Approaches to 1,1-disubstituted cinnolin-3-ylio oxides: synthesis and reactivity of a new class of heterocyclic betaines

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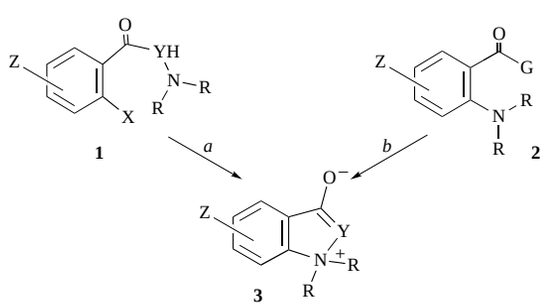
The cinnolin-3-ylio oxides 6, a new class of heterocyclic aminimide, can be prepared by intramolecular cyclization of the *N′*,*N′*-disubstituted (2-fluorophenyl)acetohydrazides 5. Attempts to prepare these betaines by an alternative route, namely cyclization of the nitrenes expected from the thermal decomposition of (2-dialkylaminophenyl)acetyl azides 11, failed, Curtius rearrangement-derived compounds being the main products isolated from these processes. Hydrochlorides of the cinnolin-3-ylio oxides 6 undergo alkyl halide elimination to yield the 1-(ω-chloroalkyl)cinnolin-3-ols 19a,b or 1-methylcinnolin-3-ol 21. Oxidation of the latter to the 3-hydroxycinnolin-4-one 22, its methylation to the corresponding *N*[1],*O*- 23 and *N*[1],*N*[2]-dimethyl 24 derivatives as well as the cyclization of 1-(5-chloropentyl)cinnolin-3-ol 19a to the diazepino[1,2-*a*]cinnolinone 20 are also reported.

Introduction

In the last few years we have been interested in the synthesis and reactivity of indole- and indazole-derived betaines **3** (Y = CH, N), which are, respectively, stabilized ammonium ylides[1] and aminimides.[2] These compounds have been prepared following two different cyclization patterns involving the formation of an N-1/C-7a bond through the aromatic nucleophilic substitution of a halogen atom (Scheme 1, path *a*) or the formation of N-1/C-2 or N-1/N-2 bonds by intramolecular quaternization of an *N*,*N*-disubstituted aniline derivative (Scheme 1, path *b*). The



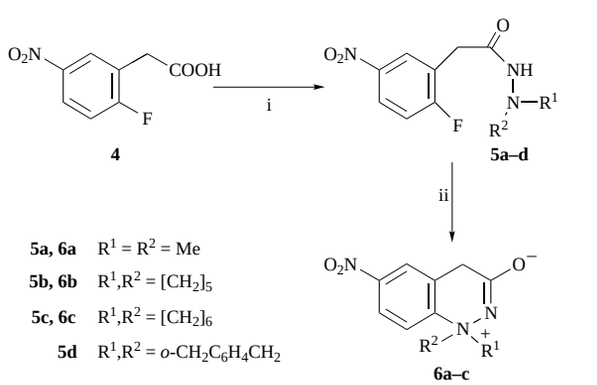
Scheme 1

indolylio oxides **3** (Y = CH, Z = H, 5-NO_2) are thus available either from the intramolecular cyclization of *N*,*N*-disubstituted 2′-halogenophenacylamines **1** (Y = CH, X = F, Cl, Z = H, 5-NO_2) or 2′-dialkylaminophenacyl halides **2** (G = CH_2Cl, CH_2Br, Z = 5-NO_2).[3] However, the indazolylio oxides **3** (Y = N; Z = H, 5-NO_2) have been initially prepared following path *a* by intramolecular cyclization[4,5] of *N′*,*N′*-disubstituted 2-halogenobenzohydrazides **1** (Y = N, X = F, Cl, Z = H, 5-NO_2). Path *b*, based on the cyclization of the nitrene arising from the decomposition of an *o*-dialkylaminobenzoyl azide **2** (G = N_3, Z = H, 3-Me, 3- and 5-NO_2, 3,5-di-NO_2), has been recently followed by Waldron *et al.*[6,7] This procedure requires appropriate substituents in the benzene ring or in the amino group[7] and, in fact, previous attempts[8] to prepare the indazolylio oxides **3** (Y = N) starting from some closely related 2-dialkylamino-5-nitrobenzoyl azides **2** (G = N_3, Z = 5-NO_2) were reported to be unsuccessful, yielding only Curtius rearrangement-derived products.

Indolylio oxides[3] and, especially, indazolylio oxides[4,9] are useful intermediates for the preparation of a number of indole and indazole derivatives some of which have been shown to possess a remarkable cytostatic activity against HeLa cells.[10]

Results and discussion

Following our research focused on the study of heterocyclic betaines we report in this paper the synthesis and reactivity of the cinnolinylio oxides **6** (Scheme 2). These cyclic aminimides[2]

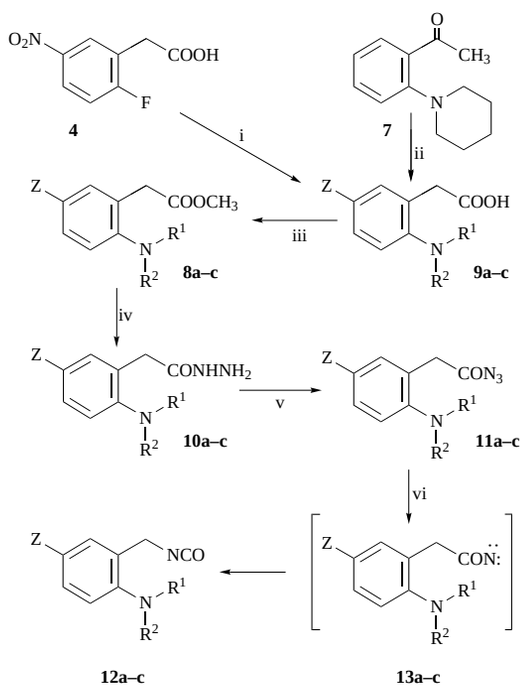


5a, 6a $R^1 = R^2 = Me$
5b, 6b $R^1,R^2 = [CH_2]_5$
5c, 6c $R^1,R^2 = [CH_2]_6$
5d $R^1,R^2 = o\text{-}CH_2C_6H_4CH_2$

Scheme 2 *Reagents and conditions:* i, *a* Cl_2SO, reflux; *b* $R^1R^2NNH_2$, aq. $NaCO_3H$, RT; ii, aq. K_2CO_3, reflux

can be considered as methylene homologues of the previously mentioned indazolylio oxides, and it was, therefore planned to synthesize them following patterns similar to those mentioned for the preparation of the latter, *i.e.* through the formation in this case of *a* N-1/C-8a or *b* N-1/N-2 bonds. Since pathway *a* is based on an intramolecular nucleophilic aromatic substitution, it requires substrates containing reactive halogen atoms such as those of *N′*,*N′*-disubstituted (2-fluorophenyl)-acetohydrazides **5a–d**, activated[11] by a 5-NO_2 group. These compounds were prepared in 70–80% yield by acylation of the corresponding hydrazines with the acid chloride of phenylacetic acid **4** (Scheme 2). The hydrazides **5a–d** are present in solution as mixtures of *Z* and *E* rotamers, duplicate signals being observed in their NMR spectra; such a conformational equilibrium is customary for hydrazides.[5,12–14] In our case, using deuteriated dimethyl sulfoxide and chloroform as solvents, *ca.* 50:50 and *ca.* 80:20 *Z*/*E* ratios respectively were observed by integration of the sharp CH_2CO signals; since this behaviour is similar to that observed in the previously studied *N′*,*N′*-

disubstituted 2-fluorobenzohydrazides,[5] the assignment of ^{1}H NMR signals for the different rotamers of the hydrazides **5** was achieved by comparison of the spectra of the two series of compounds. Cyclization of the hydrazides **5a–c** to the corresponding cinnolin-3-ylio oxides **6a–c** was easily achieved in 65–85% yield by refluxing each substrate with aqueous potassium carbonate; several attempts to cyclize *N*-aminoisoindoline-derived hydrazide **5d** using different bases and solvents were not, however, successful. To our knowledge, this obvious approach to the 3-hydroxycinnoline ring based on the cyclization of a (2-halogenophenyl)acetohydrazide has not previously been described. A '1,4-dihydrocinnoline' structure (*vs.* the corresponding '1,2-dihydrocinnoline' isomer) must be assigned to compounds **6a–c** according to their ^{13}C and ^{1}H NMR spectra. In the latter, the spiro derivatives **6b**,**c** show the characteristic anisochrony of the NCH_2 protons previously reported for related indole-, pyrazole-, benzothiadiazole- and indazole-derived betaines;[3,5] the axial (NCH_a) and equatorial (NCH_e) protons in the piperidine and azepane rings of these compounds were assigned on the basis of earlier reported results for indazolylio oxides,[5] in which H_a was shown to appear at lower field than H_e. As with other aminimides,[2,6,15] some delocalization of the depicted negative charge of compounds **6a–c** towards N-2 must also be taken into account. Since approach *b* to cinnolinylio oxides was based on the reactivity expected for (2-dialkylaminophenyl)acetyl azides **11** (Scheme 3), it presents



8a–13a $R^1,R^2 = [CH_2]_5$; Z = NO_2

8b–13b $R^1,R^2 = o\text{-}[CH_2]_2C_6H_4CH_2$; Z = NO_2

8c–13c $R^1,R^2 = [CH_2]_5$; Z = H

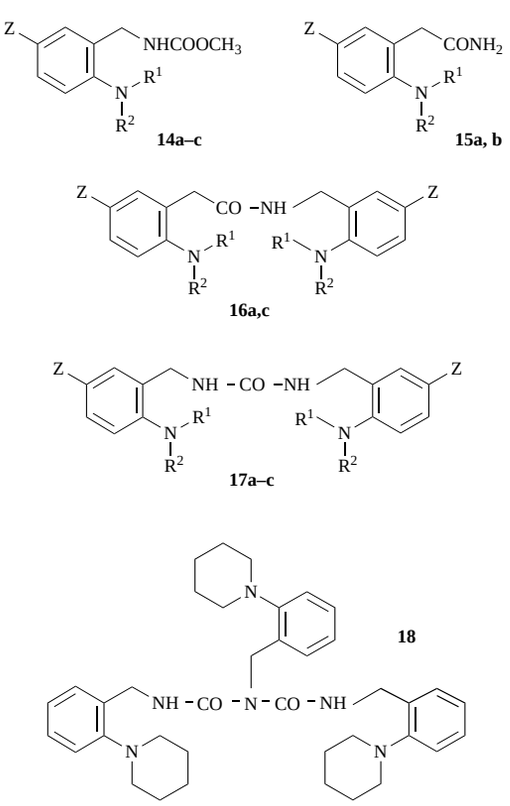
Scheme 3 *Reagents and conditions:* i, R^1R^2NH, aq. $NaCO_3H$, reflux; ii, Willgerodt reaction conditions; iii, MeOH, H_2SO_4, RT; iv, NH_2NH_2, RT; v, $NaNO_2$, aq. HCl, 0 °C; vi, C_6H_6, reflux or C_6H_6–MeOH, reflux

an additional interest owing to the variable and substituent-dependent decomposition patterns observed for the closely related 2-dialkylaminobenzoyl azides.[6–8] The starting (2-dialkylamino-5-nitrophenyl)acetic acids **9a**,**b** were prepared (Scheme 3) from the corresponding 2-fluoro analogue **4** and the required secondary amines, while (2-piperidinophenyl)acetic acid **9c** was obtained from 2′-piperidinoacetophenone **7** through a Willgerodt reaction.[16] The acids **9a–c** were stepwise transformed into the azides **11a–c** *via* the corresponding esters **8a–c** and hydrazides **10a–c**, following standard Curtius reaction procedures.[17]

Pyrolysis of the azides **11a–c** in refluxing benzene yielded complex reaction mixtures from which we were able to detect or isolate (Table 1, method A) the starting acids **9a,b**, the amides **15a,b** and **16a,c**, the urea derivatives **17a–c** and the biuret derivative **18**; no traces of the expected cinnolinylio oxides **6** could, however, be detected. Previous addition of methanol to the benzene solutions of the azides **11** gave somewhat more clear-cut pyrolyses, from which we isolated (Table 1, method B) the starting acids **9a,b**, the methyl esters **8a,c**, the urethanes **14a,c**, the amides **15a,b** and **16c** and the urea derivative **17c**. For identification purposes, the amides **15a,b** were also prepared in an alternative method from (2-fluoro-5-nitrophenyl)acetamide and the corresponding secondary amines.

The azides **11a,b**, carrying a ring nitro substituent, seem to be more stable than the azide **11c**; decomposition of the latter in the benzene solution starts before addition of methanol and/or heating and thus, the amide **16c** and the substituted urea **17c** are formed under both sets of experimental conditions.

Some compounds such as the urethanes **14** or the urea derivatives **17** are similar to those previously obtained in the thermolysis of related 2-dialkylaminobenzoyl azides[7,8] but some others seem to be unique to this kind of process. The esters **8** and the acids **9** can be directly derived from the azides **11** by nucleophilic displacement of the azido group assisted by the anchimeric effect of the neighbouring dialkylamino group.[8] The other compounds can be considered to be derived from the nitrenes **13**, directly (the amides **15**) or through a previous



14a, 15a, 16a, 17a $R^1,R^2 = [CH_2]_5$; Z = NO_2

14b, 15b, 17b $R^1,R^2 = o\text{-}[CH_2]_2C_6H_4CH_2$; Z = NO_2

14c, 16c, 17c $R^1,R^2 = [CH_2]_5$; Z = H

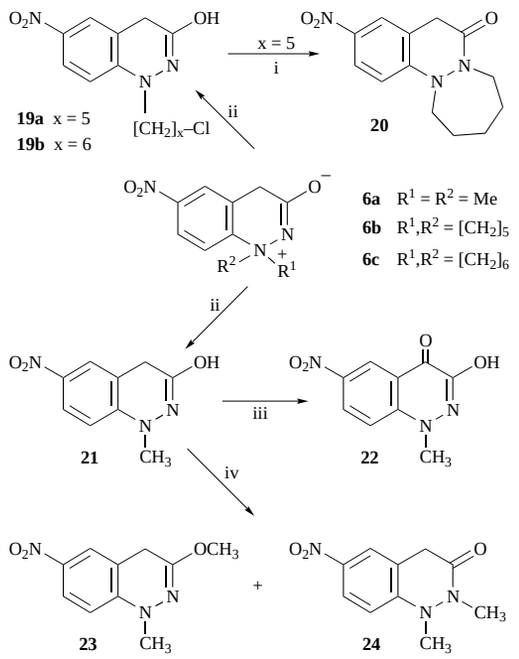
Curtius rearrangement (Scheme 3) to the isocyanates **12** (the urethanes **14**, the urea derivatives **17** and the biuret derivative **18**); 'mixed' (rearranged–unrearranged) compounds, *i.e.* the *N*-substituted amides **16a,c**, were also obtained.

Returning to the cinnolin-3-ylio oxides **6**, only the piperidine

Table 1 Products and yields arising from thermolysis of the azides **11a–c** in benzene (A) and in benzene–methanol (B)

Starting azide	Method	Overall yield (%)	Individual yields (%)						
			8	**9**	**14**	**15**	**16**	**17**	**18**
11a	A	96	—	(**9a**) 11	—	(**15a**) 6	(**16a**) 55	(**17a**) 24	—
	B	89	(**8a**) 23	(**9a**) 21	(**14a**) 41	(**15a**) 4	—	—	—
11b	A	67	—	(**9b**) —[a]	—	(**15b**) 3	—	(**17b**) 64	—
	B	91	—	(**9b**) 5	(**14b**) 79	(**15b**) 7	—	—	—
11c	A	48	—	—	—	—	(**16c**) 20	(**17c**) 13	15
	B	49	(**8c**) 17	—	(**14c**) 21	—	(**16c**) 3	(**17c**) 8	—

[a] Compound detected by TLC but not isolated.



Scheme 4 *Reagents and conditions:* i, K_2CO_3, butan-2-one, reflux; ii, *a* aq. HCl; *b* $PhNO_2$, heat; iii, H_2O_2, aq. $NaCO_3H$, RT; iv, MeI, K_2CO_3, reflux

derivative **6b** seems to be indefinitely stable at room temperature. Compounds **6a,c** decompose slowly with time, traces of 3-methoxy-1-methylcinnoline **23** (Scheme 4) being detected (TLC) among the decomposition products of the former. The reactivity of the cinnolin-3-ylio oxides **6a–c** was found to be somewhat different from that of the related indazol-3-ylio oxides.[4,9] Thus, when heated they failed to give the expected Wawzonek rearrangement products producing, instead, intractable complex mixtures. Nevertheless (Scheme 4), they could be transformed into the corresponding alkyl halide elimination products, *i.e.* 1-(ω-chloroalkyl)-1,4-dihydrocinnolin-3-ols **19a,b** and 1-methyl-1,4-dihydrocinnolin-3-ol **21**, by thermal decomposition of their hydrochlorides. The behaviour of these 1-substituted cinnolin-3-ols is, however, related to that observed for 1-substituted indazol-3-ols.[9,18,19] Thus, intramolecular alkylation at N-2 of compound **19a** to give the corresponding tricyclic fused product **20** was achieved, although in moderate yield, by heating under reflux in potassium carbonate–butan-2-one. Furthermore, 1-methylcinnolin-3-ol **21** could be easily alkylated by methyl iodide to give a mixture of 3-methoxy-1-methylcinnoline **23** and 1,2-dimethylcinnolin-3-one **24**. Additionally, the 4-methylene group of 1-substituted cinnolinols seems to be very sensitive to oxidation, partial decomposition to the 4-oxo derivative taking place when the compounds were stored in solution, or by contact with chromatographic supports, *etc.*; from a preparative point of view, 1-methylcinnolin-3-ol **21** could be easily transformed into the corresponding 3-hydroxycinnolin-4-one **22** by treatment with hydrogen peroxide in basic medium.

Experimental

Mps were determined in a Reicher-Jung hot-stage microscope and are uncorrected. IR spectra were obtained on a Perkin-Elmer 681 spectrophotometer. ^{1}H (200 or 300 MHz) and ^{13}C NMR (50 or 75 MHz) spectra were recorded on a Varian Gemini-200 or on a Varian XL-300 spectrometer using the signal of the solvent as reference. *J* Values are given in Hz. Most mass spectra (electron impact) were obtained at 70 eV on a VG 12-250 (VG Masslab) spectrometer; only the FAB mass spectrum of compound **18** was obtained on a VG AutoSpec spectrometer using a *m*-nitrobenzyl alcohol matrix. DC-Alufolien silica gel 60 PF_{254} (Merck, layer thickness 0.2 mm) and silica gel 60 PF_{254} (Merck, 20 × 20 cm plates, layer thickness 2 mm) were used, respectively, for TLC and preparative TLC (PLC). Flash column chromatography was performed on silica gel 60 (Merck, particle size 0.040–0.063 mm). Microanalyses were performed by the Departamento de Análisis, Centro de Química Orgánica 'Manuel Lora Tamayo', C.S.I.C., Madrid, Spain.

Preparation of (2-fluoro-5-nitrophenyl)acetic acid 4 and its acid chloride

The desired acid was prepared by nitration of (2-fluorophenyl)acetic acid following the method reported by Sindelar *et al.*[20] for the corresponding 2-chloro analogue; yield 85%; mp 149–151 °C (dil. AcOH) (Found: C, 48.5; H, 3.1; N, 7.2. $C_8H_6FNO_4$ requires C, 48.25; H, 3.0; N, 7.0%); ν_{max}(KBr)/cm^{-1} 3400–2400 (OH), 1715 (CO) and 1530 and 1360 (NO_2); δ_H[$(CD_3)_2SO$] 8.35 (1 H, dd, J_{mF} 6, J_m 3, 6′-H), 8.26–8.18 (1 H, m, 4′-H), 7.48 (1 H, t, J_o 9, J_{oF} 9, 3′-H) and 3.80 (2 H, d, $J^4_{F,H}$ 1.5, 2-H).

The corresponding acid chloride was prepared in good yield by treatment of the acid with refluxing thionyl chloride. After partial concentration of the reaction mixture, the crystallized product was filtered off, washed with hexane, vacuum-dried and used without further purification.

Preparation of (2-fluoro-5-nitrophenyl)acetamide

A suspension of (2-fluoro-5-nitrophenyl)acetyl chloride (1.52 g, 7 mmol) in conc. aq. ammonia (20 cm^3) was stirred for 2 h at room temperature. The solid in suspension was filtered off, washed with water and air-dried to afford the desired product (1.29 g, 93%); mp 150–152 °C (MeOH) (Found: C, 48.25; H, 3.5; N, 14.0. $C_8H_7FN_2O_3$ requires C, 48.5; H, 3.6; N, 14.1%); δ_H[$(CD_3)_2SO$] 8.29 (1 H, dd, J_{mF} 6, J_m 3, 6′-H), 8.23–8.15 (1 H, m, 4′-H), 7.60 (1 H, br s, NH_a), 7.45 (1 H, t, J_o 9, J_{oF} 9, 3′-H), 7.09 (1 H, br s, NH_b) and 3.61 (2 H, s, 2-H).

Preparation of the substituted phenylacetohydrazides 5a–d

For compounds **5a–c**, a solution of (2-fluoro-5-nitrophenyl)-acetyl chloride (6.52 g, 30 mmol) in chloroform (200 cm^3) was slowly added (~1 h) to a stirred mixture of the corresponding hydrazine (30 mmol) and 5% aq. sodium hydrogen carbonate (100 cm^3). After 2 h at room temperature, the chloroform layer was separated and the hydrazide extracted with several portions (50 cm^3) of 10% aq. hydrochloric acid (extraction was followed by TLC). In the case of compound **5c**, some hydrazide hydrochloride was precipitated after the first addition

of acid; this solid was filtered off and added to the final acid extract. This latter was neutralized with solid sodium hydrogen carbonate, and the hydrazide extracted with chloroform. This solution was dried ($MgSO_4$) and evaporated to dryness to yield chromatographically homogeneous materials. The hydrazide **5d** was prepared following exactly the method A_2 of ref. 5 starting from *N*-aminoisoindoline hydrochloride.[21]

(2-Fluoro-5-nitrophenyl)-*N*′,*N*′-dimethylacetohydrazide 5a. Yield 69%; mp 168–170 °C (Pr^iOH) (Found: C, 49.8; H, 5.1; N, 17.6. $C_{10}H_{12}FN_3O_3$ requires C, 49.8; H, 5.0; N, 17.4%); ν_{max}(KBr)/cm^{-1} 3190, 3160 and 3090 (NH) and 1680 (CO); δ_H[$(CD_3)_2SO$] 9.19 (*E* rot.) and 8.66 (*Z* rot.) (1 H, s, NH), 8.34–8.19 (2 H, m, 4′-, 6′-H, *Z* + *E*), 7.53–7.43 (1 H, m, 3′-H, *Z* + *E*), 3.91 (*Z*) and 3.54 (*E*) (2 H, s, 2-H), 2.51 (6 H, s, CH_3, *Z* + *E*) (*Z*/*E* ratio 52:48); δ_H($CDCl_3$) 8.24–8.11 (2 H, m, 4′-, 6′-H, *Z* + *E*), 7.24–7.12 (1 H, m, 3′-H, *Z* + *E*), 6.57 (*E*) and 6.39 (*Z*) (1 H, br s, NH), 3.90 (*Z*) and 3.50 (*E*) (2 H, s, 2-H) and 2.59 (*E*) and 2.53 (*Z*) (6 H, s, CH_3) (*Z*/*E* ratio 73:27); *m*/*z* 242 (M^+ + 1, 11%), 241 (M^+, 5), 199 (19), 108 (9), 107 (11) and 59 (100).

(2-Fluoro-5-nitrophenyl)-*N*-piperidinoacetamide 5b. Yield 75%; mp 141–143 °C (Pr^iOH) (Found: C, 55.6; H, 5.75; N, 14.9. $C_{13}H_{16}FN_3O_3$ requires C, 55.5; H, 5.7; N, 14.9%); δ_H[$(CD_3)_2SO$] 9.14 (*E* rot.) and 8.69 (*Z* rot.) (1 H, s, NH), 8.35–8.15 (2 H, m, 4′-, 6′-H, *Z* + *E*), 7.50–7.40 (1 H, m, 3′-H, *Z* + *E*), 3.85 (*Z*) and 3.52 (*E*) (2 H, s, 2-H), 3.10–2.20 (4 H, br m, 2″-, 6″-H, *Z* + *E*) and 1.80–1.25 (6 H, br m, 3″-, 4″-, 5″-H, *Z* + *E*) (*Z*/*E* ratio 55:45); δ_H($CDCl_3$) 3.88 (*Z*) and 3.50 (*E*) (2 H, s, 2-H) (*Z*/*E* ratio 85:15); *m*/*z* 282 (M^+ + 1, 26%), 281 (M^+, 7), 154 (9), 108 (18), 107 (17), 99 (100) and 83 (83).

***N*-(Azepan-1-yl)(2-fluoro-5-nitrophenyl)acetamide 5c.** Yield 81%; mp 131–133 °C (Pr^iOH) (Found: C, 57.1; H, 6.3; N, 14.3. $C_{14}H_{18}FN_3O_3$ requires C, 56.9; H, 6.1; N, 14.2%); δ_H[$(CD_3)_2SO$] 9.41 (*E* rot.) and 8.90 (*Z* rot.) (1 H, s, NH), 8.30–8.17 (2 H, m, 4′-, 6′-H, *Z* + *E*), 7.50–7.40 (1 H, m, 3′-H, *Z* + *E*), 3.90 (*Z*) and 3.51 (*E*) (2 H, s, 2-H), 3.05–2.70 (4 H, br m, 2″-, 7″-H, *Z* + *E*) and 1.70–1.40 (8 H, br m, 3″-, 4″-, 5″-, 6″-H, *Z* + *E*) (*Z*/*E* ratio 53:47); δ_H($CDCl_3$) 3.91 (*Z*) and 3.49 (*E*) (2 H, s, 2-H) (*Z*/*E* ratio 81:19).

***N*-(1,3-Dihydroisoindol-2-yl)(2-fluoro-5-nitrophenyl)acetamide 5d.** Yield 89%; mp 182–184 °C (Pr^iOH) (Found: C, 60.7; H, 4.35; N, 13.1. $C_{16}H_{14}FN_3O_3$ requires C, 60.95; H, 4.5; N, 13.3%); δ_H[$(CD_3)_2SO$] 9.67 (*E* rot.) and 9.01 (*Z* rot.) (1 H, s, NH), 8.40–8.17 (2 H, m, 4′-, 6′-H, *Z* + *E*), 7.50–7.40 (1 H, m, 3′-H, *Z* + *E*), 7.24 and 7.21 (4 H, s, 4″-, 5″-, 6″-, 7″-H, *Z* + *E*), 4.25 (4 H, s, 1″-, 3″-H, *Z* + *E*) and 3.99 (*Z*) and 3.61 (*E*) (2 H, s, 2-H) (*Z*/*E* ratio 53:47).

Preparation of the cinnolin-3-ylio oxides 6a–c

A mixture of the corresponding hydrazide **5a–c** (10 mmol) and potassium (or sodium) carbonate (11 mmol) in water (100 cm^3) was refluxed during 3 h (for **6a**) or 6 h (for **6b,c**). After evaporation of mixture, the solid residue was mixed with silica gel and applied to the top of a chromatography column, which was eluted with (10:1 to 3:1) chloroform–methanol mixtures; R_F values [TLC, (10:1) chloroform–methanol] for compounds **6a–c** are given in their description.

1,1-Dimethyl-6-nitro-1,4-dihydrocinnolin-3-ylio oxide 6a. Yield 82%; R_F = 0.02; mp 173–175 °C (decomp.) (EtOH) (Found: C, 54.15; H, 5.2; N, 19.0. $C_{10}H_{11}N_3O_3$ requires C, 54.3; H, 5.0; N, 19.0%); δ_H[$(CD_3)_2SO$] 8.31 (1 H, d, J_m 2.5, 5-H), 8.26 (1 H, dd, J_o 9, J_m 2.5, 7-H), 8.12 (1 H, d, J_o 9, 8-H), 3.66 (2 H, s, 4-H) and 3.55 (6 H, s, CH_3); *m*/*z* 221 (M^+, 100), 220 (77), 206 (29), 192 (20), 178 (14), 174 (59), 162 (12), 160 (11), 146 (10), 132 (31), 117 (26), 104 (11) and 89 (22).

6-Nitro-1,4-dihydrocinnoline-1-spiro-1′-piperidin-3-ylio oxide 6b. Yield 89%; R_F = 0.11; mp 202–205 °C (decomp.) (water) (Found: C, 52.8; H, 6.35; N, 14.3. $C_{13}H_{15}N_3O_3{\cdot}2H_2O$ requires C, 52.5; H, 6.4; N, 14.1%); ν_{max}(KBr)/cm^{-1} 3640, 3480 and 3360 (OH) and 1620 and 1540 (C=N, C=C); δ_H[$(CD_3)_2SO$] 8.30 (1 H, d, J_m 2.5, 5-H), 8.27 (1 H, dd, J_o 9, J_m 2.5, 7-H), 8.14 (1 H, d, J_o 9, 8-H), 3.86 [2 H, m, J_{gem} (−) 11, $J_{a,a}$ 11, 2′-, 6′-H_a], 3.64 (2 H, s, 4-H), 3.54 [2 H, br d, J_{gem} (−) 11, 2′-, 6′-H_e], and 2.59–2.30 (m) and 1.85–1.40 (m) (6 H, 3′-, 4′-, 5′-H); δ_C[$(CD_3)_2SO$] 172.21 (C-3), 149.03, 147.27 (C-6, -8a), 134.36 (C-4a), 124.02, 122.50, 120.55 (C-5, -7, -8), 64.86 (C-2′, -6′), 34.88 (C-4) and 20.71 (C-3′, -4′, -5′); *m*/*z* 261 (M^+, 100), 246 (20), 232 (35), 218 (39), 217 (49), 205 (24), 178 (37), 173 (25), 130 (23), 117 (32) and 89 (49).

6-Nitro-1,4-dihydrocinnoline-1-spiro-1′-azepan-3-ylio oxide 6c. Yield 74%; R_F = 0.16; mp 142–144 °C (decomp.) (MeOH) (Found: C, 57.8; H, 6.5; N, 13.7. $C_{14}H_{17}N_3O_3{\cdot}0.5CH_3OH{\cdot}0.5H_2O$ requires C, 58.0; H, 6.7; N, 14.0%); δ_H[$(CD_3)_2SO$] 8.29 (1 H, d, J_m 2.5, 5-H), 8.27 (1 H, dd, J_o 9, J_m 2.5, 7-H), 8.11 (1 H, d, J_o 9, 8-H), 4.20–4.00 (2.5 H, m, 2′-, 7′-H_a + 1/2CH_3OH), 3.80–3.64 (2 H, m, 2′-, 7′-H_e), 3.60 (2 H, s, 4-H), 3.16 (1.5 H, d, *J* 5, 1/2CH_3OH) and 2.35–2.06 (m) and 1.95–1.63 (m) (8 H, 3′-, 4′-, 5′-, 6′-H); *m*/*z* 275 (M^+, 59), 234 (12), 217 (16), 206 (100), 192 (25), 160 (17), 118 (18), 117 (18) and 89 (26).

Preparation of substituted phenylacetic acids 9a–c

For compounds **9a,b**, a mixture of (2-fluoro-5-nitrophenyl)-acetic acid **4** (4.00 g, 20 mmol), the corresponding secondary amine (piperidine or 1,2,3,4-tetrahydroisoquinoline) (22 mmol) and sodium hydrogen carbonate (3.78 g, 45 mmol) in water (100 cm^3) was refluxed for 24 h. After cooling of the mixture it was filtered to remove some insoluble material and treated with acetic acid to give the products; these were filtered off. Analytical samples were prepared by redissolution of the product in 0.25 M aqueous sodium hydroxide followed by reprecipitation with acetic acid.

The acid **9c** was obtained from 2′-fluoroacetophenone following a reported procedure.[16]

Since the acids **9a,b** are also produced in the thermolysis of the azides **11**, their R_F values (TLC) in chloroform and in chloroform–methanol (10:1), respectively, are given in the description of the products.

(3-Nitro-6-piperidinophenyl)acetic acid 9a. Yield 92%; R_F = 0.05, 0.43; mp 139–142 °C (previous softening) (Found: C, 59.2; H, 6.3; N, 10.8. $C_{13}H_{16}N_2O_4$ requires C, 59.1; H, 6.1; N, 10.6%); ν_{max}(KBr)/cm^{-1} 3300–2500 (OH) and 1700 (CO); δ_H[$(CD_3)_2SO$] 8.15–8.05 (2 H, m, 2′-, 4′-H), 7.21 (1 H, d, J_o 9, 5′-H), 3.70 (2 H, s, 2-H), 2.93–2.80 (4 H, m, 2″-, 6″-H) and 1.73–1.43 (6 H, m, 3″-, 4″-, 5″-H).

[3-Nitro-6-(1,2,3,4-tetrahydro-2-isoquinolyl)phenyl]acetic acid 9b. Yield 98%; R_F = 0.03, 0.45; mp 153–156 °C (previous softening) (Found: C, 65.2; H, 5.0; N, 8.8. $C_{17}H_{16}N_2O_4$ requires C, 65.4; H, 5.2; N, 9.0%); δ_H[$(CD_3)_2SO$] 8.18 (1 H, d, J_m 3, 2′-H), 8.12 (1 H, dd, J_o 9, J_m 3, 4′-H), 7.33 (1 H, d, J_o 9, 5′-H), 7.20–7.10 (4 H, m, 5″-, 6″-, 7″-, 8″-H), 4.21 (2 H, s, 1″-H), 3.75 (2 H, s, 2-H), 3.27 (2 H, t, $J_{3,4}$ 6, 3″-H) and 2.96 (2 H, t, $J_{3,4}$ 6, 4″-H).

Preparation of the substituted methyl phenylacetates 8a–c

A mixture of the corresponding acid **9** (10 mmol) and sulfuric acid (2 cm^3) in methanol (50 cm^3) was stored at room temperature for 24 h after which it was concentrated to 10 cm^3 and poured into 10% aq. sodium hydrogen carbonate (200 cm^3). Extraction of the mixture with chloroform yielded each product as an oil which solidified with time.

Since the esters **8a–c** are also produced in the thermolysis of the azides **11**, their R_F values (TLC) in chloroform and in chloroform–methanol (10:1), respectively are given in the description of each product.

Methyl (3-nitro-6-piperidinophenyl)acetate 8a. Yield 95%; R_F = 0.70, 0.85; mp 56–57 °C (hexane) (Found: C, 60.6; H, 6.8; N, 10.3. $C_{14}H_{18}N_2O_4$ requires C, 60.4; H, 6.5; N, 10.1%); ν_{max}(KBr)/cm^{-1} 1735 (CO); δ_H[$(CD_3)_2SO$] 8.16–8.08 (2 H, m, 2′-, 4′-H), 7.25 (1 H, d, J_o 9, 5′-H), 3.80 (2 H, s, 2-H), 3.62 (3 H, s, CH_3), 2.90–2.78 (4 H, m, 2″-, 6″-H) and 1.70–1.45 (6 H, m, 3″-,

4″-, 5″-H); δ_C[$(CD_3)_2SO$] 171.34 (CO), 158.85 (C-6′), 141.98 (C-3′), 130.70 (C-1′), 126.55, 123.61 (C-2′, -4′), 120.31 (C-5′), 52.58 (C-2″, -6″), 51.64 (CH_3), 36.53 (C-2), 26.50 (C-3″, -5″) and 23.50 (C-4″); *m*/*z* 278 (M^+, 94%), 263 (78), 249 (100), 231 (16), 217 (39), 189 (37), 173 (63), 117 (61), 90 (79), 89 (93) and 84 (97).

Methyl [3-nitro-6-(1,2,3,4-tetrahydro-2-isoquinolyl)phenyl]-acetate 8b. Yield 96%; R_F = 0.66, 0.89; mp 83–84 °C (hexane) (Found: C, 66.5; H, 5.6; N, 8.9. $C_{18}H_{18}N_2O_4$ requires C, 66.25; H, 5.6; N, 8.6%); δ_H[$(CD_3)_2SO$] 8.20 (1 H, d, J_m 3, 2′-H), 8.15 (1 H, dd, J_o 9, J_m 3, 4′-H), 7.35 (1 H, d, J_o 9, 5′-H), 7.20–7.05 (4 H, m, 5″-, 6″-, 7″-, 8″-H), 4.16 (2 H, s, 1″-H), 3.86 (2 H, s, 2-H), 3.52 (3 H, s, CH_3), 3.22 (2 H, t, $J_{3,4}$ 6, 3″-H) and 2.92 (2 H, t, $J_{3,4}$ 6, 4″-H).

Methyl (2-piperidinophenyl)acetate 8c. Yield 89%; R_F = 0.70, 0.86; mp 61–63 °C (hexane) (Found: C, 72.3; H, 8.3; N, 6.2. $C_{14}H_{19}NO_2$ requires C, 72.1; H, 8.2; N, 6.0%); δ_H[$(CD_3)_2SO$] 7.28–6.96 (4 H, m, 3′-, 4′-, 5′-, 6′-H), 3.64 (2 H, s, 2-H), 3.59 (3 H, s, CH_3), 2.75–2.62 (4 H, m, 2″-, 6″-H) and 1.68–1.40 (6 H, m, 3″-, 4″-, 5″-H).

Preparation of the substituted phenylacetohydrazides 10a–c

A mixture of the corresponding methyl ester **8** (10 mmol) and hydrazine hydrate (20 cm^3) was stirred at room temperature for 24 h and then diluted with water (50 cm^3). The solid in suspension was filtered off, washed with cold water and air-dried to afford the chromatographically (TLC) pure products.

(3-Nitro-6-piperidinophenyl)acetohydrazide 10a. Yield 91%; mp 140–142 °C (dil. EtOH) (Found: C, 56.0; H, 6.6; N, 19.9. $C_{13}H_{18}N_4O_3$ requires C, 56.1; H, 6.5: N, 20.1%); ν_{max}(KBr)/cm^{-1} 3315 (NH) and 1635 (CO); δ_H[$(CD_3)_2SO$] 9.32 (1 H, br s, NH), 8.12–8.02 (2 H, m, 2′-, 4′-H), 7.18 (1 H, d, J_o 9, 5′-H), 4.30 (2 H, br s, NH_2), 3.49 (2 H, s, 2-H), 3.00–2.84 (4 H, m, 2″-, 6″-H) and 1.86–1.48 (6 H, m, 3″-, 4″-, 5″-H); δ_C[$(CD_3)_2SO$] 169.29 (CO), 158.86 (C-6′), 141.52 (C-3′), 131.09 (C-1′), 126.01, 123.06 (C-2′, -4′), 119.57 (C-5′), 52.87 (C-2″, -6″), 35.37 (C-2), 25.70 (C-3″, -5″) and 23.62 (C-4″); *m*/*z* 278 (M^+, 10%), 247 (100), 219 (22), 217 (17), 173 (28), 171 (20), 163 (11), 144 (9), 117 (16), 89 (16) and 84 (17).

[3-Nitro-6-(1,2,3,4-tetrahydro-2-isoquinolyl)phenyl]aceto-hydrazide 10b. Yield 89%; mp 182–184 °C (EtOH) (Found: C, 62.3; H, 5.6: N, 17.0. $C_{17}H_{18}N_4O_3$ requires C, 62.6; H, 5.6; N, 17.2%); δ_H[$(CD_3)_2SO$] 9.33 (1 H, br t, $J_{NH,NH}$ 4, NH), 8.16 (1 H, d, J_m 2.5, 2′-H), 8.10 (1 H, dd, J_o 9, J_m 2.5, 4′-H), 7.30 (1 H, d, J_o 9, 5′-H), 7.24–7.11 (4 H, m, 5″-, 6″-, 7″-, 8″-H), 4.29 (2 H, br d, $J_{NH,NH}$ 4, NH_2), 4.26 (2 H, s, 1″-H), 3.55 (2 H, s, 2-H), 3.32 (2 H, br t, $J_{3,4}$ 5, 3″-H) and 2.98 (2 H, br t, $J_{3,4}$ 5, 4″-H).

(2-Piperidinophenyl)acetohydrazide 10c. Yield 85%; mp 79–80 °C (hexane) (Found: C, 66.8; H, 8.1; N, 18.2. $C_{13}H_{19}N_3O$ requires C, 66.9; H, 8.2; N, 18.0%); δ_H[$(CD_3)_2SO$] 9.13 (1 H, br s, NH), 7.26–6.90 (4 H, m, 3′-, 4′-, 5′-, 6′-H), 4.20 (2 H, br s, NH_2), 3.44 (2 H, s, 2-H), 2.85–2.65 (4 H, m, 2″-, 6″-H) and 1.73–1.40 (6 H, m, 3″-, 4″-, 5″-H).

Preparation and thermolysis of substituted phenylacetyl azides 11a–c

A solution of the corresponding hydrazide **10** (2 mmol) in 2 M aqueous hydrochloric acid (40 cm^3) was cooled in an ice-bath. To this, a cold solution of sodium nitrite (166 mg, 2.4 mmol) in water (2 cm^3) was then slowly added. After the mixture had been stirred for 15 min it was neutralized with solid sodium hydrogen carbonate, and extracted with benzene (3 × 50 cm^3) to give a solution of the azide **11**. **CAUTION:** Attempts to isolate some related 2-dialkylaminobenzoyl azides resulted in explosions even for working conditions <0 °C;[6,7] analogues containing nitro groups in the ring seem, however, to be less sensitive,[7] and some isolated compounds have been reported to decompose smoothly at room temperature to isocyanates or urea derivatives.[8] The benzene solution of the azide was dried ($MgSO_4$) and then either heated for 1 h under reflux (method A) or diluted with methanol (25 cm^3) and then heated under reflux for 1 h (method B). After extraction of the so formed acids **9** with aq. sodium hydrogen carbonate, the benzene solution was concentrated to 5–10 cm^3 (the corresponding urea derivative can be directly recovered by filtration at this stage), and the components of the remaining mixture were separated by preparative TLC (PLC) (*ca.* 5 plates) using chloroform–hexane (2:1), chloroform or chloroform–methanol (30:1) as developing solvents [R_F values (TLC) in chloroform and in chloroform–methanol (10:1), respectively, are given in the description of products arising from thermolysis of the azides **11**]. Recrystallization of crude materials or rechromatography (PLC) in the case of the oily biuret derivative **18** afforded pure products. The compounds obtained and yields are gathered in Table 1.

Substituted methyl benzylcarbamates 14a–c

Methyl (3-nitro-6-piperidinobenzyl)carbamate 14a. R_F = 0.45, 0.82; mp 151–153 °C (Pr^iOH) (Found: C, 57.6; H, 6.7; N, 14.5. $C_{14}H_{19}N_3O_4$ requires C, 57.3; H, 6.5; N, 14.3%); ν_{max}(KBr)/cm^{-1} 3340 and 3300 (NH) and 1695 (CO); δ_H[$(CD_3)_2SO$] 8.15–8.00 (2 H, m, 2′-, 4′-H), 7.84 (1 H, br t, $J_{CH,NH}$ 6, NH), 7.16 (1 H, d, J_o 9.5, 5′-H), 4.24 (2 H, d, $J_{CH,NH}$ 6, CH_2NH), 3.57 (3 H, s, CH_3), 3.00–2.89 (4 H, m, 2″-, 6″-H) and 1.78–1.50 (6 H, m, 3″-, 4″-, 5″-H); δ_C[$(CD_3)_2SO$] 157.44 (C-6′), 157.15 (CO), 141.62 (C-3′), 134.00 (C-1′), 123.19, 122.82 (C-2′, -4′), 119.03 (C-5′), 52.67 (C-2″, -6″), 51.61 (CH_3), 39.44 (CH_2NH), 25.71 (C-3″, -5″) and 23.56 (C-4″); *m*/*z* 293 (M^+, 20%), 276 (34), 264 (13), 224 (39), 217 (100), 205 (39), 189 (32), 176 (45), 171 (43), 162 (24), 143 (23), 130 (34), 125 (69), 117 (53), 97 (32), 90 (29) and 84 (61).

Methyl [3-nitro-6-(1,2,3,4-tetrahydro-2-isoquinolyl)benzyl]-carbamate 14b. R_F = 0.38, 0.86; mp 102–104 °C (Pr^iOH) (Found: C, 63.6; H, 5.9; N, 12.4. $C_{18}H_{19}N_3O_4$ requires C, 63.3; H, 5.6; N, 12.3%); δ_H[$(CD_3)_2SO$] 8.16–8.06 (2 H, m, 2′-, 4′-H), 7.91 (1 H, br t, $J_{CH,NH}$ 6, NH), 7.28 (1 H, d, J_o 9, 5′-H), 7.18 (4 H, s, 5″-, 6″-, 7″-, 8″-H), 4.31 (2 H, d, $J_{CH,NH}$ 6, CH_2NH), 4.29 (2 H, s, 1″-H), 3.56 (3 H, s, CH_3), 3.32 (2 H, br t, $J_{3,4}$ 6, 3″-H) and 2.97 (2 H, br t, $J_{3,4}$ 6, 4″-H).

Methyl (2-piperidinobenzyl)carbamate 14c. R_F = 0.53, 0.86; mp 85–86 °C (Pr^iOH) (Found: C, 67.5; H, 8.4; N, 11.6. $C_{14}H_{20}N_2O_2$ requires C, 67.7; H, 8.1; N, 11.3%); δ_H[$(CD_3)_2SO$] 7.53 (1 H, br t, $J_{CH,NH}$ 6, NH), 7.22–6.98 (4 H, m, 3′-, 4′-, 5′-, 6′-H), 4.25 (2 H, d, $J_{CH,NH}$ 6, CH_2NH), 3.56 (3 H, s, CH_3), 2.81–2.69 (4 H, m, 2″-, 6″-H) and 1.71–1.43 (6 H, m, 3″-, 4″-, 5″-H).

Substituted phenylacetamides 15a,b

(3-Nitro-6-piperidinophenyl)acetamide 15a. R_F = 0.10, 0.55; mp 186–189 °C (Pr^iOH) (Found: C, 59.15; H, 6.7; N, 15.8. $C_{13}H_{17}N_3O_3$ requires C, 59.3; H, 6.5; N, 16.0%); ν_{max}(KBr)/cm^{-1} 3430 and 3180 (NH) and 1690 (CO); δ_H[$(CD_3)_2SO$] 8.12–8.00 (2 H, m, 2′-, 4′-H), 7.62 (1 H, br s, NH_a), 7.16 (1 H, d, J_o 9, 5′-H), 7.08 (1 H, br s, NH_b), 3.54 (2 H, s, 2-H), 2.98–2.82 (4 H, m, 2″-, 6″-H) and 1.78–1.48 (6 H, m, 3″-, 4″-, 5″-H); *m*/*z* 263 (M^+, 45%), 246 (33), 234 (26), 217 (100), 205 (52), 189 (31), 178 (60), 173 (49), 143 (28), 130 (22), 117 (77), 89 (50) and 84 (93).

[3-Nitro-6-(1,2,3,4-tetrahydro-2-isoquinolyl)phenyl]acet-amide 15b. R_F = 0.08, 0.59; mp 181–184 °C (Pr^iOH) (Found: C, 65.85; H, 5.8; N, 13.7. $C_{17}H_{17}N_3O_3$ requires C, 65.6; H, 5.5; N, 13.5%); δ_H[$(CD_3)_2SO$] 8.18–8.05 (2 H, m, 2′-, 4′-H), 7.65 (1 H, br s, NH_a), 7.29 (1 H, d, J_o 9, 5′-H), 7.22–7.05 (5 H, m, 5″-, 6″-, 7″-, 8″-H and NH_b), 4.25 (2 H, s, 1″-H), 3.60 (2 H, s, 2-H), 3.28 (2 H, br t, $J_{3,4}$ 6, 3″-H) and 2.99 (2 H, br t, $J_{3,4}$ 6, 4″-H).

These compounds could be prepared in an alternative way according to the following procedure. A mixture of (2-fluoro-5-nitrophenyl)acetamide (see above) (0.30 g, 1.5 mmol) and the corresponding secondary amine (piperidine or 1,2,3,4-tetrahydroisoquinoline) (4.5 mmol) was heated at 100 °C for 20 min (**15a**) or 2 h (**15b**). After cooling and trituration of the mixture with 10% aq. acetic acid (5 cm^3) the solid in suspension was filtered off to afford **15a** (0.37 g, 94%) and **15b** (0.39 g, 84%).

Substituted *N*-benzylphenylacetamides 16a,c

***N*-(3-Nitro-6-piperidinobenzyl)(3-nitro-6-piperidinophenyl)-acetamide 16a.** $R_F = 0.23$, 0.85; mp 162–164 °C (Pr^iOH) (Found: C, 62.2; H, 6.7; N, 14.4. $C_{25}H_{31}N_5O_5$ requires C, 62.4; H, 6.5; N, 14.5%); ν_{max}(KBr)/cm^{-1} 3260 (NH) and 1640 (CO); δ_H[$(CD_3)_2SO$] 8.84 (1 H, br t, $J_{CH,NH}$ 6, NH), 8.03–8.11 (4 H, m) and 7.25–7.14 (2 H, m) (arom. H), 4.34 (2 H, d, $J_{CH,NH}$ 6, CH_2NH), 3.69 (2 H, s, CH_2CO) and 3.00–2.85 (8 H, m) and 1.74–1.45 (12 H, m) (piperidine rings); δ_C[$(CD_3)_2SO$] 170.17 (CO), 158.80, 157.56 (C-6), 141.59, 141.53 (C-3), 133.58, 130.94 (C-1), 126.46, 123.19, 123.09 (C-2, -4), 119.62, 119.04 (C-5) (arom. C), 52.80, 52.71 (C-2, -6, piperidine rings), 37.99, 37.38 (*C*H_2CO, CH_2NH), 25.69, 25.63 (C-3, -5, piperidine rings) and 23.54 (C-4, piperidine rings); *m*/*z* 481 (M^+, 15%), 464 (100), 247 (17), 219 (34), 217 (39), 201 (10), 173 (46), 171 (34), 130 (14), 117 (18) and 90 (13).

***N*-(2-Piperidinobenzyl)-(2-piperidinophenyl)acetamide 16c.** $R_F = 0.17$, 0.81; mp 102–104 °C (c-C_6H_{12}) (Found: C, 76.5; H, 8.7; N, 10.6. $C_{25}H_{33}N_3O$ requires C, 76.7; H, 8.5; N, 10.7%); δ_H[$(CD_3)_2SO$] 8.26 (1 H, br t, $J_{CH,NH}$ 6, NH), 7.22–6.96 (8 H, m, arom. H), 4.35 (2 H, d, $J_{CH,NH}$ 6, CH_2NH), 3.57 (2 H, s, CH_2CO), and 2.82–2.68 (8 H, m) and 1.70–1.40 (12 H, m) (piperidine rings).

Substituted urea derivatives 17a–c

***N*,*N*′-Bis(3-nitro-6-piperidinobenzyl)urea 17a.** $R_F = 0.14$, 0.74; mp 207–209 °C (PrOH) (Found: 60.7; H, 6.3; N, 17.0. $C_{25}H_{32}N_6O_5$ requires C, 60.5; H, 6.5; N, 16.9%); ν_{max}(KBr)/cm^{-1} 3370 (NH) and 1630 (CO); δ_H[$(CD_3)_2SO$] 8.14–8.00 (4 H, m, 2′-, 4′-H), 7.15 (2 H, d, J_o 9.5, 5′-H), 6.84 (2 H, br t, $J_{CH,NH}$ 6, NH), 4.29 (4 H, d, $J_{CH,NH}$ 6, CH_2NH), 3.00–2.87 (8 H, m, 2″-, 6″-H) and 1.85–1.47 (12 H, m, 3″-, 4″-, 5″-H).

***N*,*N*′-Bis[3-nitro-6-(1,2,3,4-tetrahydro-2-isoquinolyl)benzyl]-urea 17b.** $R_F = 0.11$, 0.83; mp 174–177 °C (PrOH) (Found: C, 66.6; H, 5.2; N, 14.0. $C_{33}H_{32}N_6O_5$ requires C, 66.9; H, 5.4; N, 14.2%); δ_H[$(CD_3)_2SO$] 8.18–8.04 (4 H, m, 2′-, 4′-H), 7.26 (2 H, d, J_o 9, 5′-H), 7.16 (8 H, s, 5″-, 6″-, 7″- 8″-H), 6.89 (2 H, br t, $J_{CH,NH}$ 6, NH), 4.34 (4 H, d, $J_{CH,NH}$ 6, CH_2NH), 4.27 (4 H, s, 1″-H), 3.32 (4 H, br t, $J_{3,4}$ 6, 3″-H) and 2.96 (4 H, br t, $J_{3,4}$ 6, 4″-H).

***N*,*N*′-Bis(2-piperidinobenzyl)urea 17c.** $R_F = 0.05$, 0.62; mp 140–143 °C (toluene) (Found: C, 74.1; H, 8.4; N, 13.6. $C_{25}H_{34}N_4O$ requires C, 73.9; H, 8.4; N, 13.8%); δ_H[$(CD_3)_2SO$] 7.25–6.95 (8 H, m, 3′-, 4′-, 5′-, 6′-H), 6.35 (2 H, br t, $J_{CH,NH}$ 6, NH), 4.26 (4 H, d, $J_{CH,NH}$ 6, CH_2NH), 2.84–2.65 (8 H, m, 2″-, 6″-H) and 1.71–1.40 (12 H, m, 3″-, 4″-, 5″-H); δ_C[$(CD_3)_2SO$] 158.60 (CO), 151.78 (C-2′), 134.85 (C-1′), 127.97, 127.43 (C-4′, -6′), 123.17 (C-5′), 119.37 (C-3′), 53.72 (C-2″, -6″), 38.66 (CH_2NH), 26.19 (C-3″, -5″) and 23.86 (C-4″); *m*/*z* 406 (M^+, 1%), 217 (12), 216 (15), 188 (35), 172 (100), 144 (15), 131 (22), 118 (29), 106 (10) and 91 (41).

1,3,5-Tris(2-piperidinobenzyl)biuret 18

$R_F = 0.26$, 0.90; an oil (Found: $M^+ + 1$, 623.406 788. $C_{38}H_{51}N_6O_2$ requires 623.407 350) (Found: C, 73.1; H, 8.4; N, 13.5. $C_{38}H_{50}N_6O_2$ requires C, 73.3; H, 8.1; N, 13.5%); ν_{max}(KBr)/cm^{-1} 3250 (NH) and 1690 (CO); δ_H[$(CD_3)_2SO$] 8.74 (2 H, br t, $J_{CH,NH}$ 5, NH), 7.40–6.85 (12 H, m, arom. H), 4.94 (2 H, s, 3-CH_2), 4.41 (4 H, d, $J_{CH,NH}$ 5, 1- and 5-CH_2) and 2.75–2.45 (12 H, m) and 1.70–1.30 (18 H, m) (piperidine rings); δ_C[$(CD_3)_2SO$] 156.12 (CO), 151.92, 150.81 (C-2), 133.20, 132.51 (C-1), 128.38, 128.21, 127.56, 127.23 (C-4, -6), 124.25, 123.06 (C-5), 119.53, 119.33 (C-3) (arom. C), 54.37, 53.44 (C-2, -6, piperidine rings), 39.49 (*C*H_2Ar), 26.06, 25.74 (C-3, -5, piperidine rings) and 23.74 and 23.43 (C-4, piperidine rings); δ_C($CDCl_3$) 39.99 and 38.80 (*C*H_2Ar); *m*/*z* (FAB-MS) 623 ($M^+ + 1$, 65%), 407 (16), 260 (6), 217 (91), 188 (14), 174 (100), 154 (14), 136 (13), 118 (17) and 91 (18).

Preparation of 1-substituted 1,4-dihydrocinnolin-3-ols 19a,b and 21

A suspension of the corresponding cinnolinylio oxide **6** (5 mmol) in 10% aq. hydrochloric acid (10 cm^3) was evaporated to dryness *in vacuo*. The resulting residue was suspended in nitrobenzene (10 cm^3) and heated for 7 min at 160 °C (for **19a,b**) or at 130 °C (for **21**). In the first case, the solvent was evaporated to dryness and the solid obtained after trituration of the residue with some methanol was filtered off. For compound **21**, the solid appeared after cooling of nitrobenzene solution was directly filtered off and washed with toluene.

1-(5-Chloropentyl)-6-nitro-1,4-dihydrocinnolin-3-ol 19a. Yield 47%; mp 141–143 °C (Pr^iOH) (Found: C, 52.5; H, 5.6; N, 14.2. $C_{13}H_{16}ClN_3O_3$ requires C, 52.4; H, 5.4; N, 14.1%); ν_{max}(KBr)/cm^{-1} 3250–2500 (OH) and 1660, 1605 and 1585 (C=N, C=C); δ_H[$(CD_3)_2SO$] 10.51 (1 H, br s, OH), 8.10–7.95 (2 H, m, 5-, 7-H), 7.04 (1 H, d, J_o 9, 8-H), 3.61 (4 H, t, *J* 6, 1′-, 5′-H), 3.57 (2 H, s, 4-H) and 1.85–1.30 (6 H, m, 2′-, 3′-, 4′-H); δ_C[$(CD_3)_2SO$] 163.65 (C-3), 146.66 (C-8a), 139.29 (C-6), 124.50, 123.54 (C-5, -7), 119.98 (C-4a), 112.09 (C-8), 51.13 (C-1′), 45.20 (C-5′), 33.26 (C-4) and 31.64, 24.77 and 23.32 (C-2′, -3′, -4′); *m*/*z* 299 ($M^+ + 2$, 4%), 297 (M^+, 13), 206 (100), 160 (23), 146 (11), 118 (22), 91 (11), 90 (14) and 89 (17).

1-(6-Chlorohexyl)-6-nitro-1,4-dihydrocinnolin-3-ol 19b. Yield 27%; mp 147–150 °C (MeCN) (Found: C, 54.1; H, 5.7; N, 13.3. $C_{14}H_{18}ClN_3O_3$ requires C, 53.9; H, 5.8; N, 13.5%); δ_H[$(CD_3)_2SO$] 10.57 (1 H, br s, OH), 8.07–7.92 (2 H, m, 5-, 7-H), 7.04 (1 H, d, J_o 9, 8-H), 3.60 (4 H, t, *J* 6, 1′-, 6′-H), 3.57 (2 H, s, 4-H) and 1.80–1.20 (8 H, m, 2′-, 3′-, 4′-, 5′-H); *m*/*z* 313 ($M^+ + 2$, 4%), 311 (M^+, 12), 206 (100), 160 (14), 146 (8), 118 (20), 91 (9), 90 (11) and 89 (13).

1-Methyl-6-nitro-1,4-dihydrocinnolin-3-ol 21. Yield 85%; mp >350 °C ($MeNO_2$ or dil. DMF) (Found: C, 52.4; H, 4.2; N, 20.2. $C_9H_9N_3O_3$ requires C, 52.2; H, 4.4; N, 20.3%); ν_{max}(KBr)/cm^{-1} 3300–2600 (OH) and 1675, 1610 and 1595 (C=N, C=C); δ_H[$(CD_3)_2SO$] 10.63 (1 H, br s, OH), 8.10–8.00 (2 H, m, 5-, 7-H), 7.00 (1 H, d, J_o 10, 8-H), 3.57 (2 H, s, 4-H) and 3.20 (3 H, s, CH_3); δ_C[$(CD_3)_2SO$] 163.43 (C-3), 148.12 (C-8a), 139.68 (C-6), 123.93, 123.59 (C-5, -7), 120.25 (C-4a), 111.14 (C-8), 38.49 (CH_3) and 33.72 (C-4); *m*/*z* 207 (M^+, 100%), 178 (15), 161 (19), 160 (27), 146 (12), 132 (41), 118 (51), 104 (12), 91 (21), 90 (22) and 89 (24).

Preparation of 2-nitro-7,8,9,10,12,13-hexahydro-6*H*-[1,2]-diazepino[1,2-*a*]cinnolin-12-one 20

A mixture of 1-(5-chloropentyl)cinnolinol **19a** (59 mg, 0.2 mmol) and potassium carbonate (120 mg) in butan-2-one (10 cm^3) was refluxed for 3 h. After evaporation of the mixture, the residue was diluted with water and extracted with chloroform. The complex mixture contained in the organic layer was applied to two preparative plates, which were developed with chloroform (two runs). Elution of a yellow band of $R_F = 0.16$ (TLC, $CHCl_3$) afforded the desired compound (28 mg, 54%); mp 129–131 °C (water) (Found: C, 59.6; H, 6.0; N, 16.0. $C_{13}H_{15}N_3O_3$ requires C, 59.8; H, 5.8; N, 16.1%); ν_{max}(KBr)/cm^{-1} 1655 (CO); δ_H($CDCl_3$) 8.10 (1 H, dd, J_o 9, J_m 2, 3-H), 8.00 (1 H, d, J_m 2, 1-H), 7.06 (1 H, d, J_o 9, 4-H), 3.76 (2 H, t, *J* 5) and 3.52 (2 H, t, *J* 5) (6-, 10-H), 3.60 (2 H, s, 13-H) and 2.00–1.70 (6 H, m, 7-, 8-, 9-H); *m*/*z* 261 (M^+, 100), 232 (42), 205 (14), 193 (13), 178 (19), 177 (27), 176 (38), 164 (6), 117 (6) and 89 (13).

Preparation of 3-hydroxy-1-methyl-6-nitro-1,4-dihydrocinnolin-4-one 22

A suspension of 1-methylcinnolinol **21** (0.52 g, 2.5 mmol) in a mixture of water (5 cm^3), 33% aq. hydrogen peroxide (10 cm^3) and sodium hydrogen carbonate (0.50 g) was stirred at room temperature for 3 h. The resulting dark orange solution was acidified with dilute hydrochloric acid, and the precipitated solid was filtered off; an additional amount of compound **22** was obtained after extraction of the aqueous phase with chloroform; yield 0.45 g (81%); mp 263–266 °C (MeOH) (Found: C, 49.0; H, 3.2; N, 19.3. $C_9H_7N_3O_4$ requires C, 48.9; H, 3.2; N, 19.0%); ν_{max}(KBr)/cm^{-1} 3400–2800 (OH) and 1630, 1615 and

1590 (C=N, C=C); δ_H[$(CD_3)_2SO$] 11.55 (1 H, br s, OH), 8.81 (1 H, d, J_m 3, 5-H), 8.40 (1 H, dd, J_o 10, J_m 3, 7-H), 7.82 (1 H, d, J_o 10, 8-H) and 4.00 (3 H, s, CH_3); δ_C[$(CD_3)_2SO$] 164.70 (C-4), 153.86 (C-3), 143.10, 141.30 (C-6, -8a), 126.29, 121.90 (C-5, -7), 119.76 (C-4a), 118.04 (C-8) and 43.29 (CH_3); *m*/*z* 221 (M^+, 100), 193 (19), 175 (18), 163 (21), 147 (36), 119 (17), 104 (21) and 92 (27).

Methylation of 1-methyl-6-nitro-1,4-dihydrocinnolin-3-ol 21

A mixture of 1-methylcinnolinol **21** (0.29 g, 1.4 mmol), potassium carbonate (0.30 g) and an excess of methyl iodide (2 cm^3) in acetone (30 cm^3) was refluxed for 8 h. After evaporation of the mixture the residue was diluted with water (50 cm^3) and extracted with chloroform. The mixture of methylated compounds was separated by column chromatography, compound **23** being eluted with chloroform, and compound **24** with chloroform–methanol (60 : 1).

3-Methoxy-1-methyl-6-nitro-1,4-dihydrocinnoline 23. Yield 26%; R_F = 0.69 (TLC, $CHCl_3$); mp 156–159 °C (Pr^iOH) (Found: C, 54.6; H, 5.0; N, 18.9. $C_{10}H_{11}N_3O_3$ requires C, 54.3; H, 5.0; N, 19.0%); ν_{max}(KBr)/cm^{-1} 1655, 1600 and 1590 (C=N, C=C); δ_H[$(CD_3)_2SO$] 8.06–7.95 (2 H, m, 5-, 7-H), 6.86 (1 H, d, J_o 10, 8-H), 3.68 (3 H, s, OCH_3), 3.61 (2 H, s, 4-H) and 3.30 (3 H, s, 1-CH_3); δ_C[$(CD_3)_2SO$] 152.72 (C-3), 145.81 (C-8a), 138.95 (C-6), 124.19, 124.11 (C-5, -7), 117.24 (C-4a), 109.59 (C-8), 53.96 (CH_3O), 40.48 (1-CH_3) and 27.07 (C-4); *m*/*z* 221 (M^+, 100), 175 (21), 174 (35), 132 (31), 131 (18), 117 (19), 104 (11), 91 (16), 90 (17) and 89 (22).

1,2-Dimethyl-6-nitro-1,2,3,4-tetrahydrocinnolin-3-one 24. Yield 68%; R_F = 0.16 (TLC, $CHCl_3$); mp 129–131 °C (Pr^iOH) (Found: C, 54.5; H, 5.2; N, 19.3. $C_{10}H_{11}N_3O_3$ requires C, 54.3; H, 5.0; N, 19.0%); ν_{max}(KBr)/cm^{-1} 1655 (CO); δ_H[$(CD_3)_2SO$] 8.17–8.04 (2 H, m, 5-, 7-H), 7.30 (1 H, d, J_o 9, 8-H), 3.72 (2 H, s, 4-H) and 3.15 (3 H, s) and 3.10 (3 H, s) (1-, 2-CH_3); δ_C[$(CD_3)_2SO$] 166.99 (C-3), 151.22 (C-8a), 143.50 (C-6), 127.87 (C-4a), 123.47, 122.79 (C-5, -7), 120.59 (C-8), 42.74 (1-CH_3), 34.02 (C-4) and 32.64 (2-CH_3); *m*/*z* 221 (M^+, 100), 206 (12), 178 (8), 146 (12), 132 (48), 117 (10), 104 (11), 91 (10), 90 (9) and 89 (12).

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