SYNTHESIS OF SOME QUINONES OF RELEVANCE TO A SYNTHETIC APPROACH TO AMPHIMEDINE. CRYSTAL STRUCTURE DETERMINATION OF 1-METHYLPYRIDO[4,3-g]QUINOLINE-4,5,10-TRIONE 5-N,N-DIISOPROPYLHYDRAZONE

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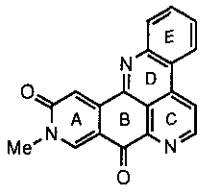
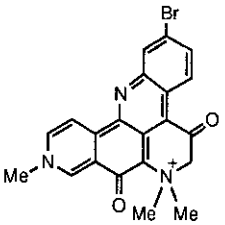
Abstract - Tricyclic quinones are formed by the intramolecular strong acid catalysed cycli-acylation of 2-(2-carboxyphenylcarbonyl)-1-methyl-4-pyridone and of 2-(4-methoxycarbonylpyridin-3-ylcarbonyl)-1-methyl-4-pyridone. Pyrido[4,3-g]quinoline-4,5,10-trione **6**, thus produced, gives the 5-imine on reaction with ammonia; this imine reacts with lithium diisopropylamide to produce the 5-diisopropylhydrazone of **6**.

Pentacyclic, cytotoxic amphimedine **1** was isolated[1] from an *Amphimedon* species of sponge collected near Guam. Subsequently, another sponge, a *Petrosia* species collected at Belize, yielded a substance petrosamine **2**,[2] which has the same skeleton as amphimedine, but at a different oxidation level. Three total syntheses of amphimedine have been described[3,4,5] the first two[3,4] of which employed an aza-Diels-Alder cycloaddition on a BCE-precursor (B-quinonoid) to produce the A ring. This, too, was to be the means for adding ring A in an approach[6] which reached a tetracycle having all rings, save A, completed. The third successful synthesis[5] proceeded *via* an ACDE intermediate generated from an initial aza-fluorene. We describe here an approach to the benzo[b]pyrido[4,3,2-de][1,8]phenanthroline system present in amphimedine in which a pyrido[4,3-g]quinoline-4,5,10-trione is to be an intermediate.

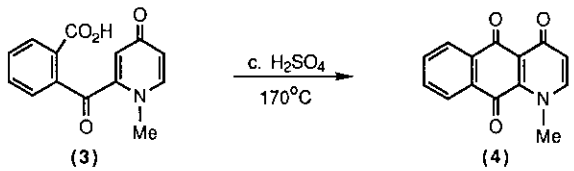


(1)



(2)

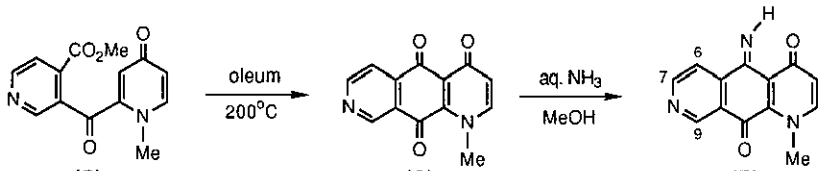
We have described[7] the 2-lithiation of 1-substituted 4-pyridones and the utilisation of these lithiated species for the production of 1,2-disubstituted 4-pyridones, for example reaction of 2-lithio-1-methyl-4-pyridone with phthalic anhydride produced keto acid **3**.



(3) (4)

Attempts to cyclise the acid chloride of **3**[7] were unsuccessful under a variety of conditions, in some cases resulting in de-acylation[8] and the reformation of 1-methyl-4-pyridone. However, treatment of **3** with concentrated sulphuric acid at 170°C yielded the tricyclic quinone **4** in 97% yield as an orange crystalline solid. The ring closure must have the character of an electrophilic intramolecular acylation (a cycli-acylation) of the pyridone, at its β-position. Although there seem to be no examples of intermolecular 4-pyridone acylations, two 3-alkylations have been described;[9,10] 4-pyrones have been C-3-acylated in good yields.[11] That no Hayashi rearrangement[12] occurs in the present cycli-acylation is consistent with the anticipation that initial ring-closing attack will occur only at the pyridone 3-position, or, viewing a portion of the pyridone as an enamide, at the β-carbon of this moiety.

The pyridyl keto ester **5**[7] was similarly cyclised to **6**, in 61% yield, the closure requiring the use of oleum at 200°C. The more vigorous conditions necessary in this case are presumably associated with the presence of protonated pyridine nitrogen in the ring whereon an acylium ion must form.



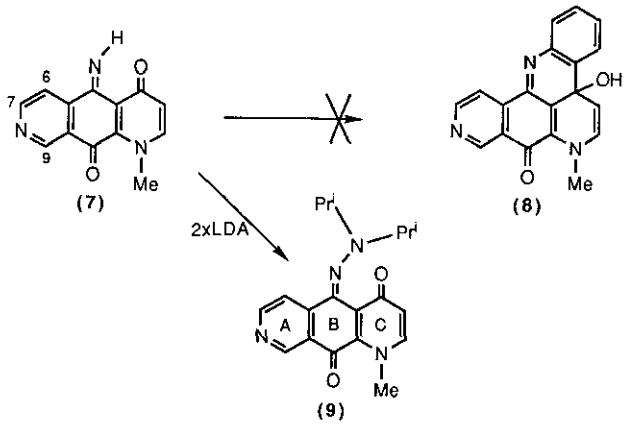
(5) (6) (7)

Reaction of quinone **6** with methanolic 35% aqueous ammonia at room temperature led to the regiospecific formation of a yellow quinone mono-imine **7** in quantitative yield, which by ^{1}H nmr analysis was shown to be a mixture, at least in solution, of the two geometrical isomers (only the major, Z isomer, **7**, shown) in a ratio of 5:1. Treatment of **7** with aqueous acid resulted in rapid hydrolysis and reformation of quinone **6**.

The regiochemistry of imine formation followed from a consideration of the ^{1}H nmr spectrum of the geometrically isomeric mixture : two exchangeable signals for the two N-hydrogens occurred at δ 14.60 and 14.48 (5:1), but only full, one-proton signals, a δ 9.42 singlet and a 9.05 doublet, J 5 Hz, were seen for the protons at C-9 and C-7 respectively. Doublets, J 5 Hz, at δ 8.50 and 7.92, in a ratio of 5:1 and

integrating together for one proton, correspond to the C-6 proton in different magnetic environments according to the geometry of the imine link, the major isomer, **7**, showing the deshielding effect of the adjacent nitrogen lone pair on the C-6-hydrogen.

This fortuitous synthetic result afforded an intermediate, **7**, in which the third nitrogen required for amphimedine had been installed; it seemed that it remained only to introduce the remaining benzenoid ring to complete the skeleton. Envisioning that a reaction of the anion of imine 7 with benzyne would be followed by intramolecular carbon-carbon bonding, and the formation of **8**, or a pyridinium salt to be derived by dehydration of this, the imine was treated with a mixture of lithium diisopropylamide (LDA) and bromobenzene (1:2:1) at -78°C; a deep purple colour was produced rapidly, and persisted as the reaction mixture was warmed to room temperature. Chromatographic isolation gave starting material and a red-purple crystalline material. Spectroscopic analysis of the new product immediately showed that no benzene moiety had been incorporated, and indeed we subsequently showed that this substance was produced (29%), with 60% recovery of starting material, when imine **7** was treated with two equivalents of LDA alone; the coloured product was not formed on treatment with only one equivalent of LDA. The structure of the isolated product was established, by X-ray crystallography, as 1-methylpyrido[4,3-g]quinoline-4,5,10-trione 5-N,N-di-isopropylhydrazone **9**.



The entirely unexpected, and extraordinary formation of a diisopropylhydrazone from an imine on treatment with LDA seems to be totally unprecedented. Not the least surprising aspect is the geometry of the imine link in **9**, which intuition would have suggested to be the lesser thermodynamically stable of the possible geometrical isomers.

Ring A and its associated substituents C1 and C8 (in this paragraph the atom numbers refer to the Figure)

are essentially planar. The other two rings take up shallow boat conformations such that the two ring distortions are *trans* to one another. The eight torsion angles involved in this arrangement, typified by O15-C3-C4-C5, have a mean value of 162.5° (of the modulus) whilst individual values vary between -156.7° and -171.5°. The arrangement not only relieves what would otherwise be a close approach between N18 and O15 and between O17 and C16, but together with the torsional rotation about the formal double bond C1-N18, *e.g.* C2-C1-N18-N19 -21.3°, brings N19 still further away from O15. A final rotation about N18-N19, *e.g.* C1-N18-N19-C20 -24.1°, completes the spiral between O15 and C20.

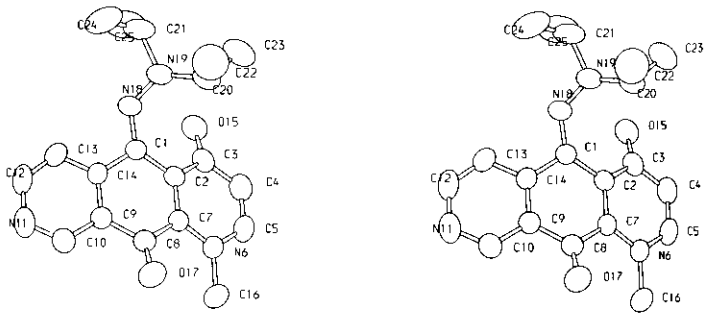
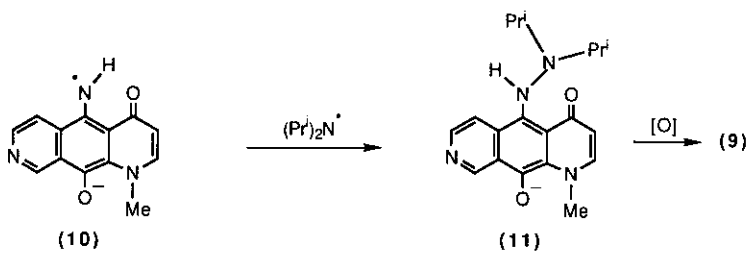


Figure Stereoscopic drawing of
1-methylpyrido[4,3-g]quinoline-4,5,10-trione 5-N,N-di-isopropylhydrazone **9**

One interpretation for the formation of geometrical isomer **7** would propose no loss of geometrical integrity in a transformation of the major isomer of starting imine into product. However we tentatively suggest that **9** may arise *via* an initial single electron transfer from $(Pr^i)_2N^-$ to the quinone, which would generate $(Pr^i)_2N\cdot$ together with the radical anion **10** of the quinone; coupling to produce **11** and then oxidation, perhaps during aerial work-up, would afford **9**.



EXPERIMENTAL

1-Methylbenzo[g]quinoline-4,5,10-trione **4** . - A solution of the keto acid **3**[7] (18 mg, 0.07 mmol) in concentrated sulphuric acid (2 ml) was heated at 170°C for 2 h. After cooling to room temperature, the reaction mixture was poured onto ice and rendered just basic with solid potassium carbonate. Extraction with chloroform and evaporation of the dried (over anhydrous potassium carbonate) extract gave the quinone **4** as a bright yellow solid (17 mg, 97 %), mp 238-239°C (from THF), ν_{max} (Nujol) 1685, 1670, 1630, and 1590 cm^{-1}; λ_{max} (EtOH) 215, 252, 287, 314, and 396 nm (log ε 4.33, 4.20, 4.00, 3.62, and 3.42); δ_H ($CDCl_3$) 8.20 (1H, d, J 6 Hz, 6-H), 8.08 (1H, d, J 6 Hz, 9-H), 7.84 (1H, t, J 6 Hz, 7-H), 7.74 (1H, t, J 6 Hz, 8-H), 7.38 (1H, d, J 8 Hz, 2-H), 6.72 (1H, d, J 8 Hz, 3-H), and 4.08 (3H, s, NCH_3); *m/z* (EI) 239 (41%, $M^{\cdot+}$), 210 (39), 133 (26), and 124 (22) (Found C, 70.6; H, 4.0; N, 5.5. $C_{14}H_9NO_3$ requires C, 70.29; H, 3.79; N, 5.86).

1-Methylpyrido[4,3-g]quinoline-4,5,10-trione **6** . - The keto ester **5**[7] (0.11 g, 0.39 mmol) in oleum (1 ml) was heated at 200°C for 5 h. The cooled reaction mixture was poured onto ice and the yellow solution made just basic with solid potassium carbonate. Extraction with chloroform then evaporation of the dried (over anhydrous potassium carbonate) extract gave a bright orange solid which was recrystallised from THF to give the quinone **6** (57 mg, 61%), as orange needles, mp 220-230°C, ν_{max} (Nujol) 1690, 1665, 1620, and 1580 cm^{-1}; λ_{max} (EtOH) 223, 258, 282, 320, and 406 nm (log ε 4.39, 3.97, 4.00, 3.55, and 3.47); δ_H ($CDCl_3$) 9.40 (1H, s, 9-H), 9.16 (1H, d, J 5 Hz, 7-H), 8.04 (d, J 5 Hz, 6-H), 7.44 (1H, d, J 8 Hz, 2-H), 6.79 (1H, d, J 8 Hz, 3-H), and 4.14 (3H, s, NCH_3); *m/z* (CI) 241 (32%, MH^+), 226 (51), 211 (18), 198 (7), 170 (5), and 77 (6) (Found C, 64.8; H, 3.3; N, 11.4. $C_{13}H_8N_2O_3$ requires C, 65.00; H, 3.36; N, 11.66).

5-Imino-1-methylpyrido[4,3-g]quinoline-4,10-dione **7** . - To a solution of quinone **6** (52 mg) in methanol (5 ml) was added 35% aqueous ammonia (5 ml) and the mixture was allowed to stand at room temperature over night. Evaporation of the solvent at room temperature *in vacuo* gave the imine **7** (49 mg, 100%), as a bright yellow crystalline solid, mp 215-219°C (from THF), ν_{max} (film) 3600-3000, 1685, 1665, 1630, and 1574 cm-1; λ_{max} (EtOH) 218, 271, 320sh, and 381 nm (log ε 4.36, 4.06, 3.60, and 3.50); δ_H ($CDCl_3$) 14.60(5/6H, bs, NH), 14.48(1/6H, bs, NH), 9.42 (1H, s, 9-H), 9.05 (1H, d, J 5 Hz, 7-H), 8.50 (5/6H, d, J 5 Hz, 6-H in Z-isomer), 7.92 (1/6H, d, J 5 Hz, 6-H in E isomer), 7.52 (1H, d, J 8 Hz, 2-H), 6.80 (1H, d, J 8 Hz, 3-H), and 4.19 (3H, s, NCH_3); *m/z* (EI) 239 (100%, $M^{\cdot+}$), 238 (43), 210 (68), 184 (20), 97 (44), 83 (46), 69 (55), and 57 (19) (Found C, 65.1; H, 3.7; N, 17.3. $C_{13}H_9N_3O_2$ requires C, 65.26; H, 3.79; N, 17.59).

5-Diisopropylaminoimino-1-methylpyrido[4,3-g]quinoline-4,10-dione **9** . - To a stirred solution of dry diisopropylamine (53 µl, 0.38 mmol) in dry THF (5 ml) under nitrogen was added n-butyllithium (2.5M in hexane, 151 µl, 0.38 mmol) at -78°C. The resulting mixture was brought to 0°C, returned to -78°C, then a solution of the imine **7** (43 mg, 0.18mmol) in dry THF (10 ml) was added all at once; an immediate purple colour was produced. After 1 h the solution was brought to room temperature for 10 min, then re-cooled to -78°C before quenching with water. The volatile solvents were removed *in vacuo* at room temperature and the residue was purified by chromatography over silica gel. Elution with $CHCl_3$-MeOH (2:1) gave the hydrazone **9**, mp 204-06°C (18 mg, 29%) closely followed by starting imine **7** (26 mg,

Table 1 Crystal Coordinates for Structure **9**

Atom	*x/a*	*y/b*	*z/c*
C1	0.4815(3)	0.1031(2)	0.3888(2)
C2	0.4360(3)	0.0926(2)	0.4601(2)
C3	0.5169(3)	0.1127(2)	0.5191(2)
C4	0.4567(4)	0.1053(2)	0.5850(2)
C5	0.3488(4)	0.0676(2)	0.5926(2)
N6	0.2857(3)	0.0376(1)	0.5384(1)
C7	0.3273(3)	0.0515(2)	0.4720(2)
C8	0.2541(3)	0.0211(2)	0.4126(2)
C9	0.3272(3)	0.0121(2)	0.3486(2)
C10	0.2844(3)	-0.0362(2)	0.2971(2)
N11	0.3421(3)	-0.0475(2)	0.2371(2)
C12	0.4471(4)	-0.0076(2)	0.2265(2)
C13	0.4958(3)	0.0414(2)	0.2720(2)
C14	0.4375(3)	0.0519(2)	0.3368(2)
O15	0.6288(2)	0.1319(1)	0.5118(1)
C16	0.1814(4)	-0.0136(2)	0.5547(2)
O17	0.1423(2)	0.0049(2)	0.4164(1)
N18	0.5606(3)	0.1522(2)	0.3630(2)
N19	0.5912(3)	0.2157(2)	0.3885(2)
C20	0.5123(4)	0.2589(2)	0.4369(2)
C21	0.6873(5)	0.2534(3)	0.3452(3)
C22	0.4270(6)	0.3106(3)	0.3964(3)
C23	0.5919(5)	0.2997(3)	0.4900(3)
C24	0.6528(7)	0.2550(4)	0.2701(4)
C25	0.8133(5)	0.2184(3)	0.3578(4)
H4	0.5000(33)	0.1238(17)	0.6248(17)
H5	0.3058(31)	0.0570(18)	0.6392(17)
H10	0.2089(26)	-0.0626(16)	0.3059(15)
H12	0.4905(35)	-0.0163(19)	0.1830(18)
H13	0.5662(30)	0.0691(16)	0.2591(17)
H20	0.4579(27)	0.2248(15)	0.4608(14)
H21	0.6899(37)	0.2989(21)	0.3648(20)
H161	0.1011	0.0069	0.5375
H162	0.1761	-0.0206	0.6051
H163	0.1973	-0.0607	0.5319
H221	0.4782	0.3495	0.3750
H222	0.3654	0.3331	0.4286
H223	0.3815	0.2837	0.3603
H231	0.6391	0.3388	0.4667
H232	0.6515	0.2653	0.5117
H233	0.5362	0.3205	0.5255
H241	0.7072	0.2914	0.2472
H242	0.5643	0.2689	0.2656
H243	0.6677	0.2067	0.2499
H251	0.8781	0.2447	0.3310
H252	0.8111	0.1670	0.3432
H253	0.8327	0.2215	0.4075

60%). A crystal of **9**, suitable for X-ray crystallographic examination, was grown from ethyl acetate. The hydrazone **9** had ν_{max} (film) 1614, 1600, and 1587 cm^{-1}; λ_{max} (EtOH) 227, 275, 344, and 527 nm (log ε 4.26, 4.14, 3.76, and 3.90); δ_H ($CDCl_3$) 9.35 (1H, s, 9-H), 8.54 (1H, d, J 5 Hz, 7-H), 8.14 (1H, d, J 5 Hz, 6-H), 7.44 (1H, d, J 8 Hz, 2-H), 6.43 (1H, d, J 8 Hz, 3-H), 4.20 (3H, s, NCH_3), 4.1 (2H, bm, 2xNCH), and 2.00-1.00 (12H, bm, $2xC(CH_3)_2$); *m/z* (EI) 338(12%, $M^{\cdot+}$), 294 (4), 239 (68), 225 (27), 210 (32), 98 (70), and 84 (100) (Found C, 67.5; H, 6.5; N, 16.6. $C_{19}H_{22}N_4O_2$ requires C, 67.43; H, 6.55; N, 16.56).

X-Ray Structure Determination of 5-Diisopropylaminoimino-1-methylpyrido[4,3-g]quinoline-4,10-dione **9** . - *Crystal data* . $C_{19}H_{22}N_4O_2$, M = 338, orthorhombic, a = 10.538(1), b = 18.235(2), c = 19.193(5) Å; U = 3688 $Å^3$, Z = 8, ρ_c = 1.22, μ(Mo - $K\alpha$) = 0.97 cm^{-1}, space group Pbca (no. 61), 2354 unique reflexions with $F > 3\sigma(F)$, R = 5.04%.

Table 2 Geometry of Structure **9**

For numbering scheme see Figure

Atoms				Bond Lengths			Bond Angles		Torsion
A	B	C	D	AB	BC	CD	ABC	BCD	Angle
C1	C2	C3	C4	1.4619(46)	1.4640(47)	1.4216(51)	119.96(28)	113.88(30)	175.1(3)
C1	C2	C3	O15			1.2378(43)		122.60(31)	-7.3(5)
C1	C2	C7	N6		1.3876(44)	1.3709(41)	119.71(29)	121.12(28)	176.7(3)
C1	C2	C7	C8			1.4829(46)		120.30(29)	-2.8(5)
C1	C14	C9	C8	1.4449(46)	1.3895(45)	1.4599(47)	119.56(29)	121.32(29)	0.2(5)
C1	C14	C9	C10			1.3983(49)		118.89(30)	178.7(3)
C1	C14	C13	C12		1.3986(48)	1.3509(53)	124.19(30)	119.92(33)	-179.6(3)
C1	N18	N19	C20	1.3202(44)	1.2968(43)	1.4746(53)	128.34(30)	125.06(32)	-24.1(6)
C1	N18	N19	C21			1.4791(62)		111.90(33)	177.7(4)
C2	C1	C14	C9				117.21(28)		21.1(5)
C2	C1	C14	C13						-162.1(3)
C2	C1	N18	N19				130.38(30)		-21.3(6)
C2	C3	C4	C5			1.3372(52)		121.65(34)	14.8(5)
C2	C7	N6	C5			1.3503(45)		118.92(28)	3.1(5)
C2	C7	N6	C16			1.4759(49)		123.53(28)	-171.5(3)
C2	C7	C8	C9					114.53(28)	23.2(4)
C2	C7	C8	O17			1.2168(43)		123.23(31)	-156.7(3)
C3	C2	C1	C14						148.3(3)
C3	C2	C1	N18						-30.3(5)
C3	C2	C7	N6				119.25(29)		8.6(5)
C3	C2	C7	C8						-170.9(3)
C3	C4	C5	N6					122.92(33)	-4.0(6)
C4	C3	C2	C7						-16.8(5)
C4	C5	N6	C7						-5.7(5)

Continued

C4	C5	N6	C16			117.34(29)	169.3(3)
C5	C4	C3	O15			123.47(33)	-162.8(4)
C5	N6	C7	C8			118.57(28)	-177.4(3)
N6	C7	C8	C9				-156.4(3)
N6	C7	C8	O17				23.7(5)
C7	C2	C1	C14				-19.7(4)
C7	C2	C1	N18				161.7(3)
C7	C2	C3	O15				160.8(3)
C7	C8	C9	C10			119.77(30)	159.5(3)
C7	C8	C9	C14				-22.0(4)
C8	C7	N6	C16				8.0(5)
C8	C9	C10	N11	1.3174(49)		124.51(34)	178.9(3)
C8	C9	C14	C13			116.17(30)	-176.8(3)
C9	C10	N11	C12	1.3405(51)		115.48(33)	-1.4(5)
C9	C14	C1	N18			112.40(29)	-160.0(3)
C9	C14	C13	C12				-2.7(5)
C10	C9	C8	O17			122.24(31)	-20.6(5)
C10	C9	C14	C13				1.7(5)
C10	N11	C12	C13			124.96(36)	0.3(6)
N11	C10	C9	C14				0.4(5)
N11	C12	C13	C14				1.8(6)
C13	C14	C1	N18				16.7(5)
C14	C1	N18	N19				160.0(3)
C14	C9	C8	O17				157.9(3)
N18	N19	C20	C22	1.5165(71)		110.13(37)	-91.2(5)
N18	N19	C20	C23	1.5154(70)		112.02(36)	144.0(4)
N18	N19	C21	C24	1.4862(87)		112.73(45)	49.8(5)
N18	N19	C21	C25	1.4936(85)		108.61(44)	-75.7(5)
C20	N19	C21	C24		119.40(34)		-109.8(5)
C20	N19	C21	C25				124.7(4)
C21	N19	C20	C22				65.5(5)
C21	N19	C20	C23				-59.3(5)

The typical habit of the dark red crystals was hexagonal prismatic with oblique end faces. Intensity data were collected from a specimen of dimensions 0.10 x 0.13 x 0.2 mm out to $\theta = 30^{o}$ on an Enraf Nonius CAD-4 computer-controlled Kappa axis single-crystal diffractometer. No absorption correction was applied as $\mu R < 0.07$.

Application of the MULTAN 80 suite of programs revealed a 23 atom partial solution, and the two remaining non-hydrogen atoms were located by difference Fourier synthesis at R = 20%. Seven non-methyl hydrogen atoms were assigned and the 25 non-hydrogen atoms refined with anisotropic temperature factors to R = 7.57%. At this point a second difference synthesis revealed the expected

methyl hydrogen atoms. The weighting scheme $w^{-1} = 0.55 + 0.028F$ was used to obtain a uniform distribution of $w \times \Delta F^2$ over the F range.

A stereoscopic drawing of the molecule is shown in the Figure, the positional co-ordinates are given in Table 1, and bond lengths, bond angles, and torsion angles in **9** are given in Table 2.

REFERENCES AND NOTES

1. F. J. Schmitz, S. K. Agarwal, S. P. Gunasekera, P. G. Schmidt, and J. N. Shoolery, *J. Amer. Chem. Soc.*, 1983, **105**, 4835.
2. T. F. Molinski, E. Fahy, D. J. Faulkner, G. D. Van Duyne, and J. Clardy, *J. Org. Chem.*, 1988, **53**, 1340.
3. A. M. Echavarren and J. K. Stille, *J. Amer. Chem. Soc.* , 1988, **110**, 4051.
4. A. Kubo and S. Nakahara, *Heterocycles*, 1988, **27**, 2095.
5. R. H. Prager and C. Tsopelas, *Heterocycles*, 1989, **29**, 847.
6. C. V. Labavca, A. R. MacKenzie, C. J. Moody, C. W. Rees, and J. J. Vaquero, *J. Chem. Soc., Perkin Trans. 1*, 1987, 927.
7. P. Meghani and J. A. Joule, *J. Chem. Soc., Perkin Trans 1*, 1988, 1.
8. The deacylation of acyl pyridones is precedented : V. S. Giri, B. C. Maitz, and S. C. Pakrashi, *Heterocycles*, 1985, **23**, 71.
9. H. Tomisawa, H. Hongo, H. Kato, and R. Fujita, *Chem. Pharm. Bull.*, 1971, **19**, 2414.
10. F. M. Saidova and A. D. Magai, *Zh. Org. Khim.*, 1979, **15**, 447 (*Chem. Abs.* , 1979, **91**, 5076t).
11. L. L. Woods, *J. Org. Chem.*, 1957, **22**, 341; *ibid.*, 1959, **24**, 1804; *ibid.*, 1962, **27**, 696.
12. S. J. Cristol, *Acc. Chem. Res.*, 1971, **4**, 393.

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