Functionalised Enaminones and their Use in Heterocyclic Synthesis

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A series of enaminones derived from 2,4-dioxocyclohexane carboxylic acid esters has been prepared. The use of some of the new derivatives in the synthesis of some quinazolones and imidazoloquinazolines is illustrated.

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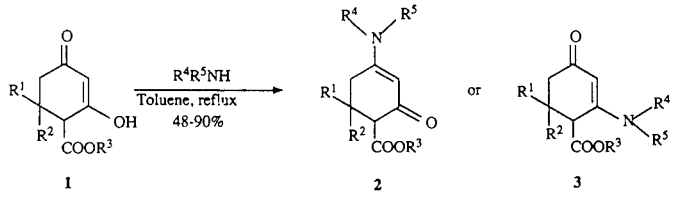
Introduction.

Enaminones in general and those derived from dimedone and cyclohexane-1,3-dione in particular have found wide use in the preparation of new heterocyclic systems [1]. Examples of such systems include quinoline [2-6], acridine [3,5,6], 2-azatricyclo[7.3.1.0^{3,8}]tridecane [7], benzoxazine [5,6], triazine [8] and quinazoline [8] derivatives. A recent review cites many examples of heterocyclic syntheses from cyclohexane-1,3-diones, many of which use enaminone intermediates [9].

Syntheses.

A need for some new bi- and tri-cyclic heterocycles stimulated an investigation of primary and secondary amine derivatives of the readily available methyl and ethyl 2,4-dioxocyclohexane carboxylates **1** [10-13]. Refluxing the diketoesters **1** with primary or secondary amines in toluene under a Dean and Stark water separator gave good yields of single products which proved to be enaminones. The ir spectra showed bands for the ester group and C=O and C=C of the enaminone system (Table 3). These and the nmr (Table 2) and uv (Table 3) spectra were consistent with either structure **2** or **3**. It was not possible to distinguish between these two structures although it seemed reasonable that steric hindrance would prevent attack at C-2 to give enaminones **3**. In addition to the simple amines, hydrazines and methyl carbazoate reacted in ethanol or diglyme to give derivatives **2e**, **2o**, **2p**, **2r** and **2s**. It is well known that 3-ketoesters condense with hydrazines to give pyrazolones [14,15]. As there was not ring closure with these derivatives it was very unlikely that the hydrazone had formed from the C-2 carbonyl group. This was confirmed when the diketo diester **4** readily gave the pyrazoloindazole **5** with hydrazine. The structure was established by the elemental analysis, mass, and nmr spectra. The proton nmr showed three singlets at δ 1.43 (6 H), 2.52 (2 H) and 8.22 (4 H) confirming the tautomerism shown on the formula. Unfortunately, the solubility of this material was too low to allow us to obtain a ^{13}C-nmr spectrum.

Scheme 1



1	R^1	R^2	R^3
a	H	H	Me
b	Me	H	Me
c	Me	Me	Me
d	Ph	H	Me
e	Ph	H	Et

2/3	R^1	R^2	R^3	R^4	R^5
a	H	H	Me	H	Me
b	H	H	Me	H	CH_2Ph
c	H	H	Me	H	CH_2CH_2Ph
d	H	H	Me	H	1-adamantyl
e	H	H	Me	H	NHCOOMe
f	H	H	Me	-$(CH_2)_4$-	
g	Me	H	Me	H	CH_2Ph
h	Me	H	Me	H	CH_2CH_2Ph
i	Me	H	Me	-$(CH_2)_4$-	
j	Me	Me	Me	H	CH_2Ph

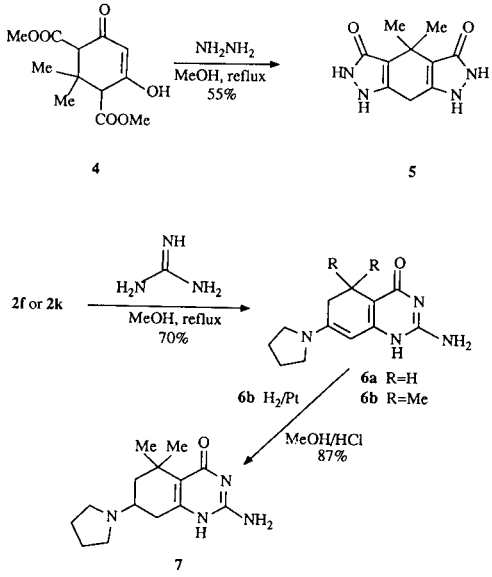
2/3	R^1	R^2	R^3	R^4	R^5
k	Me	Me	Me	-$(CH_2)_4$-	
l	Ph	H	Me	H	Pr^i
m	Ph	H	Me	-$(CH_2)_4$-	
n	Ph	H	Me	-$CH_2CH_2OCH_2CH_2$-	
o	Ph	H	Me	H	NH_2
p	Ph	H	Me	H	NHCOOMe
q	Ph	H	Et	-$(CH_2)_4$-	
r	Ph	H	Et	H	NH_2
s	Ph	H	Et	H	NHMe

Table 1

Enaminone-Esters

No.	R^1	R^2	R^3	R^4	R^5	Method	Yield %	Mp (°C)	Solvent
2a	H	H	Me	H	Me	A	83	131-132	AcOEt
2b	H	H	Me	H	CH_2Ph	B	96	160-161	Toluene
2c	H	H	Me	H	CH_2CH_2Ph	B	60	119-121	Toluene
2d	H	H	Me	H	1-adamantyl	B	22	214-215	AcOEt
2e	H	H	Me	H	NHCOOMe	C	62	145-146	*i*-PrOH
2f	H	H	Me	-$(CH_2)_4$-		B	86	113-114	AcOEt-PE
2g	H	Me	Me	H	CH_2Ph	B	90	154-155	AcOEt
2h	H	Me	Me	H	CH_2CH_2Ph	B	73	118-119	Toluene
2i	H	Me	Me	-$(CH_2)_4$-		B	76	138-139	AcOEt
2j	Me	Me	Me	H	CH_2Ph	B	79	139-140	AcOEt
2k	Me	Me	Me	-$(CH_2)_4$-		B	77	112-113	AcOEt-PE
2l	H	Ph	Me	H	*i*-Pr	B	70	193-194	Toluene
2m	H	Ph	Me	-$(CH_2)_4$-		B	84	178-179	Toluene
2n	H	Ph	Me	-$(CH_2CH_2OCH_2CH_2)$-		B	63	194-195	IPA
2o	H	Ph	Me	H	NH_2	D	76	180-181	EtOH
2p	H	Ph	Me	H	NHCOOMe	C	50	212-213	EtOH
2q	H	Ph	Et	-$(CH_2)_4$-		B	48	168-169	EtOH
2r	H	Ph	Et	H	NH_2	D	55	195-196	EtOH
2s	H	Ph	Et	H	NHMe	D	50	137-138	AcOEt

Scheme 2



X-ray crystallographic studies of two of the products confirmed them to be **2g** (Figure 1) and **2m** (Figure 2). The other members of the series of enaminones **2a** to **2s** were prepared *via* similar reactions and in no case was any trace of a second product derived from attack at C-2 detected. Treatment of either of the enaminone-esters **2f** or **2k** with guanidine base in refluxing alcohol gave the derived quinazolone **6a** or **6b** respectively in about 70% yield. It was not possible to attempt reduction of the carbonyl groups because of the very poor solubility of these compounds. However, hyrogenation of **6b** in concentrated hydrochloric acid/methanol gave the dihydro derivative **7**.

Table 2

Enaminone Ester ^{1}H-NMR (Deuteriochloroform)

No. [a]	Signal (multiplicity, integral)
2a	2.30 (m, 5 H), 2.76 (d, 3 H), 3.68 (s, 3 H), 5.00 (s, 1 H), 6.55 (s, 1 H)
2b	2.30 (m, 4 H), 3.20 (m, 1 H), 3.70 (s, 3 H), 4.20 (d, 2 H), 5.13 (s, 1 H), 5.60 (s, 1 H), 7.30 (s, 5 H)
2d	1.65 (m, 7 H), 2.00 (m, 13 H), 3.70 (s, 3 H), 4.45 (s, 1 H), 5.47 (s, 1 H)
2e	2.12 (s, 2 H), 2.45 (m, 3 H), 3.17 (s, 3 H), 3.19 (s, 3 H), 5.20 (s, 1 H) [b]
2f	1.94 (m, 4 H), 2.25 (m, 4 H), 2.50 (m, 1 H), 3.24 (m, 4 H), 3.70 (s, 3 H), 5.00 (s, 1 H)
2g	0.95 (d, 3 H), 2.30 (m, 4 H), 3.65 (s, 3 H), 4.11 (d, 2 H), 4.98 (s, 1 H), 6.35 (s, 1 H), 7.23 (s, 5 H)
2h	1.00 (d, 3 H), 2.30 (m, 4 H), 3.00 (m, 4 H), 3.68 (s, 3 H), 5.05 (s, 1 H), 6.10 (s, 1 H), 7.16 (s, 5 H)
2i	1.10 (d, 3 H), 1.95 (m, 4 H), 2.45 (AB system, 2 H), 3.02 (s, 1 H), 3.30 (m, 4 H), 3.65 (s, 3 H), 5.00 (s, 1 H)
2j	1.05 (s, 6 H), 2.40 (AB system, 4 H), 2.98 (s, 1 H), 3.60 (s, 3 H), 4.15 (d, 2 H), 5.00 (s, 1 H), 6.55 (d, 1 H), 7.25 (s, 5 H)
2k	1.10 (s, 6 H), 1.92 (m, 4 H), 2.47 (AB system, 4 H), 3.02 (s, 1 H), 3.30 (m, 4 H), 3.65 (s, 3 H), 5.00 (s, 1 H)
2l	1.15 (d, 6 H), 2.40 (m, 1 H), 3.25 (s, 3 H), 3.50 (m, 4 H), 4.96 (s, 1 H), 5.80 (d 1 H), 7.22 (s, 5 H)
2m	1.95 (m, 4 H), 2.70 (m, 2 H), 3.30 (m, 6 H), 3.52 (s, 3 H), 5.10 (s, 1 H), 7.28 (s, 5 H)
2n	2.60 (m, 2 H), 3.30 (m, 6 H), 3.60 (m, 4 H), 3.92 (s, 3 H), 5.25 (s, 1 H), 7.25 (s, 5 H)
2o	2.45 (m, 2 H), 3.35 (s, 3 H), 3.57 (m, 2 H), 4.38 (s, 2 H), 5.25 (s, 1 H), 7.30 (s, 5 H), 8.35 (s, 1 H) [c]
2q	0.98 (t, 3 H), 1.92 (m, 4 H), 2.70 (m, 2 H), 3.30 (m, 6 H), 3.95 (q, 2 H), 5.08 (s, 1 H), 7.28 (s, 5 H)
2r	1.00 (t, 3 H), 2.65 (s, 2 H), 3.60 (m, 2 H), 3.95 (q, 2 H), 4.50 (s, 2 H), 5.38 (s, 1 H), 7.42 (s, 5 H), 8.48 (s, 1 H) [c]
2s	0.95 (t, 3 H), 2.50 (m, 1 H), 2.58 (s, 3 H), 3.60 (m, 4 H), 3.82 (q, 2 H), 5.55 (s, 1 H), 6.90 (s, 1 H), 7.27 (s, 5 H)

[a] Compounds **2c** and **2p** were too insoluble to provide satisfactory spectra. [b] Solvent perdeuteriomethanol. [c] Solvent DMSO-d_6.

Table 3
Enaminone Ester IR and UR Absorptions

No.	from	NH	IR cm^{-1} COOR	C=O	C=C	Other	UV (ETOH) λ nm	ε
2a	$CHCl_3$	3330	1740	1610	1595	1530, 1430	288	28300
2b	$CHCl_3$	3430	1735	1620	1590	1520	287	38500
2c	$CHCl_3$	3430	1738	1620	1595	1515	290	32400
2d	$CHCl_3$	3400	1730	1605	1580	1520, 1160	295	29500
2e	KBr	3280	1730		1580	1760 (NHCOOMe)	283	26000
2f	$CHCl_3$		1740	1610	1550	1450	302	34200
2g	$CHCl_3$	3300	1740	1620	1580	1520, 1205	289	31100
2h	$CHCl_3$	3310	1740	1620	1595	1530, 1260	290	31000
2i	$CHCl_3$		1740	1610	1560	1450, 1300	302	33900
2j	$CHCl_3$	3300	1740	1620	1580	1510, 1205	295	29500
2k	$CHCl_3$		1730	1600	1560	1440, 1160	302	32100
2l	KBr	3260	1740	1610	1540	1260, 1155	291	28400
2m	KBr	3400	1737	1615	1550	1420, 1150	302	32200
2n	KBr		1740	1615	1540	1440, 1140	302	29200
2o	KBr	3320	1735		1540	1260	289	24200
2p	KBr	3280	1730	1580	1540	1240, 1020	280	23900
			1760 (NHCOOMe)					
2q	$CHCl_3$		1735	1610	1550	1445, 1160	302	33100
2r	KBr	3330	1737		1540	1422, 1264	290	25000
2s	KBr	3330	1737		1540	1422, 1264	257	14700

Table 4
Elemental Analyses of Enaminones

		MW	Calcd. %C	%H	%N	Found %C	%H	%N
2a	$C_9H_{38}NO_3$	183.2	59.00	7.15	7.65	59.12	7.25	7.61
2b	$C_{15}H_{17}NO_3$	259.3	69.48	6.61	5.40	69.60	6.62	5.34
2c	$C_{16}H_{19}NO_3$	273.3	70.31	7.01	5.12	70.45	7.08	5.29
2d	$C_{18}H_{25}NO_3$	303.4	71.26	8.31	4.62	70.99	8.39	4.74
2e	$C_{10}H_{14}N_2O_5$	242.2	49.59	5.83	11.56	49.71	6.02	11.50
2f	$C_{12}H_{17}NO_3$	223.3	64.55	7.67	6.27	64.61	7.72	6.25
2g	$C_{16}H_{19}NO_3$	273.3	70.31	7.01	5.12	70.60	7.01	5.15
2h	$C_{17}H_{21}NO_3$	287.4	71.06	7.37	4.87	71.19	7.55	4.95
2i	$C_{13}H_{19}NO_3$	237.3	65.80	8.07	5.90	65.65	8.26	5.97
2j	$C_{17}H_{21}NO_3$	287.4	71.06	7.37	4.87	71.16	7.67	4.96
2k	$C_{14}H_{21}NO_3$	251.3	66.91	8.42	5.57	66.90	8.58	5.71
2l	$C_{17}H_{21}NO_3$	287.4	71.06	7.37	4.87	71.00	7.54	4.71
2m	$C_{18}H_{21}NO_3$	299.4	72.22	7.07	4.68	72.13	7.26	4.79
2n	$C_{18}H_{21}NO_4$	315.4	68.55	6.71	4.44	68.72	6.85	4.41
2o	$C_{14}H_{16}N_2O_3$	260.3	64.60	6.20	10.76	64.36	6.30	10.58
2p	$C_{16}H_{18}N_2O_5$	318.3	60.37	5.70	8.80	60.26	5.80	8.63
2q	$C_{19}H_{23}NO_3$	313.4	72.82	7.40	4.47	72.88	7.55	4.54
2r	$C_{15}H_{18}N_2O_3$	274.3	65.68	6.61	10.21	65.62	6.76	10.10
2s	$C_{16}H_{20}N_2O_3$	288.4	66.65	6.99	9.72	66.51	7.08	9.67

Table 5
Crystal Data and X-ray Experimental Details

	2g	**2m**	**11**	**15**
Formula	$C_{16}H_{19}NO_3$	$C_{18}H_{21}NO_3$	$C_{13}H_{17}N_3O_2$	$C_{11}H_{21}N_3O_2$
Formula Mass	273.3	299.4	247.3	259.3
Crystal System	monoclinic	orthorhombic	monoclinic	monoclinic
Space Group	$P2_1/n$	Pbca	$P2_1/c$	C2/c
a (Å)	8.808(3)	8.756(6)	10.903(7)	24.173(13)
b (Å)	7.096(3)	17.535(9)	10.632(7)	7.200(4)
c (Å)	22.618(10)	20.286(11)	11.589(8)	15.904(11)
β (°)	90.58(3)	90	112.07(5)	108.37(5)
V (Å^3)	1414(1)	3115(3)	1245(1)	2627(3)
D_c (G cm^{-3})	1.28	1.28	1.32	1.31
Z	4	8	4	8
F(000)	584	1280	528	1120
μ (cm^{-1})	0.83	0.81	0.85	0.94
Diffractometer	Nicolet R3m	Nicolet R3m	Nicolet R3m	Nicolet R3m
Radiation	MoKα	MoKα	MoKα	MoKα
Wavelength (Å)	0.71069	0.71069	0.71069	0.71069
Temperature (°C)	-100	-100	-100	-100
Crystal Size (MM)	.59 x .38 x .03	.58 x .21 x .05	.48 x . 43 x .30	.81 x .13 x .02
Scan Mode	ω	ω	ω	ω
2θRange (°)	3-52	3-52	3-60	3-52
Collected Data	2844	3041	4905	2682
Unique Data	2773	3041	2460	2580
Observed Data	1338	682	1338	732
Parameters refined	184	207	163	181
g	0.0007	0.0002	0	0.0001
Residual Peaks (e.Å^{-3})	<0.22	<0.22	<0.26	<0.20
R	0.043	0.056	0.043	0.050
wR	0.050	0.052	0.036	0.041

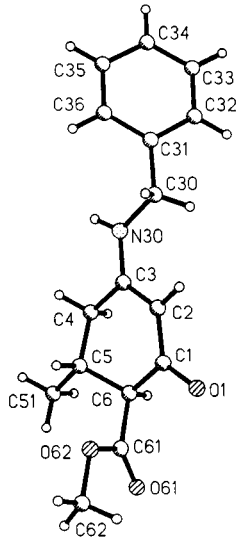


Figure 1. Perspective view and atom labelling of **2g**.

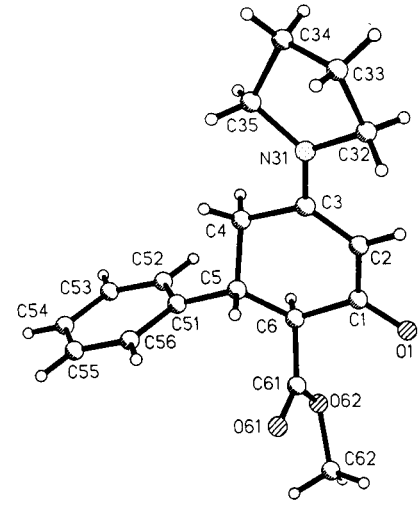
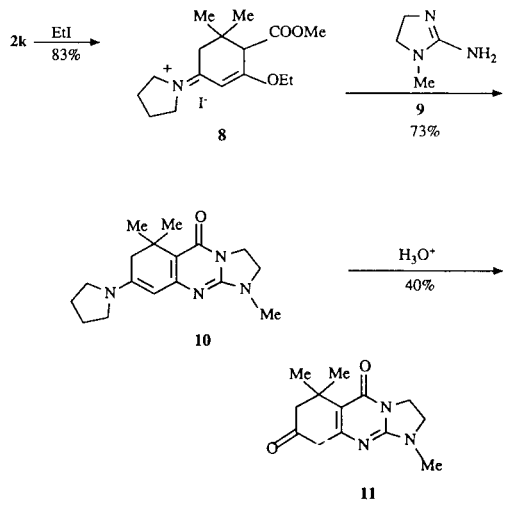


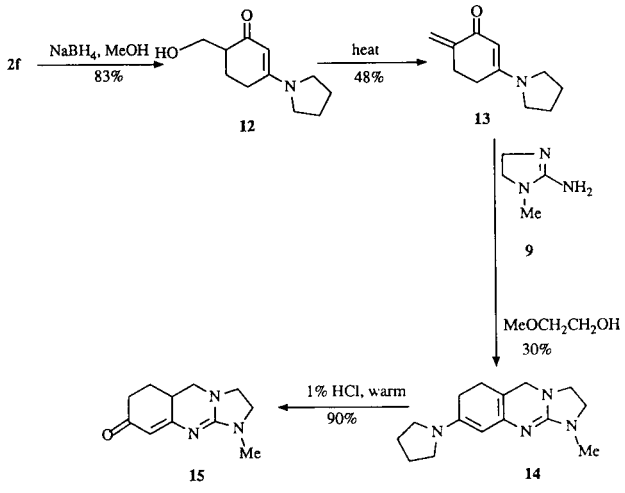
Figure 2. Perspective view and atom labelling of **2m**.

Scheme 3



Compound **2k** failed to react with 2-amino-4,5-dihydro-1-methylimidazole (**9**) so it was treated with iodoethane to give the *O*-alkylated salt **8**. This did react with the cyclic guanidine to give the required imidazoquinazolinone **10** which could be hydrolysed to the vinacylguanidine **11**. Attack of the imidazole **9** in the opposite mode (*i.e.* the primary amino group condenses with the ester) could have given the angular product instead of the linear molecule **10**. That the structures shown are correct was demonstrated by an X-ray crystal structure determination on the dione **11** (Figure 3).

Scheme 4



The enaminone-ester **2f** was reduced to the alcohol **12** by sodium borohydride in dry methanol. On vacuum distillation this lost water to give the olefine **13** which reacted with 2-amino-1-methylimidazoline (**9**) in a refluxing mixture of ethoxyethanol and methanol to give the tricyclic compound **14**. Mild hydrolysis then gave the vinacylguanidine **15**, the structure of which was confirmed by X-ray crystallography (Figure 4).

Table 6

Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Coefficients ($Å^2$ x 10^3) for **2g** and **2m**

2g	x	y	z	U_{eq} [a]
O(1)	2589(3)	2544(3)	4697(1)	31(1)
C(1)	2897(3)	839(4)	4631(1)	22(1)
C(2)	2301(3)	-605(4)	4989(1)	21(1)
C(3)	2710(3)	-2474(4)	4924(1)	20(1)
C(4)	3809(4)	-3061(4)	4457(1)	25(1)
C(5)	3864(4)	-1721(4)	3936(1)	23(1)
C(6)	4024(4)	311(4)	4150(1)	25(1)
N(30)	2205(3)	-3826(4)	5282(1)	22(1)
C(30)	1258(4)	-3437(4)	5796(1)	26(1)
C(31)	1111(3)	-5120(4)	6197(1)	21(1)
C(32)	1511(3)	-4950(5)	6790(1)	26(1)
C(33)	1333(4)	-6451(5)	7176(2)	30(1)
C(34)	759(4)	-8134(5)	6973(2)	31(1)
C(35)	358(3)	-8338(5)	6382(2)	30(1)
C(36)	524(3)	-6819(4)	5997(1)	26(1)
C(51)	5131(4)	-2254(4)	3510(2)	28(1)
C(61)	3925(4)	1745(5)	3656(1)	24(1)
O(61)	4915(3)	2815(3)	3522(1)	35(1)
O(62)	2568(2)	1653(3)	3382(1)	34(1)
C(62)	2299(4)	3056(5)	2930(2)	46(1)
2m	x	y	z	U_{eq} [a]
O(1)	2500(9)	914(3)	4594(3)	46(3)
C(1)	1108(12)	1002(5)	4715(5)	29(4)
C(2)	-58(12)	867(4)	4249(4)	25(3)
C(3)	-1559(11)	870(5)	4408(4)	27(4)
C(4)	-2119(11)	1044(5)	5103(4)	31(4)
C(5)	-931(12)	1495(7)	5482(4)	59(5)
C(6)	656(12)	1259(6)	5403(5)	48(4)
N(31)	-2677(10)	726(4)	3967(3)	32(3)
C(32)	-2323(12)	626(5)	3256(4)	41(4)
C(33)	-3930(10)	641(6)	2952(4)	48(4)
C(34)	-4948(12)	335(6)	3474(4)	52(4)
C(35)	-4276(12)	646(5)	4114(4)	38(4)
C(51)	-1469(12)	1715(7)	6150(5)	37(4)
C(52)	-1688(12)	1204(5)	6663(4)	46(4)
C(53)	-2296(14)	1421(6)	7259(4)	52(5)
C(54)	-2671(14)	2169(6)	7369(4)	51(5)
C(55)	-2435(14)	2688(5)	6868(5)	51(4)
C(56)	-1860(13)	2469(6)	6276(5)	48(5)
C(61)	1902(15)	1720(7)	5694(5)	44(5)
O(61) [b]	1852(11)	2450(5)	5552(4)	41(3)
C(62) [b]	2999(11)	1428(5)	6005(4)	36(4)
O(61') [c]	2245(36)	974(16)	6110(12)	50(9)
O(62') [c]	2764(44)	2116(20)	5686(16)	51(11)
C(62)	4312(13)	1926(5)	6117(4)	50(4)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor. [b] Site occupancy 0.75. [c] Site occupancy 0.25.

EXPERIMENTAL

The uv spectra were obtained on a Pye-Unicam SP800 and the ir spectra on a Perkin-Elmer 297 spectrophotometer. The ^{1}H-nmr

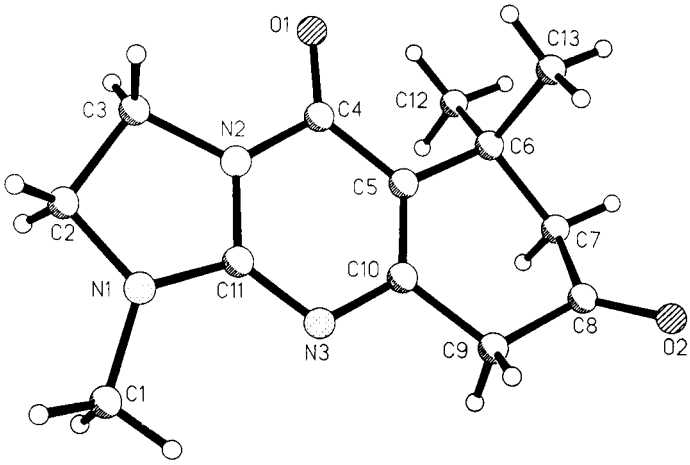


Figure 3. Perspective view and atom labelling of **11**.

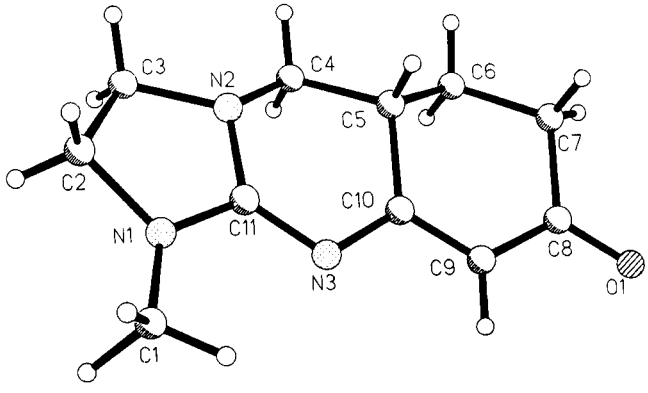


Figure 4. Perspective view and atom labelling of **15**.

Table 7

Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Coefficients ($Å^2$ x 10^3) for **11** and **15**

11	x	y	z	U_{eq} [a]
O(1)	10984(2)	3519(2)	10529(2)	26(1)
O(2)	12758(2)	-1245(2)	8565(2)	34(1)
N(1)	7001(1)	1839(2)	8371(2)	22(1)
N(2)	9024(2)	2616(2)	9360(2)	20(1)
N(3)	8799(2)	836(2)	8055(2)	20(1)
C(1)	5973(3)	1298(3)	7289(3)	27(1)
C(2)	6784(3)	3018(3)	8935(3)	28(1)
C(3)	8187(3)	3416(3)	9801(3)	26(1)
C(4)	10396(3)	2715(3)	9740(3)	21(1)
C(5)	10967(3)	1807(3)	9141(3)	18(1)
C(6)	12463(3)	1858(3)	9440(3)	19(1)
C(7)	12813(3)	1015(3)	8522(3)	24(1)
C(8)	12154(3)	-248(3)	8351(3)	24(1)
C(9)	10670(3)	-188(3)	7868(3)	24(1)
C(10)	10154(3)	902(3)	8395(3)	19(1)
C(11)	8306(3)	1712(3)	8549(3)	20(1)
C(12)	12922(3)	3210(3)	9297(3)	28(1)
C(13)	13210(3)	1371(3)	10767(3)	26(1)

15	x	y	z	U_{eq} [a]
O(1)	973(2)	3930(8)	6285(3)	47(2)
N(1)	4053(2)	4071(9)	8032(3)	45(3)
N(2)	3530(2)	4004(9)	8947(3)	41(3)
N(3)	3037(2)	3931(8)	7375(3)	28(2)
C(1)	4220(3)	4516(10)	7254(4)	49(3)
C(2)	4491(3)	4247(11)	8925(4)	54(3)
C(3)	4132(3)	3669(12)	9512(4)	55(4)
C(4)	3016(3)	3416(10)	9158(4)	45(3)
C(5)	2493(3)	4254(10)	8477(3)	31(3)
C(6)	1926(3)	3561(10)	8584(4)	39(3)
C(7)	1395(3)	4281(11)	7863(3)	42(3)
C(8)	1440(3)	3977(10)	6938(4)	31(3)
C(9)	2006(3)	3821(10)	6849(4)	29(3)
C(10)	2512(3)	3945(10)	7538(4)	25(3)
C(11)	3513(3)	4014(11)	8088(4)	34(3)
O(2)	942(3)	3318(10)	4536(3)	75(3)
O(3)	1984(3)	1825(8)	4430(3)	53(2)
O(4)	87(2)	5512(12)	3392(3)	89(3)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

spectra were determined on a Perkin-Elmer R12 spectrometer at 60 MHz and the ^{13}C-nmr spectra on a Varian XL 300 spectrometer at 75 MHz. Ethyl 2-hydroxy-4-oxo-6-phenylcyclohex-2-enecarboxylate [13], methyl 2-hydroxy-6-methyl-4-oxocyclohex-2-enecarboxylate [11], methyl 6,6-dimethyl-2-hydroxy-4-oxocyclohex-2-enecarboxylate [12] and methyl 2-hydroxy-4-oxo-6-phenylcyclohex-2-enecarboxylate [13] were prepared according to literature methods.

Methyl 2-Hydroxy-4-oxocyclohex-2-enecarboxylate (**1a**).

But-3-en-2-one (35 g, 0.5 mole) was added to a mixture of dimethyl malonate (66 g, 0.5 mole) and anhydrous potassium carbonate (6 g, 43 mmoles) and the product stirred at 40-50° for 3 hours. The cooled product was neutralised with 2.5 *M* hydrochloric acid (60 ml) and the organic layer separated and dried to give dimethyl 2-(3-oxobutyl)malonate, yield 80.8 g (80%), bp 50-53°/0.5 mm; ir (neat): ν = 1740 (C=O), 1720 (C=O) cm^{-1}; ^1H-nmr (deuteriochloroform): δ = 2.10 (s, 3 H, CH_3), 2.50 (m, 5 H, 2 x CH_2 + CH), 3.70 (s, 6 H, 2 x OCH_3).

A sample of this ketodiester (50.0 g, 0.25 mole) was added to a solution of sodium (5.7 g, 0.25 mole) in methanol (65 ml) on an ice bath, and stirred on the ice bath for 1 hour followed by 8 hours reflux. The product was partitioned between saturated sodium chloride solution (250 ml) and ether (250 ml). The aqueous layer was acidified with 1 *M* sulfuric acid (150 ml) and extracted with dichloromethane (2 x 250 ml). The extracts were dried (magnesium sulfate) and the solvent evaporated, yield 24 g (57%), mp 82-84° (toluene), (lit [16] mp 81-82° prepared by reduction of 2,4-dihydroxybenzoic acid).

Dimethyl 6,6-Dimethyl-2-hydroxy-4-oxocyclohex-2-ene-1,5-dicarboxylate (**4**).

Methyl acetoacetate (6.9 g, 60 mmoles) followed by dimethyl 2-propylidinylmalonate (10.2 g, 60 mmoles) was added to a stirred solution of sodium (1.4 g, 0.06 g-atom) in methanol (25 ml) and the mixture refluxed 10 hours and cooled. The product was acidified with sulfuric acid (1 *M*, 50 ml), extracted with dichloromethane (2 x 100 ml), dried (magnesium sulfate) and the solvent re-

moved, yield 5.4 g (35%), mp 159-160° (ethyl acetate); ir (potassium bromide): ν = 1730, 1620, 1550, 1440 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ = 1.10 (s, 6 H, 2 x CH_3), 3.45 (s, 2 H, 2 x CH), 3.68 (s, 6 H, 2 x OCH_3), 4.35 (s, 1H, =CH-).

Anal. Calcd. for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29. Found: C, 56.50; H, 6.40.

Diethyl 6-Methyl-2,4-dioxocyclohexane-1,5-dicarboxylate.

By a similar procedure to the above was obtained an oil which was distilled, bp 180-190°/2 mm, yield 10%, mp 80-82° (ethanol); ir (chloroform): ν = 1735, 1680, 1660, 1620 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 0.95 (d, 3 H, J = 8 Hz, CH_3), 1.10 (t, 6 H, J = 7 Hz, 2 x CH_3), 2.00 (s, 2 H, CH_2), 3.10 (m, 2 H, 2 x CH), 3.50 (m, 1 H, CH), 4.00 (q, 4 H, J = 7 Hz, 2 x CH_2).

Anal. Calcd. for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.42; H, 6.65.

Preparation of Enaminones.

Method A.

A solution of methylamine (33% in ethanol, 20 ml) was added to a solution of methyl 2-hydroxy-4-oxocyclohex-2-enecarboxylate (5.6 g, 33 mmoles) in ethanol (50 ml) and the mixture stirred at room temperature 2 hours. The solvent was evaporated under vacuo and the residue azeotroped with toluene to give the enaminone-ester (5 g, 83%), Table 1.

Method B.

A solution of the diketo ester (10 mmoles) and the amine (10 mmoles) in toluene (30 ml) was refluxed under a Dean/Stark water separator until the theoretical volume of water had collected (2 to 4 hours). The solvent was evaporated and the residue recrystallised to give the enaminone-ester, Table 1.

Method C.

A mixture of the diketo-ester (10 mmoles) and methyl carbazate (1.8 g, 20 mmoles) in diglyme (10 ml) was heated in an oil bath maintained at 110-120° for 1.5 hours. The reaction mixture was refrigerated for several days to give the enamido-ester, Table 1.

Method D.

A solution of the diketo-ester (4 mmoles) and hydrazine (0.13 g, 4 mmoles) in ethanol (30 ml) was refluxed for 4 hours and the solvent evaporated to give the enaminone-ester, Table 1.

4,8-Dihydro-4,4-dimethylpyrazolo[4,5-*f*]indazole-3(2*H*),5(6*H*)-dione (**5**).

A solution of dimethyl 6,6-dimethyl-2,4-dioxocyclohexane-1,5-dicarboxylate (0.48 g, 2 mmoles) and hydrazine (0.07 g, 2 mmoles) in methanol (10 ml) was stirred at ambient temperature for 2 hours and refluxed for 10 hours. After cooling and standing overnight, the product was collected, yield 0.12 g (55%), mp >300° dec (glacial acetic acid); ir (potassium bromide): ν = 3150 (br), 1630, 1580, 1560, 1510, 1440, 1400, 820 cm^{-1}; uv (ethanol): λ = 227 nm (ϵ 7400), 249 nm (ϵ 5100); ^{1}H-nmr (DMSO-d_6): δ = 1.43 (s, 6 H, 2 x CH_3), 2.52 (s, 2 H, CH_2), 8.22 (s, 4 H, 4 x NH).

Anal. Calcd. for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.50; H, 5.45; N, 25.34.

2-Amino-5,6-dihydro-7-(1-pyrrolidinyl)quinazolin-4(1*H*)-one (**6a**).

A solution of guanidine hydrochloride (7.3 g, 76 mmoles) in methanol (70 ml) was added to a solution of sodium (1.75 g) in methanol (20 ml). After standing for 15 minutes the solution was filtered to remove sodium chloride and methyl 2-oxo-4-pyrrolidinocyclohex-3-enecarboxylate (10 g, 45 mmoles) was added to the filtrate. The resulting clear solution was refluxed for 3 hours during which time the product precipitated. After cooling it was collected and washed with hot methanol, yield 7.3 g (70%), mp >340° dec; ir (potassium bromide): ν = 3350, 1650, 1580, 1520, 1500 cm^{-1}. The solubility was too low for nmr spectra to be obtained.

Anal. Calcd. for $C_{12}H_{16}N_4O$: C, 62.05; H, 6.94; N, 24.12. Found: C, 62.25; H, 7.11; N, 24.33.

2-Amino-5,6-dihydro-5,5-dimethyl-7-(1-pyrrolidinyl)quinazolin-4(1*H*)-one (**6b**).

Prepared by a similar procedure, yield 71%, mp >320° dec (methanol); ir (potassium bromide): ν 3450, 1650, 1550, 1420, 800 cm^{-1}. The solubility was too low for nmr spectra to be obtained.

Anal. Calcd. for $C_{14}H_{20}N_4O$: C, 64.59; H, 7.74; N, 21.52. Found: C, 64.47; H, 8.04; N, 21.36.

2-Amino-5,5-dimethyl-7-(1-pyrrolidinyl)-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one (**7**) Dihydrochloride.

A solution of compound **6b** (1 g, 4 mmoles) in methanol (100 ml) and concentrated hydrochloric acid (10 ml) was hydrogenated over platinum(IV) oxide (0.1 g) at room temperature and pressure. One equivalent of hydrogen was absorbed over 22 hours and the uptake ceased. The solution was filtered and the solvent evaporated, yield 1.0 g (87%), mp 235-236° (ethanol); ir (potassium bromide): ν = 3400, 3300, 1650, 1560, 1100 cm^{-1}; ^{1}H-nmr (perdeuteriomethanol): δ = 1.30 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 2.00 (m, 6 H, 3 x CH_2), 3.00 (m, 4 H, 2 x CH_2), 3.55 (m, 2 H, CH_2).

Anal. Calcd. for $C_{14}H_{24}Cl_2N_4O$: C, 50.15; H, 7.22; Cl, 21.15; N, 16.71. Found: C, 50.06; H, 7.40; Cl, 21.15; N, 16.63.

N-(5,5-Dimethyl-3-ethoxy-4-methoxycarbonylcyclohex-2-eneylidene)pyrrolidinium Iodide (**8**).

A solution of compound **2k** (1.25 g, 5 mmoles) in iodoethane (10 ml) was refluxed for 6 hours. After the product had cooled to room temperature the yellow crystals were collected, yield (1.7 g, 83%), mp 144-145° (2-propanol); ir (potassium bromide): ν = 1740, 1600, 1260 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 1.16 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.40 (t, 3 H, CH_2CH_3), 2.20 (m, 6 H, 3 x CH_2), 2.85 (s, 4 H, 2 x CH_2), 3.70 (s, 3 H, OCH_3), 3.90 (s, 1 H, CH), 4.20 (q, 2 H, CH_2CH_3), 6.00 (s, 1 H, =CH-).

Anal. Calcd. for $C_{16}H_{26}INO_3$: C, 47.18; H, 6.43; I, 31.16; N, 3.44. Found: C, 46.88; H, 6.34; I, 30.90; N, 3.41.

8-(1-Pyrrolidinyl)-2,3,6,7-tetrahydro-1,6,6-trimethylimidazolo[2,3-*b*]quinazolin-5-one (**10**).

A solution of 1-methyl-2-amino-2-imidazoline (**9**) hydrobromide (1.35 g, 7.5 mmoles) in methanol (10 ml) was added to a solution of sodium (0.17 g) in methanol (10 ml) and allowed to stand until the sodium bromide precipitate had settled. The solution was filtered, a solution of compound **8** (2 g, 5 mmoles) in 2-methoxyethanol (25 ml) added to the filtrate and the mixture refluxed 4 days. The solvent was evaporated and the residue recrystallised, yield 1.1 g (73%), mp 213-215° (ethanol/water); ir (chloroform): ν = 1660, 1580, 1560, 1530, 1410 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 1.35 (s, 6 H, 2 x CH_3), 1.90 (m, 4 H, 2 x CH_2), 2.30 (s, 2 H, CH_2), 2.89 (s, 3 H, NCH_3), 3.30 (m, 6 H, 3 x CH_2), 3.95 (m, 2 H, CH_2), 4.82 (s, 1 H, =CH-).

Anal. Calcd. for $C_{17}H_{24}N_4O$: C, 67.97; H, 8.05; N, 18.65. Found:

C, 67.75; H, 8.12; N, 18.78.

2,3,6,7-Tetrahydro-1,6,6-trimethylimidazolo[2,3-*b*]quinazoline-5(1*H*),8(9*H*)-dione (**11**).

A solution of compound **10** (1.5 g, 5 mmoles) in hydrochloric acid (50 ml, 1 *M*) was kept on a boiling water bath for 20 hours during which time the uv maximum at 397 nm completely disappeared to be replaced by a new maximum at 330 nm. The solution was cooled, basified (5 *M* sodium hydroxide, 12 ml) and washed with dichloromethane (2 x 10 ml) which was rejected. The aqueous solution was then carefully brought to *p*H 7 by the addition of a few drops of dilute hydrochloric acid and extracted with dichloromethane (2 x 100 ml). The organic phase was dried (magnesium sulfate), evaporated and recrystallised, yield 0.5 g (40%), mp 157-159° (dichloromethane/ethyl acetate); ir (chloroform): ν = 1730, 1660, 1610, 1560, 1300 cm^{-1}; ^{1}H-nmr: δ = 1.37 (s, 6 H, 2 x CH_3), 2.45 (s, 2 H, CH_2), 2.95 (s, 3 H, NCH_3), 3.32 (s, 2 H, CH_2), 3.80 (m, 4 H, 2 x CH_2).

Anal. Calcd. for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 62.78; H, 6.90; N, 16.83.

6-Hydroxymethyl-3-pyrrolidinocyclohex-2-enone (**12**).

Sodium borohydride (15 g, 0.40 mole) was added to a solution of methyl 2-oxo-4-pyrrolidinocyclohex-3-enecarboxylate (3 g, 0.013 mole) in dry methanol (150 ml) in small portions (0.2-0.3 g at a time) over 6 hours with cooling to control the effervescence. The resulting mixture was stirred at room temperature for 1 hour and refluxed for 4 hours, cooled and the solvent removed. The residue was dissolved in the minimum of water (20 ml), basified with sodium hydroxide (2 ml of 5 *M*) and extracted with dichloromethane (2 x 25 ml). The organic solution was dried (magnesium sulfate), the solvent evaporated, yield 2.2 g (83%), mp 98-100° (toluene); ir (chloroform): ν = 3390, 1590, 1550 cm^{-1}; uv (ethanol): λ = 301 nm (ϵ = 34 200); ^{1}H-nmr (deuteriochloroform): δ = 1.95 (m, 6 H, 3 x CH_2), 2.50 (m, 2 H, CH_2), 3.30 (m, 4 H, 2 x CH_2), 3.68 (m, 2 H, CH_2), 4.55 (m, 1 H, CH), 5.00 (s, 1 H, =CH-).

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.70; H, 8.92; N, 7.23.

6-Methylidenyl-3-pyrrolidinocyclohex-2-enone Hydrobromide (**13**).

Freshly recrystallized compound **12** (2 g, 10 mmoles) was distilled (190-194°/0.6 mm) to give a yellow oil, yield 0.87 g (48%); ir (chloroform): ν = 1580, 1550 cm^{-1}; uv (ethanol): λ = 232 nm (ϵ 6 400), 327 nm (ϵ 24 000); ^{1}H-nmr (deuteriochloroform): δ = 1.95 (m, 6 H, 3 x CH_2), 2.60 (m, 2 H, CH_2), 3.30 (m, 4 H, 2 x CH_2), 5.12 (s, 2 H, $=CH_2$), 5.85 (s, 1 H, =CH-).

A sample was taken up in ethanol, treated with hydrogen bromide and the solvent evaporated to give the hydrobromide, mp 202-203° (ethanol/toluene).

Anal. Calcd. for $C_{11}H_{16}BrNO$: C, 51.18; H, 6.25; Br, 30.95; N, 5.43. Found: C, 51.10; H, 6.31; Br, 30.90; N, 5.45.

1-Methyl-8-pyrrolidino-1,2,3,5,6,7-hexahydroimidazolo[2,3-*b*]-quinazoline (**14**).

A solution of 2-amino-1-methyl-2-imidazoline hydrobromide (2.7 g, 15 mmoles) in methanol (20 ml) was added to sodium (0.34 g, 0.016 g-atom) in methanol (20 ml) and stirred 15 minutes. The product was filtered and the filtrate added to a solution of freshly distilled compound **13** (2.7 g, 15 mmoles) in 2-methoxyethanol (30 ml) and refluxed for 50 hours. The solvent was evaporated and the residue shaken with sodium hydroxide solution (5 ml of 5 *M*) and extracted with dichloromethane (4 x 25 ml). The organic solution was dried (magnesium sulfate) and the solvent evaporated, yield 1.2 g (30%), mp 202-204° (ethyl acetate/ethanol); ir (chloroform): ν = 1604, 1550, 1535, 1485, 1330 cm^{-1}; uv (ethanol): λ = 335 nm (50 600); ^{1}H-nmr (deuteriochloroform): δ = 2.00 (s, 2 H, CH_2), 2.40 (m, 4 H, 2 x CH_2), 2.80 (m, 4 H, 2 x CH_2), 2.95 (s, 3 H, N-CH_3), 3.40 (m, 8 H, 4 x CH_2), 5.58 (s, 1 H, =CH-).

Anal. Calcd. for $C_{15}H_{22}N_4$: C, 69.73; H, 8.58; N, 21.68. Found: C, 69.33; H, 8.60; N, 21.77.

1,2,3,5,5a,6-Hexahydro-1-methylimidazolo[2,3-*b*]quinazolin-8(7*H*)-one (**15**).

A solution of compound **14** (1.0 g, 4 mmoles) in 1% hydrochloric acid (10 ml) was allowed to stand on a boiling water bath for 15 minutes, cooled and neutralised by the careful addition of sodium bicarbonate. The product was extracted with dichloromethane (3 x 100 ml), dried (magnesium sulfate) and the solvent removed, yield 0.9 g (90%), mp 206-207° (ethanol); ir (potassium bromide): ν = 1678, 1572, 1547, 1525 cm^{-1}; uv (ethanol): λ = 328 nm; ^{1}H-nmr (deuteriochloroform): δ = 1.65 (s, 6 H, 3 x H_2O), 2.03 (m, 1 H, CH), 2.44 (m, 2 H, CH_2), 2.80 (m, 2 H, CH_2), 2.99 (s, 3 H, CH_3), 3.22-3.57 (m, 6 H, 3 x CH_2), 5.70 (s, 1 H, =CH-); ^{13}C-nmr (DMSO-d_6): δ = 26.6, 31.1, 32.8, 36.4, 46.4, 46.8, 47.3, 109.4, 159.4, 168.8, 197.4.

Anal. Calcd. for $C_{11}H_{15}N_3O \cdot 3H_2O$: C, 50.95; H, 8.16; N, 16.20. Found: C, 50.70; H, 7.93; N, 16.04.

X-Ray Crystallography.

Table 5 lists the experimental details. Data were collected with a Nicolet R3m diffractometer using graphite monochromatized MoKα radiation. Throughout data collections the intensities of three standard reflections were monitored at regular intervals and this indicated no significant crystal decomposition. Full sets of unique data were collected within the given scan ranges. Intensities were corrected for Lorentz and polarization effects but not for absorption. Reflections with $I > 3\sigma(I)$ were used for structure solutions and refinement.

All structures were solved by direct methods, and refined by full-matrix least-squares procedures. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were included in calculated positions with isotropic displacement parameters equal to the isotropic equivalent of their carrier atoms. The locations of OH and NH hydrogens and the conformations of *N*-methyl groups were deduced from Fourier difference maps. The methoxycarbonyl group of **2m** was disordered over two conformations with site occupancies of 0.75 and 0.25. The assymetric unit of **15** contains three molecules of water all of which are involved in a complex network of hydrogen bonding. The functions minimized were $\Sigma w(|F_o|-|F_c|)^2$, with $w = [\sigma^2(Fo)+gFo^2]^{-1}$. All calculations were performed using SHELXTL PC™ (version 4.1) [17]. Tables 6 and 7 list the final atom coordinates and equivalent isotropic displacement parameters for the four structures. There are no unusual features in the bond lengths or angles. Tabulations of bond lengths and angles, hydrogen atom coordinates, anisotropic thermal parameters, structure factors and equations of mean planes are available from the author (PJS).

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