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BENZOXADIAZOCINES, BENZOTHIADIAZOCINES AND BENZOTRIAZOCINES—V

THE SYNTHESIS OF SOME 2-AMINO-6-METHYL- AND 2-AMINO-6-PHENYL-5,6-DIHYDRO-4H-3,1,6-BENZOTHIADIAZOCINES

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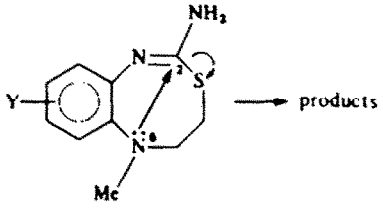
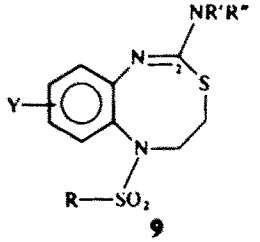
Abstract- A method is described for the synthesis of hydrochlorides of some type **8** title compounds in which the nucleophilicity of N-2 is reduced or completely lost so as to prevent ring contraction reactions and, as a result, making these compounds comparatively stable.

In the preceding paper[1] we have predicted that (i) 2-amino-6-methyl-5,6-dihydro-4H-3,1,6-benzothiadiazocines (**1**) in which the nucleophilicity of N-6 is sufficiently reduced by electron attracting substituents in appropriate positions of the benzene ring should be accessible by cyclisation methods which require comparatively low reaction temperatures and that (ii) type **1** compounds which do not contain such substituents should be accessible by methods which, in addition to ring closure, lead to protonation of N-6 in the products, i.e. to complete loss of the nucleophilicity of N-6, because in both cases subsequent ring contraction (as depicted in **1**) would be prevented. Here we wish to describe a method applicable to both cases (i) and (ii).



1

Reaction of the appropriate 2-chloronitrobenzenes with 2-methylaminoethanol furnished the 2-(2-nitranilino)ethanols **2A** which were allowed to react with thionyl chloride, phosphorus tribromide and methanesulfonyl chloride to obtain the corresponding chlorides (**3A**),[1] bromides (**4A**) and methanesulfonates (**5A**), respectively (Scheme 1). While the chlorides **3A** hardly reacted with potassium thiocyanate under the conditions tested, the bromides **4A** could be brought to react with this reagent in DMF and smooth reaction took place in refluxing ethanolic solution between the methanesulfonates **5A** and KSCN. The resulting thiocyanates **6A** were reduced in the presence of Pd-C catalysts to obtain the diamines **7A**. Since the latter proved to be exceedingly sensitive to air no attempts were made at their isolation. Instead, the reaction mixtures were, after removal of the catalyst, saturated with dry hydrogen chloride at 0° to obtain the hydrochlorides of the cyclised products **8A** directly. Depending on the nature and position of the substituents attached to the benzene ring, the aminodihydrobenzothiadiazocines **8A** furnished either di- (**8Aa**, **8Ab**) or monohydrochlorides (**8Ac**, **8Ad** and **8Ae**). The structures **8** are unambiguously proved by the ^{13}C-NMR spectra which exhibit diagnostic signals around 31, 56 and 170 ppm assigned to the *S*-CH_2, the *N*-CH_2 and the isothiuronium carbon atoms, respectively, in good agreement with the chemical shifts of the corresponding carbon atoms of some type **9**



9

compounds described in Part III.[2] The position of the C-2 signals (170 ppm) as compared with that of the C-2 signals of the model compounds **9** (150 ppm) shows that the isothiourea moiety is protonated both in the di- and monohydrochlorides, i.e. that N-6 of **8Ac**·HCl, **8Ad**·HCl and **8Ae**·HCl is *not* protonated. Here the basicity and the nucleophilicity of N-6 are apparently

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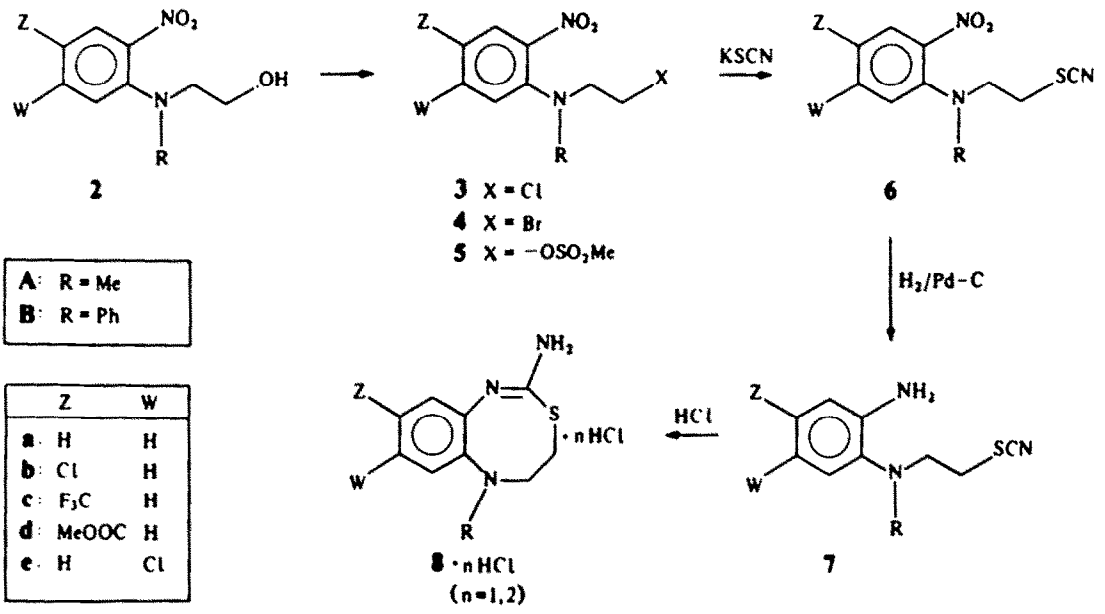
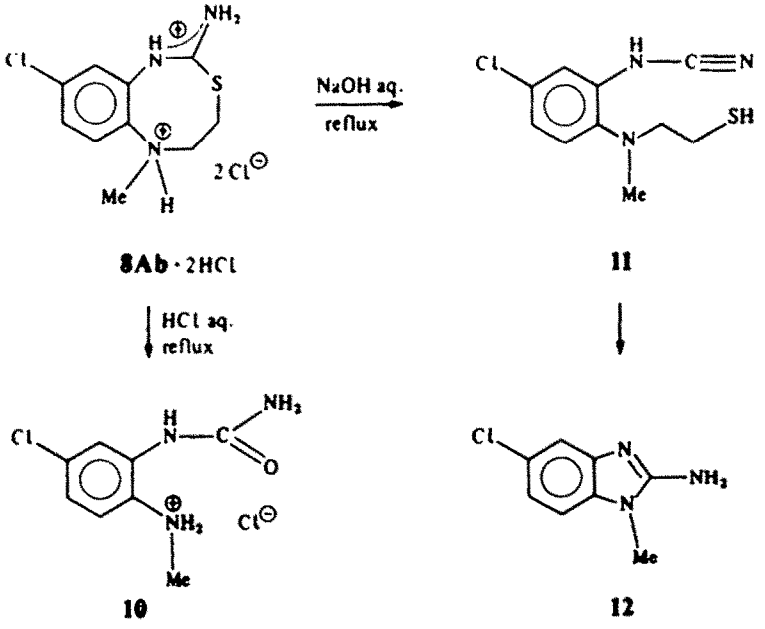


Scheme 1.

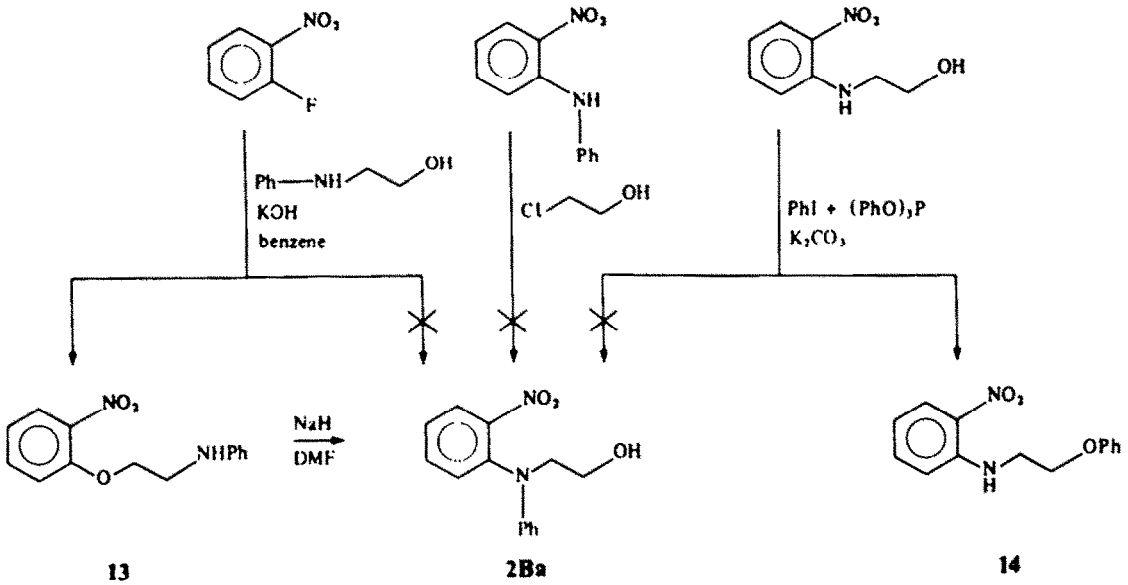
reduced by the 9-F_3C, the 9-MeOOC and the 8-Cl substituents to such an extent that both protonation of and ring contraction initiated by N-6 are prevented.

Further proof for structure **8** comes, in the case of compound **8Ab** · 2 HCl, from the results of hydrolysis studies (Scheme 2). While refluxing with aqueous hydrochloric acid afforded the urea derivative **10**, alkaline hydrolysis furnished the 2-aminobenzimidazole **12**. Because of the $OH^{\ominus}$ ions present in great excess and capable of acting as external nucleophiles, the ring contraction **8Ab** → **12** appears *not* to be initiated by intramolecular nucleophilic attack of N-6 at C-2 (as depicted in **1**) but rather to take place via the N-cyano derivative **11**. Indeed, when the reaction is disrupted at an early stage, the IR spectrum of the crude reaction mixture exhibits a cyanoamine band at 2160 cm^{-1}.

The same method was applicable also to the synthesis of the 6-phenyl analogue **8Ba** · HCl. However, here the synthesis of the starting substance **2Ba** presented some difficulties (Scheme 3). All attempts to obtain 2-(2-nitrodiphenylamino)ethanol **2Ba** directly by (i) N-(2-nitrophenylation) of 2-anilinoethanol with 2-fluoronitrobenzene (2-chloronitrobenzene did not react with 2-anilinoethanol), (ii) N-phenylation of 2-(2-nitranilino)ethanol and (iii) 2-hydroxyethylation of 2-nitrodiphenylamine with 2-chloroethanol failed. In the



Scheme 2.



Scheme 3.

first two cases the isomers of the desired compound **2Ba**, viz. N-[2-(2-nitrophenoxy)ethyl] aniline (**13**) and 2-nitro-N-(2-phenoxyethyl)aniline (**14**), respectively, were obtained while in the last case either no reaction took place at all or very complex mixtures were formed which, according to TLC, did not contain the desired compound **2Ba**. That the isomers **13** and **14**, respectively, were obtained was clearly shown by the IR spectra of the acetylation products which exhibited amide I bands (at 1650 and 1665 cm^{-1}, respectively) rather than an ester carbonyl band. (The carbonyl band of the acetyl derivative of **2Ba** appears at 1735 cm^{-1}.) Finally the isomer **13** was converted into the desired compound **2Ba** by a rearrangement induced by sodium hydride and akin to the well-known Smiles rearrangement.[3] Starting with compound **2Ba** compound **8Ba** · HCl was obtained via the bromide **4Ba** and the thiocyanate **6Ba**. The basicity of N-2 in the cyclised product **8Ba** is considerably lowered by the attached phenyl group so as to prevent protonation of N-2. The monohydrochloride of **8Ba** is stable at room temperature but decomposes on attempted recrystallisation probably as a result of processes initiated by intramolecular nucleophilic attack of N-2 at C-6 (*cf* 1).

EXPERIMENTAL

The IR spectra were obtained with a Spektromom instrument (Hungarian Optical Works, Budapest) using KBr pellets, the 60 MHz ^{1}H-NMR spectra of the intermediates, if not otherwise stated, were obtained with a Perkin–Elmer R12 spectrometer in $CDCl_3$ soln, using Me_4Si as the internal reference. The 100 MHz ^{1}H- and the ^{13}C-NMR spectra of the 2-amino-5,6-dihydro-4H-3,1,6-benzothiadiazocine salts (**8** · n HCl) were obtained with a JEOL FX 100 spectrometer.

2-(N-Methyl-2-nitranilino)ethanols (**2A**)

(a) For the preparation of **2Aa**, its 4-chloro derivative (**2Ab**) and **2Ad**, see Ref. 1.

(b) 4-*Trifluoromethyl derivative* (**2Ac**). The mixture of 1-chloro-2-nitro-4-trifluoromethylbenzene (4.5 g, 20 mmol), 2-(methylamino)ethanol (1.5 g, 20 mmol) and EtOH (20 ml) was refluxed for 4 hr and evaporated to dryness *in vacuo*. The oily residue was taken up in ether (150 ml). The ethereal soln was washed with 5% HCl aq (15 ml) and water, dried and evaporated to dryness *in vacuo* to obtain 5.0 g (94%) of the title compound as a red oil. (Calc for $C_{10}H_{11}F_3N_2O_3$ (264.2): N, 10.60%. Found: N, 10.64%) which was used in the following step without further purification.

(c) 5-*Chloro derivative* (**2Ae**). The mixture of 2,4-dichloronitrobenzene (38.4 g, 0.2 mol), 2-(methylamino)ethanol (18.6 g, 0.24 mol) and dry pyridine was refluxed for 4 hr and evaporated to dryness *in vacuo*. The ethanolic (50 ml) soln of the residue was saturated with dry HCl at 0° to obtain 32 g (60%) of the hydrochloride of the title compound as a yellow crystalline powder, m.p.: 178–180° (dec; from EtOH–ether). (Calc for $C_9H_{10}Cl_2N_2O_3$ (265.1): Cl, 26.75; N, 10.57%. Found: Cl, 26.94; N, 10.34%.)

The free base was obtained in 96% yield by treating the aqueous soln of the salt with 20% NaOH aq (pH 9) and conventional work-up, and proved to be pure according to TLC.

N-(2-Mesyloxyethyl)-N-methyl-2-nitranilines (**5A**)

(a) Mesyl chloride (4 ml, 50 mmol) was added dropwise to the soln of **2Aa** · HCl[1] (4.65 g, 20 mmol) in pyridine (20 ml) with continuous stirring at −5° to 0°. The mixture was stirred for 1 hr at this temp and poured into ice-water (120 ml) to obtain, after conventional work-up, 5.4 g (99%) of **5Aa** as a yellow oil. (Calc for $C_{10}H_{14}N_2O_5S$ (274.2): C, 43.79; H, 5.14; N, 10.21; S, 11.69%. Found: C, 44.01; H, 5.12; N, 10.31; S, 11.87%.)

(b) The 4-chloro (**5Ab**), 4-trifluoromethyl (**5Ac**) and 5-chloro derivative (**5Ae**) as well as **5Ad** were similarly obtained.

Compound **5Ab**: yield 85% [starting with 15 g (65 mmol) of **2Ab**[1]], red oil. (Calc for $C_{10}H_{13}ClN_2O_5S$ (308.8): Cl, 11.51; N, 9.07; S, 10.38%. Found: Cl, 11.44; N, 9.34; S, 10.27%.)

Compound **5Ac**: yield 70% [starting with 4 g (15 mmol) of **2Ac**], yellow oil. (Calc for $C_{11}H_{13}F_3N_2O_5S$ (342.3): N, 8.18; S, 9.36%. Found: N, 8.26; S, 8.92%.)

Compound **5Ad**: yield 85% [starting with 35.5 g (0.12 mol) of compound **2Ad** · HCl[1]], red oil. (Calc for $C_{12}H_{16}N_2O_5S$ (332.3): N, 8.43; S, 9.65%. Found: N, 8.42; S, 9.93%.)

Compound **5Ae**: yield 92% [starting with 12 g (52 mmol) of **2Ad**], orange oil. (Calc for $C_{10}H_{13}ClN_2O_5S$ (308.8): Cl, 11.50; N, 9.07%. Found: Cl, 11.37; N, 9.28%.)

N-Methyl-2-nitro-N-(2-thiocyanatoethyl)anilines (**6A**)

(a) The mixture of **5Aa** (27.4 g, 0.1 mol), EtOH (400 ml) and KSCN (20 g, 0.2 mol) was refluxed for 2 hr. The resulting salt

was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was taken up in CH_2Cl_2 and water (200 ml, each) to obtain, by conventional work-up, 20.1 g (85%) of **6Aa** as an orange oil. (Calc for $C_{10}H_{11}N_3O_2S$ (237.3): C, 50.62; H, 4.67; N, 17.71; S, 13.51%. Found: C, 50.75; H, 4.55; N, 17.68; S, 13.25%.) IR: 2200 cm^{-1} (—SCN).

(b) The 4-chloro (**6Ab**), 4-trifluoromethyl (**6Ac**) and 5-chloro derivatives (**6Ad**) were similarly obtained.

Compound **6Ab**: yield 74% [starting with 17 g (55 mmol) of **5Ab**], light yellow needles, m.p.: 75° from ethanol. (Calc for $C_{10}H_{10}ClN_3O_2S$ (271.7): Cl, 13.08; N, 15.46; S, 11.80%. Found: Cl, 13.45; N, 14.98; S, 11.70%.) IR: 2150 cm^{-1}.

Compound **6Ac**: yield 78% [starting with 2.5 g (7.6 mmol) of **5Ac**], light yellow needles, m.p.: 60–61° (from MeOH). (Calc for $C_{11}H_{10}F_3N_3O_2S$ (305.3): N, 13.76; S, 10.50%. Found: N, 13.90; S, 10.82%.) IR: 2250 cm^{-1}.

Compound **6Ad**: yield 81% [starting with 2.5 g (7.5 mmol) of **5Ad**, and performing the reaction in refluxing 2-propanol], red oil. (Calc for $C_{12}H_{13}N_3O_4S$ (295.3): N, 14.23; S, 10.86%. Found: N, 14.27; S, 10.39%.)

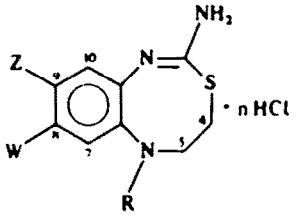
Compound **6Ae**: yield 91% [starting with 15 g (49 mmol) of **5Ae**], yellow crystalline powder, m.p.: 53–54° (from a small amount of MeOH). (Calc for $C_{10}H_{10}ClN_3O_2S$ (271.8): Cl, 13.06; N, 15.46; S, 11.80%. Found: Cl, 13.21; N, 15.17; S, 12.07%.) IR: 2200 cm^{-1}.

2 - Amino - 6 - methyl - 5,6 - dihydro - 4H - 3,1,6 - benzothiadiazocine (**8A**) *hydrochlorides*

(a) Compound **6Aa** (2.37 g, 10 mmol) was reduced in anhyd dioxane (80 ml) soln in the presence of a 10% Pd–C catalyst (1.6 g) at room temp and normal pressure. The catalyst was filtered off under argon and washed with anhyd dioxane. The colourless filtrate, containing **7Aa**, was sat at room temp with dry HCl and evaporated to dryness *in vacuo*; care was taken that the bath-temp did not exceed 40°. The crystalline residue was triturated with EtOH to obtain 2.0 g (70%) of **8Aa** · 2 HCl as a colourless crystalline powder, m.p.: 155 156° dec; from MeOH–ether. (Calc for $C_{10}H_{13}Cl_2N_3S$ (280.2): C, 42.86; H, 5.40; Cl, 25.30; N, 15.00; S, 11.41%. Found: C, 42.72; H, 5.51; Cl, 25.54; N, 15.16; S, 11.72%.) For the ^{1}H- and ^{13}C-NMR spectra, see Tables 1 and 2, respectively.

(b) Compounds **8Ab** · 2 HCl and **8Ae** · HCl were obtained by

Table 1. ^{1}H-NMR spectra (δ scale) of some 2-amino-5,6-dihydro-4H-3,1,6-benzothiadiazocine salts (**8** · n HCl)



Compound	**8Aa** · 2 HCl	**8Ab** · 2 HCl	**8Ac** · HCl	**8Ad** · HCl	**8Ae** · HCl	**8Ba** · HCl
R	Me	Me	Me	Me	Me	Ph
Z	H	Cl	F_3C	MeOOC	H	H
W	H	H	H	H	Cl	H
n	2	2	1	1	1	1
Solvent	DMSO-d_6[a] (+CD_3OD)	DMSO-d_6[a]	CD_3OD	CD_3OD	DMSO-d_6	CD_3OD [pyridine-d_5][b]
N-Me	2.84s (3.11s)	2.80s	2.91s	2.96s	2.80s	– –
4-H_2	3.02[c] (3.07t)	3.04s[c]	3.02t	3.03t	3.03s[c]	3.42t [3.11t]
5-H_2	3.02s[c] (3.49t)	3.04s[c]	3.30t	3.42t	3.03s[c]	4.04t [3.88t]
7-H		7.3–7.5m	7.4–7.7m	7.35d (8.5 Hz)	7.63d (2 Hz)	
8-H	7.2–7.65m (7.2–7.7m)			7.93dd		7.25–7.6m [7.0–7.6m]
9-H						
10-H		7.22d (2 Hz)	7.4–7.7m	7.79d (2 Hz)	7.2 7.45m	
NH_2[d]	7.0bs (–)	5.55bs		--	9.6bs	-
NH[d]	9.60s (—)	9.62s	—	—	12.44s	— —
Other						

[a] Because of the basicity of the solvent the spectrum of the *mono*hydrochloride is obtained.

[b] Because of the basicity of the solvent the spectrum of the free base is obtained.

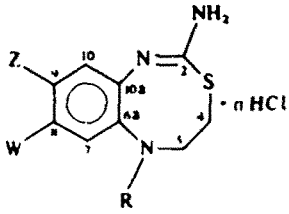
[c] In solvent DMSO-d_6 the protons of the S—CH_2—CH_2—N system become, by chance, isochronous with the result that an A_4 type spectrum is obtained.

[d] The presence of two NH signals (the high field signal being twice as intensive as the low field signal) indicates that N-1 is protonated in all cases. This is supported by the considerable paramagnetic shifts of the N-Me and N-CH_2 signals of compound **8Aa** · 2 HCl when replacing the solvent DMSO-d_6[a] by CD_3OD.

[e] COOMe: 3.88s.

[f] N-Ph, solvent CD_3OD: 6.38d (2H), 6.70t (1H), 7.13t (2H); solvent pyridine-d_5: 6.62d (2H), 6.68t (1H), 7.0–7.6m (2H; merged with the signals of 7-H–10H).

Table 2. ^{13}C-NMR spectra (δ scale) of some 2-amino-5,6-dihydro-4H-3,1,6-benzothiadiazocine salts (**8**·n HCl)[a]



Compound	**8Aa**·2 HCl	**8Ab**·2 HCl	**8Ac**·HCl	**8Ad**·HCl	**8Ae**·HCl	**8Ba**·HCl
R	Me	Me	Me	Me	Me	Ph
Z	H	Cl	F_3C	MeOOC	H	H
W	H	H	H	H	Cl	H
n	2	2	1	1	1	1
Solvent	DMSO-d_6[b]	DMSO-d_6[b]	CD_3OD	CD_3OD	DMSO-d_6	CD_3OD
N-Me	43.6	44.5	43.5	42.7	42.7	
C-2	169.3	170.6	171.2	170.5	168.7	169.8[d]
C-4	29.9	31.0	31.6	31.4	29.1	36.0
C-5	57.7	58.2	57.1	56.2	56.4	52.2
C-6a	142.8	143.3	149.1	150.0	144.2	143.0
C-7	124.9	124.8	125.7	123.4	125.3	131.8
C-8	129.8	130.2	127.3	131.5	132.3	132.1
C-9	124.5	131.5	129.6	126.6	124.6	126.1
C-10	127.5	127.9	123.4	128.2	126.2	129.8
C-10a	133.3	135.9	133.5	131.1	131.7	138.5
Other		..	[e]	[f]		[g]

[a] The signals of the aromatic carbon atoms were assigned on the basis of their multiplicities in the off-resonance spectra and the well-known additivity rules, using substituent constants reported.[c] In the case of compound **8Ac**·HCl use was made furthermore of the phenomenon of C–F spin coupling causing splitting of the signals of C-9 ($^2J_{C,F}$), C-8 and C-10 ($^3J_{C,F}$).

[b] Because of the basicity of the solvent the spectrum of the *mono*hydrochloride is obtained.

[c] L. M. Jackman and T. Jen, *J. Am. Chem. Soc.* **97**, 2811 (1975); D. F. Ewing, *Org. Magn. Reson.* **12**, 499 (1979); G. Tóth and A. Almásy, unpublished results.

[d] In pyridine-d_5 this signal is shifted to 159.0 ppm. This diamagnetic shift of about 10 ppm is in agreement with deprotonation of the thiouronium group.

[e] F_3C: 125.0.

[f] MeOOC: 52.8, 167.1.

[g] N-Ph: 147.9 (C-1'), 113.3 (C-2', C-6'), 130.6 (C-3', C-5'), 119.7 (C-4').

essentially the same method (the reduction, however, being carried out in ethanolic soln and the crude product being triturated with acetone) in 67 and 68% yield, respectively.

Compound **8Ab**·2 HCl: colourless crystalline powder, m.p.: 140–145° dec; from EtOH–ether. (Calc for $C_{10}H_{14}Cl_3N_3S$ (314.7): Cl, 33.80; N, 13.35; S, 10.19%. Found: Cl, 33.63; N, 13.55; S, 10.77%.)

Compound **8Ae**·HCl: colourless crystalline powder, m.p.: 258–260° dec; from MeOH–ether. (Calc for $C_{10}H_{13}Cl_2N_3S$ (278.2): Cl, 25.48; N, 15.10; S, 11.52%. Found: Cl, 25.86; N, 14.95; S, 11.50%.) For the ^{1}H- and ^{13}C-NMR spectra of these two compounds, see Tables 1 and 2, respectively.

(c) Compound **8Ac**·HCl was obtained similarly (the reduction being carried out in dioxane, and the crude salt being precipitated from its anhyd ethanolic soln by the addition of ether) in 40% yield in the form of a colourless crystalline powder, m.p.: 145° dec; from EtOH–ether. (Calc for $C_{11}H_{13}F_3ClN_3S$ (311.8): Cl, 11.38; N, 13.48; S, 10.29%. Found: Cl, 11.55; N, 13.50; S, 10.67%.) For the ^{1}H- and ^{13}C-NMR spectra, see Tables 1 and 2, respectively.

(d) Compound **8Ae**·HCl was obtained similarly (the reduction, however, being carried out in MeOH, and crystallisation of the crude product being induced by trituration with ether) in the form of a colourless crystalline powder, m.p.: 161–162° from MeOH–ether in 62% yield. (Calc for $C_{12}H_{16}ClN_3O_2S$ (301.8): C, 47.75; H, 5.34; Cl, 11.75; N, 13.5%. Found: C, 47.52; H, 5.44; Cl, 12.01; N, 13.95%.) For the ^{1}H- and ^{13}C-NMR spectra, see Tables 1 and 2, respectively.

4 - *Chloro* - N - *methyl* - 2 - *ureidoanilinium chloride* (**10**)

Compound **8Ab**·2 HCl (0.2 g, 0.6 mmol) was refluxed with 20% HCl aq (3 ml) for 1 hr. The mixture was allowed to cool to obtain 0.15 g (89%) of the title compound in the form of colourless crystals, m.p.: 200–202° from EtOH. (Calc for $C_8H_9Cl_2N_3O$ (233.7): C, 41.11; H, 3.45; Cl, 30.34; N, 18.02%. Found: C, 40.83; H, 3.67; Cl, 29.94; N, 17.90%.) IR: 3150b (NH's), 1725 ($\oplus NH_2$), 1685 (urea).

2 - *Amino* 5 - *chloro* - 1 - *methylbenzimidazole* (**12**)

The mixture of **8Ab**·2 HCl (1.25 g, 4 mmol), EtOH (10 ml) and 10% NaOH aq (5 ml) was refluxed for 1 hr. Most of the EtOH was distilled off and the aqueous soln was allowed to cool to obtain 0.5 g (69%) of the title compound as colourless crystals, m.p.: 213–214° from nitromethane. (Calc for $C_8H_8ClN_3$ (181.6): C, 52.90; H, 4.44; Cl, 19.52; N, 23.14%. Found: C, 52.70; H, 4.15; Cl, 19.36; N, 23.04%.) Mass spectrum: *m/z* 181 (M^+), 166, 165. ^{1}H-NMR (DMSO-d_6): δ 3.5 (*N*-Me), 6.65 bs (NH's), 6.88 dd (6-H), 6.98d ($J_o \approx 9$ Hz, 7-H), 7.16d ($J_m \approx 2$ Hz, 4-H).

N-[2-(2-*Nitrophenoxy*)*ethyl*]*aniline* (**13**)

2-Fluoronitrobenzene (55 g, 0.39 mol) was added dropwise with continuous stirring and external cooling to the mixture of 2-anilinoethanol[4] (56 g, 0.41 mol), dry benzene (100 ml) and finely pulverised KOH (24 g, 0.43 mol) at such a rate that the temp did not exceed 20°. The mixture was stirred subsequently for 3 hr at room temp and for 20 hr at 100°. Water (60 ml) was

added to obtain, after conventional work-up, 85 g (85%) of the title compound as an oily product which turned crystalline when triturated with EtOH (20 ml), m.p.: 67° from EtOH. (Calc for $C_{14}H_{14}N_2O_3$ (258.3): C, 65.11; H, 5.46; N, 10.86%. Found: C, 65.05; H, 5.69; N, 11.00.) ^{1}H-NMR ($CDCl_3$ + D_2O): δ 3.52t (b in the absence of D_2O; N-CH_2), 4.26t (J = 5 Hz, O-CH_2), 6.6–6.8 m (ArH's); IR: 3380 cm^{-1} (NH).

Acetyl derivative, oil, IR: 1650 cm^{-1}.

2-*Nitro*-N-(2-*phenoxyethyl*)*aniline* (**14**)

The mixture of iodobenzene (274 g, 1.34 mol) and triphenyl phosphite (85 g, 0.28 mol) was refluxed for 6 hr and allowed to cool to about 50°. 2-(2-Nitranilino)ethanol[3] (50 g, 0.28 mol) and finely pulverised K_2CO_3 (38 g, 0.28 mol) were added, and the mixture was gently refluxed for 0.5–1 hr until it started to darken. The excess iodobenzene was removed by steam-distillation to obtain an oily residue which solidified when allowed to cool. Recrystallisation from EtOH furnished 51 g (72%) of the title compound, m.p.: 80–81°. (Calc for $C_{14}H_{14}N_2O_3$ (258.3): C, 65.11; H, 5.46; N, 10.85%. Found: C, 64.90; H, 5.60; N, 10.97%.) IR: 3350 cm^{-1} (NH); ^{1}H-NMR: δ 3.65t + 4.12t (J = 5 Hz; —CH_2—CH_2—), 6.5–7.5 m (8H) + 8.1 dd (1H, J = 9 and 2 Hz, ArH's), 8.3 bs (NH).

Acetylation: the mixture of **14** (1.6 g, 6.2 mmol), Ac_2O (5 ml) and anhyd $ZnCl_2$ (0.1 g) was heated for 1 hr to obtain the N-acetyl derivative as an oil which turned crystalline when treated with EtOH (5 ml). Yield: 1.3 g (70%), m.p.: 72° from aqueous EtOH. (Calc for $C_{16}H_{16}N_2O_4$ (300.3): C, 63.69; H, 5.37; N, 9.33%. Found: C, 63.50; H, 5.06; N, 9.62%.) IR: 1665 cm^{-1}.

Attempted reaction of 2-nitrodiphenylamine with 2-chloroethanol

2-Nitrodiphenylamine[6] was refluxed with excess 2-chloroethanol in the presence of $ZnCl_2$ for 8–10 hr; according to TLC, the resulting complex mixture did not contain the desired **2Ba**. No reaction took place when the two reactants were refluxed in DMF in the presence of K_2CO_3, nor when the amine was first treated with MeMgI and subsequently with 2-chloroethanol.

2-(2-*Nitrodiphenylamino*)*ethanol* (**2Ba**)

NaH (80%; 0.25 g, 8.5 mmol) was added to the soln of **13** (2.0 g, 7.8 mmol) in dry DMF (20 ml) with continuous stirring and ice-cooling. The mixture was stirred for 0.5 hr with ice-cooling and for 3 hr at room temp. Water (100 ml) was added and the mixture was slightly acidified (pH 6) with AcOH. Extraction with benzene furnished 1.5 g of a red oil which was worked up by preparative TLC (Kieselgel G; benzene–MeOH, 4:1) to obtain, in decreasing order of their R_f values, an orange oil [probably N,O-bis-(2-nitrophenyl)-2-anilinoethanol, 5–10%, obtained also by 2-nitrophenylation of **2Ba** with 2-fluoronitrobenzene] and the title compound [1.0–1.2 g (50–60%)] in the form of a red oil; IR: 3370 cm^{-1} (OH); ^{1}H-NMR (100 MHz, $CDCl_3$): δ 2.7 bs (OH), 3.7–4.1 m (—CH_2—CH_2—), 6.65–7.8 m (ArH's); ^{13}C-NMR ($CDCl_3$): δ 55.0 (N-CH_2), 59.8 (O-CH_2), 128.9 d, 125.8 d, 134.2 d, 120.5 d (C-3–C-6), 140.3 s (C-2), 146.3 s or 147.3 s (C-1), 147.3 s or 146.3 s, 116.5 d, 129.1 d, 125.0 (phenyl, C-1, o-C's, m-C's, p-C); IR spectrum of the acetyl derivative (orange oil), obtained by the conventional method: 1735 cm^{-1}]. **2Ba** was used without further purification in the following step.

N-(2-*Bromoethyl*)-2-*nitrodiphenylamine* (**4Ba**)

PBr_3 (8 ml, 85 mmol) was added dropwise to the benzene (200 ml) soln of **2Ba** (12 g, 46 mmol) with continuous stirring and ice-cooling. The resulting mixture was allowed to stand for 1 hr at room temp and then refluxed until, according to TLC (Kieselgel G; benzene–MeOH, 4:1) the starting substance completely disappeared (4–6 hr). Ice-water (300 ml) was added to obtain, after conventional work-up of the benzene layer, 12 g (80%) of the crude title compound in the form of a red oil which was used without further purification in the following step.

N-(2-*Thiocyanatoethyl*)-2-*nitrodiphenylamine* (**6Ba**)

The mixture of crude **4Ba** (15.7 g, 49 mmol), KSCN (8.0 g, 0.12 mmol) and 2-propanol (80 ml) was refluxed for 12 hr and evaporated to dryness *in vacuo*. The residue was taken up in water (40 ml) and ether (80 ml) to obtain, after conventional work-up of the ethereal layer, the crude product in the form of a red oil which was purified by column chromatography (Kieselgel G; benzene). The purified product (10 g, 68%) turned crystalline on standing, m.p.: 68° from ether. (Calc for $C_{15}H_{13}N_3O_2S$ (299.4): C, 60.20; H, 4.38; S, 10.69%. Found: C, 60.36; H, 4.30; S, 10.96%.) IR: 2200 cm^{-1} (—SCN); ^{1}H-NMR: δ 3.02t + 4.03t (J = 7 Hz; —CH_2—CH_2—), 6.5–7.9 m (ArH's).

2-*Amino*-6-*phenyl*-5,6-*dihydro*-4H-3,1,6-*benzothiadiazocine hydrochloride* (**8Ba** · HCl)

Compound **6Ba** (10 g; 34 mmol) was reduced in a mixture of benzene (20 ml) and EtOH (110 ml) in the presence of a 10% Pd–C catalyst at room temp and normal pressure. The catalyst was filtered off, the filtrate was acidified with 20% ethanolic HCl and evaporated to dryness *in vacuo*. The residue was taken up in dry dioxane (50 ml) and the soln was saturated with dry HCl and kept in a refrigerator until crystallisation of the product started. Ether (200 ml) was added, the product (6.0 g, 58%; m.p.: 235°; decomposes during attempted recrystallisation) was filtered off and washed with ether. (Calc for $C_{15}H_{15}N_3S$ · HCl (305.8): C, 58.91; H, 5.27; Cl, 1.59; N, 13.74%. Found: C, 58.54; H, 5.70; Cl, 11.52; N, 13.44%.) For the ^{1}H- and ^{13}C-NMR spectra, see Tables 1 and 2, respectively.

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