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HETISINE DERIVATIVES PART 3. REARRANGEMENT OF 11-ACETYL-2,13-DIDEHYDROHETISINE AND 13-DEHYDRO-2,11-DIACETYLHETISINE

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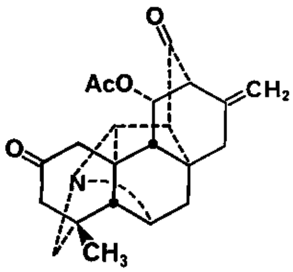
Abstract — *Heating 11-Acetyl-2,13-didehydrohetisine (1) with aqueous potassium carbonate in methanol afforded a rearrangement product,* $C_{20}H_{25}NO_4$*, mp 313-315°C. The structure of this compound has been shown to be 4 by an X-ray crystallographic study. Mild treatment of 13-dehydro-2,11-diacetylhetisine (5) with base gave 2-acetyl-13-dehydro-11-*<u>*epi*</u>*hetisine (7). Under refluxing conditions, 5 gave the rearrangment compound 8. The structure of 8 was assigned by chromium-trioxide-pyridine oxidation to give 4.*

We have described in an earlier communication[1] the preparation of 11-acetyl-2,13-didehydrohetisine (1) by Sarett oxidation of 11-acetylhetisine (2). The compound (2) was prepared by mild (-6°C) or vigorous (reflux) acetylation of hetisine (3) followed by chromatographic separation. When 1 was heated under reflux with aqueous potassium carbonate in methanol, a crystalline compound, $C_{20}H_{25}NO_4$, mp 313-315°C, ms: m/z 343 was obtained. The infrared spectrum showed the presence of a hydroxyl group (3070 cm^{-1}), a keto group (1710 cm^{-1}) and a lactone moeity (1720 cm^{-1}). The ^1H nmr spectrum indicated two three-proton singlets at δ 1.15 and 1.41 attributed to the tertiary C(4)-methyl and a tertiary methyl group attached to an oxygen function, respectively. The singlet at δ 2.78 can be assigned to C(9)-H and the signals at δ 3.10-3.50 (3H, multiplet) can be attributed to the overlap of the C(6), C(13) and C(20) protons. In addition, the absence of the



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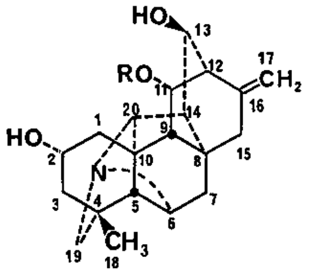
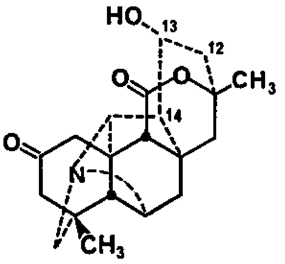


2 R = Ac

3 R = H



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olefinic protons of the C(17)-methylene group usually located at δ 5.00 strongly suggested that this compound is a rearranged product.

The rearranged product formed a crystalline perchlorate salt as colorless prisms ($C_{20}H_{25}NO_4.HClO_4$, mp 305-306°C) suitable for X-ray crystal structure determination. The cell dimensions determined by least squares fit of 25 strong reflections were as follows: a = 841.66(2), b = 841.66(2), c = 2846.94(6) pm, $\alpha = \beta = \gamma = 90.00(3)°$. Examination of the systematic absences (oko k = 4n+1) and consideration of the equivalence of the a- and b- axes indicated the tetragonal space group $P4_1$.[2] The calculated density was 1.468 g/cm^3, the cell volume 2.0175 x 10^9 pm^3 and z = 8. A total of 4540 reflections were measured, of which 4138 were above the I>3 (I) threshold. Of these, 2734 unique reflexions were used in the least square refinement. Crystal exposure time was 52.8 h and while the net change in control reflection intensity was only 1.2%, the data were corrected for anisotropic decay. The initial normalization routine selected the 374 strongest reflections for MULTAN (minimum E value of 1.407) and showed an unexceptional distribution of Es. From these data MULTAN found 12423 phase relationships and produced 28 distinct phase sets. Four of these sets were developed (EXFFT and DMS) and one (set 19, cfom 2.927) consisted of an intricate reticulation of peaks having substantial, although incorrect, structure; this set was chosen for attempted refinement. Full-matrix least square refinement (LSFM) of peak coordinates suspected of corresponding to eighteen atoms (the most intense peak presumed to be chlorine, the others carbons) utilizing isotropic temperature factors resulted in an R = 0.316 after seven cycles. A difference map (DIALOG, FOUR) revealed an additional five atoms, and after four more LSFM cycles (R = 0.249) another difference map was produced. At this juncture, four additional atoms could be discerned and four atoms were relabeled as oxygens. Most of the structure was now correctly interpretable, and atoms were renamed appropriately. The positions of the two remaining perchlorate oxygens were computed and incorporated into the structure file (HYDRO, ATOMS). A third difference Fourier revealed the remaining non-hydrogens, and permitted correct assignment of all atoms. Eight additional refinement cycles decreased R_w to 0.086 after adoption of a weighting scheme and conversion to anisotropic temperature factors. A difference map now revealed sixteen hydrogen atoms, including the hydroxyl and ammonium protons and the positions of ten others were calculated (HYDRO). Symmetry operations were applied to transform all coordinates to the same asymmetric unit (ATOMS). Five final LSFM cycles resulted in an unshifting $R(R_w)$ = 0.044 (0.055). A final difference map showed no residual peaks. Table 1 gives the final atomic parameters; bond lengths are given in Table 2.

Figure 1 shows an ORTEP drawing of the perchlorate salt of the rearrangement product (**4**) (H^+, $ClO_4^{\ominus}$ are not shown) and Figure 2 shows an ORTEP plot of the **4** perchlorate unit cell. The interesting feature of this structure is the skeletal rearrangement which occurred, resulting in the C-ring lactone formation under the alkaline hydrolysis conditions.

13-Dehydro-2,11-diacetylhetisine (**5**) was prepared by Sarett oxidation of 2,11-diacetylhetisine.[1] Treatment of **5** with methanolic potassium carbonate at 25°C gave a mixture of products from which the normal deacetylation product (**6**) could not be isolated in a pure state. However, an isomeric compound was obtained by preparative tlc which has been shown to be 2-acetyl-13-dehydro-11-*epi*hetisine (**7**). The structure assignment of **7** was based on its ^1H nmr spectrum which showed the C(11)- αproton as a doublet at δ 4.14 with a coupling constant of 5.1 Hz.

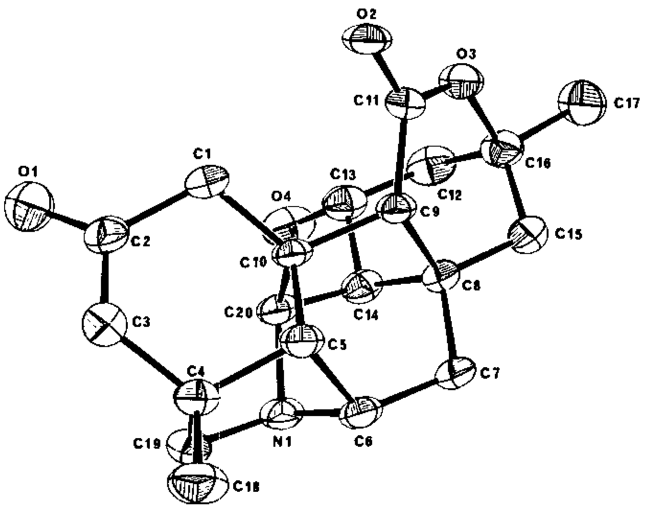
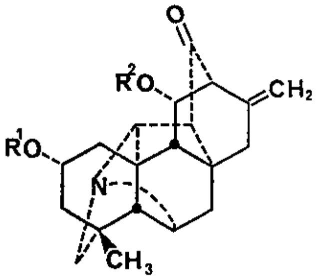
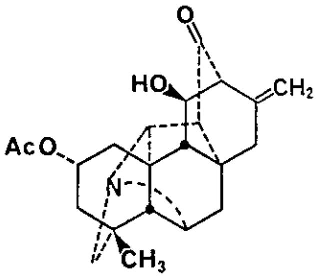


Figure 1. ORTEP Plot of Compound **4**·Perchlorate ($HClO_4$ not shown).



5 $R^1 = R^2 = Ac$

6 $R^1 = Ac$; $R^2 = H$



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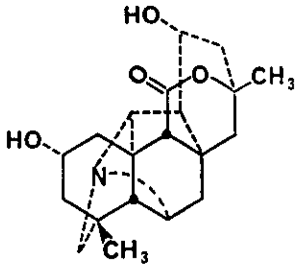

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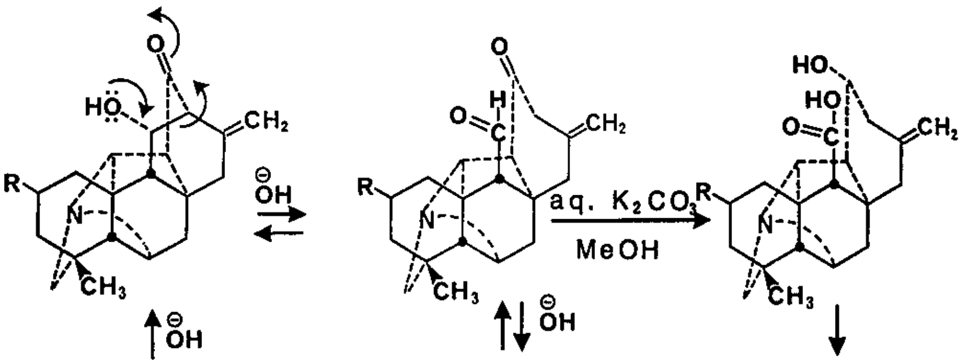
This small coupling constant indicated a β-hydroxyl group at C(11). An α-hydroxyl group at C(11) shows a doublet with a large coupling (J = ~ 9.0 Hz) due to the C(11)-β proton.[3] A smaller coupling is in agreement with a dihedral angle of ~ 120° between C(11)-α and C(9)-β protons. The coupling relation between C(11)-αH and C(9)-βH was shown by irradiation of C(11)-αH (δ 4.14), when the doublet of C(9)-βH at δ 3.11 (J = 5.1 Hz) became a singlet. Reaction of **5** with aqueous methanolic potassium carbonate under refluxing conditions gave the rearrangement product (**8**). This structure assignment was assigned by oxidation of **8** with chromium trioxide-pyridine to afford compound **4**.



1 or 5 **7** **4 or 8**

A plausible mechanism for the formation of the rearrangements products **4** and **8** is shown above. The first step appears to be the hydrolysis of the C(11)-acetyl group under mild (25°C) conditions. The C(11)-acetyl group appears to be more susceptible to hydrolysis than the C(2)-acetyl function. The hydrolysis is accompanied by a reverse aldol condensation as is evident from the formation of the C(11)-epimer on work-up of the reaction (vide supra). Under refluxing conditions, a Cannizzaro-like process, involving attack of hydroxide on the formyl moeity followed by intramolecular hydride transfer, takes place.[4,5] On work up under mildly alkaline conditions, the rearranged lactone (**4**) or (**8**) is obtained.

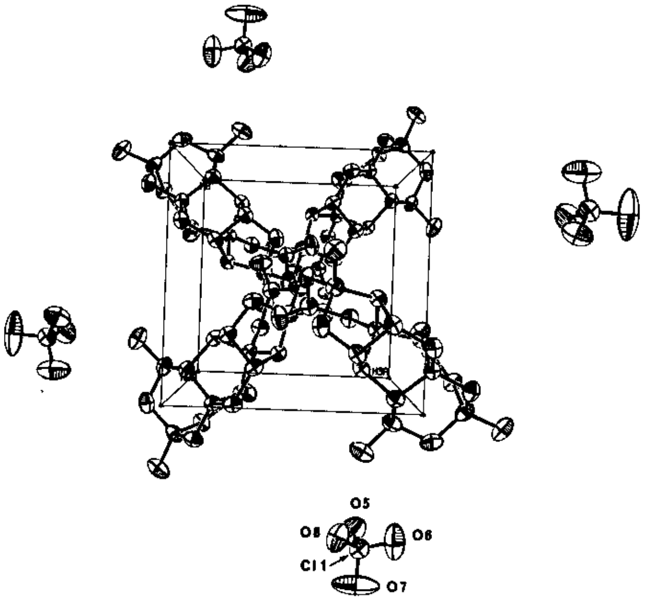


Figure 2. ORTEP Plot of **4**·Perchlorate Unit Cell

Table 1. Positional Parameters and Their Estimated Standard Deviations

Atom	x	y	z	B(A2)
CL1	0.8273(1)	-0.7096(1)	0.489	4.11(1)
O5	0.9843(4)	-0.6661(7)	0.5034(2)	9.9(1)
O6	0.817(1)	-0.8724(4)	0.4891(2)	12.8(2)
O7	0.7961(5)	-0.6432(5)	0.4450(1)	7.52(9)
O8	0.7267(4)	-0.6493(5)	0.5249(1)	6.65(8)
C1	0.3466(3)	0.2798(3)	0.5797(1)	2.59(5)
C2	0.3912(4)	0.4468(3)	0.5946(1)	2.72(5)
C3	0.5080(4)	0.4592(3)	0.6343(1)	3.05(5)
C4	0.4733(3)	0.3500(3)	0.6762(1)	2.67(5)
C5	0.4327(3)	0.1780(3)	0.6617(1)	2.35(4)
C6	0.3339(3)	0.1184(3)	0.70314(9)	2.53(5)
C7	0.2481(4)	-0.0411(3)	0.69675(9)	2.68(5)
C8	0.1562(3)	-0.0485(3)	0.65045(9)	2.34(4)
C9	0.2731(3)	-0.0033(3)	0.61133(9)	2.21(4)
C10	0.3060(3)	0.1758(3)	0.62209(9)	2.10(4)
C11	0.2212(3)	-0.0527(3)	0.56197(9)	2.39(4)
C12	-0.1378(4)	-0.0658(4)	0.5965(1)	3.55(6)
C13	-0.0646(3)	0.0972(4)	0.6061(1)	2.94(5)
C14	0.0398(3)	0.0927(3)	0.6497(1)	2.55(5)
C15	0.0783(4)	-0.2068(3)	0.6404(1)	3.08(5)
C16	-0.0127(4)	-0.1955(4)	0.5946(1)	3.05(5)
C17	-0.0796(5)	-0.3537(4)	0.5792(2)	4.49(7)
C18	0.6163(4)	0.3545(4)	0.7095(1)	3.76(6)
C19	0.3187(1)	0.3995(3)	0.7026(1)	2.98(5)
C20	0.1536(3)	0.2324(3)	0.65014(9)	2.32(4)
O1	0.3388(3)	0.5634(3)	0.5746(1)	4.12(5)
O2	0.2967(3)	-0.0157(3)	0.52737(7)	3.16(4)
O3	0.0999(2)	-0.1507(2)	0.55616(7)	2.85(4)
O4	-0.1832(3)	0.2148(3)	0.61336(9)	4.03(5)
N1	0.2158(3)	0.2542(3)	0.69940(8)	2.53(4)
H1A	0.242(5)	0.285(5)	0.558(2)	5*
H1B	0.449(5)	0.230(5)	0.563(2)	5*
H3A	0.519(5)	0.569(4)	0.641(2)	5*
H3B	0.616(5)	0.423(5)	0.622(2)	5*
H5	0.530(5)	0.105(5)	0.657(2)	5*
H6	0.398(5)	0.135(5)	0.736(2)	5*
H7A	0.178(5)	-0.055(5)	0.721(2)	5*
H7B	0.342(5)	-0.121(5)	0.700(2)	5*
H9	0.367(5)	-0.055(5)	0.614(2)	5*
H12A	-0.230(5)	-0.085(5)	0.619(2)	5*
H12B	-0.207(5)	-0.052(5)	0.563(2)	5*
H13	0.008(5)	0.138(5)	0.575(2)	5*

Table 1 - continued

Atom	x	y	z	B(A2)
H14	-0.037(5)	0.101(5)	0.679(2)	5*
H15A	0.010(5)	-0.231(5)	0.663(2)	5*
H15B	0.159(5)	-0.298(4)	0.635(2)	5*
H17A	0.005(5)	-0.445(5)	0.576(2)	5*
H17B	-0.156(5)	-0.346(5)	0.546(2)	5*
H17C	-0.143(5)	-0.398(5)	0.602(2)	5*
H18A	0.625(5)	0.478(5)	0.719(2)	5*
H18B	0.716(5)	0.332(5)	0.691(2)	5*
H18C	0.595(5)	0.276(5)	0.737(2)	5*
H19A	0.260(5)	0.501(5)	0.687(2)	5*
H19B	0.338(5)	0.420(5)	0.737(2)	5*
H20	0.100(5)	0.334(5)	0.639(2)	5*
H21N	0.149(5)	0.260(5)	0.719(2)	5*
H220	-0.217(5)	0.242(5)	0.586(2)	5*

Starred atoms were refined isotropically.

Anisotropically refined atoms are given in the form of the isotropic equivalent thermal parameter defined as: (4/3) * [a2*B(1,1) + b2*B(2,2) + c2*B(3,3) + ab(cos gama)*B(1,2) + ac(cos beta)*B(1,3) + bc(cos alpha)*B(2,3)]

Table 2. Bond Distances in Å

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
CL1	O5	1.429(3)	C5	H5	1.03(4)	C12	H12A	1.02(4)
CL1	O6	1.373(3)	C6	C7	1.535(3)	C12	H12B	1.12(4)
CL1	O7	1.405(3)	C6	N1	1.518(3)	C13	C14	1.523(3)
CL1	O8	1.415(3)	C6	H6	1.09(4)	C13	O4	1.421(3)
C1	C2	1.515(3)	C7	C8	1.529(3)	C13	H13	1.13(4)
C1	C10	1.530(3)	C7	H7A	0.93(4)	C14	C20	1.516(3)
C1	H1A	1.08(4)	C7	H7B	1.04(4)	C14	H14	1.05(4)
C1	H1B	1.07(4)	C8	C9	1.534(3)	C15	C16	1.513(3)
C2	C3	1.501(3)	C8	C14	1.540(3)	C15	H15A	0.88(4)
C2	O1	1.218(3)	C8	C15	1.513(3)	C15	H15B	1.04(4)
C3	C4	1.535(3)	C9	C10	1.563(3)	C16	C17	1.511(3)
C3	H3A	0.95(3)	C9	C11	1.529(3)	C16	O3	1.497(3)
C3	H3B	1.02(4)	C9	H9	0.91(4)	C17	H17A	1.05(4)
C4	C5	1.543(3)	C10	C20	1.584(3)	C17	H17B	1.15(4)
C4	C19	1.559(3)	C11	O2	1.213(3)	C17	H17C	0.91(4)
C4	C18	1.532(3)	C11	O3	1.323(3)	C18	H18A	1.07(4)
C5	C6	1.528(3)	C12	C13	1.529(4)	C18	H18B	1.00(4)
C5	C10	1.552(3)	C12	C16	1.518(4)	C18	H18C	1.04(4)

Table 2 - continued

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
C19	N1	1.501(3)	N1	H21-N	0.80(4)	H17B	H17C	1.66(6)
C19	H19A	1.08(4)	H3A	H3B	1.58(5)	H19A	H19B	1.71(5)
C19	H19B	1.02(4)	H7A	H7B	1.61(5)	H18A	H18B	1.65(5)
C20	N1	1.508(3)	H12A	H12B	1.62(5)	H18B	H18C	1.71(5)
C20	H20	1.01(4)	H15A	H15B	1.58(5)			
O4	H22-O	0.85(4)	H17A	H17C	1.50(5)			

Numbers in parentheses are estimated standard deviations in the least significant digits.

EXPERIMENTAL

Melting points were taken on a Thomas-Kofler hot stage fitted with a microscope and are corrected. ^1H Nmr spectra were determined in $CDCl_3$ with TMS as an internal standard on a Varian EM-390 spectrometer. ^{13}C Nmr spectra were run in $CDCl_3$ solutions on a JEOL FX-60 or FX-90 Q spectrometer. Mass spectra were recorded on a Finnegan Quadrupole 4023 spectrometer.

Hydrolysis of 13-Dehydro-2,11-diacetylhetisine (5) to 2-Acetyl-13-dehydro-11-*epi*hetisine (7) — A solution of 13-dehydro-2,11-diacetylhetisine (**5**, 25 mg) in 5% aqueous methanol (2 ml) was stirred with potassium carbonate (20 mg) at 25°C for 1.5 h. Usual work up gave a residue consisting of a mixture of two major closely moving compounds as seen on tlc (silica gel). Separation of the two major compounds on a thick layer tlc plate (10 cm x 20 cm, 3 mm thick silica gel) gave (**7**, 3 mg); ms: M^+ m/z 369 ($C_{22}N_{27}NO_4$) (10%), 354(2), 340(75), 310(15), 280(30), 43(100); ^1H nmr: δ 1.04 (3H, *s*, C(4)-CH_3), 2.07 (3H, *s*, OAc), 3.11 (1H, *d*, J = 5.1 Hz, C(9)-αH), 4.14 (1H, *d*, J = 5.1 Hz, C(11)-αH), 5.08 (2H, br*s*, C=CH_2), 5.21 (1H, br*m*, w1/2 = 10.3 Hz, C(2)-βH).

Rearrangement of 13-Dehydro-2,11-diacetylhetisine (5) to 8 — A solution of 13-dehydro-2,11-diacetylhetisine (**5**, 100 mg) in methanol (2 ml), water (0.1 ml) and potassium carbonate (50 mg) was stirred at 25° for 46 h and then heated under reflux for 2 h. The solution was evaporated under reduced pressure, washed with water (10 ml) and the residue collected (71 mg); ms: M^+ 345 ($C_{20}H_{27}NO_4$) (20%), 328(20), 177(50), 162(40), 43(100); ir (nujol): ν max 3360, 3060, 1720, 1460, 1375, 1322, 1300, 1290, 1272, 1240, 1220, 1200, 1170, 1160, 1120, 1100, 1065, 1055, 1035, 1010, 990, 970, 960, 940, 920, 900 cm^{-1}; ^1H nmr: δ 0.97 (3H, *s*, C(4)-CH_3), 1.37 (3H, *s*, C(16)-CH_3), 3.07-3.21 (2H, *m*, C(6)-H C(13)-H), 3.79 (1H, br*s*, C(20)-H), 4.22 (1H, br*m* w1/2 9.0 Hz, C(2)-βH).

Rearrangement of 11-Acetyl-2,13-didehydrohetisine (1) to 4 — A solution of 11-acetyl-2,13-didehydrohetisine (**1**, 40 mg) in methanol (2 ml) and water (0.1 ml) was heated under reflux with potassium carbonate (50 mg) for 3 h. The reaction mixture was evaporated under reduced pressure, the residue extracted with chloroform (3 x 50 ml), dried over sodium sulfate and the solvent removed under reduced pressure. Crystallization of the residue from ether afforded colorless needles, mp 313-315°C; ms: M^+ m/z 343(40%), 315(10), 300(15), 270(10), 178(30), 43(100); ir (nujol):

ν max 3070, 1720, 1710, 1455, 1370, 1330, 1300, 1285, 1270, 1205, 1210, 1175, 1155, 1125, 1110, 1080, 1052, 1020, 970, 945, 920, 898 cm^{-1}; ^{1}H nmr: δ 1.15 (3H, s, C(4)-CH$_3$), 1.41 (3H, s, C(16)-CH$_3$), 2.78 (1H, s, C(9)-H), 3.10-3.50 (3H, m, C(6), C(13) and C(20)-H); ^{13}C nmr: ppm 210.6 C(2), 168.9 C(11), 81.8 C(16), 73.4 C(13), 66.3 C(18), 65.7 C(19), 64.6 C(6), 62.2 C(9), 58.1 C(5), 57.3 C(12), 54.8 C(10), 50.2 C(3), 46.0 C(8), 44.2 C(14), 43.3 C(1), 42.4 C(4), 39.40 C(15), 38.2 C(7), 28.2 C(17), C(20).

Chromium Trioxide-pyridine Oxidation of (8) to **4** — Compound **8** (10 mg) in pyridine (2 ml) was stirred with Sarett reagent (100 mg CrO$_3$ in 1 ml pyridine) (0.3 ml) at 25° for 1.5 h. To the reaction mixture was added water (4 ml), 5% hydrochloric acid (3 ml) and the solution was extracted with ether (2 x 10 ml) and chloroform (8 x 10 ml). The aqueous layer was basified with aq. ammonia to pH 9.0 and extracted with chloroform (4 x 100 ml). The chloroform extract was dried over sodium sulfate and the solvent evaporated under reduced pressure to afford a residue (3 mg). Crystallization from ether gave colorless needles, mp 313-315°C, identical with **4** by comparison of tlc behavior and ir and ms spectra.

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