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THROUGH-SPACE ELECTROSTATIC CONTROL IN A NOVEL REGIOSPECIFIC RING TRANSFORMATION OF 1,3,4-TRISUBSTITUTED MALEIMIDES

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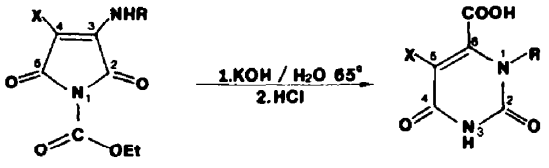
Abstract—Ring transformation of 1-ethoxycarbonyl-3,4-disubstituted maleimide in alkaline solution yielded exclusively 1,5-disubstituted orotic acid. No hydantoin derivatives were detected. These findings can be best explained by assuming that the initial attack of the hydroxylate anion occurs at C2 and not at C5. X-ray diffraction and quantum chemical investigations indicate that stereospecificity is mainly due to through-space electrostatic effects.

In the hope of achieving favorable biological properties we synthesized 1,5-disubstituted derivatives of orotic acid (uracil-6-carboxylic acid **2a**). We used 1-carbethoxy-3,4-disubstituted maleimides (**1**) as starting materials. They reacted on adding potassium hydroxyde as shown in Scheme 1.



1a: R=Ph X=H
1b: R=Ph X=Cl

2a: R, X=H
2b: R=Ph X=H
2c: R=Ph X=Cl

Scheme 1.

Molecular diagrams and some relevant bond lengths and angles for 1-ethoxycarbonyl-3-phenylamino-4-chloro-maleimide (**1b**) and 1-phenyl-uracil-6-carboxylic acid (**2b**) as obtained from X-ray diffraction measurements, are given in Figs. 1 and 2.

The following mechanism for the transformation can be proposed: The **1**→**2** rearrangement starts with a nucleophilic attack of the hydroxide anion at C2. After forming a tetrahedral complex (**3**), the ring opens.

In **4** a rotation around a double bond occurs (for similar examples see Kalinowski and Kessler[1]) and after elimination of ethanol ring closure follows. On adding acid the corresponding derivative of orotic acid is obtained. This rearrangement can be followed by UV spectroscopy (Fig. 3). The maximum at 368 nm, which is assigned to the maleimide ring, is shifted instantly to 334 nm as KOH is added indicating that delocalization is diminished. The maximum at 334 nm disappears gradually and a band, due to the disubstituted orotic acid, appears at 275 nm.

If the attack occurred at C5 instead of C2, compound **1a** would yield 1-phenyl-5-carboxymethylene-hydantoin,

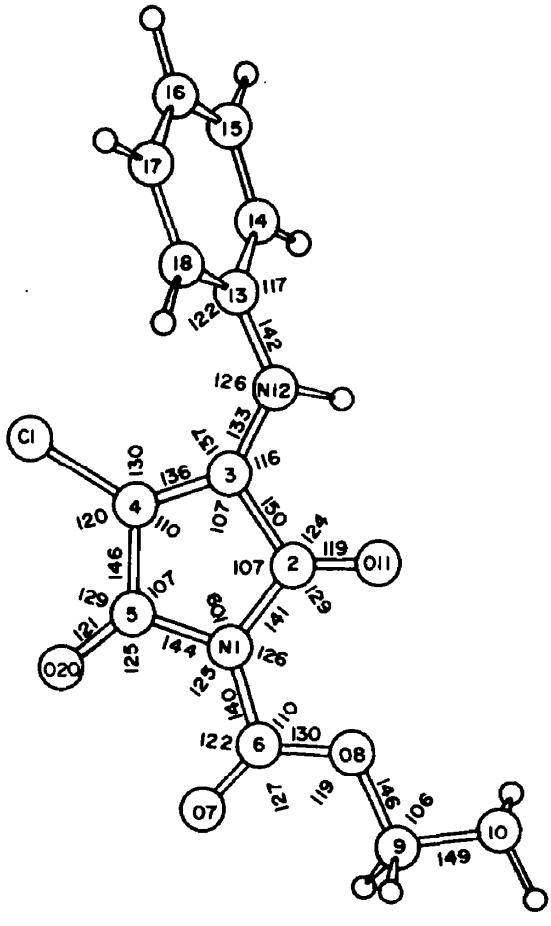


Fig. 1. Molecular diagram for 1-ethoxycarbonyl-3-phenylamino-4-chloro-maleimide **1b**. Mean e.s.d.'s for bond lengths and angles involving non-hydrogen atoms are 0.4 pm and 0.3°, respectively (Only one molecule of the asymmetric unit is shown with bond distances and angles averaged over two molecules of the asymmetric unit).

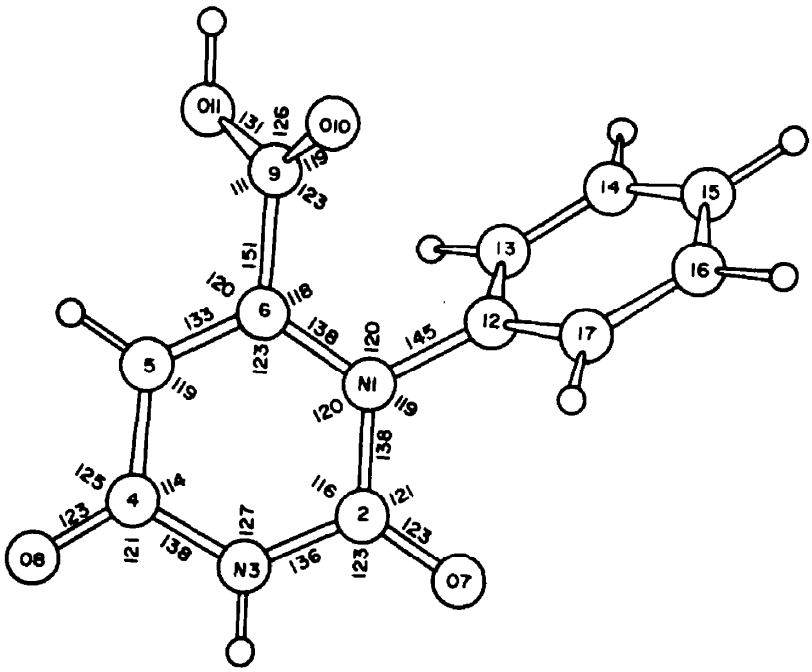


Fig. 2. Molecular diagram for 1-phenyl-uracil-6-carboxylic-acid **2b**. Mean e.s.d.'s for bond lengths and angles involving non-hydrogen atoms are 0.7 pm and 0.5°, respectively.

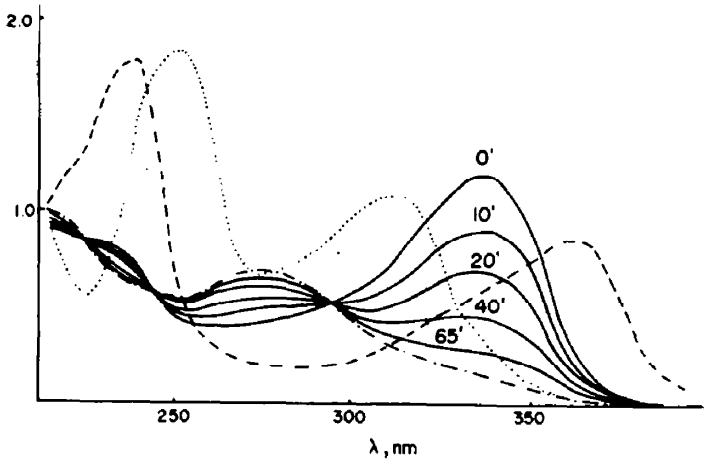
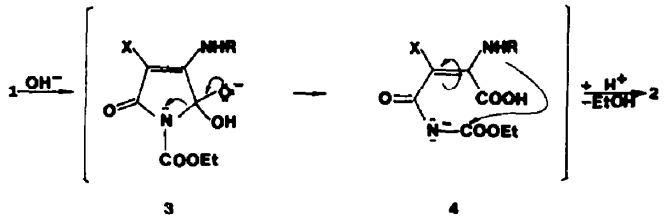


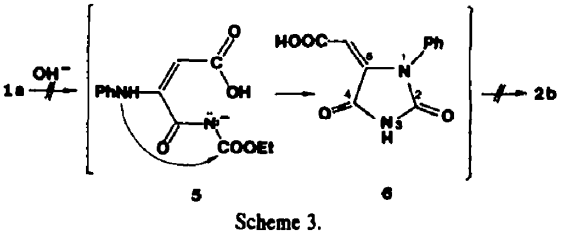
Fig. 3. Electronic spectra: ---**1a**, ——**1a** + KOH time dependence, -.-**2b**, ... **10** (Ref.[3]).



Scheme 2.

6, via **5**, and a further ring transformation of **6** would result **2b**.

According to Ralph *et al.*[2] the transformation **6**→**2b** does not take place under diverse experimental conditions, either. The presence of a hydantoin derivative in the reaction mixture during transformation of **1** to **2** should have been detected spectroscopically. The spectrum of 5-carboxymethylene-hydantoin (**10**) the parent compound of **6**, as recorded by Mitchell and Nyc,[3] is

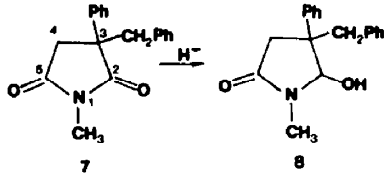


Scheme 3.

given in Fig. 3. The striking difference excludes the formation of hydantoin.

Amide hydrolysis is regarded as a typically charge controlled reaction.[4] Accordingly the preferred reaction site should be the carbon atom which bears the more positive net charge. A CNDO/2 molecular orbital calculation was performed.[5] We modelled **1a** by the hypothetical 1-carboxy-3-vinylamino-maleimide. The net charges on C2 and C5 of the model compound are 0.323 and 0.364 electrons, respectively. Consequently charge control is not responsible for regiospecificity in this case. In addition to that, N1–C2 is somewhat shorter than the N1–C5 bond.

Regioselectivity and stereo-selectivity in the reduction of asymmetrically substituted succinimides has been explained by Bürgi *et al.*[6,7] with a rearside attack of the H^- anion at the C2 atom and not at C5 because of bulky substituents at C3.[8] Although the dihedral angle between the maleimide ring and the phenyl ring is 59° in **1b**, such a



Scheme 4.

pronounced hindrance is absent because C3 is an sp^3 atom. A space filling model of **1b** is shown in Fig. 4. We assume that beside steric factors this regiospecificity is due to the through-space electrostatic effect of the ethoxycarbonyl group attached to N1. The electrostatic approach to chemical reactivity was proposed by Scrocco and Tomasi.[9] The importance of through-space interactions in organic reaction mechanisms has been stressed recently by several authors.[12] Electrostatic isopotential maps are generally used to give a crude in-

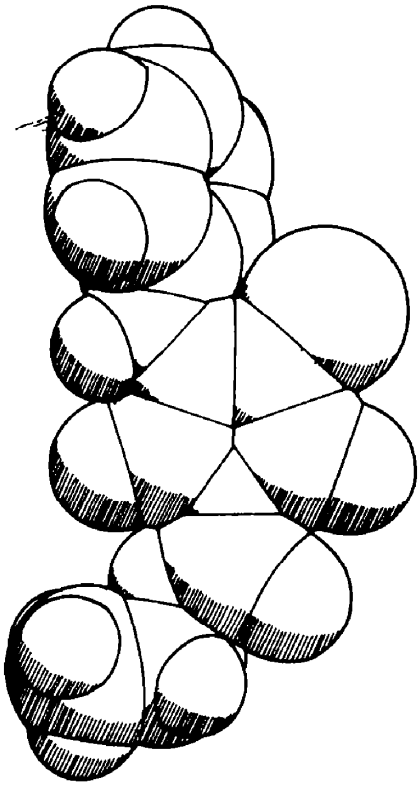


Fig. 4. Space filling model of **1b**.

formation about possible sites and directions of an electrophilic attack. Negative regions of the potential are preferred by the positively charged electrophile. We used a simplified method[10] for the construction of the map of the hypothetical 1-carboxy-3-vinylamino-maleimide. Its sections, containing the carbonyl groups are depicted in Fig. 5.

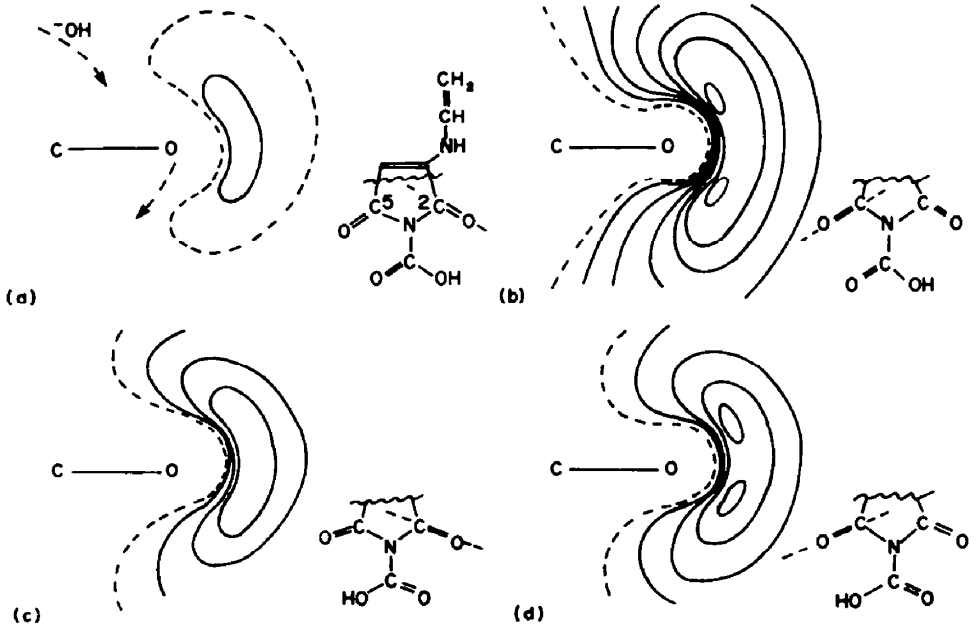


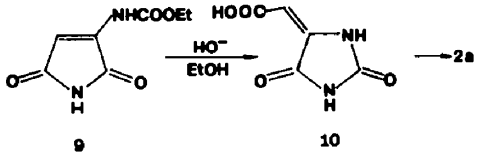
Fig. 5. Sections of electrostatic isopotential maps around carbonyl oxygen atoms of the hypothetical 1-carboxy-3-vinylamino-maleimide. Full lines correspond from the outermost to 400, 800, 1200, 1600, 2000 and 2500 kJ . mol^{-1}. Dashed lines indicate zero potential energy contours. Schematic reaction path of the hydroxylate anion is depicted in part a.

The conformation of this molecule was taken from the crystal structure analysis of **1b**. Map sections, given in Fig. 5a–b, indicate that the attack of the negatively charged nucleophile is considerable hindered at C5 by the large negative region of the potential around the carbonyl oxygen. On the other hand, no such electrostatic hindrance is present in the vicinity of C2.

If the carboxy group is rotated by 180° about the N1–C6 bond both regions of the isopotential map become almost identical (Fig. 5c–d).

Due to unfavourable electrostatic interaction the transition complex formed at C5 is of the higher energy than its counterpart at C2. Consequently, the rate of ring opening at C5 is lower than at C2 and an orotic acid derivative is formed exclusively. We assume that stability difference between intermediates **4** and **5** is insignificant and it does not give account of regiospecificity.

The importance of the position of the ethoxycarbonyl group in governing the ring transformation is further supported by the observation of Atkinson *et al.*[11] Thus 3-ethoxycarbonylamino-maleimide (**9**) yields 5-carboxymethylene-hydantoin (**10**) on adding potassium hydroxide. The first step of this reaction should be a nucleophilic attack at C5.



Scheme 5.

CONCLUSIONS

The ring transformation of 1-ethoxycarbonyl-3-phenylamino-4-substituted maleimide may be controlled mainly by three factors. These are:

(i) net charges on the carbonyl carbon atoms;
(ii) steric effect of the 3-phenylamino group;
(iii) through-space electrostatic hindrance due to the proximity of the ethoxycarbonyl group at N1.

If net charges are dominant, hydantoin derivatives should be obtained. In fact, our reaction yielded exclusively substituted orotic acid. This indicates that steric and especially through-space electrostatic factors control the reaction.

EXPERIMENTAL

UV spectra were recorded on a Unicam SP-8-100 spectrophotometer, IR spectra were measured on a Zeiss UR-20 equipment in KBr pellets. A Perkin Elmer R 12 NMR apparatus was used.

1-Ethoxycarbonyl-3-phenylamino-maleimide (**1a**). 752 g (0.04 M) 3-phenylamino-maleimide[13] was dissolved during stirring in 280 ml acetone. 6.48 g (0.06 M) ethyl chlorformate and 6.06 g (0.06 M) triethylamine were added simultaneously and dropwise during stirring. Meanwhile, salt precipitated and the temperature of the mixture was raised by about 10°. After completing the addition the mixture was stirred for 1.5 hr then heated under reflux for 10 minutes. After one night standing, the precipitated triethylammonium hydrochloride was removed and the mixture was evaporated to dryness. The yellow, crystalline material was washed with water, filtered and dried. The product was recrystallized from ethylacetate or absolute alcohol and 7.6 g (73%) **1a** was obtained, m.p. 168–172°. λ_{max} nm ($CHCl_3$) 368 (log ϵ 4.01); ν_{max} cm^{-1} 3300 (NH), 1800, 1760 (C=O); τ (DMSO): 7.5 (1H, s, NH), 5.56 (1H, s, 4-H), 4.3 (2H, q, OCH_2), 1.33 (3H, t, CH_3). (Found: C, 60.02; H, 4.62; N, 10.70. $C_{13}H_{12}N_2O_4$ requires: C, 60.00; H, 4.65; N, 10.77%). (No suitable crystals for X-ray analysis could be obtained from **1a**.)

1-Ethoxycarbonyl-3-phenylamino-4-chloro-maleimide (**1b**). 3.33 g (0.015 M) 3-phenylamino-4-chloro-maleimide[14] was dissolved during stirring at room temperature in 80 ml acetone. 2.43 g (0.0225 M) ethyl chlorformate and 2.28 g (0.00225 M) triethylamine were added dropwise simultaneously. Meanwhile salt precipitated and the temperature raised by about 10°. The reaction mixture was stirred at room temperature for about 1.5 hr then heated up to reflux for 10 min. After cooling the precipitated triethylammonium hydrochloride was filtered and the reaction mixture was evaporated to dryness. The oily residue crystallized from 96% ethanol m.p. 120–126° (3.72 g, 84%). λ_{max} nm (ethanol) 326 (log ϵ 4.01); ν_{max} cm^{-1} 3278 (NH), 1800, 1758, 1712 (C=O); τ (DMSO); 9.82 (1H, s, NH), 4.2 (2H, q, OCH_2), 1.31 (3H, t, CH_3). (Found: C, 53.71; H, 3.79; N, 9.37; Cl, 12.10. $C_{13}H_{11}N_2O_4Cl$ requires: C, 52.98; H, 3.76; N, 9.50; Cl, 12.02%).

X-ray investigation. 2644 independent reflections were collected on a STOE diffractometer with CuK_α radiation. 36 of the most intense reflections were redetermined applying a Ni filter. The structure was solved and refined using SHELX.[15] 1778 reflections with $F > 10\sigma(F)$ gave a final agreement of $R = 0.095$. The crystal data are: a = 79.3.7 (2), b = 2163.7 (6), c = 1535.3 (4) pm, $V = 2.6366\ nm^3$, $C_{13}H_{11}N_2O_4Cl$, $M_r = 294.6$, $D_x = 1.482\ Mgm^{-3}$, $\lambda(CuK_\alpha) = 154.18$ nm, $\mu = 25.9\ cm^{-1}$, space group Pbca (rhombic), Z = 8. The atomic coordinates are given in Table 1.

1-Phenyl-uracil-6-carboxylic acid (**2b**). 2.6 g (0.01 M) **1a** was suspended in 52 ml 1 M KOH/water (0.052 M). The mixture was kept at 65° for 2 hr. A clear, colorless solution was obtained. After evaporating the reaction mixture to about 15 ml it was acidified with 5 N HCl. The obtained, white, crystalline material was filtered and after drying recrystallized from water or water/ethanol m.p. 254–263° (dec.) (2.1 g, 90.5%). λ_{max} nm (ethanol) 275 (log ϵ 3.95); ν_{max} cm^{-1} 3185 (NH), 1750, 1715, 1650 (C=O); τ (DMSO): 11.7 (1 H, s, NH), 9.45 (1 H, s, OOOH), 6.1 (1 H, s, 5-H). (Found: C, 57.25; H, 3.45; N, 12.00. $C_{11}H_8N_2O_4$ requires: C, 56.87; H, 3.47; N, 12.06%).

X-ray investigation. 5159 independent reflections were collected on a Siemens AED diffractometer with Mo K_α radiation. The

Table 1. Fractional coordinates (× 10^4) for **1b**. e.s.d.'s are given in parentheses

Atom	x	y	z
N1	3471(7)	2142(3)	1876(3)
C2	3605(8)	2217(3)	2785(4)
C3	2730(7)	1676(3)	3201(4)
C4	2172(8)	1306(3)	2548(4)
C5	2587(8)	1574(3)	1704(4)
C6	4094(9)	2546(3)	1237(4)
O7	3698(7)	2504(2)	480(3)
O8	5136(7)	2939(2)	1582(3)
C9	5850(11)	3423(3)	1030(5)
C10	6253(14)	3948(4)	1622(6)
O11	4235(7)	2632(2)	3181(3)
N12	2677(7)	1680(3)	4067(3)
C13	2224(8)	1177(3)	4613(3)
C14	1115(8)	1303(4)	5299(4)
C15	819(10)	834(4)	5895(5)
C16	1530(9)	274(4)	5810(5)
C17	2632(9)	153(3)	5123(5)
C18	2963(10)	608(3)	4531(4)
C1	1137(2)	622(1)	2597(1)
O20	2272(7)	1378(3)	983(3)
H9A	6946(11)	3260(3)	683(5)
H9B	4907(11)	3574(3)	570(5)
H10A	6897(14)	4288(4)	1229(6)
H10B	7117(14)	3758(4)	2095(6)
H10C	5208(14)	4164(4)	1955(6)
H12	2824(7)	2110(3)	4293(3)
H14	523(8)	1750(4)	5368(4)
H15	-17(10)	919(4)	6437(5)
H16	1252(9)	-81(4)	6283(5)
H17	3198(9)	-298(3)	5054(5)
H18	3824(10)	525(3)	3999(4)

Table 2. Fractional coordinates ($\times 10^4$) for **2a**. e.s.d.'s are given in parentheses

	Molecule I			Molecule II		
Atom	x	y	z	x	y	z
N1	−1340(3)	8078(4)	983(3)	3390(2)	−1700(3)	6442(3)
C2	−994(3)	6141(5)	1437(4)	2945(3)	185(4)	6085(3)
N3	−247(3)	5183(4)	2546(4)	1968(2)	1011(3)	5243(3)
C4	214(3)	5958(5)	3231(4)	1394(3)	162(4)	4690(3)
C5	−210(4)	7965(5)	2726(4)	1840(3)	−1841(4)	5185(3)
C6	−922(3)	8949(5)	1629(4)	2798(3)	−2672(4)	6006(3)
O7	−1352(3)	5338(4)	881(3)	3439(2)	1056(3)	6494(3)
O8	923(3)	4953(4)	4180(3)	584(2)	1116(3)	3830(3)
C9	−1151(3)	11102(5)	964(4)	3208(3)	−4805(4)	6591(3)
O10	−963(3)	12016(4)	−85(3)	3411(2)	−5838(3)	7712(3)
O11	−1490(3)	11764(4)	1733(3)	3241(3)	−5336(3)	5712(3)
C12	−2235(3)	9176(5)	−107(4)	4557(3)	−2536(4)	7088(3)
C13	−3224(4)	10044(6)	89(4)	4835(3)	−2841(5)	8303(4)
C14	−4063(4)	11212(7)	−964(5)	5958(4)	−3643(6)	8881(4)
C15	−3900(4)	11423(7)	−2131(5)	6753(3)	−4154(6)	8272(5)
C16	−2906(5)	10484(8)	−2288(5)	6453(3)	−3853(6)	7054(5)
C17	−2047(4)	9339(7)	−1259(5)	5344(3)	−3010(5)	6449(4)
H3	6	3954	2813	1665	2158	5105
H5	89	8606	3161	1447	−2565	4898
H11	−1449	13106	1230	3272	−4008	4786
H13	−3349	9818	1050	4179	−2463	8794
H14	−4852	11960	−853	6209	−3882	9842
H15	−4555	12356	−2950	7637	−4804	8763
H16	−2792	10644	−3237	7092	−4254	6547
H17	−1242	8570	−1352	5083	−2718	5471

structure was solved and refined using SHELX.[15] 3347 reflections of the initial set with $F > 3\sigma(F)$ were retained in the final refinement (R = 0.0558). The crystal data are: a = 1206.3 (3), b = 805.9 (2), c = 1198.4 (3) pm, $\alpha = 62.61$ (5), $\beta = 93.64$ (10), $\gamma = 80.80$ (6)°, V = 1.0085 nm^3, $C_{11}H_8N_2O_4$, $M_r = 232.2$, $D_x = 1.529$, Mg.m^{-3}, λ(Cu K_α) = 71.07 nm, $\mu = 0.85$ cm^{-1}, space group: $P\bar{1}$, Z = 4. Atomic coordinates for **2b** are given in Table 2.

1-Phenyl-5-chloro-uracil-6-carboxylic acid (**2c**). 2.94 g (0.01 M) **1b** was suspended in 52 ml 1 M KOH/water. The mixture was heated to 65° and kept at this temperature for 2 hr. A clear, colourless solution was obtained. The solvent was partially evaporated and acidified by 5 N HCl. The precipitated product was filtered and after drying it was recrystallized from water m.p. 259–262° (2.4 g, 85%). λ_{max} nm (ethanol) 280 (log ϵ 3.98); ν_{max} cm^{-1} 3190 (NH), 1710, 1700, 1690 (C=O). ^{1}H NMR could not be recorded because of poor solubility. (Found: C, 46.42; H, 3.18; N, 9.93; Cl, 12.26. $C_{11}H_7N_2O_4Cl$ requires: C, 46.41; H, 3.18; N, 9.84; Cl, 12.45%).

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