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Synthesis of Pyrrolo[1,2-c]quinazoline Derivatives.

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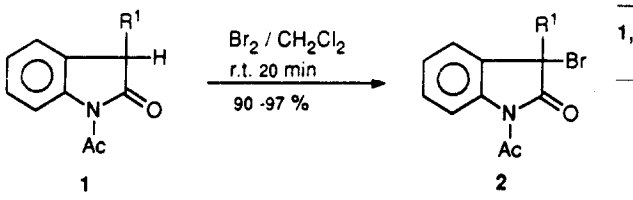
Abstract: *Δ^2-Pyrrolin-4-ones **12** and **13**, prepared from 1-acyl-3-alkyl-1,3-dihydro-2H-indol-2-ones **1**, via the corresponding 3-bromo-, **2** and **6**, 3-azido, **7** and **8**, and 3-iminophosphorane **9** and **10**, were cyclized to the corresponding pyrrolo[1,2-c]quinazoline derivatives **14** and **15**.*

In recent years substituted pyrrolo[1,2-c]quinazoline derivatives have received, only limited attention[1]. Recently a variety of pyrrolo[1,2-c]quinazolines were prepared by reacting the appropriate quinazolines or quinazolones with α-halopyruvates or α-haloketones[2]; dipolar cycloaddition reactions of quinazolinium yilids also gave pyrrolo[1,2-c]quinazoline derivatives[3]. We report a new synthesis of pyrrolo[1,2-c]quinazolin-1-ones **14** and (6*H*)pyrrolo[1,2-c]quinazolin-1,5-diones **15** starting, respectively, from 1-acetyl-3-alkyl-3-bromo-1,3-dihydro-2*H*-indol-2-ones **2** and 3-alkyl-3-bromo-1-ethoxycarbonyl-1,3-dihydro-2*H*-indol-2-ones **6**[4]. The reaction of 1-acetyl-3-alkyl-1,3-dihydro-2*H*-indol-2-ones **1** with bromine, in dichloromethane at r. t., gave the corresponding 3-bromoderivatives **2** in nearly quantitative yield (Scheme 1, Table 1).

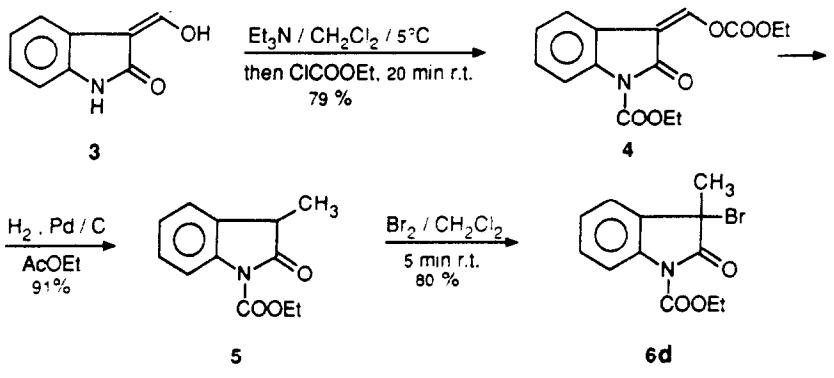
The 3-alkyl-3-bromo-1-ethoxycarbonyl-1,3-dihydro-2*H*-indol-2-ones **6** were prepared as previously reported[4]. The 3-bromo-3-methyl-1-ethoxycarbonyl-1,3-dihydro-2*H*- indol-2-one **6d**, a compound for which the reported general synthesis[4] is not applicable, was prepared from 3-(hydroxymethylene)indol-2-one **3**[5] following scheme 2 (see Experimental).

Scheme 1

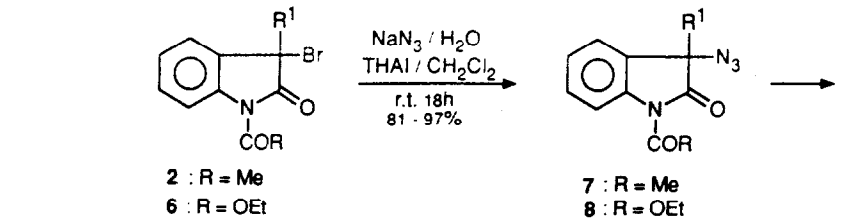


1, 2	R^1
a	Bn
b	Et
c	CH_2COOEt

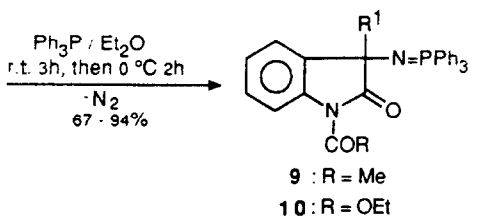
Scheme 2



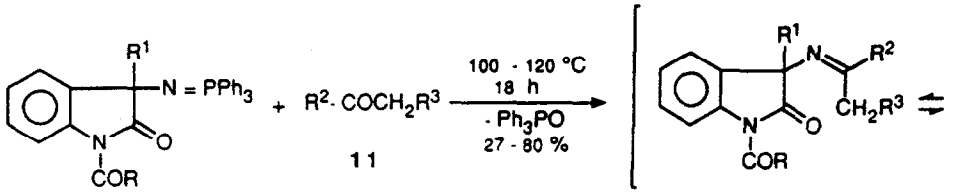
Scheme 3



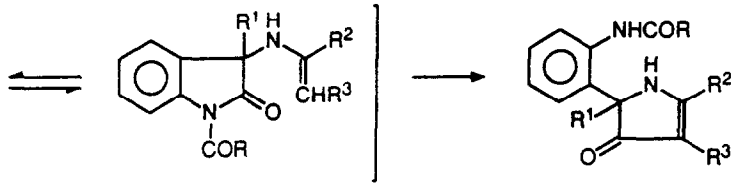
2, 7, 9	R^1	6, 8, 10
a	Bn	a
b	Et	b
c	CH_2COOEt	-
-	Me	d
-	n-Pr	e



Scheme 4



9 : R = Me
10 : R = OEt



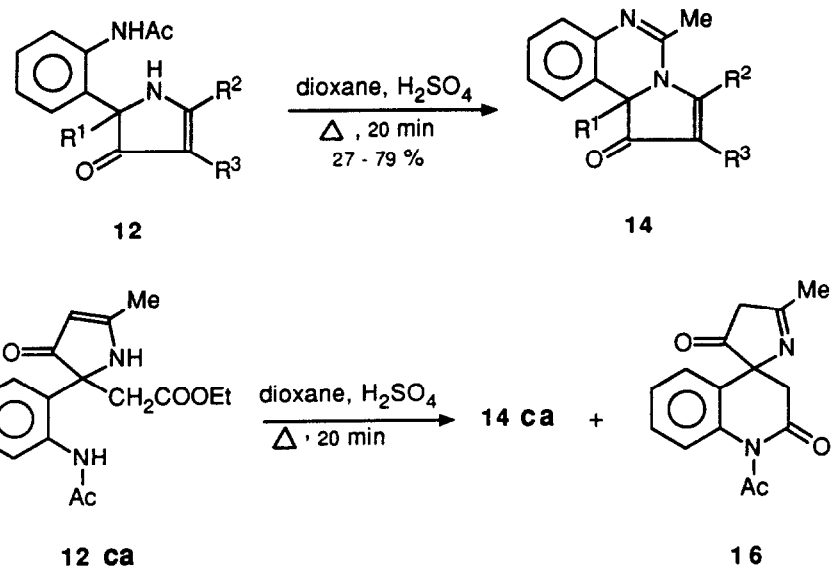
12 : R = Me
13 : R = OEt

11	R^2	R^3	12, 14	R^1	R^2	R^3	13
a	Me	H	**aa**	Bn	Me	H	**aa**
b	Me	Ph	**ab**	Bn	Me	Ph	**ab**
c	-$(CH_2)_6$-		**ac**	Bn	-$(CH_2)_6$-		**ac**
d	Et	Me	**ad**	Bn	Et	Me	--
e	Ph	H	**ae**	Bn	Ph	H	--
			ba	Et	Me	H	--
			bb	Et	Me	Ph	**bb**
			bc	Et	-$(CH_2)_6$-		**bc**
			ca	CH_2COOEt	Me	H	--
			cb	CH_2COOEt	Me	Ph	--
			--	Me	Me	H	**da**
			--	Me	Me	Ph	**db**
			--	n-Pr	Me	H	**ea**
			--	n-Pr	Me	Ph	**eb**

When the bromoderivatives **2** and **6** were treated, at r. t., with sodium azide in dichloromethane-water and in the presence of tetrahexylammonium iodide (THAI), the corresponding 3-azido-2*H*-indol-2-ones **7** and **8** were formed in good yields.

These compounds proved to be very stable: they melt without decomposing and can be stored at room temperature for long times. Their reaction with triphenylphosphine in ether at r. t., resulted in the formation of the corresponding iminophosphoranes **9** and **10** which crystallized out, pure and in high yields, from the reaction mixture (Scheme 3, Table 1). The reaction, at 100-120 °C for 18 h in a closed vessel, of the iminophosphoranes **9** and **10** with an excess of an anhydrous ketone **11**, resulted in the formation of the Δ^2-pyrrolin-4-ones **12** and **13** (Scheme 4, Table 2). The formation of these compounds clearly involves the enamine tautomer of the first formed imine. Compounds **12**, when heated under reflux in dioxane solution and in the presence of a catalytic amount of concentrated sulfuric acid, cyclize to the pyrrolo [1,2-c]quinazolin-1-ones **14** (Scheme 5, Table 3). No cyclization was observed with basic catalysis. Compound **12ca** resulted in **14ca** and another compound in equivalent amount. This last compound was tentatively assigned structure **16** on the basis of analytical and spectroscopic data.

Scheme 5



12 **14**

12 ca **16**

Instead, compounds **13**, in acidic conditions are very stable and cannot be cyclized in this way. However, when heated under reflux in ethanol solution and in the presence of a catalytic amount of EtONa, they cyclize to the (6*H*)pyrrolo[1,2-c]quinazolin-1,5-diones **15** (Scheme 6, Table 3); alkaline hydrolysis using KOH/$H_2$0, leads to the same result: also in this case only derivatives **15** were obtained. The structure of the new compounds was assigned on the basis of analytical and spectroscopic data (Table 4) as well as x-ray diffraction analysis[6] for compounds **12ca**, **14ba** and **15da**. Figures 1, 2, 3 show an ORTEP view of the molecules with the atomic numbering scheme of heavy atoms; thermal ellipsoids of C, N, and O atoms are drawn at 20%

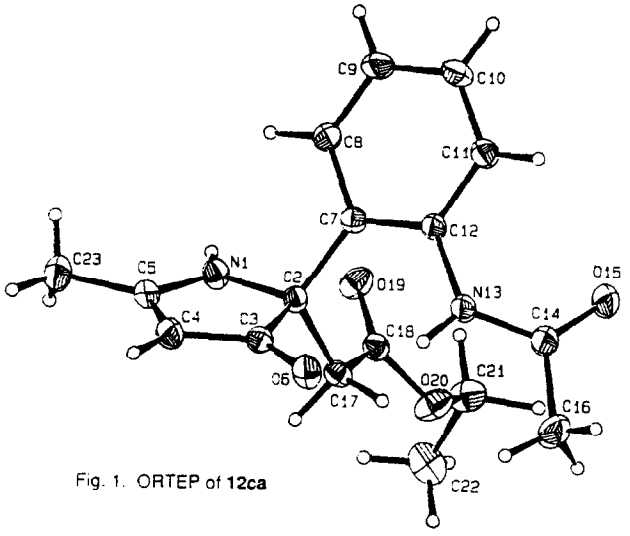


Fig. 1. ORTEP of **12ca**

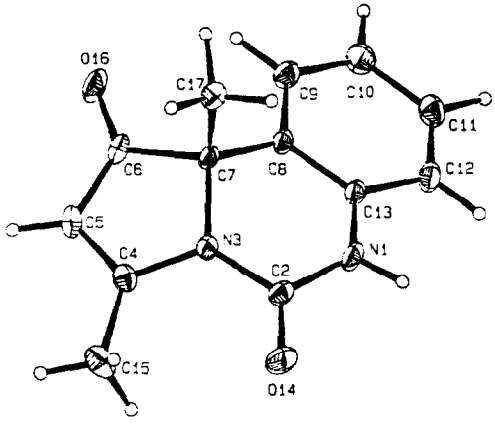


Fig. 3. ORTEP of **15da**

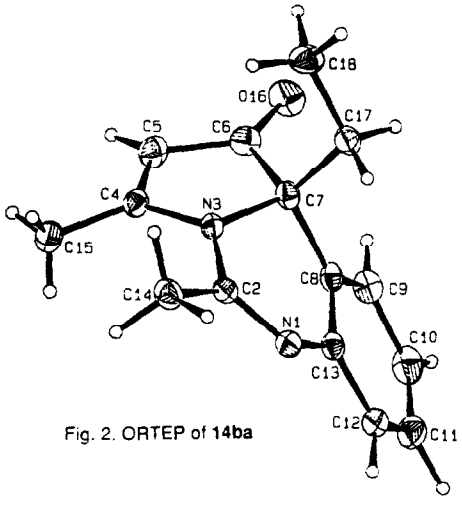
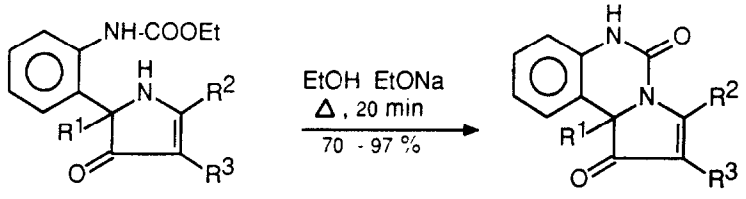


Fig. 2. ORTEP of **14ba**

probability level. Bond distances and angles in all the structures are in the normal range. The five membered ring is planar in **12ca**, while it presents an envelope conformation in **14ba** (q=0.123(1)Å^2, following Cromer and Pople[12]); **15da** shows an intermediate situation (q=0.0631(3) and 0.034(3)Å^2, respectively, for the two independent molecules). The N1, C2, N3, C7, C8, C13 hetero-ring present the same distorted boat conformation (^{1,4}B) both in **14ba** and in **15da**. No particularly relevant difference is found between equivalent geometrical parameters between the two independent molecules of **15da**: any difference can be due to packing forces. The packing of all three structures is essentially determined by a network of hydrogen bonds.

Scheme 6



13 **15**

13, 15	R^1	R^2	R^3
aa	Bn	Me	H
ab	Bn	Me	Ph
ac	Bn	-(CH$_2$)$_6$-	
bb	Et	Me	Ph
bc	Et	-(CH$_2$)$_6$-	
da	Me	Me	H
db	Me	Me	Ph
ea	n-Pr	Me	H
eb	n-Pr	Me	Ph

EXPERIMENTAL

Melting points were determined on a Buchi apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 instrument, in nujol mull for solids and as liquid film for oils. ^{1}H-NMR were recorded on a Bruker AC 300 spectrometer in $CDCl_3$ solution unless otherwise stated.

Column chromatography was performed on Merck Kieselgel 60, 0.063 - 0.2 mm and on Florisil 0.150 - 0.250 mm. Evaporation was carried out under vacuum in a rotary evaporator.

Compounds **1a**[7] and **1b**[8] were prepared according to the literature procedure. Compounds **6a,b,e** were prepared as previously reported [4].

Ethyl 1-Acetyl-1,3-dihydro-2H-Indol-2-one-3-acetate **1c.**
E-Ethyl 1-Acetyl-2*H*-indol-2-one-3-ylidene acetate [9] (2.5 g, 10 mmol) was dissolved in EtOAc (60 mL), 10% Pd/C (200 mg) was added and the mixture hydrogenated at r. t. and atmospheric pressure; After 15 min the catalyst was filtered off and the solvent evaporated. Crystallization from Et_2O - hexane gaves pure **1c**, 2.38 g (91 %), mp 79-80 °C.

1-Acetyl-3-Alkyl-3-Bromo-1,3-dihydro-2H-indol-2-ones **2**; *General Procedure*:
The 1-acetyl-3-alkyl-1,3-dihydro-2*H*-indol-2-one **1** (20 mmol) was dissolved in CH_2Cl_2 (60 mL) and then Br_2 (21 mmol) in CH_2Cl_2 (20 mL) was added. After 5 min at r. t. the solution was evaporated and the residue crystallized (Table 1).

1-Carbethoxy-3-(ethoxycarbonyloxymethylene)indol-2-one **4.**
Compound **3**[5] (4.83 g, 30 mmol) was dissolved in CH_2Cl_2 (100 mL) and Et_3N (16.7 mL, 120 mmol) was added. The solution was cooled at 0-5 °C and ethyl chloroformate (8.6 mL, 90 mmol) in CH_2Cl_2 (25 mL) was added. After 20 min at r. t. the mixture was washed with water (2 x 60 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was crystallized from Et_2O to give pure compound **4**, 7.24 g (79 %), mp 115 °C. Anal. calc. for $C_{15}H_{15}NO_6$: C 59.01 , H 4.95 , N 4.59 . Found: C 58.95 , H 5.01 , N 4.62 .

1-Carbethoxy-3-methyl-1,3-dihydro-2H-indol-2-one **5.**
Compound **4** (6.1 g, 20 mmol) was dissolved in AcOEt (150 mL), 10 % Pd/C (300 mg) was added and the mixture hydrogenated at r. t. and atmospheric pressure. After 3 h the catalyst was filtered off, the solvent evaporated and the residue purified by column chromatography on silica gel (eluent: CH_2Cl_2) to give pure compound **5**, 3.2 g (91 %), mp 75-76 °C from Et_2O-hexane. Anal. calc. for $C_{12}H_{13}NO_3$: C 65.74 , H 5.98 , N 6.39 . Found: C 65.68 , H 6.02 , N 6.43 .

3-Bromo-3-Methyl-1-Ethoxycarbonyl-1,3-dihydro-2H-indol-2-one **6d.**
Compound **5** (3.5 g, 20 mmol) was dissolved in CH_2Cl_2 (80 mL) and then Br_2 (1.13 mL, 22 mmol) in CH_2Cl_2 (20 mL) was added under stirring at r. t.. After 10 min the solution was evaporated and the residue purified by column chromatography on Florisil (eluent: CH_2Cl_2 / Et_2O 40 : 1), mp 59-60 °C from hexane, 4.8 g (80 %). Anal. calc. for $C_{12}H_{12}BrNO_3$: C 48.34 , H 4.06 , N 4.69 . Found: C 48.21 , H 4.01 , N 4.87 .

1-Acetyl-3-Alkyl-3-Azido-1,3-dihydro-2H-indol-2-ones **7** *and 3-Alkyl-3- Azido-1-carbethoxy-1,3-dihydro-2H-indol-2-ones* **8**; *General Procedure*:

Compound **2** or **6** (20 mmol) was dissolved in CH_2Cl_2 (50 mL) and then NaN_3 (6.5 g, 100 mmol) in H_2O (25 mL) and THAI (200 mg) were added. The mixture was stirred at room temperature for 18 h. The organic layer was washed with H_2O (40 mL), dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2 / hexane 1 : 1) and crystallized (Table 1).

Iminophosphoranes **9** *and* **10**; *General Procedure*:
Compound **7** or **8** (20 mmol) was dissolved in Et_2O (60 mL) and then Ph_3P (5.8 g, 22 mmol) in Et_2O (60 mL) was added under stirring at r. t.. N_2 was evolved and after 30 min crystallization occurs. After 3 h at r. t., the mixture was cooled at 0 °C for 2 h, filtered and washed with Et_2O (Table 1).

Δ^2-Pyrrolin-4-ones **12** *and* **13**; *General Procedure*:
A mixture of iminophosphorane **9** or **10** (3 mmol), appropriate anhydrous ketone **11** (4 mL) and activate molecular sieves (5 g, 4A, Aldrich) was placed in a closed steel vessel at 120 °C (100 °C for compounds **9b** and **10b** with **11c**), for 18 h. After this time, the reaction mixture was diluted with CH_2Cl_2 (20 mL), filtered and the residue purified by column chromatography (Table 2).

Pyrrolo[1,2-c]quinazolin-1-ones **14**; *General Procedure*:
A mixture of Δ^2-pyrrolin-4-one **12** (1 mmol), dioxane (20 mL) and H_2SO_4 97% (0.1 mL) was heated under reflux for 15'. After solvent evaporation, water was added (20 mL) and the residue extracted with CH_2Cl_2 (2 x 15 mL), dried (Na_2SO_4), filtered and evaporated. The crude mixture was purified by crystallization (Table 3).

(6H)-Pyrrolo[1,2-c]quinazolin-1,5-diones **15**; *General Procedure*:
The Δ^2-pyrrolin-4-one **13** (1 mmol) was dissolved in EtOH (30 mL) and a solution of EtONa in EtOH (5 mL, 3 mg/mL) was added. The mixture was heated under reflux for 30'. After solvent evaporation, water was added and the residue extracted with CH_2Cl_2 (2 x 15 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated and then purified by crystallization (Table 3).

X-ray structure determination of ***12ca, 14ba*** *and* ***15da.***
All single crystal X-ray measurements were performed on a *Nonius CAD-4* diffractometer, using graphite-monochromated Mokα radiation (λ=0.71073 Å). Data were corrected for Lorentz-polarization coefficient (Lp). The three structures were solved by direct methods (program MULTAN[10]); **15da** presented some problems because of the presence of 8 molecules in the unit-cell; despite the indications of the acentric group $Pca2_1$, given by statistic analysis, we attempted to solve the structure in the centrosymmetric space group *Pcam*. In fact no solution was obtained in the centrosymmetric group, while all C, N, O atoms of the two independent molecule were derived from the 'best' *E*-map in the acentric one; subsequent refinement has confirmed the acentric group. The refinements were made by minimizing the function $\Sigma w(F_o\text{-}k\ F_c)^2$, with

weights $w=1/\sigma^2(F_o)$, where $\sigma^2(F_o)=[\sigma^2(I)+0.0009I^2]/(2F_oLp)^2$. Scattering factors were taken from Ref 11; C, N, and O atoms were refined anisotropically, H atoms isotropically. Final difference Fourier maps showed no particular feature. Crystal data and some details of the data collection and full-matrix least-squares refinement are given in table 5.

Table 1. Compounds **2, 7, 8, 9, 10** Prepared.

Starting Material	Product	R^1	Yield (%)	mp (°C) (solvent)[a]
1a	**2a**	Bn	92	89-90 (Hx)
1b	**2b**	Et	97	79-80 (Hx-Et_2O)
1c	**2c**	CH_2COOEt	80	88-89 (Hx)
2a	**7a**	Bn	85	59-60 (Hx-Et_2O)
2b	**7b**	Et	94	19-20 (Hx)
2c	**7c**	CH_2COOEt	88	33-34 (Hx-Et_2O)
6a	**8a**	Bn	92	58-60 (Hx-Et_2O)
6b	**8b**	Et	97	45-46 (Hx)
6d	**8d**	Me	84	72-73 (Et_2O)
6e	**8e**	n-Pr	81	oil
7a	**9a**	Bn	91	166-168 (Et_2O)
7b	**9b**	Et	83	133-135 (Et_2O)
7c	**9c**	CH_2COOEt	94	174-176 (Et_2O)
8a	**10a**	Bn	70	183-185 (Et_2O)
8b	**10b**	Et	90	135-136 (Et_2O)
8d	**10d**	Me	88	175-176 (Et_2O)
8e	**10e**	n-Pr	67	117-118 (Et_2O)

[a] Hx: hexane.

Table 2. Δ^2-Pyrrolin-4-ones **12** and **13** Prepared.

Starting Material	Product	Eluent	Yield %	mp (°C) (solvent)[a]
9a	**12aa**	CH_2Cl_2/Et_2O (3:1)	51	258-260 (CH_3COCH_3)
9a	**12ab**	CH_2Cl_2/AcOEt (5:1)	75	221-222 (CH_2Cl_2-Et_2O)
9a	**12ac**	CH_2Cl_2/Et_2O (5:1)	70	216-218 (Et_2O)
9a	**12ad**	Hx/CH_3COCH_3 (2:1)	37	192-193 (Et_2O)
9a	**12ae**	CH_2Cl_2/AcOEt (3:1)	48	235-237 (CH_2Cl_2-Et_2O)
9b	**12ba**	CH_2Cl_2/MeOH (20:1)	64	227-229 (Et_2O)
9b	**12bb**	CH_2Cl_2/Et_2O (4:1)	60	128-130 (Et_2O)
9b	**12bc**	CH_2Cl_2/CH_3COCH_3 (2:1)	65	234-236 (CH_2Cl_2-Et_2O)
9c	**12ca**	CH_2Cl_2/Et_2O (4:1)	55	169-170 (CH_2Cl_2-Et_2O)
9c	**12cb**	CH_2Cl_2/AcOEt (2:1)	39	175-176 (CH_2Cl_2-Et_2O)
10a	**13aa**	CH_2Cl_2/MeOH (80:1)	31	233-234 (Et_2O)
10a	**13ab**	CH_2Cl_2/Et_2O (50:1)	47	163-165 (Hx-Et_2O)
10a	**13ac**	CH_2Cl_2/Et_2O (10:1)	50	200-202 (Et_2O)
10b	**13bb**	CH_2Cl_2/Et_2O (20:1)	39	151-152 (Et_2O)
10b	**13bc**	CH_2Cl_2/Et_2O (20:1)	48	205-207 (Et_2O)
10d	**13da**	CH_2Cl_2/CH_3COCH_3 (20:1)	43	194-195 (CH_2Cl_2-Et_2O)
10d	**13db**	CH_2Cl_2/Et_2O (6:1)	27	158-160 (CH_2Cl_2-Et_2O)
10e	**13ea**	CH_2Cl_2/Et_2O (5:1)	80	200-201 (Et_2O)
10e	**13eb**	CH_2Cl_2/Et_2O (20:1)	53	147-148 (Hx-Et_2O)

[a] Hx: hexane.

Table 3. Pyrrolo[1,2-c]quinazolin-1-ones **14** and (6H)Pyrrolo[1,2-c]-quinazolin-1,5- diones **15** Prepared.

Starting material	Product	Yield %	mp (°C) (solvent)[a]
12aa	**14aa**	54	243-245 (Hx-Et_2O)
12ab	**14ab**	78	214-216 (CH_2Cl_2-Et_2O)
12ac	**14ac**	75	191-192 (Et_2O)
12ad	**14ad**	79	95-96 (Et_2O)
12ae	**14ae**	43	119-120 (Hx-Et_2O)
12ba	**14ba**	63	97-98 (Hx-Et_2O)
12bb	**14bb**	75	168-169 (Et_2O)
12bc	**14bc**	45	114-115 (Hx)
12ca	**14ca**	27	oil
12ca	**16**	27	210-212 (Et_2O)
12cb	**14cb**	42	91-92 (Hx-Et_2O)
13aa	**15aa**	94	237-239 (CH_2Cl_2-Et_2O)
13ab	**15ab**	97	198-200 (CH_2Cl_2-Et_2O)
13ac	**15ac**	95	221-223 (Et_2O)
13bb	**15bb**	96	213-215 (Hx-Et_2O)
13bc	**15bc**	97	168-170 (Et_2O)
13da	**15da**	70	223-224 (CH_2Cl_2-Et_2O)
13db	**15db**	78	163-165 (Hx-Et_2O)
13ea	**15ea**	83	182-184 (Et_2O)
13eb	**15eb**	94	204-206 (Et_2O)

[a] Hx: hexane.

Table 4. Spectral Data of New Compounds

Product	IR (Nujol or film) ν cm^{-1}	^1H - NMR δ, J (Hz)
1c	1758, 1728, 1702	1.13 (t, 3H, 7.0), 2.67 (s, 3H), 3.03 (2H, m), 3.90(1H, t, 5.5), 4.06 (2H, q, 7.0), 7.22 (3H, m), 8.20 (1H, d, 8.0)
2a	1760, 1712	2.65 (3H, s), 3.82 and 3.86 (2H, AB, 15), 7.13 (7H, m), 7.50 (1H, m), 8.05 (1H, m)
2b	1775, 1731	0.79 (3H, t, 7.0), 2.50 (2H, m), 2.71 (3H, s), 7.27 (1H, dt, 7.5 and 0.9), 7.36 (1H, dd, 8.0 and 1.5), 7.43 (1H, dt, 8.0 and 1.5), 8.22 (1H, d, 8.0)
2c	1777, 1730	1.00 (3H, t, 7.0), 2.72 (3H, s), 3.57 and 3.72 (2H, AB, 17), 3.90 (2H, m), 7.20 (1H, d, 7.3), 7.37 (2H, m), 8.23 (1H, d, 8.0)
4	1785, 1738, 1688	1.44 (3H, t, 7.0), 1.46 (3H, t, 7.0), 4.46 (2H, q, 7.0), 4.51 (2H, q, 7.0), 7.26 (1H, m), 7.40 (1H, m), 7.85 (1H, d, 8.0), 7.98 (1H, d, 8.0), 8.38 (1H, s)
5	1772, 1736	1.45 (3H, t, 7.0), 1.53 (3H, d, 7.5), 3.59 (1H, q, 7.5), 4.47 (2H, q, 7.0), 7.18 (2H, m), 7.30 (1H, m), 7.80 (1H, d, 8.0)
6d	1789, 1750, 1615	1.47 (3H, t, 7.0), 1.54 (3H, s), 4.49 (2H, q, 7.0), 7.23 (1H, m), 7.39 (1H, m), 7.48 (1H, d, 7.5), 7.91 (1H, d, 8.2)
7a	2105, 1760, 1720	2.72 (3H, s), 3.43 (2H, s), 6.90 (2H, m), 7.22 (6H, m), 8.08 (1H, d, 8.0)
7b	2120, 1770, 1730	0.78 (3H, t, 7.5), 2.15 (2H, m), 2.70 (3H, s), 7.30 (2H, m), 7.40 (1H, m), 8.25 (1H, d, 8.0)
7c	2103, 1770,1738, 1720	1.04 (3H, t, 7.0), 2.78 (3H, s), 3.22 and 3.40 (2H, AB, 17), 3.98 (2H, q, 7.0), 7.35 (3H, m), 8.30 (1H, d, 8.0)
8a	2118, 2080, 1768, 1735	1.41 (3H, t, 7.1), 3.31 and 3.35 (2H, AB, 13), 4.41 (2H, q, 7.1), 6.89 (2H, m), 7.15 (5H, m), 7.32 (1H, m), 7.73 (1H, d, 8.1)
8b	2118, 2100, 1771, 1750	0.78 (3H, t, 7.5), 1.44 (3H, t, 7.2), 2.14 (2H, m), 4.77 (2H, q, 7.2), 7.25 (2H, m), 7.39 (1H, m), 7.93 (1H, d, 8.3)
8d	2130, 2080, 1779, 1750	1.47 (3H, t, 7.0), 1.73 (3H, s), 4.48 (2H, q, 7.0), 7.23 (1H, m), 7.34 (1H, m), 7.39 (1H, m), 7.93 (1H, d, 8.2)
8e	2100, 1775, 1740	0.85 (3H, t, 7.2), 1.10 (2H, m), 1.42 (3H, t, 7.1), 2.08 (2H, m), 4.45 (2H, q, 7.1), 7.30 (3H, m), 7.92 (1H, d, 8.2)
9a	1752, 1704	2.18 (3H, s), 3.40 (2H, bs), 6.75-7.75 (24H, m)
9b	1770, 1710	0.68 (3H, t, 7.5), 2.12 (2H, m), 2.25 (3H, s), 6.98 (1H, m), 7.09 (1H, m), 7.26-7.58 (15H, m), 7.66 (1H, m), 7.89 (1H, d, 8.0)
9c	1761, 1721, 1700	0.73(3H, t, 7.5), 2.32 (3H, s), 3.20 and 3.37 (2H, AB, 15), 3.73 (2H, q, 7.5), 6.90-7.70 (18H, m), 7.91 (1H, d, 8.0)
10a	1765, 1718	1.26 (3H, t, 7.1), 3.34 (2H, m), 4.18 (2H, q, 7.1), 6.89 (3H, m), 7.02 (4H,

		m), 7.12 (1H, m), 7.28 (8H, m), 7.39 (2H, m), 7.57 (6H, m)
10b	1776, 1730 (CCl_4)	0.69 (3H, t, 7.4), 1.33 (3H, t, 7.1), 2.11 (2H, m), 4.26 (2H, q, 7.1), 6.94 (1H, m), 7.06 (1H, m), 7.30 (7H, m), 7.40 (4H, m), 7.55 (6H, m)
10d	1765, 1728	1.33 (3H, t, 7.0), 1.64 (3H, s), 4.27 (2H, q, 7.0), 6.97 (1H, m), 7.08 (1H, m), 7.45 (17H, m)
10e	1765, 1725	0.76 (3H, t, 7.2), 1.10 (2H, m), 1.34 (3H, t, 7.5), 2.05 (2H, m), 4.25 (2H, q, 7.5), 6.94 (1H, m), 7.06 (1H, m), 7.26-7.59 (17H, m)
12aa	3190, 1690, 1619	DMSO: 2.15 (3H, s), 2.35 (3H, s), 3.40 and 3.51 (2H, AB, 15), 4.67 (1H, d, 1.5, s after D_2O), 7.14 (8H, m), 8.00 (1H, d, 8.0), 8.83 (1H, bs)[a], 12.5 (1H, bs)[a]
12ab	3240, 1667, 1632	2.21 (3H, s), 2.31 (3H, s), 3.45 and 3.56 (2H, AB, 13.5), 6.21 (1H, bs)[a], 7.00 (4H, m), 7.22 (9H, m), 8.03 (1H, d, 8.0), 12.05 (1H, bs)[a]
12ac	3280, 1677, 1647	1.20-1.80 (8H, m), 2.21 (2H, m), 2.33 (3H, s), 2.55 (2H, m), 3.30 and 3.57 (2H, AB, 13.5), 5.51 (1H, bs)[a], 6.92 (3H, m), 7.15 (4H, m), 7.27 (1H, m), 8.03 (1H, d, 8.0), 12.3 (1H, bs)[a]
12ad	3258, 1679, 1648	1.13 (3H, t, 7.5), 1.61 (3H, s), 2.34 (3H, s), 2.47 (2H, q, 7.5), 3.20 (1H, d, 14),3.66 (1H, d, 14), 5.35 (1H, bs)[a], 6.90 (3H, m), 7.13 (4H, m), 7.28 (1H, m), 8.03 (1H, d, 8.0), 12.15 (1H, bs)[a]
12ae	3280, 1666, 1641	2.33 (3H, s), 3.27 (1H, d, 13.3), 3.88 (1H, d, 13.3), 5.45 (1H, d, 1.5, s after D_2O), 5.94 (1H, bs)[a], 6.90 (3H, m), 7.20 (4H, m), 7.60 (6H, m), 8.06 (1H, d, 8.3), 11.90 (1H, bs)[a]
12ba	3190, 1695, 1622	0.71 (3H, t, 7.0), 2.10 (2H, m), 2.21 (3H, s), 2.29 (3H, s), 4.94 (1H, s), 6.43 (1H, bs)[a], 6.97 (1H, t, 7.5), 7.21 (2H, m), 7.91 (1H, d, 8.0), 11.73 (1H, bs)[a]
12bb	3258, 1675, 1648	0.77 (3H, m), 2.18 (2H, m), 2.24 (3H, s), 2.43 (3H, s), 6.57 (1H, bs)[a], 7.01 (1H, m), 7.21 (2H, m), 7.35 (5H, m), 7.91 (1H, m), 11.78 (1H, bs)[a]
12bc	3262, 1673, 1662	0.76 (3H, t, 7.0), 1.45 (6H, m), 1.90 (2H, m), 2.10 (2H, m), 2.25 (3H, s), 2.30 (2H, m), 2.68 (2H, m), 5.95 (1H, bs)[a], 7.00 (1H, m), 7.30 (2H, m), 7.97 (1H, d, 8.0), 11.96 (1H, bs)[a]
12ca	3300, 1732, 1675, 1640	1.05 (3H, t, 7.0), 2.32 (3H, s), 2.38 (3H, s), 2.73 (1H, d, 17), 3.66 (1H, d, 17), 3.95 (2H, q, 7.0), 5.00 (1H, d, 1.5, s after D_2O), 6.95-7.42 (4H, m, 3H after D_2O), 8.00 (1H, d, 8.0), 11.50 (1H, bs)[a]
12cb	3220, 1765, 1695, 1649	1.13 (3H, t, 7.1), 2.26 (3H, s), 2.34 (3H, s), 2.69 (1H, d, 16.5), 3.14 (1H, d, 16.5), 4.11 (2H, m), 5.78 (1H, bs)[a], 6.82 (1H, d, 8.0), 7.05 (2H, m), 7.25-7.45 (5H, m), 7.90 (1H, d, 8.2), 9.68 (1H, bs)[a]
13aa	3150, 3050, 1728, 1618	1.33 (3H, t, 7.0), 2.16 (3H, s), 3.41 and 3.51 (2H, AB, 13), 4.25 (2H, q, 7.0), 4.75 (1H, d, 1.5, s after D_2O), 7.03-7.28 (8H, m), 7.67 (1H, bs)[a], 7.91 (1H, d, 8.0), 11.50 (1H, bs)[a]
13ab	3280br, 1740, 1613	1.29 (3H, t, 7.0), 2.20 (3H, s), 3.47 and 3.64 (2H, AB, 13), 4.22 (2H, m), 5.89 (1H, bs)[a], 6.92 (3H, m), 7.05-7.38 (10H, m), 7.93 (1H, d, 8.0), 11.17 (1H, bs)[a]

13ac	3280 br, 1699, 1615	1.20-1.40 (9H, m), 1.70 (2H, m), 2.20 (2H, m), 2.54 (2H, m), 3.31 and 3.65 (2H, AB, 13.7), 4.24 (2H, m), 5.35 (1H, bs)[a], 6.92 (3H, m), 7.16 (4H, m), 7.25 (1H, m), 7.95 (1H, d, 8.0), 11.48 (1H, bs)[a]
13bb	3250, 1730, 1695, 1642	0.82 (3H, t, 7.4), 1.29 (3H, t, 7.1), 2.22 (1H, m), 2.38 (1H, m), 2.42 (3H, s), 4.21 (2H, m), 5.89 (1H, bs)[a], 7.01 (1H, m), 7.18-7.38 (7H, m), 7.80 (1H, d, 8.1), 10.84 (1H, bs)[a]
13bc	3320, 1736, 1705, 1649	0.77 (3H, t, 7.4), 1.32 (3H, t, 7.1), 1.50 (6H, m), 1.85 (2H, m), 2.10 (1H, m), 2.27 (2H, m), 2.32 (1H, m), 2.66 (2H, t, 6.4), 4.21 (2H, m), 5.50 (1H, bs)[a], 6.96 (1H, m), 7.23 (1H, m), 7.32 (1H, m), 7.89 (1H, d, 8.0), 11.13 (1H, bs)[a]
13da	3190, 3080, 1737, 1628	1.31 (3H, t, 7.0), 1.74 (3H, s), 2.26 (3H, s), 4.21 (2H, q, 7.0), 4.94 (1H, s), 5.97 (1H, bs)[a], 6.98 (1H, m), 7.28 (2H, m), 7.81 (1H, d, 8.0), 11.30 (1H, bs)[a]
13db	3260 br, 1740, 1688	1.29 (2H, t, 7.0), 1.83 (3H, s), 2.40 (3H, s), 4.21 (2H, q, 7.0), 5.89 (1H, bs)[a], 7.02 (1H, m), 7.24-7.55 (7H, m), 7.94 (1H, d, 8.0), 10.34 (1H, bs)[a]
13ea	3190, 3090, 1728, 1629	0.90 (3H, m), 1.19 (2H, m), 1.34 (3H, t, 7.0), 2.15 (2H, m), 2.31 (3H, s), 4.22 (2H, q, 7.0), 4.93 (1H, s), 5.87 (1H, bs)[a], 6.95-7.35 (3H, m), 7.79 (1H, m), 10.70 (1H, bs)[a]
13eb	3280, 3240, 1729, 1698	0.90 (3H, m), 1.32 (2H, m), 1.34 (3H, t, 7.0), 2.17 (2H, m), 2.42 (3H, s), 4.23 (2H, q, 7.0), 6.02 (1H, bs)[a], 6.98-7.41 (8H, m), 7.86 (1H, m), 10.70 (1H, bs)[a]
14aa	1698	2.14 (3H, s), 2.48 (3H, s), 2.98 and 3.20 (2H, AB, 13.5), 4.97 (1H, s), 7.04 (2H, m), 7.22 (5H, m), 7.32 (1H, m), 7.86 (1H, d, 7.5)
14ab	1678	2.12 (3H, s), 2.57 (3H, s), 3.07 and 3.28 (2H, AB, 13.3), 6.94 (2H, m), 7.07 (2H, m), 7.20-7.40 (9H, m), 8.08 (1H, d, 7.5)
14ac	1675	0.45-1.80 (8H, m), 2.40-2.60 (4H, m), 2.57 (3H, s), 2.98 and 3.23 (2H, AB, 13.4), 7.07 (2H, m), 7.17-7.34 (6H, m), 7.94 (1H, dd, 8 and 1)
14ad	1680	0.80 (3H, t, 7.5), 1.51 (3H, s), 2.42 (2H, m), 2.50 (3H, s), 2.99 and 3.21 (2H, AB, 13.5), 7.02 (2H, m), 7.25 (6H, m), 7.96 (1H, d, 7.5)
14ae	1694	1.76 (3H, s), 3.05 (1H, d, 13.5), 3.32 (1H, d, 13.5), 5.03 (1H, s), 6.86 (2H, m), 7.12 (2H, m), 7.30 (9H, m), 8.04 (1H, d, 7.5)
14ba	1697	0.77 (3H, t, 7.5), 1.86 (2H, m), 2.40 (3H, s), 2.51 (3H, s), 5.18 (1H, s), 7.20 (3H, m), 7.80 (1H, d, 7.5)
14bb	1670	0.83 (3H, t, 7.5), 1.94 (2H, m), 2.48 (3H, s), 2.60 (3H, s), 7.19 (1H, m), 7.28 (5H, m), 7.40 (2H, m), 7.90 (1H, d, 7.5)
14bc	1680	0.74 (3H, t, 7.5), 1.50 (6H, m), 1.86 (4H, m), 2.18 (1H, m), 2.42 (1H, m), 2.54 (3H, s), 2.83 (2H, m), 7.18 (3H, m), 7.77 (1H, d, 7.4)
14ca	1740, 1690	1.15 (3H, t, 7.2), 2.35 (3H, s), 2.50 (3H, s), 2.75 and 2.85 (2H, AB, 14.3), 4.02 (2H, q, 7.2), 5.23 (1H, s), 7.21 (3H, m), 7.76 (1H, d, 7.5)
14cb	1731, 1678	1.13 (3H, t, 7.1), 2.44 (3H, s), 2.60 (3H, s), 2.84 and 2.96 (2H, AB, 14.4), 4.03 (2H, q, 7.1), 7.20-7.40 (8H, m), 7.85 (1H, d, 7.7)

15aa	3190, 1719, 1668	2.35 (3H, s), 3.16 (2H, s), 5.07 (1H, s), 6.79 (1H, d, 8.0), 7.00-7.30 (7H, m), 7.67 (1H, bs)[a], 8.08 (1H, d 8.0)
15ab	3220, 1701, 1683	2.36 (3H, s), 3.24 (2H, s), 6.88 (3H, m), 7.00-7.30 (10H, m), 7.40 (1H, bs)[a], 8.17 (1H, m)
15ac	3200, 1692, 1678	0.25 (1H, m), 1.05 (3H, m), 1.50 (1H, m), 1.65 (3H, m), 1.90 (1H, m), 2.40 (1H, m), 2.70 (1H, m), 3.08 (1H, m), 3.16 and 3.22 (2H, AB, 13.3), 6.83 (1H, d, 7.8), 7.10 (3H, m), 7.19 (3H, m), 7.27 (1H, m), 7.86 (1H, bs)[a], 8.02 (1H, d, 7.6)
15bb	3200, 1695, 1679	0.90 (3H, t, 7.4), 2.08 (2H, m), 2.72 (3H, s), 6.85 (1H, d, 7.8), 7.08 (1H, m), 7.26 (1H, m), 7.32 (3H, m), 7.42 (2H, m), 8.00 (1H, d, 7.7), 8.05 (1H, bs)[a]
15bc	3220, 1700, 1681	0.80 (3H, t, 7.3), 1.50 (6H, m), 1.98 (4H, m), 2.21 (1H, m), 2.43 (1H, m), 3.15 (2H, m), 6.78 (1H, d, 7.7), 7.02 (1H, m), 7.21 (1H, m), 7.80 (1H, bs)[a], 7.89 (1H, d, 7.8)
15da	3190, 1720, 1668	1.60 (3H, s), 2.60 (3H, s), 5.36 (1H, s), 6.81 (1H, d, 8.0), 7.06 (1H, m), 7.22 (1H, m), 7.68 (1H, bs)[a], 7.93 (1H, d, 8.0)
15db	3220, 1715, 1694	1.68 (3H, s), 2.72 (3H, s), 6.90-7.60 (8H, m), 8.01 (1H, d, 8.0), 8.32 (1H, bs)[a]
15ea	3240, 1700, 1668	0.82 (3H, t, 7.0), 1.30 (2H, m), 1.91 (2H, m), 2.60 (3H, s), 5.36 (1H, s), 6.81 (1H, d, 8.0), 7.05 (1H, m), 7.24 (1H, m), 7.76 (1H, bs)[a], 7.91 (1H, d, 8.0)
15eb	3220, 1692, 1604	0.85 (3H, t, 7.0), 1.36 (2H, m), 2.04 (2H, m), 2.69 (3H, s), 6.81 (1H, m), 7.00-7.38 (7H, m), 7.84 (1H, bs)[a], 8.01 (1H, m)
16	1798, 1688, 1652	2.07 (3H, s), 2.42 (3H, s), 3.11 and 3.14 (2H, AB, 18.6), 3.35 and 3.52 (2H, AB, 18.6), 7.15 (1H, m), 7.32 (1H, m), 7.44 (1H, d, 7.3), 8.19 (1H, m)

[a] Exchange with D_2O.

Table 5. Details of crystallographic data, data collection and structure refinement

	12ca	**14ba**	**15da**
System	monoclinic	monoclinic	orthorombic
space group	$P2_1/n$	$P2_1/n$	$Pca2_1$
a, Å	9.033(2)	7.870(1)	15.926(3)
b, Å	14.153(3)	19.033(1)	6.936(1)
c, Å	12.974(4)	7.730(1)	23.230(2)
β, deg	93.42(2)	107.51(1)	
Volume, $Å^3$	1655.7(7)	1104.2(2)	2566.1(7)
Z	4	4	8

Table 5. Details of crystallographic data, data collection and structure refinement

	12ca	**14ba**	**15da**
D_x, g. cm^{-3}	1.269	1.373	1.244
ϑ_{max} of data collection, deg	25.0	27.5	25.0
No. unique reflections collected	2912	2520	2318
No. observed reflections [I>σ(I)]	1793	2243	2017
R	0.039	0.043	0.044
R_w	0.038	0.042	0.039
$(\Delta/\sigma)_{max}$ in the last least-square cycle	0.07	0.01	0.01
maximum residue in Δ map, e/Å^{-3}	0.21	0.18	0.20

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