93. 2*H*-Benzimidazoles

Part 5[1])

Convenient Synthons for Tricyclic Heterocycles

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Dedicated to *Salo Gronowitz* on the occasion of his 65th birthday

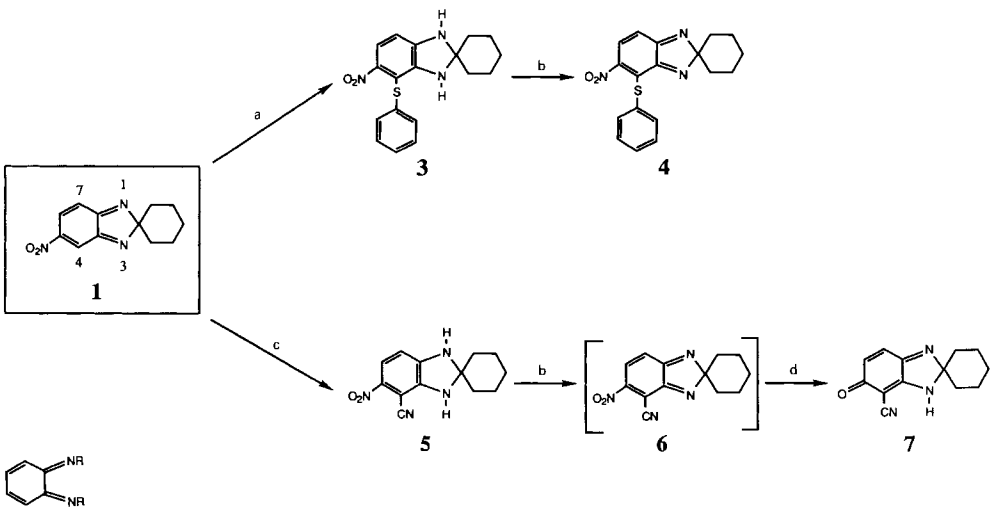
The readily available 5-nitrospiro[2*H*-benzimidazole-2,1′-cyclohexane] (**1**) was converted into the carbonitrile **5** and the 4-phenylthio derivative **4**. The NO_2 or the PhS substituents in **4** could be replaced regiospecifically by reaction with Me_3SiN_3 or NaN_3, respectively. The 5-azido derivative **8**, resulting from NO_2-group replacement was made to cyclize photolytically to give the angular spiro[cyclohexane-imidazophenothiazine] **18**. The azide **9** obtained from the PhS replacement in **4** cyclized spontaneously to give the angular spiro[cyclohexane-imidazobenzoxadiazole] **10** which, on reductive hydrolysis, furnished benzofurazan-4,5-diamine **14**. The diamine **14** was converted by conventional methods into a imidazobenzoxadiazole **15**, oxadiazoloquinoxaline **16**, and selenadiazoloxadiazole **17**. The carbonitrile **5** was converted, in simple steps, into the 'stretched-out', angular pteridine and purine analogues, **25** and **28**, respectively.

Introduction. – We will report here on some new synthetic applications of 2*H*-benzimidazoles [1] [2] which are readily obtained by condensation of cyclohexanone with *o*-phenylenediamine followed by oxidation with MnO_2. The resulting 2*H*-benzimidazoles (*e.g.* **1**) behave as protected phenylenediamines, but they are, unlike their unprotected counterparts, amenable to nucleophilic substitution by *Michael* addition [2 b]. This reversal of reactivity ('Umpolung'), which is undoubtedly due to their inherent structure of a 'stable' quinone diimine (*cf.* **2**) endows 2*H*-benzimidazoles with a considerable synthetic potential, particularly for preparing other heterocycles.

Results. – *Preparation of Starting Materials.* Our strategy involved essentially the easily prepared 5-nitro-2*H*-benzimidazole **1**. Reaction with an aqueous solution of NaCN in presence of catalytic amount of as PTC gave the carbonitrile **5** *(Scheme 1)*. The yield (43%) was not improved by using other sources of CN (*e.g.* Me_3SiCN) or in a non-aqueous medium (*e.g.* THF/15-crown-5-ether). Oxidation of **5** with active MnO_2 produced the moisture-sensitive 2*H*-benzimidazole **6**. Even short exposure to air caused hydrolysis to 5-hydroxy-2*H*-benzimidazole-4-carbonitrile followed by prototropic rearrangement to the 5-oxo derivative **7**.

[1]) Part 4: [1].

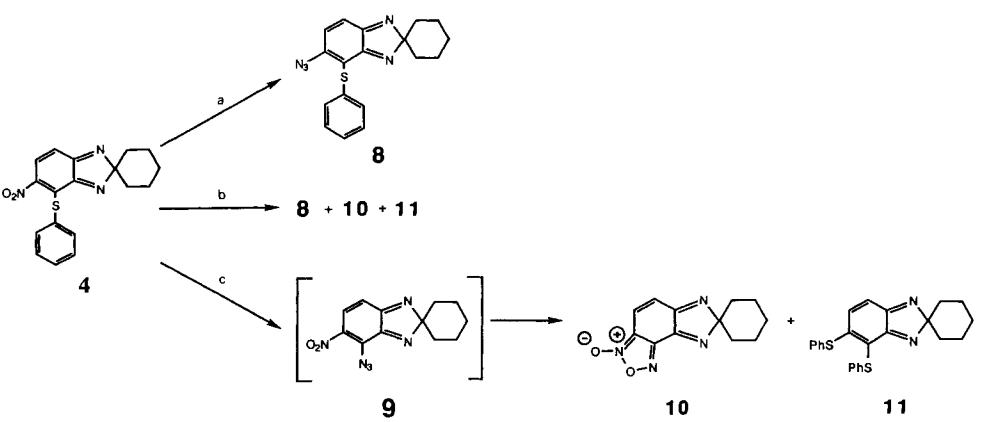
Scheme 1



a) AcOH, PhSH. b) MnO_2. c) NaCN, $(t\text{-Bu})_4NBr$. d) H_2O.

The other required starting material 5-nitro-4-(phenylthio)-2*H*-benzimidazole **4** was obtained from **1** by treatment with thiophenol followed by MnO_2 oxidation. Its behaviour towards azide nucleophiles is noteworthy *(Scheme 2)*. When made to react with $(CH_3)_3SiN_3$, a regiospecific replacement of the NO_2 group gave the light-sensitive 5-azido derivative **8**. In contrast, treatment with NaN_3 in presence of 15-crown-5-ether led first, *via* a regiospecific replacement of the PhS substituent, to the unstable 4-azido derivative **9**. Assisted decomposition of the N_3 by the NO_2 group [3] caused cyclisation to the furazan derivative **10**. A roughly equal amount of the 4,5-di(phenylthio) compound **11**

Scheme 2



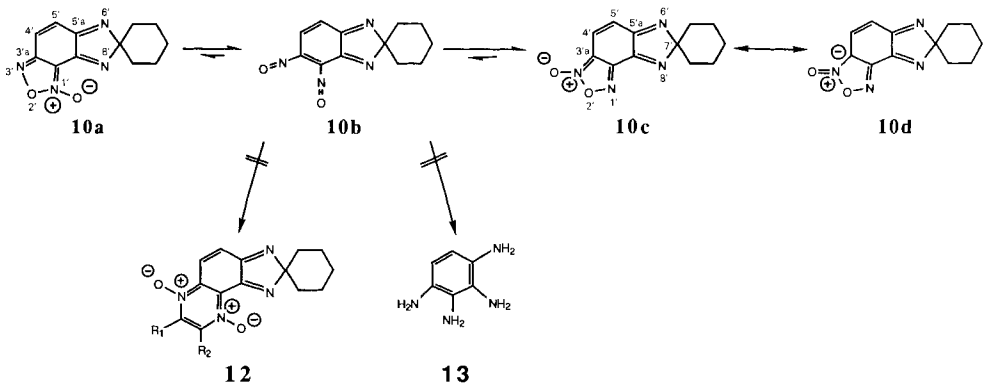
a) $(CH_3)_3SiN_3$ in CH_2Cl_2. b) NaN_3/Bu_4NBr in CH_2Cl_2. c) NaN_3, THF, 15-crown-5-ether.

was also formed, presumably as the result of a liberated and strongly nucleophilic phenylthiolate ion competing with the N_3 for substrate **4**.

The regiospecificity of the two azide reagents producing **8** or **9** can best be rationalized on steric grounds rather than on the concept of hard and soft bases ('HSAB' principle [4]). Under the reaction conditions (crown ether), NaN_3 provides small, linear, 'naked' anions which are able to approach the shielded but more easily replaceable PhS substituent. By contrast, the bulky ion pair derived from Me_3SiN_3 will preferentially substitute the less hindered NO_2 group.

Imidazobenzoxadiazole **10**: *Structure and Reactions.* Compound **10** was found to display a tautomeric equilibrium **10a**⇌**10c** *(Scheme 3)*. Its ^{1}H-NMR spectrum ($CHDCl_2$) shows 4 *doublets* corresponding to the protons H–C(4) and H–C(5) in **10c**,

Scheme 3



and H–C(4) and H–C(5) in **10a** at low field (7.15–7.4 ppm) in a ratio of *ca.* **10a**/**10c** 1:18.6 at 295°K, but, in (D_6)DMSO, only **10c** is observable at this temperature. While the tautomeric tendency of imidazobenzoxadiazoles is well established [5], the equilibrium distribution in this case is noteworthy. Calculated from the NMR data (based on the ratio of the proton populations), the free-energy difference (enthalpy) between the tautomers amounts to *ca.* 7.17 KJ/mol (1712 cal/mol) [6]. This value is in agreement with the equilibrium favouring one side, when compared with monocyclic and condensed oxadiazoles for which enthalpy figures of 2.09 KJ/mol (500 cal/mol) are quoted [7]. A value of 3.98 KJ/mol (950 cal/mol), already regarded as high, was found for the tautomeric equilibrium of 5:1 for quinolino[7,8-*c*]furoxane [7].

The preference for the *N*-oxide form **10c** is undoubtedly due to the lone pair of electrons on the imidazole N-atom repelling the polar O-atom of the *N*-oxide group. The structural assignment of **10c** was made by a $^{13}C\{^1H\}$NOE difference spectrum. Selective irradiation of the two protons H–C(4) and H–C(5) was not possible because of their close chemical shifts. A clear NOE in the ^{13}C-NMR at 158.6 and 111.7 ppm was discernible. The former signal is assigned to C(5) in accord with other 2*H*-benzimidazoles, while the upfield peak can be ascribed to C(3a) in **10c**, *i.e.* to the ring C-atom which is part of the $\succeq C{=}N^+{-}O^-$ moiety in the oxadiazole ring. Only the resonance hybrid **10d**

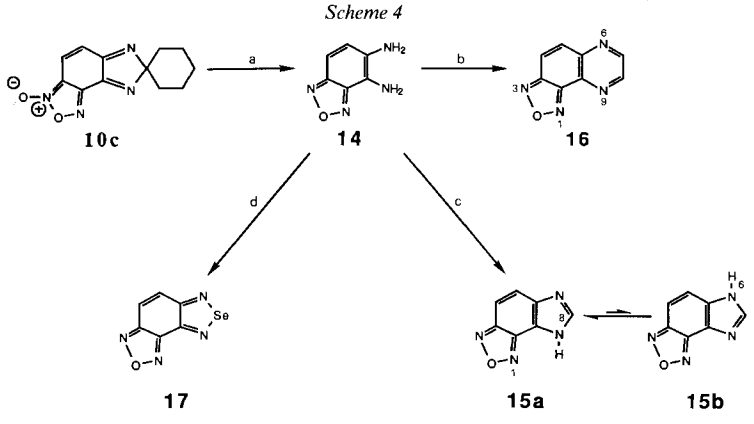
derived from **10c** can plausibly account for the observed shielding in C(3a) [8] by the *N*-oxide group. In the other isomer **10a**, a signal well downfield from 111.7 ppm would be expected for C(3a).

The stability of the imidazobenzoxadiazole **10c** is also shown in its chemical behaviour. Thus, we were unable to reduce the compound to the benzene-1,2,3,4-tetraamine **13** or to convert it into the corresponding quinoxaline 1,4-dioxide **12** by the procedure described in [9], since both reactions would entail ring-opening of **10c** to the dinitroso compound **10b**.

Conversion of **10c** *into Angular Tricycles.* While the oxadiazole ring in **10c** resisted cleavage, reductive fission of the 2*H*-imidazole moiety of the molecule with sodium dithionite [1] [2] was successful. The reductive step not only removed the cyclohexane ring, but also the exocyclic O-atom in **10c** producing benzoxadiazole-4,5-diamine **14** *(Scheme 4)* [10].

The 4,5-diamine functions in **14** can be used for various heterocyclisations as is illustrated by three examples *(Scheme 4)*. Heating of **14** in HCOOH gave imidazol[4,5-*e*]-[1,2,5]benzoxadiazole in its preferred tautomeric form **15a** owing to an intramolecular H-bond between H–N(8) and N(1). Condensation of **14** with the bisulfite compound of glyoxal yielded [1,2,5]oxadiazolo[3,4-*f*]quinoxaline (**16**), and treatment with SeO_2 led to [1,2,5]selenadiazolo[3,4-*e*][1,2,5]oxadiazole (**17**).

Scheme 4



a) $Na_2S_2O_4$. b) CHO–CHO·$NaHSO_3$. c) HCOOH, ΔT. d) SeO_2.

*Cyclisation of 5-Azido-4-(phenylthio)spiro[2*H*-benzimidazole-2,1′-cyclohexane]* (**8**). In view of the nature of the substituents in **8**, decomposition of the N_3 group should provide the phenothiazine **18** *(Scheme 5)*. The mechanism of such cyclisations has been extensively studied [11], and it was found that intermediate triplet or singlet nitrenes can give rise to the same products [12]. Variations in the yield are due to a combination of factors such as solvent, reaction temperature, and mode of N_3 decomposition.

The optimum yield of the dark-blue 2*H*-imidazo[4,5-*c*]phenothiazine **18** was obtained from photolysis at 25° in acetophenone, a triplet sensitizer. In contrast, thermolysis in this solvent suppressed phenothiazine formation in favour of the amine **19**, while

Scheme 5

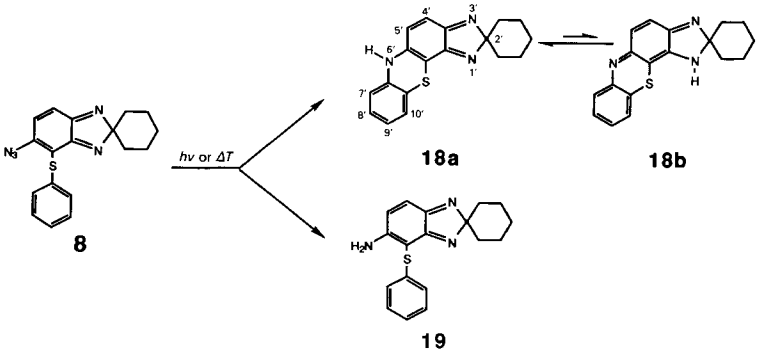
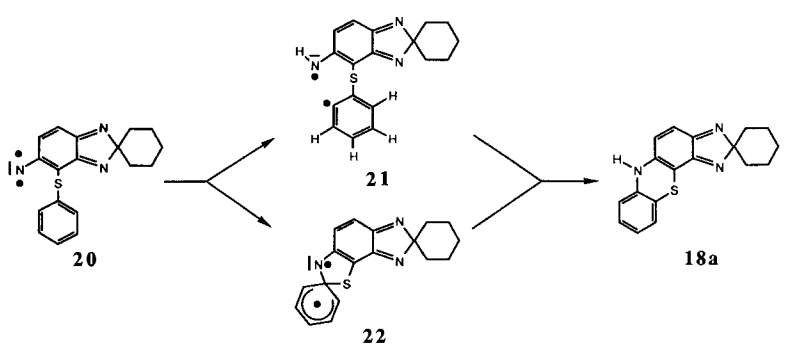


Table. *Experimental Results of the Thermal and Photolytic Decomposition of* **8** *in Various Solvents*

Method	Yield of **18** [%]	Solvent	Temp. [°C]	Yield **19** of [%]
hν	53.4	Acetophenone	25	6.0
hν	39.5	THF	25	8.4
hν	4.8	CH_2Cl_2/Pyrene	25	–
ΔT	22.5	$(EtO)_3PO$	40	42.3
ΔT	11.5	99% EtOH	62	59.0
ΔT	19.5	Acetophenone	85	51.3
ΔT	27.9	Chlorobenzene	130	44.5

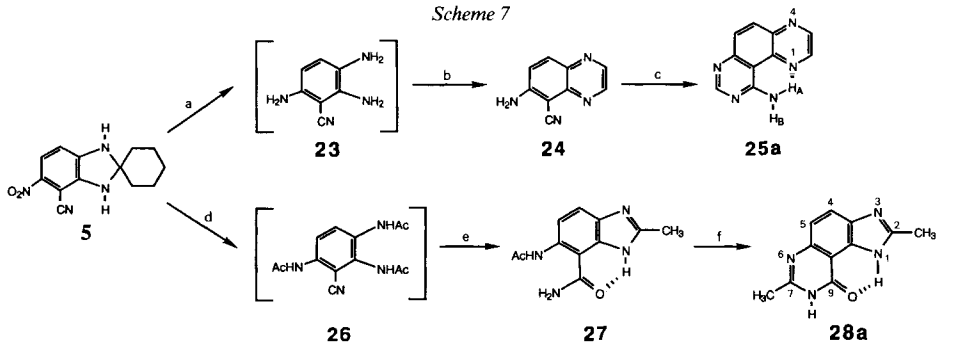
photolysis in pyrene, a singlet promoter, gave a very small yield of **18** (*cf.* the *Table*). Deoxygenation with $(EtO)_3PO$ of the appropriate nitro derivative **4** provided only a small yield of **18**. Our optimum conditions (*hν*/acetophenone) imply the participation of a triplet nitrene in the phenothiazine formation (*Scheme 6*). The mechanism may involve coupling of the diradical **21** or ring expansion of an intermediate thiazole **22** as observed in some cases [11].

Scheme 6



Synthesis of the Angular Pteridine Analogue **25** *and Purine Analogue* **28**. The above described benzimidazole-carbonitrile **5**, which can be regarded a tetrasubstituted benzene equivalent, was designed as a potential intermediate for the synthesis of a stretched-out pteridine or purine analogues of possible interesting biological activity [13].

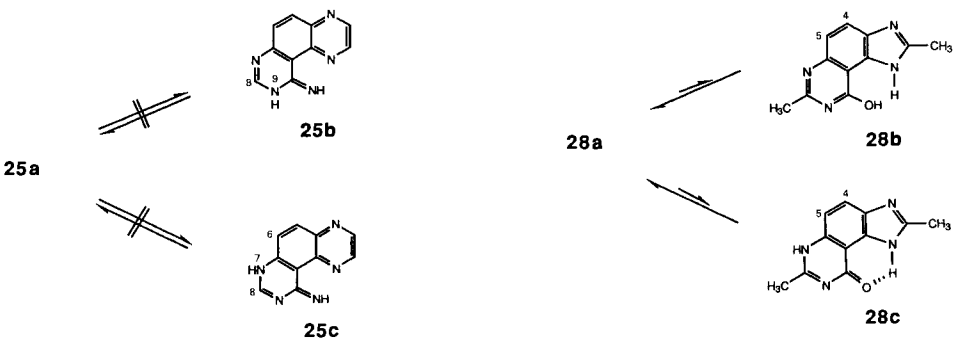
Scheme 7



a) Pd/H_2, EtOH 50%. b) $CHO-CHO \cdot NaHSO_3$. c) $HCONH_2$, 180°. d) Pd/H_2, $AcOH/Ac_2O$ 1:1. e) 1N ethanol. HCl. f) ΔT.

Reduction of **5** in 50% EtOH with Pd/H_2 in the dark gave the unstable 2,3,6-triaminobenzonitrile **23** *(Scheme 7)*. From the reaction of **23** with glyoxal sodium bisulfite, the quinoxaline **24** was obtained, which has been mentioned previously by *Schneller* and *Christ* [13b] but without any analytical data. Reflux of the **24** in formamide (180°, 8 h) gave the required angular pteridine analogue **25a**. Milder conditions using orthoformate/NH_3 or formamidine acetate [14] did not lead to cyclisation. The protons of the NH_2 group H_A and H_B are not equivalent in **25a** but appear at 9.81 and 8.49 ppm owing to an H-bond between H_A and N(1). The presence of the imino tautomers **25b** or **25c** can be excluded, since no NOE effect between H–N(9) and H–C(8), or H–C(8) and H–C(6) with H–N(7), respectively, was observed *(Scheme 8)*.

Scheme 8



Reduction of **5** as described above in a solution of AcOH and Ac_2O gave, after the usual workup, crude benzonitrile **26**. Its hydrolysis in 1N ethanolic HCl at room temperature [15] led to the benzimidazole **27** which, on short heating cyclised to produce imidazoquinazoline **28**.

Compound **28** exists predominantly in the lactam form **28a** (12.6:1) on the basis of ^{1}H-NMR: two *doublets* at 8.22 and 7.82 ppm with $J = 8.9$ Hz are assigned to H–C(5) and H–C(4) in **28a**, and signals at 2.86 and 2.57 ppm to the two Me groups at C(2) and C(7)

respectively. In addition, two faint *doublets* at 7.53 and 6.93 are best ascribed to H–C(5) and H–C(4) of tautomer **28b** or **28c**. A broad peak at 4.0–5.5 ppm (D_2O exchange) is characteristic of the imidazole-N*H*. In an NOE experiment, neither H–C(4) nor H–C(5) show interaction with the N*H* resonance, thereby excluding the presence of a proton at either N(3) or N(8) and, accordingly, the presence of other tautomers. This is moreover supported by the fact that in pyrimidin-4-one the lactam structure is dominant in aqueous as well as in DMSO solution [16].

The IR spectrum (KBr) shows two strong bands at 1695 cm^{-1} and 1660 cm^{-1} corresponding to the C=O and the >C=N moieties in **28a**. The wave number corresponding to the C=O group is more in agreement with an α,β-unsaturated ketone (*cf.* **28a**) [17] than with an $\alpha,\beta,\alpha',\beta'$-unsaturated C=O as represented by **28c**. This preference for the lactam form as a solid is also borne out by IR results obtained from studies on related systems [18].

We thank Mrs. *G. Baumann* for ^1H- and ^{13}C-NMR spectra, *H. Rudy*, *P. Weyrich*, and *G. Beutel* for MS and CHN analysis, *J.R. Thompson* (Salford) for helpful advice for HPLC, the *British Council* for a travel grant to *(A.C.)* which substantially furthered collaboration. Generous support of this work by *BASF AG*, *Bayer AG*, *Hoechst AG* for generous gifts of chemicals, the *ICN Biomedicals GmbH* (Eschwege) for providing us generously with silica gel, as well as the *Verband der Chemischen Industrie – Fonds der Chemie*, and *Deutsche Forschungsgemeinschaft* is gratefully acknowledged.

Experimental Part

General. Petroleum ether refers to the fraction of b.p. 40–60°. Irradiations were performed with a 125-W medium-pressure Hg lamp (*Hanau*, 254 nm, *T.Q. 150*) placed inside a H_2O-cooled immersion well. HPLC Separations were carried out on a *Knauer* HPLC pump *64*. Activated MnO_2 was purchased from *Fluka* (CAS No.[1313-13-9]). Column chromatography: silica gel *60 (Merck)*. M.p.: *Reichert* melting-point microscope, uncorrected. UV Spectra: *Carl Zeiss DMR 4* spectrometer. IR Spectra: *Perkin-Elmer 325* spectrometer. NMR Spectra: *Bruker WM 250* (250 MHz for ^1H and 62,89 MHz for ^{13}C); δ values relative to TMS. MS: *Varian MAT-311-A* (100 eV).

2,3-Dihydro-5-nitro-4-(phenylthio)spiro[1H-benzimidazole-2,1'-cyclohexane] (**3**). After stirring the yellow soln. of *5-nitrospiro[2H-benzimidazole-2,1'-cyclohexane]* (**1**; 1 g, 4.33 mmol) [2a], AcOH (0.25 ml, 4.33 mmol), PhSH (0.44 ml, 4.33 mmol), and CH_2Cl_2 (30 ml) at r.t. for 10 min, it turned red. The excess of solvent is now driven off on a rotary evaporator, and the residual oil chromatographed (silica gel, CH_2Cl_2). Recrystallisation from $CHCl_3$ gives pure **3** (1.13 g, 76.4%) as light red crystals. M.p. 126°. UV (MeOH): 446 (lg ε = 3.908), 262 (4.020), 241 (4.133). IR (KBr): 3325 (N–H); 1585, 1350 (NO_2). ^1H-NMR ((D_6)DMSO): 7.99 (*s*, H–C(1)); 7.41 (*d*, ^3J = 8.5, H–C(6)); 7.30–7.24 (*m*, H–C(2), H–C(6) of Ph); 7.16–7.05 (*m*, H–C(3), H–C(4), H–C(5) of Ph); 6.40 (s, H–C(3)); 6.17 (*d*, ^3J = 9.0, H–C(7)); 1.64–1.15 (*m*, C_6H_{10}). MS: 341 (53, M^+). Anal. calc. for $C_{18}H_{19}N_3O_2S$ (341.46): C 73.31, H 5.62, N 12.31; found: C 63.18, H 5.54, N 12.35.

5-Nitro-4-(phenylthio)spiro[2H-benzimidazole-2,1'-cyclohexane] (**4**). A soln. of **3** (1 g, 2.93 mmol) in 100 ml of CH_2Cl_2 is stirred with activated MnO_2 (3 g) at r.t. After 20 min, MnO_2 is filtered off, and the concentrated filtrate is chromatographed (silica, petroleum ether/AcOEt 2:1. The second band provides the pure product, recrystallisable from CH_2Cl_2/hexane (840 mg, 84.6%) as dark orange crystals. M.p. 139°. UV (MeOH): 449 (lg ε = 3.675), 254 (4.082). IR (KBr): 3090, 3070 (Ph); 1530, 1315 (NO_2). ^1H-NMR ($CDCl_3$): 7.60 (*d*, ^3J = 10.0, H–C(6)); 7.50–7.46 (*m*, H–C(2), H–C(6) of Ph); 7.33–7.24 (*m*, H–C(3), H–C(4), H–C(5) of Ph); 7.17 (*d*, ^3J = 10.0, H–C(7)); 1.74–1.04 (*m*, C_6H_{10}). MS: 339 (100, M^+). Anal. calc. for $C_{18}H_{17}N_3O_2S$ (339.44): C 63.69, H 5.06, N 12.38; found: C 63.75, H 5.17, N 12.45.

2,3-Dihydro-5-nitrospiro[1H-benzimidazole-2,1'-cyclohexane]-4-carbonitrile (**5**). To a stirred soln. of **1** (1 g, 4.33 mmol) in 25 ml of AcOEt, a soln. of NaCN (637 mg, 12.99 mmol) and $(t\text{-Bu})_4NBr$ (138 mg, 0.43 mmol) in 4 ml of H_2O is added. The colour of the mixture changes from yellow to red during the reaction time of 15 min. After filtration, the org. layer is separated and the aq. layer extracted 3 × with 30 ml of AcOEt. The combined org. layers

are dried ($MgSO_4$), concentrated, and finally subjected to FC, starting with petroleum ether/AcOEt 4:1 and gradually changing to a proportion of 1:1. The red main band is isolated and recrystallized from AcOEt/hexane to give **5** (482 mg, 43.2%) as carmine red crystals. M.p. 187°. UV (MeOH): 467 ($\lg \varepsilon = 4.093$), 302 (3.854), 236 (4.120). IR (KBr): 3270 (N–H); 2220 (CN); 1530, 1375 (NO_2). ^{1}H-NMR ((D_6)DMSO): 8.78 (*s*, H–N(1)); 8.27 (*s*, H–N(3)); 7.57 (*d*, $^3J = 10.0$, H–C(6)); 6.15 (*d*, $^3J = 10.0$, H–C(7)); 1.74–1.54 (*m*, C_6H_{10}). MS: 258 (20, M^+). Anal. calc. for $C_{13}H_{14}N_4O_2$ (258.31): C 60.44, H 5.47, N 21.69; found: C 60.30, H 5.59, N 21.63.

*2,6-Dihydro-6-oxospiro[1*H*-benzimidazole-2,1′cyclohexane]-7-carbonitrile* (**7**). Compound **5** (1 g, 3.88 mmol) is oxidized with MnO_2 (8 g) in 75 ml of THF for 15 min at r.t., in the course of which the red suspension becomes colourless, providing a mixture of impure *5-nitrospiro[2*H*-benzimidazole-2,1′-cyclohexane]-4-carbonitrile* (**6**). After removal of MnO_2, a paste is made from the filtrate with 40 g of silica, which is stirred at r.t. for 17 h and finally extracted with THF. The crude extract is chromatographed (petroleum ether/AcOEt 1:1) and the yellow main band eluted and finally recrystallized from AcOEt/hexane to provide anal. pure **7** (625 mg, 70.9%) as yellow crystals. M.p. 223°. UV (MeOH): 404 ($\lg \varepsilon = 3.677$), 259 (4.228), 212 (4.252). IR (KBr): 3190 (N–H); 2230 (CN). ^{1}H-NMR ((D_6)DMSO): 11.87 (*s*, H–N(1)); 7.45 (*d*, $^3J = 10.2$, H–C(4)); 6.63 (*d*, $^3J = 10.2$, H–C(5)); 1.78–1.64 (*m*, C_6H_{10}). MS: 227 (46, M^+). Anal. calc. for $C_{13}H_{13}N_3O$ (227.29): C 68.69, H 5.78, N 18.49; found: C 68.59, H 5.73, N 18.46.

*5-Azido-4-(phenylthio)spiro[2*H*-benzimidazole-2,1′-cyclohexane]* (**8**). To a soln. of **4** (1 g, 2.95 mmol) in 50 ml of CH_2Cl_2, Me_3SiN_3 (1.17 ml, 8.85 mmol) is added and the mixture kept stirring at r.t. under exclusion of light for 2.5 h. The carefully isolated crude product is chromatographed (silica, AcOEt/petroleum ether 1:1). The main band yields a dark yellow oil, which crystallizes on trituration with petroleum ether and rapid cooling to give **8** (600 mg, 60.7%) as yellow crystals. M.p. 85° (dec.). UV (MeOH): 371 ($\lg \varepsilon = 3.379$), 251 (4.356). IR (CH_2Cl_2): 2120, 1300 (N_3). ^{1}H-NMR ($CDCl_3$): 7.38 (*d*, $^3J = 10.0$, H–C(7)); 7.30–7.16 (*m*, Ph); 6.96 (*d*, $^3J = 10.0$, H–C(6)); 1.98–1.25 (*m*, C_6H_{10}). MS: 335 (18, M^+). Anal. calc. for $C_{18}H_{17}N_5S$: 335.1205 (MS peakmatching); found: C 335.1205 (elemental analysis proved unsatisfactory due to unstability of the product).

*Spiro[cyclohexane-1,7′-[7′*H*]-imidazo[4,5-e]-2,1,3-benzoxadiazole] 1′-Oxide* (**10**). To a soln. of **4** (1 g, 2.95 mmol) in 50 ml of THF, 15-crown-5-ether (10 drops) is added followed by NaN_3 (575 mg, 8.85 mmol). The mixture is stirred at 70° (temp. of oil bath) for 12 h. Unreacted NaN_3 is filtered off and the filtrate chromtographed (FC, petroleum ether/AcOEt 2:1). The weakly coloured main band is recrystallized from $CHCl_3$/hexane to give **10** (310 mg, 43.1%) as ochre coloured crystals. M.p. 109°. UV (MeOH): 348 ($\lg \varepsilon = 3.065$), 297 (4.162), 244 (4.106). IR (KBr): 1635 (C=N–O); 1460 [$N^+(-O^-)$–O]; 1380 (N–O). ^{1}H-NMR ($CHDCl_2$, tautomer **10c**): 7.17 (*d*, $^3J = 10.0$, H–C(5′)); 7.12 (*d*, $^3J = 10.0$, H–C(4′)); 1.98–1.73 (*m*, C_6H_{10}). ^{1}H-NMR ($CHDCl_2$, tautomer **10a**): 7.38 (*d*, 1H, $^3J = 10.0$); 7.27 (*d*, 1H, $^3J = 10.0$); 1.98–1.73 (*m*, C_6H_{10}). ^{13}C-NMR ($CDCl_3$, tautomer **10c**): 158.6 (J(H–C(5′), C(5′)) = 4.3, ^3J(H–C(4′), C(5′)) = 6.9, C(5′a)); 149.8 (^3J(H–C(4′), C(8′6)) = 4.3, C(8′b)); 147.3 (^3J(H–C(5′), C(8′)) = 1.7, C(8′a)); 126.2 (C(5)); 121.0 (C(4′)); 112.2 (C(7′)); 111.7 (^2J(H–C(4′), C(3′a)) = 4.7, ^3J(H–C(5′), C(3′a)) = 8.2, C(3′a)); 33.6 (C(2), C(6)); 25.5 (C(4)); 24.0 (C(3), C(5)). MS: 244 (100, M^+). Anal. calc. for $C_{12}H_{12}N_4O_2$ (244.28): C 59.00, H 4.96, N 22.94; found: C 58.83, H 4.89, N 22.84.

Reactions of **10**. *Benzofurazan-4,5-diamine* (**14**). Compound **10** (800 mg, 3.28 mmol) is dissolved in 50 ml of dioxane. To this soln., 50 ml of H_2O are slowly added, followed by $Na_2S_2O_4$ (14.27 g, 82 mmol). After the reduction has proceeded for 1 h under stirring, undissolved $Na_2S_2O_4$ is filtered off, and the deep-red solution is extracted with Et_2O (4 ×). The combined org. layers are dried ($MgSO_4$), excess of solvent is driven off, and the residual oil is recrystallized from $CHCl_3$/hexane to give **14** (235 mg, 47.9%) as vermilion crystals. M.p. 149° ([10]: 149–151°). ^{1}H-NMR ((D_6)DMSO): 7.15 (*d*, $^3J = 9.5$, H–C(7)); 7.10 (*d*, $^3J = 9.5$, H–C(6)); 5.27 (*s*, NH_2–C(5)); 4.94 (*s*, NH_2–C(4)).

*8*H*-Imidazo[4,5-e]-2,1,3-benzoxadiazole* (**15**). A soln. of **14** (300 mg, 2.00 mmol) in 20 ml of 99–100% HCOOH and 4N HCl (1:1) is refluxed for 1 h (oil bath: 100°) and then allowed to cool. After reaching r.t., the mixture is neutralized with aq. NH_3 and then extracted with AcOEt (4 ×). The combined org. layers are dried ($MgSO_4$) and chromatographed (silica, AcOEt). The two bands distinguished by a bright blue fluorescence under UV (365 nm) are isolated and combined. Recrystallization from AcOEt provides **15** (153 mg, 47.9%) as bright ochre coloured crystals. M.p. 248°. UV (MeOH): 324 ($\lg \varepsilon = 3.131$), 271 (3.093), 226 (4.081). IR (KBr): 3160–2590 (absorption band). ^{1}H-NMR ((D_6)DMSO): 13.47 (*s*, 0.07 H, H–N(6)); 8.37 (*s*, H–C(7)); 7.88 (*d*, $^3J = 10.0$, H–C(4)); 7.71 (*d*, $^3J = 10.0$, H–C(5)); 3.40 (*s*, 0.93 H, H–N(8)). MS: 160 (100, M^+). Anal. calc. for $C_7H_4N_4O$ (160.15): C 52.49, H 2.52, N 34.99; found: C 52.41, H 2.37, N 34.89.

[1,2,5]Oxadiazolo[3,4-f]quinoxaline (**16**). To a soln. of **14** (588 mg, 3.92 mmol) in 50 ml of dioxane/H_2O 1:1 CHO–CHO · $NaHSO_3$ (1.22 g, 4.30 mmol) dissolved in 16 ml of H_2O is added. The mixture is kept stirring at r.t. for 4 h. Addition of K_2CO_3 (1.7 g) is followed by extraction of the crude product with several portions of Et_2O 5 min later. The combined org. layers are dried ($MgSO_4$) and chromatographed (FC, elution first with CH_2Cl_2

followed by a slow change to CH_2Cl_2/AcOEt 4:1). Isolation of the main band and recrystallization from $CHCl_3$/hexane provides **16** (385 mg, 57.1%) as bright, beige needles. M.p. 162°. UV (MeOH): 282 (lg ε = 3.864), 258 (4.315). IR (KBr): 1555 (C=N–O); 1395 (N–O). ^{1}H-NMR ((D$_6$)DMSO): 9.18 (*d*, ^3J(7,8) = 2.5, 1H); 9.10 (*d*, ^3J(7,8) = 2.5, 1H); 8.27 (*d*, ^3J(4,5) = 10.0, 1H); 8.02 (*d*, ^3J(4,5) = 10.0, 1H). MS: 172 (100, M^+). Anal. calc. for $C_8H_4N_4O$ (172.16): C 55.81, H 2.35, N 32.55; found: C 55.68, H 2.47, N 32.68.

[1,2,5]Selenadiazolo[3,4-e][1,2,5]benzoxadiazole (**17**). Compound **14** (450 mg, 3.00 mmol) is dissolved in 15 ml of 96% EtOH and heated under reflux. A freshly prepared and filtered soln. of SeO_2 (366 mg, 3.30 mmol) in 2.5 ml of H_2O is added and the mixture kept boiling for 10 min. After cooling to r.t., separation is carried out by CC with petroleum ether/AcOEt 3:1. Isolation of the main band and recrystallization from CH_2Cl_2/hexane provides **17** (149 mg, 22.0%) as bright, beige crystals. M.p. 196° (subl.). UV (MeOH): 329 (lg ε = 3.937), 280 (3.823), 257 (4.106). IR (KBr): 1540 (C=N–O); 1405 (N–O). ^{1}H-NMR ((D$_6$)DMSO): 8.00 (*d*, ^3J(4,5) = 9.9, 1H); 7.91 (*d*, ^3J(4,5) = 9.9, 1H). MS: 226 (100, M^+, Se (80)). Anal. calc. for $C_6H_2N_4OSe$ (225.08): C 32.02, H 0.90, N 24.90; found: C 32.10, H 0.87, N 24.89.

Decomposition of **8**. *Photolysis (Method A)*. Compound **4** (3.0 g, 8.85 mmol) is reacted with Me_3SiN_3 (3.52 ml, 26.55 mmol) as described above to give **8**. The chromatographically pure product is dissolved in 250 ml of solvent, *i.e.* acetophenone or THF or CH_2Cl_2 plus 3 g of pyrene (see the *Table*). Photolysis is carried out at r.t. under stirring the appropriate soln. for 6 h, 2 h, and 4 h 15 min, respectively. The reaction product is chromatographed (FC; petroleum ether/AcOEt 3:2). The dark blue and the orange band are separated and purified from CH_2Cl_2/hexane to give **18** and **19**. The reaction in CH_2Cl_2/pyrene was treated as follows: after photolysis, the solvent is driven off and the product purified over silica with petroleum ether. The pyrene is retained on the short SiO_2 column (*ca.* 5 cm), while the product is eluted with MeOH. For the final chromatography, petroleum ether/AcOEt 9:1 is used.

Thermolysis (Method B) (*cf.* the *Table*). A 1% soln. of **8** (*w*/*v*) in 180 ml of PhCl or $(EtO)_3PO$ or acetophenone or 99% EtOH is stirred under exclusion of light for 3 h, 3 d, 3 h, and 5 h, respectively at 130°, 40°, 85°, and 62°, respectively. The solvent is driven off on completion of the reaction and the oily product chromatographed (petroleum ether/AcOEt 1:1) to give the dark blue **18** and the orange coloured **19** as described in *Method A*.

Spiro[cyclohexane-1,2'[2H]imidazo[4,5-c]phenothiazine] (**18a**). Dark blue crystals. M.p. 106° (dec.). UV (MeOH): 598 (lg ε = 3.324), 294 (4.123), 232 (4.181), 204 (4.410). IR (KBr): 3600–2960 (N–H absorption band). ^{1}H-NMR ((D$_6$)DMSO): 8.90 (*s*, H–N(6')); 8.29 (*s*, H–N(1')); 7.11 (*d*, ^3J = 10.0, H–C(4')); 7.15–6.75 (*m*, H–C(8'), H–C(9'), H–C(10'), H–C(4')); 7.15–6.75 (*m*, H–C(8'), H–C(9'), H–C(10'), H–C(4'), H–C(5'), H–C(7'), H–C(8'), H–C(9'), H–C(10') of **18b**); 6.78 (*d*, ^3J = 10.0, H–C(5')); 6.54 (*d*, ^3J = 10.0, H–C(7)); 1.80–1.40 (*m*, 2 C_6H_{10}). MS: 307 (100, M^+). Anal. calc. for $C_{18}H_{17}N_3S$ (307.44): C 70.32, H 5.58, N 13.67; found: C 70.44, H 5.47, N 13.49.

4-(Phenylthio)spiro[2H-benzimidazole-2,1'cyclohexane] (**19**). Orange crystals. M.p. 218°, was identical with the product described in [19].

6-Aminoquinoxaline-5-carbonitrile (**24**). A suspension of **5** (1 g, 3.88 mmol) in 100 ml of 50% EtOH is reduced in presence of 5% Pd/C (200 mg) under H_2 (1 atm) with exclusion of light at r.t. for 18 h. The catalyst is filtered off and washed with 25 ml of 50% EtOH. CHO–CHO·$NaHSO_3$ (1.10 g, 3.88 mmol) dissolved in 14 ml of H_2O is added to the combined EtOH extracts. The mixture is stirred at r.t. in the dark for 3 h and, shortly before the end of the reaction time, 1.5 g of K_2CO_3 are added. The aq. layer is extracted with Et_2O and the extract chromatographed (AcOEt/petroleum ether 3:1). The light-blue fluorescing main band (UV_{365}) is isolated and **24** obtained by recrystallization from CH_2Cl_2/petroleum ether (442 mg, 67.0%) as ochre coloured needles. M.p. 229°. UV (MeOH): 381 (lg ε = 3.342), 274 (3.282), 248 (3.952), 220 (3.718), 208 (3.836). IR (KBr): 3485, 3350, 3210 (NH_2); 2220 (CN). ^{1}H-NMR ((D$_6$)DMSO): 8.77 (*d*, ^3J(2,3) = 2.0, 1 H); 8.62 (*d*, ^3J(2,3) = 2.0, 1 H); 7.94 (*d*, ^3J = 9.3, H–C(8)); 7.35 (*d*, ^3J = 9.4, H–C(7)); 7.29 (*s*, C(6)–NH_2). MS: 170 (100, M^+). Anal. calc. for $C_9H_6N_4$ (170.19): C 63.51, H 3.56, N 32.93; found: C 63.41, H 3.52, N 32.77.

Pyrazino[2,3-f]quinazoline-10-amine (**25**). A soln. of **24** (300 mg, 1.76 mmol) in 15 ml of $HCONH_2$ is heated at 180° for 8 h. After driving off the solvent, the residual oil is dissolved in 25 ml of H_2O and extracted with AcOEt (30 ml, 10 ×). The dried combined org. layers are chromatographed (acetone/99% EtOH 1:1). Separation of the colourless main band followed by recrystallization from AcOEt yields an amorphous, yellow powder. Further purification by reverse-phase HPLC (packing: silica *RP 18*, particle size: 5µ; solvent: MeOH/H_2O 7:3, UV detector: 218 nm) provides **25** (114 mg, 32.9%) as light-yellow crystals. M.p. 232°. UV (MeOH): 356 (lg ε = 3.823), 280 (3.897), 255 (3.961), 218 (4.482). IR (KBr): 3365, 3150, 1645 (–NH_2). ^{1}H-NMR ((D$_6$)DMSO): 9.81 (*s*, H_A); 9.13 (*d*, ^3J(2,3) = 2.1, 1 H); 9.10 (*d*, ^3J(2,3) = 2.1, 1 H); 8.69 (*s*, H–C(8)); 8.49 (*s*, H_B); 8.33 (*d*, ^3J(5,6) = 9.3, 1 H); 8,04 (*d*, ^3J(5,6) = 9.3, 1 H). MS: 197 (100, M^+). Anal. calc. for $C_{10}H_7N_5$ (197.07): C 60.94, H 3.59, N 35.55; found: C 60.80, H 3.60, N 35.29.

1,8-Dihydro-2,6-dimethylimidazo[4,5-f]quinazolin-9-one (**28**). An agitated suspension of **5** (800 mg, 3.10 mmol) and 5% Pd/C (160 mg) in 50 ml of AcOH/Ac_2O 1:1 is reduced under H_2 (1 atm) and exclusion of light for 24 h. Removal of the catalyst and solvent provides crude **26**. It is taken up in 20 ml of 1N ethanolic HCl and the soln. stirred at r.t. for 15 h. A white precipitate is gradually formed, and its separation is completed by successive addition of 40 ml of Et_2O and cooling. After filtration, the residue is suspended in 15 ml of 1N ethanolic HCl and the mixture refluxed for 1 h. Crystallization from Et_2O at r.t. provides **28** (214 mg, 32.3%) as white grey crystals. M.p. 226° (dec.). UV (MeOH): 346 (lg ε = 3.604), 237 (4.190). IR (KBr): 3330, 3300 (CONHR); 3060 (N–H); 3330–2560 (band due to intermolecular aggregation); 1695 (C=O). ^{1}H-NMR ((D_6)DMSO): 8.22 (*d*, $^3J(4,5)$ = 8.9, 1 H); 7.82 (*d*, $^3J(4,5)$ = 8.9, 1 H); 4.94 (*s*, H–N(1), H–N(8)); 2.86 (*s*, CH_3); 2.57 (*s*, CH_3). MS: 214 (100, M^+). Anal. calc. for $C_{11}H_{10}N_4O$ (214.25): C 61.66, H 4.71, N 26.16; found: C 61.56, H 4.70, N 26.16.

6-(Acetylamino)-2-methyl-1H-benzimidazole-7-carboxamide (**27**). This intermediate was isolated from an experiment designed to optimize the synthesis of **28**. Reduction of **5** with 5% Pd/C under H_2 and workup is carried out as reported above. After separation of **28**, 40 ml of Et_2O are added to the remaining filtrate, causing precipitation of a brown, sticky product. Recrystallization (twice) from 70% EtOH/Et_2O gave **27** (30 mg, 4.2%) as bright green crystals. M.p. 302° (dec.). UV (MeOH): 359 (lg ε = 3.655), 324 (3.606), 244 (4.198). IR (KBr): 3460 (N–H); 3310–3230 ($CONH_2$, CH_3CONHR); 2850, 2720 (CH_3); 1690 (CONHR); 1625 ($CONH_2$). ^{1}H-NMR ((D_6)DMSO): 9.57 (*s*, NH); 7.77 (*d*, $^3J(4,5)$ = 8.3, 1 H); 6.73 (*d*, $^3J(4,5)$ = 8.8, 1 H); 4.23 (*s*, NH, $CONH_2$); 2.56 (*s*, CH_3); 2.11 (*s*, CH_3). MS: 232 (66, M^+). Anal. calc. for $C_{11}H_{12}N_4O_2$ (232.27): C 56.88, H 5.22, N 24.13; found: C 56.87, H 5.16, N 24.01.

REFERENCES

[1] B. Iddon, A.G. Robinson, H. Suschitzky, *Synthesis* **1988,** 871.

[2] a) J.A.L. Herbert, B. Iddon, A.G. Robinson, H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1* **1988,** 991; b) K.E. Davies, G.E. Domany, M. Farhat, J.A.L. Herbert, A.M. Jefferson, M. de los A. Guttierrez Martin, H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1* **1984,** 2465.

[3] E.A. Birkhimer, B. Norup, T.A. Bak, *Acta Chem. Scand.* **1960,** *14,* 1894.

[4] J. March, 'Advanced Organic Chemistry: Reactions, Mechanisms and Structure', 3rd edn., Interscience Publication, J. Wiley and Sons, New York, 1985, p. 227.

[5] a) G. Ponzio, *Gazz. Chim. Ital.* **1928,** *58,* 329; *Ber. Dtsch. Chem. Ges.* **1928,** *61,* 1316; b) G. Ponzio, *Gazz. Chim. Ital.* **1929,** *59,* 713.

[6] M. Hesse, H. Meier, B. Zeeh, 'Spektroskopische Methoden in der organischen Chemie', 2nd edn., G. Thieme Verlag, Stuttgart, 1984, p. 131.

[7] A. Rahman, A.J. Boulton, D.P. Clifford, G.J.T. Tiddy, *J. Chem. Soc. (B)* **1968,** 1516.

[8] F.A.L. Anet, I. Yavari, *Org. Magn. Reson.* **1976,** *8,* 158.

[9] C.H. Issidorides, M.J. Haddadin, *J. Org. Chem.* **1966,** *31,* 4067.

[10] a) W. Borsche, H. Weber, *Liebigs Ann. Chem.* **1931,** *489,* 270; b) J.W. Barton, M.C. Goodland, K.J. Gould, J.F.W. McOmie, W.R. Mound, S.A. Saleh, *Tetrahedron* **1979,** *35,* 241.

[11] J.I.G. Cadogan, *Acc. Chem. Res.* **1972,** *5,* 303.

[12] a) J.M. McRobbie, O. Meth-Cohn, H. Suschitzky, *J. Chem. Res. (M)* **1977,** *434, ibid. (S)* **1977,** 17; b) B. Iddon, O. Meth-Cohn, E.F.V. Scriven, H. Suschitzky, P.T. Gallagher, *Angew. Chem. Int. Ed.* **1979,** *18,* 900.

[13] a) N.J. Leonard, *Acc. Chem. Res.* **1982,** *15,* 128; b) S.W. Schneller, W.J. Christ, *J. Heterocycl. Chem. (Suppl.)* **1982,** *19,* 139.

[14] A. Albert, in 'Adv. Heterocycl. Chem.' Ed. A.R. Katritzky, Academic Press, New York, 1982, Vol. 32, p. 31.

[15] A. Marxer, *Helv. Chim. Acta* **1961,** *44,* 762.

[16] a) Y. Inone, N. Furutachi, K. Nakanishi, *J. Org. Chem.* **1966,** *31,* 175; b) L. Bauer, G.E. Wright, B.A. Mikrut, C.L. Bell, *J. Heterocycl. Chem.* **1965,** 447.

[17] N.H. Cromwell, F.A. Miller, A.R. Johnson, R.L. Frank, D.J. Wallace, *J. Am. Chem. Soc.* **1949,** *71,* 3337.

[18] a) D.J. Brown, L.N. Short, *J. Chem. Soc.* **1953,** 331; b) D.J. Brown, E. Hoerger, S.F. Mason, *ibid.* **1955,** 211.

[19] H. Suschitzky, W. Kramer, R. Neidlein, H. Uhl, *J. Chem. Soc., Perkin Trans. 1* **1988,** 983.