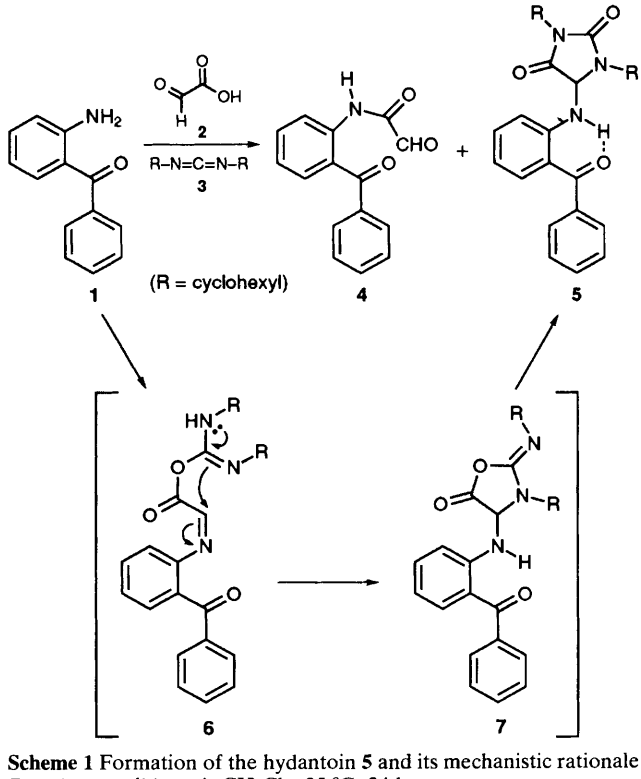
Unexpected Hydantoin Formation in the Attempted Amidation with 2-Aminobenzophenone of Glyoxylic Acid using Dicyclohexylcarbodiimide

Gerhard Bringmann,*[a] Thomas Mader,[a] Karl Peters[b] and Hans Georg von Schnering[b]

[a] *Institut für Organische Chemie der Universität Würzburg, Am Hubland, W-8700 Würzburg, Germany*
[b] *Max-Planck-Institut für Festkörperforschung, Heisenbergstr. 1, W-7000 Stuttgart 80, Germany*

The formation and structure elucidation of the hydantoin **5**, an unexpected product from 2-aminobenzophenone **1**, glyoxylic acid **2** and dicyclohexylcarbodiimide **3**, is described.

The activation of carboxylic acids for reactions with amines to give amides or peptides, using carbodiimides such as DCC (dicyclohexylcarbodiimide) **3**, is a well established procedure in organic synthesis,[2–4] owing to the mild reaction conditions required. The *N*-glyoxyl-2-aminobenzophenone **4** is a postulated[5] intermediate in the biogenesis of naturally occurring diazepam-like 1,4-benzodiazepines, presumably arising from an oxidative cleavage of the related mould metabolite viridicatine (4-phenyl-3-hydroxyquinolin-2-one). When trying to prepare **4** by the DCC method, starting from 2-aminobenzophenone **1** and glyoxylic acid **2**, we obtained, besides the desired amide **4**, a completely unexpected, rapidly eluting and thus non-polar product. NMR spectroscopy revealed structural elements of all three reaction components, *i.e.* the presence of the aromatic units of the 2-aminobenzophenone **1**, the glyoxylic acid moiety **2** (as seen, *inter alia*, by the proton signal at δ 5.27 ppm), and, unprecedentedly, the incorporation of the complete DCC entity.[1]† The possible formation of such a product might be explained in terms of a reaction of the



Scheme 1 Formation of the hydantoin **5** and its mechanistic rationale. *Reaction conditions*: i, CH_2Cl_2, 25 °C, 24 h

† *Spectral and physical data* for **5**: m.p. 156–157 °C; ^{1}H NMR ($CDCl_3$) δ 8.80 (1H, d, *J* 7.6 Hz), 6.67–7.62 (9H, m), 5.27 (1H, d, *J* 7.6 Hz), 3.71–3.99 (2H, m) and 0.98–2.17 (20H, m); ^{13}C NMR ($CDCl_3$) δ 199.4, 170.5, 155.2, 148.5, 139.9, 135.7, 134.9, 131.6, 129.5, 128.4, 119.9, 117.1, 113.7, 107.9, 65.9, 52.5, 51.8, 31.8, 30.3, 29.5, 26.0, 25.4 and 25.3; IR (KBr) ν_{max}/cm^{-1} 3200, 1750 and 1700; mass (EI) *m/z* 459 (M^+, 32%), 376 (34), 354 (27), 263 (23), 196 (21) and 181 (100); satisfactory microanalytical data were obtained for **5**.

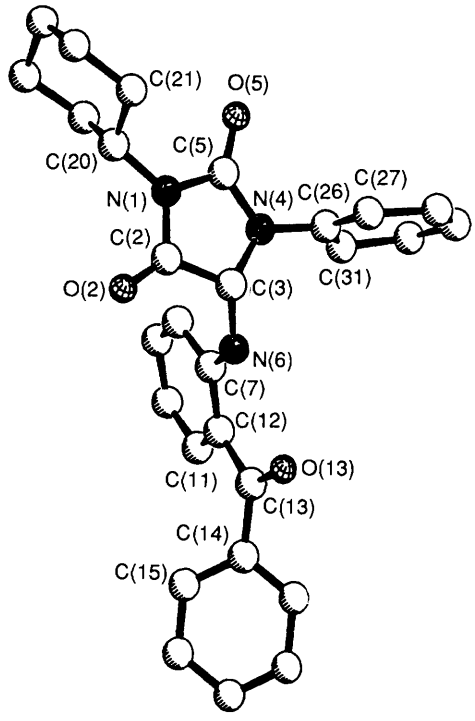


Fig. 1 Schakal plot of the molecular structure of the hydantoin **5**, as obtained by X-ray structure analysis‡

nucleophilic amine with the formyl group of glyoxylic acid **2** in the initial step, rather than with the DCC-activated carboxylic unit. The resulting imine **6**, with its reactive acid-derived functionality, would then cyclize to give the five-membered heterocycle **7**. Some spectroscopic evidence (*e.g.* the ^{13}C NMR shifts), however, hinted at the possible isomeric structure **5** for the product. The formation of this apparently thermodynamically more stable hydantoin might be explained in terms of a (nucleophile-induced) ring opening of **7** and subsequent cyclization to give **5**.

Ultimate unambiguous proof for the structure **5** was finally obtained by an X-ray structure analysis.[2]‡ Fig. 1 clearly shows the central hydantoin substructure of **5**. The planar character of one of the cyclohexyl rings [C(26)–C(31)] reflects the thermal mobility of this cycloalkyl substituent and explains the relatively high *R*-value. The near-planarity of the array O(13)–C(13)–C(12)–C(7)–N(6)–H(6), combined with the short distance (1.812 Å) between O(13) and H(6), suggests there is intramolecular hydrogen bonding in this aminobenzophenone part.

Although cyclocondensation reactions using DCC are known in the literature,[6–8] this type of hydantoin formation is unprecedented.

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‡ *Crystal data* for **5**: $C_{28}H_{33}N_3O_3$, triclinic, space group $P\bar{1}$, a = 10.714(4), b = 12.601(5), c = 9.870(3) Å, α = 96.67(3), β = 111.48(3), γ = 93.41(3)°, V = 1224.1(8) Å^3, Z = 4, D_c = 1.244 g cm^{-3}; Siemens R3m/V; Mo-Kα radiation. λ(Kα) = 0.71073 Å; 3.5° < 2θ < 55°; 5627 unique reflections, of which 3136 were treated as observed [$F_o > 3\sigma(F_o)$]; empirical absorption correction; R = 0.103, R_w = 0.068. The cyclohexyl ring at N(4) is disordered. The averaged positions in Fig. 1 give an almost planar six-membered ring. Hence, no hydrogen positions could be determined or calculated for this substituent. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.