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Short communication

Conformational analysis and inotropic activity of 2-substituted-5-cyano-1,6-dihydro-6-oxo-3-pyridine carboxylates. II*

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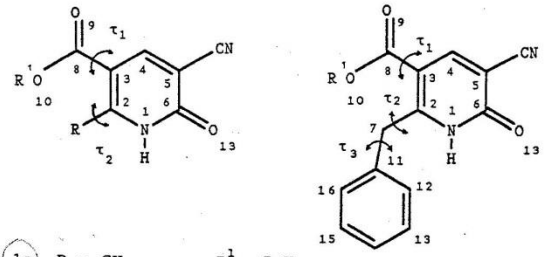
Summary — Single-crystal X-ray work has been carried out on the 2-benzyl-5-cyano-1,6-dihydro-6-oxo-3-methoxycarbonyl pyridine compound **1f.** It crystallizes in the triclinic system space group $P\bar{1}$. Minimum energy conformations of 2-(alkyl or arylalkyl) 5-cyano-1,6-dihydro-6-oxo-3-pyridine carboxylates showing different biological activity have been calculated by the semiempirical MNDO and AM1 methods. A most critical factor for the different inotropic activities (positive or negative) of compounds **1a – 1f** seems to be related to the location and the steric requirements of a 'pocket' in the receptor boundary that limit the size of the substituent at position 2.

ethyl 2-substituted-5-cyano-1,6-dihydro-6-oxo-3-pyridine carboxylates / MNDO/AM1 / inotropic activity / X-ray analysis

Introduction

Compounds **1a–1f** [1] (fig 1) exhibit different inotropic activity. They were tested on contractile activity and frequency rate of spontaneously beating atria from reserpine-treated guinea pigs and their effects were compared with the effects of milrinone. As discussed in previous papers [1, 2], ester **1a** induces greatest increase of contractile force: furthermore, the maximum inotropic effect is obtained at a concentration (10^{-4} M) lower than that of milrinone. The action on the atria is also characterized by an increase in frequency rate compared to that induced by milrinone. Compound **1b** has a positive inotropic and chronotropic effect: its influence is, however, less marked than that induced by **1a.** Compounds **1c** and **1e** are marginally active as inotropic agents whereas **1d** and **1f** induce a marked negative inotropic effect and have a negative influence on chronotropism (fig 2).

A preliminary investigation [3] on ethyl 2-alkyl-substituted-5-cyano-1,6-dihydro-6-oxo-3-pyridine carboxylates **1a, 1c, 1d** suggested a relation between the positive inotropic activity exhibited by these compounds and a nearly coplanar conformation of the $COOR^1$ group and the α-pyridone ring.



1a R = CH_3 ; R^1 = C_2H_5
1b R = CH_2-CH_3 ; R^1 = C_2H_5
1c R = $CH(CH_3)_2$; R^1 = C_2H_5
1d R = $C(CH_3)_3$; R^1 = C_2H_5
1e R = C_6H_5 ; R^1 = C_2H_5
1f R^1 = CH_3

Fig 1. Formula and numbering scheme adopted for compounds **1a–1f.**

* Part I was published in *Eur J Med Chem* (1990), 25, 425.

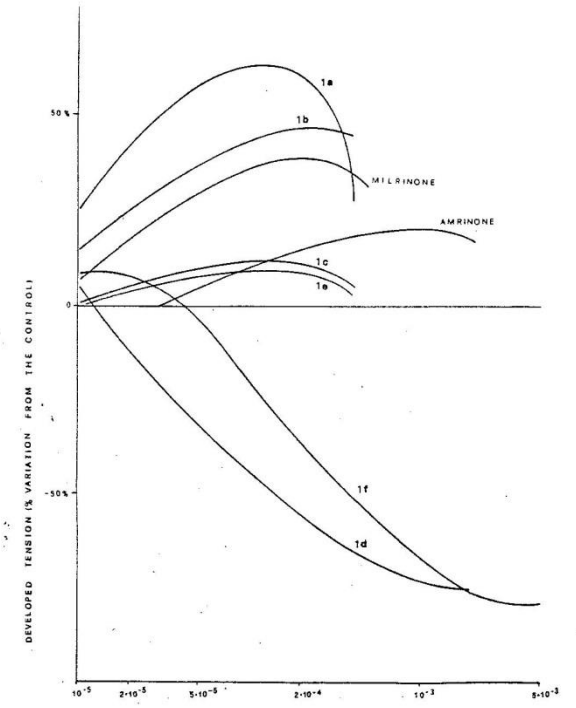


Fig 2. Effect of compounds **1a–1f** on contractile force of spontaneously beating guinea-pig isolated atria.

To verify this hypothesis further and to obtain a better understanding of the role of the substituent at position 2, we have extended our investigation to 2-ethyl-, 2- benzyl- and 2-phenyl- derivatives **1b, 1f** and **1e**.

Results

X-ray study

The X-ray analysis on compound **1f** was carried out in order to obtain a direct comparison with analogous investigation on **1a, 1d, le** [1] and **1c** [3] which have different pharmacological activities.

The crystal structure of **1f** (mp: 254–255°) is characterized by 2 independent molecules in the asymmetric unit. It_ crystallizes in the triclinic system space group P1, a = 12.220(3), b = 11.410(3), c = 12.144(3) Å, α = 119.11(3)°, β = 62.97(3)°, γ = 105.26(4)°, z = 4, V = 1314.5(8) Å^3, $R(F)$ = 0.040 [$R_w(F)$ = 0.45] (room temperature). An ORTEP plot [4] of the 2 molecules with the numbering scheme used is shown in figure 3: atomic fractional coordinates for non-hydrogen atoms are given in table I, bond distances and angles in table II. The 2 molecules do not differ significantly in the orientation of the respective benzyl substituents. The angles between the normal to the corresponding planes are A^B 79.7 (2)° and A1^B1 80.7 (2)°.

The pyridone rings of molecules I and II are planar and the dihedral angles between the carbomethoxy and the corresponding α-pyridone ring planes are 24.8

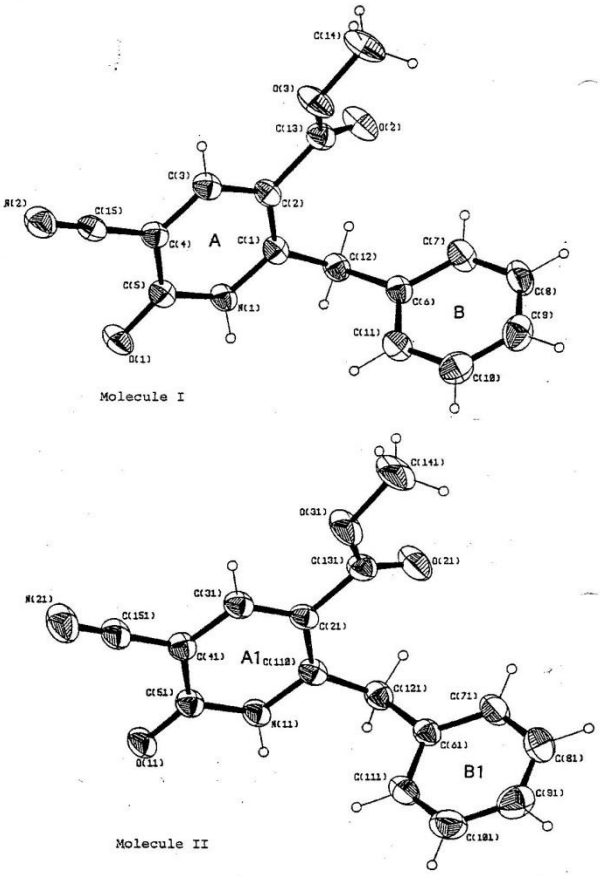


Fig 3. ORTEP figure of compound **1f.** Perspective views of the asymmetrical units with the numbering scheme adopted (the thermal ellipsoids are drawn at the 40% probability level).

Table I. Atomic coordinates (x 10^4) for non-hydrogen atoms and equivalent isotropic thermal parameters (x 10^3) with ESDs in parentheses.

Atom	x/a	y/a	z/a	Ueq(Å^2
N(1)	463(3)	-1490(3)	2706(3)	34(2)
N(2)	3459(3)	-4305(4)	1523(4)	51(2)
O(1)	630(2)	-3749(3)	1700(3)	46(2)
O(2)	1762(3)	2421(3)	5009(3)	56(2)
O(3)	3615(3)	1537(3)	3766(3)	54(2)
C(1)	832(3)	-174(4)	3335(4)	34(2)
C(2)	1935(3)	78(4)	3479(4)	34(2)
C(3)	2630(4)	-1000(4)	2979(4)	36(2)
C(4)	2220(3)	-2313(4)	2389(4)	34(2)
C(5)	1080(4)	-2600(4)	2228(4)	36(2)
C(6)	465(3)	1571(4)	2858(4)	35(2)
C(7)	600(4)	2964(4)	3428(5)	48(3)
C(8)	992(4)	3640(4)	2618(5)	57(3)
C(9)	1275(4)	2954(5)	1237(5)	54(3)
C(10)	1141(4)	1564(5)	658(5)	53(3)
C(11)	743(4)	883(4)	1465(4)	45(3)
C(12)	-22(3)	841(4)	3759(4)	37(2)
( )	2394(4)	1489(4)	4182(4)	40(2)
C(14)	4189(4)	2855(5)	4363(5)	64(3)
C(15)	2911(4)	-3422(4)	1898(4)	37(3)
N(11)	1757(3)	4289(3)	8198(3)	37(2)
N(21)	4518(4)	1503(4)	7545(5)	70(3)
O(11)	1706(3)	2069(3)	7674(3)	51(2)
O(21)	3503(3)	8216(3)	9573(3)	60(2)
O(31)	5174(3)	7136(3)	8786(4)	62(2)
C(110)	2283(3)	5570(4)	8523(4)	36(2)
C(21)	3415(3)	5803(4)	8608(4)	36(2)
C(31)	3989(4)	4738(4)	8350(4)	40(3)
C(41)	3448(3)	3454(4)	8020(4)	38(2)
C(51)	2273(4)	3195(4)	7942(4)	38(2)
C(61)	2084(3)	6851(4)	7457(4)	36(2)
C(71)	2421(4)	8150(4)	7573(5)	48(3)
C(81)	2867(5)	8419(5)	6446(6)	61(3)
C(91)	3009(4)	7391(5)	5173(5)	61(3)
C(101)	2689(5)	6087(5)	5036(5)	60(3)
C(111)	2228(4)	5818(4)	6159(5)	49(3)
C(121)	1556(4)	6555(4)	8690(4)	41(2)
C(131)	4009(4)	7201(4)	9046(4)	43(3)
C(141)	5836(5)	8431(5)	9275(6)	72(4)
C(151)	4031(4)	2365(4)	7759(5)	46(3)

(U equivalent is defined as one third of the trace of the orthogonalized Uij tensor.)

Table II. Selected bond lengths (Å) and angles (°) with ESDs in parentheses.

N(1)-C(1)	1.370(5)	N(1)-C(5)	1.377(6)
N(2)-C(15)	1.141(7)	O(1)-C(5)	1.246(5)
O(2)-C(13)	1.192(5)	O(3)-C(13)	1.336(5)
O(3)-C(14)	1.457(5)	C(1)-C(2)	1.375(7)
C(1)-C(12)	1.504(7)	C(2)-C(3)	1.398(7)
C(2)-C(13)	1.501(5)	C(3)-C(4)	1.376(5)
C(4)-C(5)	1.424(7)	C(4)-C(15)	1.427(7)
C(6)-C(7)	1.387(6)	C(6)-C(11)	1.383(6)
C(6)-C(12)	1.511(8)	C(7)-C(8)	1.382(9)
C(8)-C(9)	1.371(8)	C(9)-C(10)	1.383(7)
C(10)-C(11)	1.383(9)	N(11)-C(110)	1.371(4)
N(11)-C(51)	1.382(5)	N(21)-C(151)	1.144(8)
O(11)-C(51)	1.250(5)	O(21)-C(131)	1.194(6)
O(31)-C(131)	1.325(6)	O(31)-C(141)	1.464(6)
C(110)-C(21)	1.379(7)	C(110)-C(121)	1.494(8)
C(21)-C(31)	1.393(7)	C(21)-C(131)	1.506(6)
C(31)-C(41)	1.379(5)	C(41)-C(51)	1.426(7)
C(41)-C(151)	1.424(8)	C(61)-C(71)	1.383(6)
C(61)-C(111)	1.395(6)	C(61)-C(121)	1.509(8)
C(71)-C(81)	1.382(9)	C(81)-C(91)	1.374(7)
C(91)-C(101)	1.380(8)	C(101)-C(111)	1.376(9)

C(1)-N(1)-C(5)	126.2(5)	C(13)-O(3)-C(14)	115.7(4)
N(1)-C(1)-C(12)	115.0(4)	N(1)-C(1)-C(2)	117.6(4)
C(2)-C(1)-C(12)	127.3(5)	C(1)-C(2)-C(13)	121.1(5)
C(1)-C(2)-C(3)	119.4(5)	C(3)-C(2)-C(13)	119.6(5)
C(2)-C(3)-C(4)	121.7(5)	C(3)-C(4)-C(15)	122.2(5)
C(3)-C(4)-C(5)	119.9(5)	C(5)-C(4)-C(15)	117.9(5)
O(1)-C(5)-C(4)	125.0(5)	N(1)-C(5)-C(4)	115.1(4)
N(1)-C(5)-O(1)	119.8(5)	C(11)-C(6)-C(12)	121.4(4)
C(7)-C(6)-C(12)	120.1(4)	C(7)-C(6)-C(11)	118.4(5)
C(6)-C(7)-C(8)	120.4(5)	C(7)-C(8)-C(9)	121.0(5)
C(8)-C(9)-C(10)	119.1(5)	C(9)-C(10)-C(11)	120.1(5)
C(6)-C(11)-C(10)	121.0(5)	C(1)-C(12)-C(6)	113.2(4)
O(3)-C(13)-C(2)	109.8(4)	O(2)-C(13)-C(2)	125.2(5)
O(2)-C(13)-O(3)	125.0(5)	N(2)-C(15)-C(4)	179.1(5)
C(110)-N(11)-C(51)	125.1(4)	C(131)-O(31)-C(141)	115.5(5)
N(11)-C(110)-C(121)	114.3(4)	N(11)-C(110)-C(21)	118.2(4)
C(21)-C(110)-C(121)	127.5(5)	C(110)-C(21)-C(131)	121.0(5)
C(110)-C(21)-C(31)	119.5(5)	C(31)-C(21)-C(131)	119.4(5)
C(21)-C(31)-C(41)	121.6(5)	C(31)-C(41)-C(151)	121.7(5)
C(31)-C(41)-C(51)	119.9(5)	C(51)-C(41)-C(151)	118.4(5)
O(11)-C(51)-C(41)	124.2(5)	N(11)-C(51)-C(41)	115.8(4)
N(11)-C(51)-O(11)	120.0(5)	C(111)-C(61)-C(121)	120.7(4)
C(71)-C(61)-C(121)	121.4(4)	C(71)-C(61)-C(111)	117.8(5)
C(61)-C(71)-C(81)	121.2(5)	C(71)-C(81)-C(91)	120.4(6)
C(81)-C(91)-C(101)	119.2(5)	C(91)-C(101)-C(111)	120.5(5)
C(61)-C(111)-C(101)	120.9(5)	C(110)-C(121)-C(61)	112.0(4)
O(31)-C(131)-C(21)	109.6(5)	O(21)-C(131)-C(21)	125.3(6)
O(21)-C(131)-O(31)	125.1(5)	N(21)-C(151)-C(41)	178.8(7)

(7)° and 15.7(7)° respectively. Molecules I and II are connected by strong hydrogen bonds between the proton and the ring CO oxygen of the adjacent molecule: N(11)...O(1)' 2.775(3) Å, H-(N11)...O(1)' 1.807(3) Å, N(11)-H(N11)...O(1)' 168.9(2)° and N(1)...O(11)' 2.751(5) Å, HN(1)...O(11)' 1.772(5) Å, N(1)-H(N1)...O(11)' 176.4(5)° (' at *-x, -y, -z*) to form a dimer as shown in figure 4 which presents the molecular packing viewed down the *c* crystallographic axis. A comparison with the 2-*tert*-butyl derivative [1] **1d** indicates that in both compounds dimers of the same type are formed. A common feature of both compounds is also the *cis*oid orientation of the ester group which has the carbonyl oxygen directed towards the substituent at the position 2, whereas the orientation of the carbonyl group is *trans*oid for the isopropyl and phenyl derivatives [1] which present a very low positive inotropic activity and also for the methyl derivative which has the highest positive inotropic activity in this series of compounds. In both cases the crystal packing is not determined by molecular stacking, most likely because of the bulk of the substituent at position 2 (benzyl- in one case and *tert*-butyl- in the other): the dimers are separated by normal Van der Waals distances. In table III are summarized some significant conformational parameters of 5-cyano-1,6-dihydro-6-oxo-3-pyridine carboxylate derivatives with differently substituted 2-positions related to their pharmacological activities. It appears that the *trans*oid conformation is preferred by the positive inotropes and the *cis*oid is only found in compounds with a negative inotropic effect. The twist, *ie*, the dihedral angle between the carboalkoxy and pyridine moieties, does not influence inotropic activity. In the series of 2-substituted compounds, molecular stacking in the crystalline state packing arrangement was exhibited only by the 2-methyl derivative.

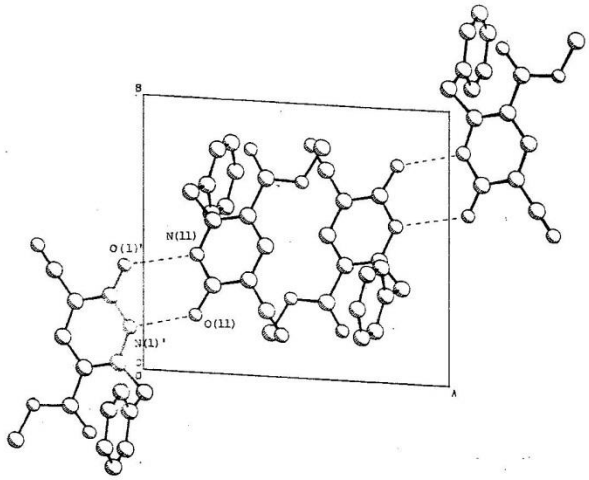


Fig 4. Crystal packing diagram as viewed along the *c*-axis for compound **1f** (' at *-x, -y, -z*).

Hydrogen bond interaction with dimer formation is common to all compounds. The distances N(2)...O(2), O(1)...R, O(1)...O(2) and O(2)...R which could be *a priori* related to a specific activity have been investigated both in the solid state and in the lowest energy conformations calculated for the free molecules. If the CN nitrogen atom, the carbonyl oxygen and the substituent at the position 2 are considered as possible recognition points, the shortest N(2)...O(2) distance appears to be related to positive inotropic activity: as the distance increases, the activity becomes a negative one*. The O(1)...O(2) distance is not correlated with the activity.

Theoretical calculations

Extensive conformational analysis was performed on **1a–1f** scanning the torsional angles τ1, τ2, τ3 and τ4 by 20° in the range 0–360°, while relaxing all the other geometric parameters: crystal structures were used, when available, for the initial conformations. Both MNDO [5] and AM1 [6] methods, as implemented in the AMPAC package [7] were used: the former appears less reliable for the study of the bioactive conformations since it overestimates the repulsions between atoms when at their Van der Waals distance and suggests minimum energy conformations with the $COOR^1$ group almost perpendicular to the C_2–C_3 bond**. Nevertheless, both methods indicate that the energy required to attain a coplanar conformation of the $COOR^1$ group and the α-pyridone ring increases in the series **1a** < **1b** < **1c** < **1d***** , suggesting a relation between positive inotropic activity and a [illegible] topography containing the dipolar moiety (COC[illegible]) and the hydrogen bonding region (CONH). However, **1e,** with a proper orientation of the phenyl moiety, can also achieve a nearly flat topography with an energy

* The N(2)...O(2) values ranges from 5.9–6. 1 Å in **1a–1e** and from 6.9–7.1 Å in **1d**, **1f**.

** The torsional angle τ1 ranges from ± 75° – ± 90° in the MNDO model and from –30° to +30° in the AM1 model except for **1d** where τ1 is + 56.15°.

*** In the AM1 model the energy difference (given in Kcal/mol) between the lowest energy conformation and a coplanar (*cis*oid or *trans*oid) conformation of the $COOR^1$ group and the α-pyridone moiety is as follows: **1a,** 0.0 (*cis*oid)-1.5(*trans*oid); **1b**, 0.0–1.9; **1c**, 0.1–2.1; **1d**, 1.7–4.3; **1e**, 0.5–2.1 and **1f**, 0.9–3.0.

Table III. Significant conformational parameters of ethyl or methyl 5-cyano-1,6-dihydro-6-oxo-pyridine carboxylate derivatives.

Substituent in 2-position	*Pharmacological activity*	*Carboethoxy orientation*+	*Molecular conformation*++	*Molecular complexity*	*Intermolecular interactions*	*Hydrogen bond*[a]
$-CH_3$ **(1a)**	Positive inotropic	1.7 13.6° 2.1 15.6°	*Trans*oid	Dimer	Among the pyridones 3.4 Å	1.61 2.04
$CH(CH_3)_2$ **(1c)**	Marginally positive inotropic	32.2°	*Trans*oid	Dimer	Absent	2.06
$-C_6H_5$ **(1e)**	Marginally positive inotropic	18°	*Trans*oid	Dimer	Absent	1.94
$-C(CH_3)_3$ **(1d)**	Negative inotropic	48.1 49.5°	*Cis*oid	Dimer	Absent	2.03 2.17
$-CH_2-C_6H_5$ **(1f)***	Negative inotropic	15.7 24.8°	*Cis*oid	Dimer	Absent	1.77 1.80

[a] Between the carbonyl oxygen and the nitrogen of the pyridone ring in all examples; * carbomethoxy; + dihedral angles between the carboethoxy and pyridone moieties; ++ referred to the carbonyl orientation with respect to the substituent in the 2 position.

cost comparable to that calculated for **1a**, **1b**: this suggests a key role for the R substituent which cannot only prevent a coplanar topography, but also collide with the steric boundary of the receptor and suggests the presence of a lipophilic pocket in the receptor that limits the size of R. Furthermore, a *trans*oid conformation of the COOR[1] group (with respect to the C_2–C_3 bond) is preferred in the solid state and accessible at a reasonable energy cost (1.5 – 2 Kcal/mol) in the free molecule for **1a–1b**, whereas a '*cis*oid' conformation is preferred for **1d** and **1f.**

Experimental protocols

X-ray analysis

X-ray structure of compound **1f** was determined on a Philips PW 1100 diffractometer using graphite-monochromated MoK_α radiation (λ = 0.71069 Å). Cell constants were determined by least-square fitting of the setting angles of the diffractometer between 20° and 26°. Intensity data were collected at room temperature (293 ± 2 K) and corrected for Lorentz and polarization factors but not for absorption. The structure was solved with the SHELX/86 [8] program using direct methods and refined by least-squares techniques. The hydrogen atom positions were derived from difference maps. All non-hydrogen atoms were refined anisotropically, while the hydrogens were refined isotropically. Atomic scattering factors were taken from reference [9].

Crystal data, final atomic coordinates and thermal parameters have been deposited at the Crystallographic Data Centre, Cambridge, UK [10].

References

1 Mosti L, Menozzi G, Schenone P, Dorigo P, Gaion RM, Benetollo F, Bombieri G (1989) *Eur J Med Chem* 24, 517–529

2 Dorigo P, Gaion RM, Borea PA, Belluco P, Mosti L, Maragno I (1990) *Gen Pharmacol* 21, 511–515

3 Orsini F, Benetollo F, Bombieri G, Mosti L (1990) *Eur J Med Chem* 25, 425–431

4 Johnson CK (1976) *Ortep Rep ORNL-5138*. Oak Ridge National Lab, Oak Ridge, TN

5 Dewar MJS, Thiel WS (1977) *J Am Chem Soc* 99, 4907–4917

6 Dewar MJS, Zoebish EG, Healy EF, Stewart JP (1985) *J Am Chem Soc* 107, 3902–3909

7 Indiana University (1985) *Quantum Chemistry Program Exchange No 527*. Indiana Univ, IA, USA

8 Sheldrick MG (1976) *'SHELX' Program for Crystal Structure Determination*. Univ Cambridge, UK

9 *International Tables for X-Ray Crystallography* (1974) Kluwer Academic Publ, USA Kynoch Press, Birmingham, UK, vol IV

10 Cambridge Univ Chemical Laboratory. *Crystallographic Data Centre*. Univ Chemical Laboratory, Cambridge, UK