.97(1H, d, J=5, 2-H), 4.28(1H, s, 20-H), 4.50(1H, s, 3-H).

Reduction of 27. Compound 27(26 mg) was dissolved in MeOH(10 ml) and treated with $NaBH_4$(20 mg). One drop of H_2O was added and the reaction mixture allowed to stand overnight, whereupon tlc indicated the complete consumption of 27. Tlc showed five spots, the one with the highest Rf being isolated(ca. 7 mg) and identified as 29, MS m/z 361(M^+, 24), 344(5), 332(16), 286(2), 258(2). ^{1}H NMR(100 MHz), 1.22(3H, d, J=7, 16-CH_3), 1.38(3H, s, 4-CH_3), 2.34(3H, s, N-CH_3), 2.50, 2.74(2H, ABq, J=11, 19-H_2), 3.22(1H, s, 3-H), 3.92(1H, d, J=5, 2-H), 4.00(1H, m, 13-H), 4.50(1H, s, 20-H).

Reversion of 27 to 25. A soln of 27(5 mg) in acetone(2 ml) was acidified with conc. HCl to pH 1-2 and allowed to stand for 5 h. The usual work-up gave a colorless gum identified as 25 by tlc(s-1 & s-2), MS and IR.

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