Tetrahedron Vol 41, No 14, pp. 2847 to 2854, 1985
Printed in Great Britain

0040-4020/85 $3.00 + .00
Pergamon Press Ltd.

BENZOXADIAZOCINES, BENZOTHIADIAZOCINES AND BENZOTRIAZOCINES—IV

RING CLOSURE OF 1-{2-[N-(2-CHLOROETHYL AND 2-HYDROXYETHYL)-N-METHYLAMINO]PHENYL}-3-PHENYLTHIOUREAS. TETRAHYDROQUINOXALINE *VS.* DIHYDRO-3,1,6-BENZOTHIADIAZOCINE AND HEXAHYDRO-1,3,6-BENZOTRIAZOCINETHIONE FORMATION

GYULA HORNYÁK*
Research Group for Alkaloid Chemistry of the Hungarian Academy of Sciences, H-1521 Budapest, Hungary

KÁROLY LEMPERT and ETELKA PÍFCZKA†
Department of Organic Chemistry, Technical University Budapest, Hungary

and

GÁBOR TÓTH
Department of General and Analytical Chemistry, Technical University Budapest, Hungary

(*Received in UK 6 February* 1984)

Abstract - While base induced ring closure of 1-{2-[N-(alkylsulfonyl and arylsulfonyl)-N-(2-chloroethyl)amino]phenyl}-3-phenylthioureas **1** had furnished the corresponding type **2** dihydro-3,1,6-benzothiadiazocine derivatives rather than the isomeric hexahydro-1,3,6-benzotriazocinethiones (**3**) or tetrahydroquinoxalines (**4**), base induced ring closure of the related N-(2-chloroethyl)-N-Me derivatives **9a–9c**, **10a** and **10b** furnishes type **14** tetrahydroquinoxalines. **14a** is obtained also by treating the N-(2-hydroxyethyl)-N-Me derivative **11** with the triphenylphosphine–diethyl azodicarboxylate (DEAD) reagent. *In situ* replacement of the chlorine atom of compound **9a** by iodine in the *absence of base* as well as treatment of 1-{2-[N-(2-hydroxyethyl)-N-methylamino]phenyl}-1-methyl-3-phenylthiourea (**18**) with the triphenylphosphine–DEAD reagent furnishes the benzimidazole derivatives **16** and **22**, respectively, whose formation may be rationalised by assuming the intermediacy of the dihydro- and tetrahydro-3,1,6-benzothiadiazocine derivatives **12a** · HI and **20**, respectively, and their subsequent ring contraction.

In part III[1] of the present series a method for the synthesis of 6-(alkylsulfonyl and arylsulfonyl)-5,6-dihydro-4H-3,1,6-benzothiadiazocines (**2**) by ring closure of type **1** thiourea derivatives has been described (Scheme 1). In principle, two additional modes of cyclisations were possible and would have lead to hexahydro-1,3,6-benzotriazocinethiones (**3**) (for R″=H) and tetrahydroquinoxaline derivatives (**4**), respectively. However, these two types of structures for the products were ruled out on the basis of both chemical and spectroscopic evidence.‡ The effect of the alkylsulfonyl and arylsulfonyl groups, respectively, was to reduce the nucleophilicity of N-6 of the product and to thereby prevent ring contraction initiated by nucleophilic attack of N-6 at C-2, i.e. reaction **2** → **5**.

Here we wish to report on our unsuccessful attempts to extend the scope of the above method to the synthesis of 6-*methyl*-2-(subst. amino)-5,6-dihydro-4H-3,1,6-benzothiadiazocines (**12**). However, these failures finally led us to the contrivance of a successful method for the synthesis of 2-amino-6-methyl-5,6-dihydro-4H-3,1,6-benzothiadiazocines (**12A**) which will be described in the accompanying paper.

Initially we attempted to obtain the desired compounds **12** by ring closure of 1-{2-[N-(2-chloroethyl or 2-hydroxyethyl)-N-methylamino]-phenyl}-3-phenylthioureas (**9**, **11**) and the related morpholine derivatives **10**, respectively, i.e. analogously to the synthesis of the 6-(alkylsulfonyl and arylsulfonyl) derivatives **2**. The methods of synthesis of the starting compounds **9–11** are shown in Scheme 2.

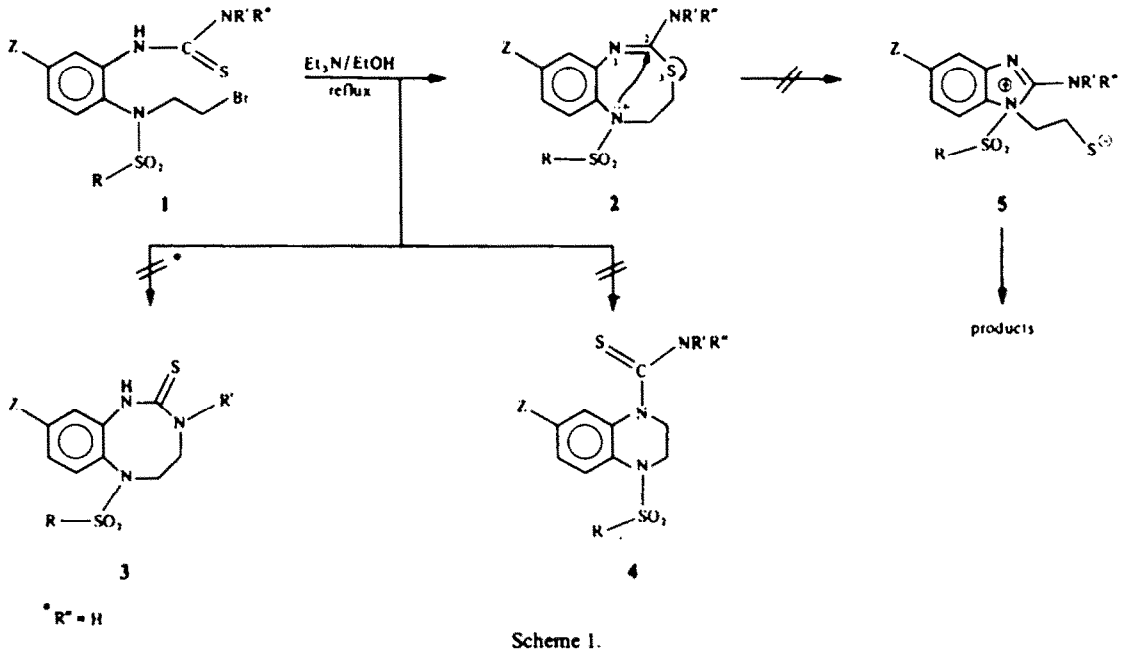
As a result of the replacement of the N-(alkylsulfonyl) and N-(arylsulfonyl) groups of the compounds **1** by an N-Me group, the direction of ring closure changed (Scheme 3); e.g. base catalysed cyclisation of thiourea **9a** furnished the tetrahydroquinoxaline derivative **14a** as the only product. Structure **14a** was proved by comparison with an authentic sample obtained by phenylthiocarbamoylation of N-methyltetrahydroquinoxaline (**15**). The same product was obtained by treating compound **8a** with phenylisothiocyanate.

The isomeric structure **12a** is ruled out for the cyclisation product of compound **9a** also by the ^{13}C-NMR spectrum: the signals at 45.5, 50.3 and 180.4 ppm indicate the presence of *two* N-CH_2 groups and of a thiourea grouping rather than of one S-CH_2 and N-CH_2 group, each, and an isothiourea grouping. (The S-CH_2, N-CH_2 and isothiourea signals in the ^{13}C-NMR spectra of some type **2** compounds described in Ref. 1 appear around 33, 50 and 151 ppm, respectively.)

Similarly, base catalysed cyclisation of **9b** and **9c** furnished the tetrahydroquinoxalines **14b** and **14c**,

† EGyT Pharmacochemical Works (Budapest) research fellow, 1980–1981.

‡ See *Note added in proof* on p. 2854.

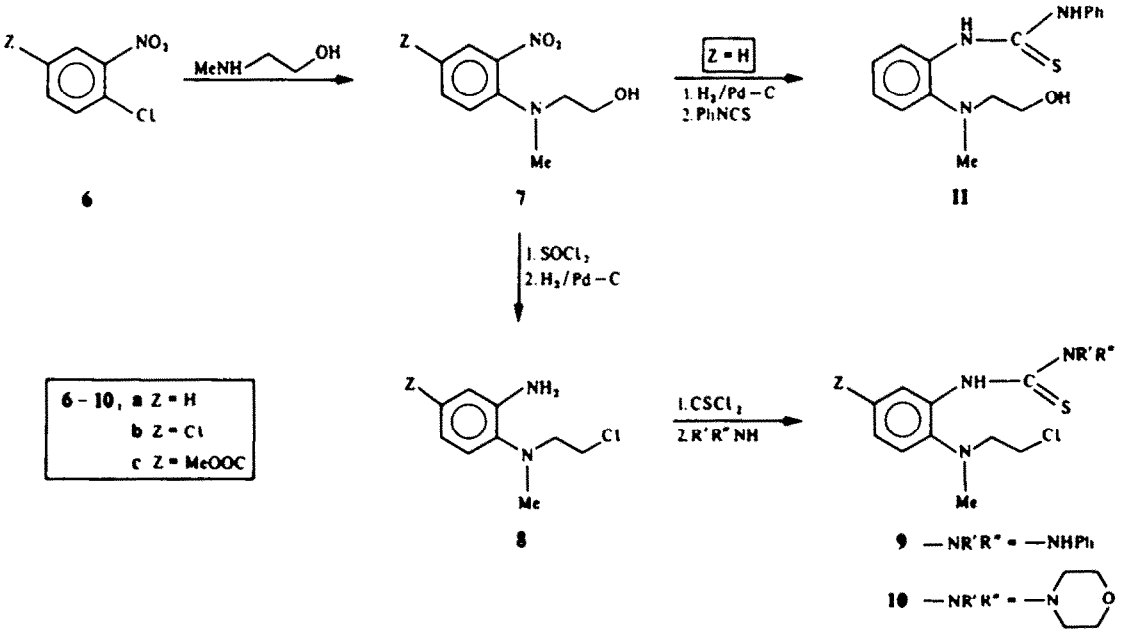


Scheme 1.

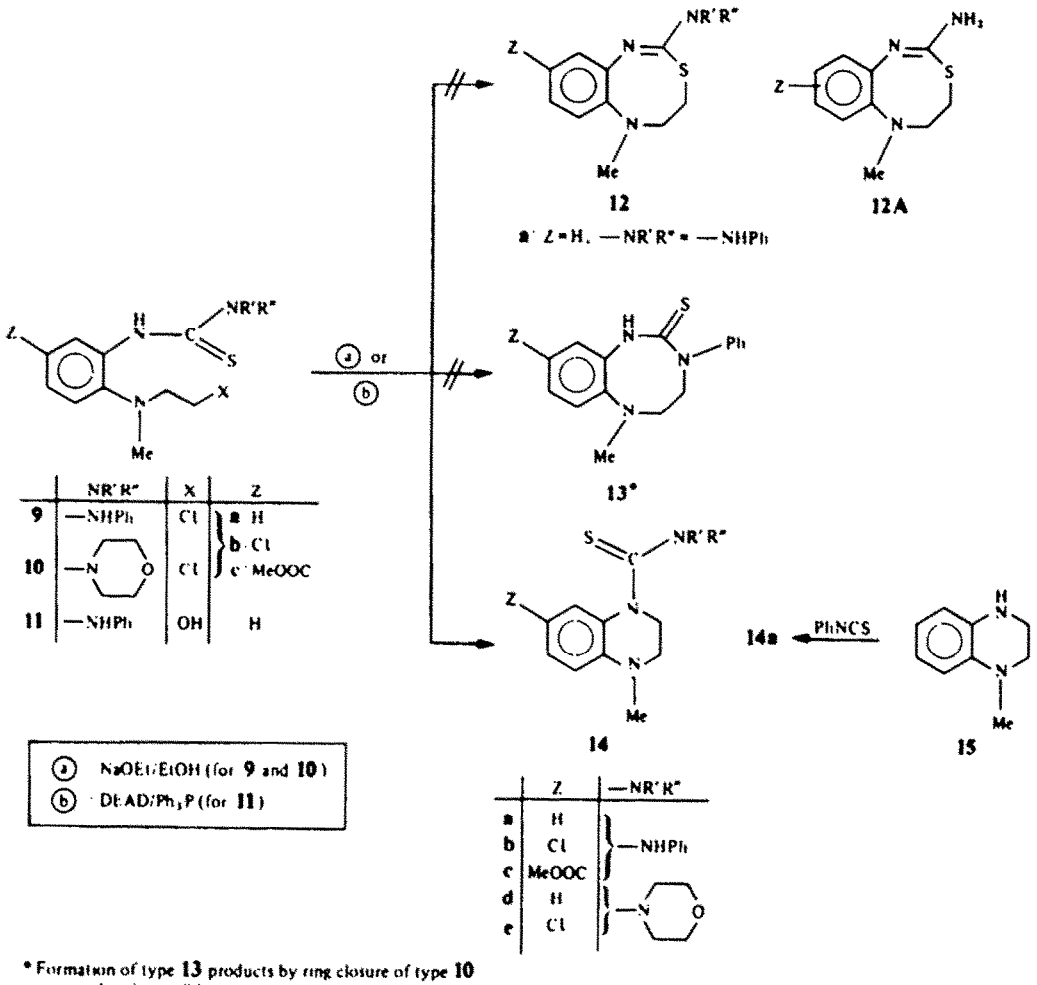
respectively, whose structure assignments were based on their ^{13}C-NMR spectra: the signals of the two N-CH_2 groups and of the thiourea grouping appear at 45.6, 49.8 and 181.1 ppm in the spectrum of **14b**, and at 44.9, 50.1 and 180.6 ppm in the spectrum of **14c**. By base catalysed cyclisation of thioureas **10a** and **10b** the N - [morpholino(thiocarbonyl)]tetrahydroquinoxalines **14d** and **14e** were also prepared.

Recently application of the diethyl azodicarboxylate (DEAD)-triphenylphosphine reagent for alkylation of thioureas has been described,[2] S-alkylisothioureas, N-alkylthioureas or their mixtures being, depending on the type of the thiourea introduced, the products of the reaction. The DEAD-triphenylphosphine reagent, applied to thiourea **11** furnished the tetrahydroquinoxaline derivative **14a** by intramolecular N-alkylation.

These observations demonstrate that, in addition to their effect mentioned above, the alkylsulfonyl or arylsulfonyl groups serve to direct (presumably by



Scheme 2.



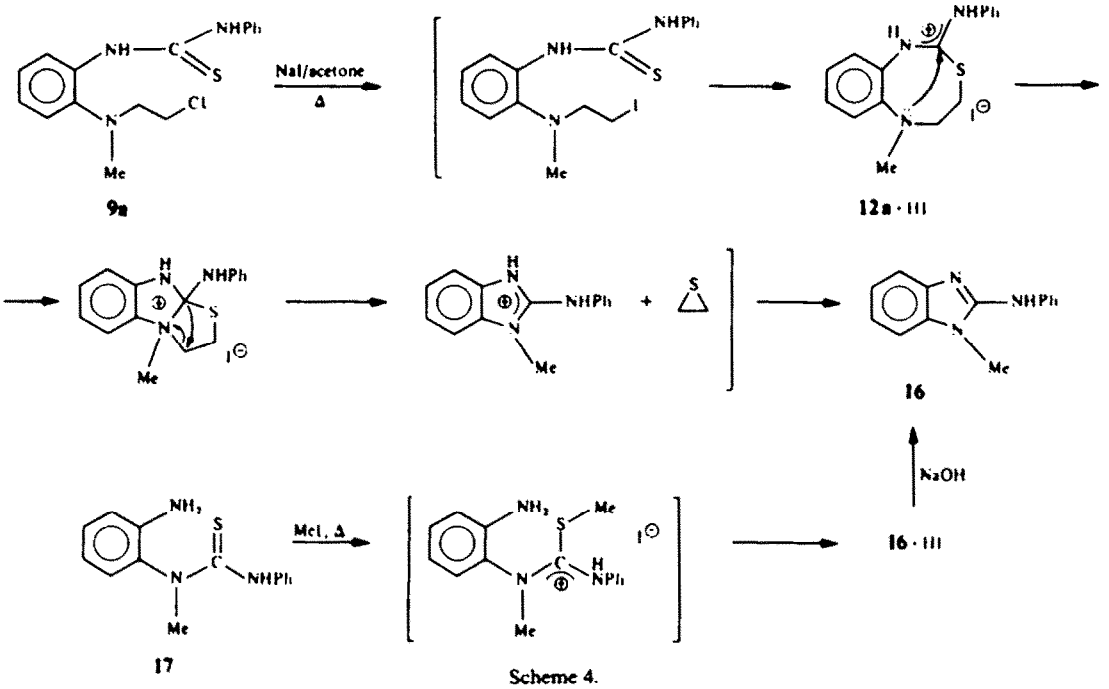
* Formation of type **13** products by ring closure of type **10** compounds is impossible even in principle

Scheme 3.

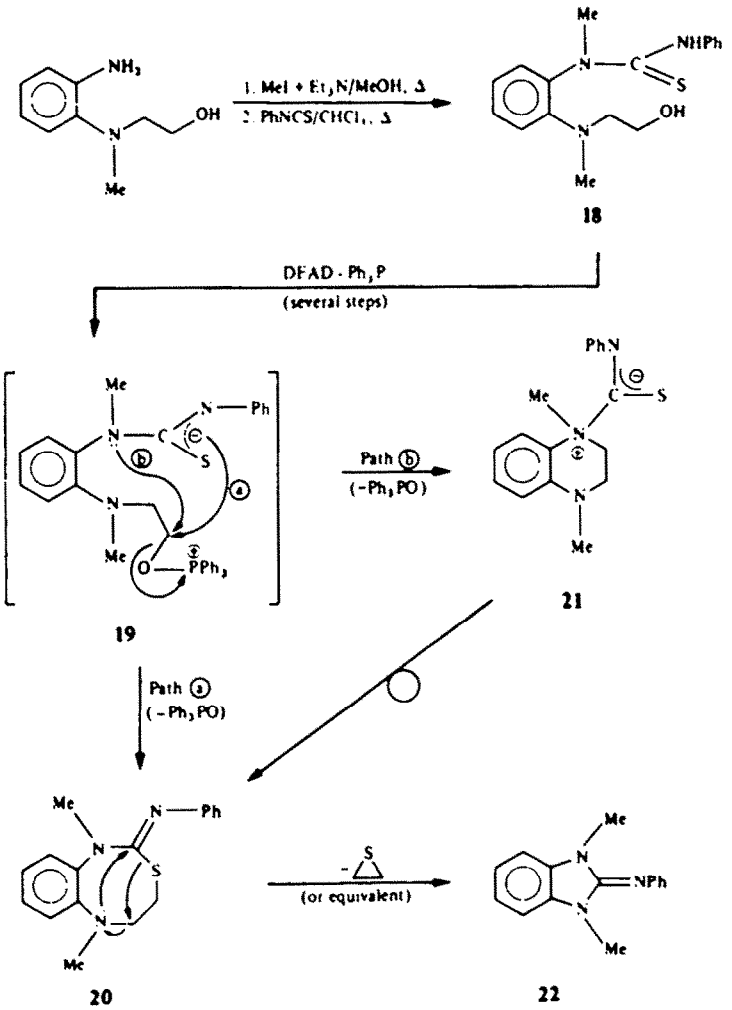
lowering the nucleophilicity of the *ortho*-N atom) the cyclisation towards formation of dihydro-3,1,6-benzothiadiazocines rather than of tetrahydroquinoxalines which are the products in the absence of such groups.

In the hope that replacement of X=Cl in compound **9a** by a better leaving group could result in permitting to effect the ring closure in the absence of base and therefore in a change of orientation, **9a** was treated with sodium iodide in acetone. No reaction took place at room temperature (100 hr); however, at 65° the benzimidazole **16** was obtained in moderate yield. Formation of this compound may be rationalised *via* **12a** · HI, as depicted in Scheme 4 where the structure proving synthesis of **16**, starting with **17** is also shown. Compound **17** was obtained by treating N-methyl-*o*-phenylenediamine with phenyl isothiocyanate; that the methylamino rather than the amino group is phenylthiocarbamoylated in this reaction, is shown by the chemical shift of the N-Me signal (δ 3.65 ppm) in the ^{1}H-NMR spectrum of the product (*cf* with the chemical shifts of the N-Me signals of N-methylaniline (2.5 ppm) and of N-methyl-N,N'-diphenylthiourea (3.7 ppm)).

Finally the ring closure of the trisubstituted thiourea **18**, the N-Me derivative of **11** was studied. The basic idea behind this was that application of the DEAD-triphenylphosphine reagent to **18** should lead to the formation of the intermediate **19**[3] (Scheme 5). The latter would then probably eliminate triphenylphosphine oxide according to path a, which would be equivalent to the reversal of the orientation experienced in the case of **11** and lead to the tetrahydro-3,1,6-benzothiadiazocine **20**. Should, on the other hand, the orientation experienced in the case of **11** be retained (path b), then the resulting dipolar **21** would probably be rather unstable and rearrange to the desired isomer **20**. The method of synthesis of **18** from **7a** is shown in Scheme 5. Although the oily product resulting from the reaction of **18** with the DEAD–triphenylphosphine reagent appeared to be homogeneous according to TLC, it was clearly shown by its ^{1}H- and ^{13}C-NMR spectra (measured on the day following its isolation) to be a 1 : 3 mixture of the desired **20** and its ring contraction product **22**. Apparently because of the higher temperatures necessary for obtaining the mass spectrum, only the ring contraction product **22** was



Scheme 4.



Scheme 5.

seen in the latter. The mechanism of the ring contraction of **20** is thought to be similar to that of **12a** · HI (shown in Scheme 4). All attempts to obtain tetrahydrobenzothiadiazocine **20** in pure form and the NMR spectra of the pure compound failed.

The results summarised in Schemes 4 and 5 demonstrate that the synthesis of dihydro- and tetrahydro-3,1,6-benzothiadiazocine derivatives lacking the alkylsulfonyl and arylsulfonyl groups in position 6 is possible; however, these compounds are, at least in form of the free bases, rather unstable and undergo ring contraction. The undesired ring contraction may, on the other hand, possibly be prevented (i) by *reducing the nucleophilicity of* N-6 with the aid of *electron attracting substituents* introduced into appropriate positions of the benzene ring and applying cyclisation methods which require comparatively *low reaction temperatures* or (ii)—in the absence of such substituents—by applying methods which, in addition to ring closure, lead to *protonation of* N-6 in the cyclised products, i.e. *complete loss of the nucleophilicity* of N-6. A method, applicable for both cases, will be described in the following paper.

EXPERIMENTAL

FT ^{1}H- and ^{13}C-NMR spectra were obtained with a JEOL FX-100 spectrometer using TMS as the internal reference; IR spectra were obtained with a Spectromom 2000 instrument (Hungarian Optical Works, Budapest) in KBr pellets.

2-(N-*Methyl*-2-*nitranilino*)*ethanol* (**7a**)

The mixture of **6a** (78 g, 0.5 mol), 2-(methylamino)ethanol (47 g, 0.62 mol) and pyridine (50 ml) was refluxed for 15 hr and evaporated to dryness *in vacuo*. The residue was taken up in heptane, again evaporated to dryness *in vacuo* and taken up in MeOH (150 ml). The methanolic soln was saturated with dry HCl to obtain 96.5 g (83%) of **7a** · HCl as light yellow crystals which were filtered off and washed with MeOH–ether (1:2) and ether; m.p.: 185° (dec; from MeOH ether). (Calc for $C_9H_{13}ClN_2O_3$ (232.7): Cl, 15.23; N, 12.04%. Found: Cl, 15.40; N, 11.88%.)

The salt was dissolved in water (250 ml), CH_2Cl_2 and crystalline Na_2CO_3 were added until the aqueous layer became neutral. From the organic layer 75 g (76%) of the title compound were obtained in the form of a red oil which was used in the following step without further purification.

2-(4-*Chloro*-N-*methyl*-2-*nitranilino*)*ethanol* (**7b**)

The mixture of **6b** (19.2 g, 0.1 mol), 2-(methylamino)ethanol (1.1 g, 0.15 mol) and pyridine (50 ml) was refluxed for 5 hr and evaporated to dryness *in vacuo*. The residue was dissolved in CH_2Cl_2 (150 ml), the soln was washed with dil AcOH, dried ($MgSO_4$) and evaporated to dryness to obtain 25.8 g (97%) of the title compound as an orange coloured oil.

HCl *Salt*, m.p.: 137–139° (from EtOH–ether). (Calc for $C_9H_{12}Cl_2N_2O_3$ (267.1): Cl, 26.54; N, 10.50%. Found: Cl, 26.07; N, 10.68%.)

Methyl 4 - [N - (2 - *hydroxyethyl*) - N - *methylamino*] - 3 - *nitrobenzoate* (**7c**)

The mixture of **6c**[4] (43.2 g, 0.2 mol), 2-(methylamino)ethanol (19 g, 0.25 mol), MeOH (150 ml) and pyridine (50 ml) was refluxed for 18 hr. The HCl salt, 35.5 g (61%), orange coloured crystals, m.p.: 99–102° (from MeOH–ether) (Calc for $C_{11}H_{15}ClN_2O_5$ (290.7): Cl, 12.19; N, 9.64%. Found: Cl, 12.00; N, 9.52%.), of the title compound was obtained as described for the HCl salt of **7a**. The free base is an orange red oil. (Calc for $C_{11}H_{14}N_2O_5$ (254.3): C, 51.96; H, 5.55; N, 11.02%. Found: C, 51.81; H, 5.39; N, 11.09%.)

N-(2-*Chloroethyl*)-N-*methyl*-2-*nitraniline*

Thionyl chloride (11 ml, 0.15 mol) was added dropwise to the soln of **7a** (13.7 g, 0.07 mol) in CH_2Cl_2 (50 ml). The soln was refluxed for 3 hr on a steam bath and evaporated to dryness *in vacuo*; this operation was repeated once again after the addition of MeOH (50 ml). The residue was taken up in CH_2Cl_2 (150 ml). The soln was washed with 5% NaOH aq and water, dried ($MgSO_4$) and evaporated to dryness to obtain 14.6 g (97%) of the title compound as a yellow oil which was used in the following step without further purification.

4 - *Chloro* - N - (2 - *chloroethyl*) - N - *methyl* - 2 - *nitraniline*. A red oil, was similarly obtained in 79% yield. (Calc for $C_9H_{10}Cl_2N_2O_2$ (249.1): C, 43.39; H, 4.05; Cl, 28.47; N, 11.25%. Found: C, 43.91; H, 4.32; Cl, 28.07; N, 11.40%.)

Methyl 4 - [N - (2 - *chloroethyl*) - N - *methylamino*] - 3 - *nitrobenzoate*. An orange oil, was similarly obtained in 73% yield. (Calc for $C_{11}H_{13}ClN_2O_4$ (272.7): C, 48.45; H, 4.80; Cl, 13.00; N, 10.27%. Found: C, 48.15; H, 5.20; Cl, 12.81; N, 10.32%.)

N-(2-*Chloroethyl*)-2-*isothiocyanato*-N-*methylaniline*

N-(2-Chloroethyl)-N-methyl-2-nitraniline (10 g, 46.5 mmol) was reduced in ethanolic soln (250 ml) in the presence of a 10% Pd–C catalyst (1 g) at normal pressure and room temp. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo*. The resulting crude **8a** was taken up in CH_2Cl_2 (150 ml) and water (100 ml), and a small amount of $Na_2S_2O_4$ was added. Subsequently thiocarbonyl dichloride (3.6 ml, 47 mmol) was added dropwise at 0° with vigorous stirring. The organic layer was washed successively with water, sat $Na_2S_2O_4$ aq, 10% Na_2CO_3 aq and water, dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The residue was purified by treatment with Norite in refluxing ether to obtain 8.6 g (82%) of the title compound as a yellow oil, IR 2100 cm^{-1} (—NCS), which was used in the following step without further purification.

4 - *Chloro* - N - (2 - *chloroethyl*) - 2 - *isothiocyanato* - N - *methylaniline*. A light yellow oil, was similarly obtained in 82% yield via **8b**; IR: 2100 cm^{-1} (—NCS).

Methyl 4 - [N - (2 - *chloroethyl*) - N - *methylamino*] - 3 - *isothiocyanatobenzoate*. A brownish yellow oil, was similarly obtained in 53% yield via **8c**; IR: 2100 and 1720 cm^{-1}.

1 - {2 - [N - (2-*Chloroethyl*) - N - *methylamino*]*phenyl*} - 3 - *phenylthiourea* (**9a**)

The mixture of N-(2-chloroethyl)-2-isothiocyanato-N-methylaniline (28 g, 12.4 mmol), aniline (1.4 ml, 15.4 mmol) and ether (25 ml) was kept at room temp overnight to obtain 1.0 g (25%) of the title compound as a colourless crystalline powder, m.p.: 135–136° from EtOH. (Calc for $C_{16}H_{18}ClN_3S$ (319.9): C, 60.08; H, 5.67; Cl, 11.08; N, 13.13; S, 10.02%. Found: C, 60.24; H, 5.37; Cl, 11.58; N, 13.32; S, 10.77%.)

1 - {5 - *Chloro* - 2 - [N - (2 - *chloroethyl*) - N - *methylamino*]*phenyl*} - 3 - *phenylthiourea* (**9b**). A light yellow crystalline powder, m.p.: 130–131° from MeOH, was similarly obtained in 53% yield. (Calc for $C_{16}H_{17}Cl_2N_3S$ (354.3): Cl, 20.01; N, 11.86%. Found: Cl, 19.52; N, 11.92%.)

N-(2-*Chloroethyl*) - N-*methyl* - N' - *morpholino*(*thiocarbonyl*) - o - *phenylenediamine* (**10a**)

The mixture of N-(2-chloroethyl)-2-isothiocyanato-N-methylaniline (3 g, 13 mmol), morpholine (1.2 ml, 14 mmol) and ether (50 ml) was refluxed for 2 hr and evaporated to dryness *in vacuo*. The residue was triturated with water and crystallised from EtOH to obtain 1.2 g (29%) of the title compound as a light yellow crystalline powder, m.p.: 107–108° from EtOH. (Calc for $C_{14}H_{20}ClN_3OS$ (313.9): Cl, 11.30; N, 12.38; S, 10.22%. Found: Cl, 11.25; N, 13.10; S, 10.70%.)

5 - *Chloro* - N - (2 - *chloroethyl*) - N - *methyl* - N' - *morpholino*(*thiocarbonyl*) - o - *phenylenediamine* (**10b**). Light yellow needles, m.p.: 110–111° from EtOH, was similarly obtained in 76% yield. (Calc for $C_{14}H_{19}Cl_2N_3OS$ (348.3): Cl, 20.36; N, 12.07; S, 9.20%. Found: Cl, 20.05; N, 11.84; S, 9.11%.)

2-(2-Amino-N-methylanilino)ethanol

Compound **7a** (5.0 g, 26 mmol) was reduced in EtOH (150 ml) in the presence of a 10% Pd–C catalyst (0.5 g) at normal pressure and room temp. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo* to obtain 4.1 g (97%) of the title compound as a light yellow oil.

Dihydrochloride, m.p.: 114–117° from EtOH–light petroleum. (Calc for $C_9H_{16}Cl_2N_2O$ (239.2): C, 45.20; H, 6.74; Cl, 29.65; N, 11.71%. Found: C, 45.42; H, 7.07; Cl, 29.71; N, 12.30%.)

1 - Methyl - 4 - phenyl(thiocarbamoyl) - 1,2,3,4 - tetrahydroquinoxaline (**14a**)

Compound **7a** (9.8 g, 50 mmol) was reduced and worked up as described above. The resulting oily product was added to the mixture of phenyl isothiocyanate (6 ml, 50 mmol) and $CHCl_3$ (50 ml). After being kept overnight at room temperature the mixture was evaporated to dryness *in vacuo*. The residue was triturated with a small amount of 2-propanol to obtain 9.85 g (65%) of the title compound, m.p.: 116–117° from 2-propanol. (Calc for $C_{16}H_{19}N_3OS$ (301.4): C, 63.75; H, 6.35; N, 13.94; S, 10.63%. Found: C, 63.60; H, 6.24; N, 14.07; S, 10.58%.)

1 - Methyl - 4 - phenyl(thiocarbamoyl) - 1,2,3,4 - tetrahydroquinoxaline (**14a**)

(a) Compound **9a** (1.0 g, 3.1 mmol) was stirred with the ethanolic (20 ml) soln of NaOEt (212 mg, 3.1 mmol) for 0.5 hr at 50°. The mixture was evaporated to dryness *in vacuo* and the residue was taken up in CH_2Cl_2 (50 ml) and water (20 ml) to obtain, after conventional work-up of the organic layer, 0.48 g (55%) of the title compound as a light yellow crystalline powder, m.p.: 144–145° from EtOH–acetone, 1:1. (Calc for $C_{16}H_{17}N_3S$ (283.4): C, 67.81; H, 6.04; N, 14.82%. Found: C, 68.36; H, 5.96; N, 14.64%.)

For the ^{1}H- and ^{13}C-NMR spectra, see Tables 1 and 2, respectively.

(b) The mixture of **15**[5] (0.3 g, 2 mmol), phenyl isothiocyanate (0.5 ml, 4 mmol) and CH_2Cl_2 (15 ml) was refluxed for 1 hr to obtain, after the same work-up as described under (a), 0.17 g (30%) of the title compound, light yellow crystals, m.p.: 144–145° from EtOH–acetone, 1:1.

(c) Compound **8a**, obtained by catalytic reduction of N-(2-chloroethyl)-N-methyl-2-nitraniline (10 g, 46.5 mmol) as described above, was treated with phenyl isothiocyanate (5.6 ml, 47 mmol) in CH_2Cl_2 soln (50 ml). The mixture was kept overnight at room temp and evaporated to dryness *in vacuo*. The residue was triturated with two portions of light petroleum (20 ml, each) and crystallised from 2-propanol to obtain 2.25 g (17%) of **14a**, m.p.: 144–145° from EtOH–acetone, 1:1.

(d) The soln of diethyl azodicarboxylate (2.6 g, 15 mmol) in THF (20 ml) was added with stirring at ambient temps dropwise to the mixture of **11** (2.6 g, 9.0 mmol), triphenyl phosphine (3.9 g, 15 mmol) and THF (50 ml). The mixture was allowed to stand for 24 hr and evaporated to dryness *in vacuo*. The residue was purified by column chromatography (Kieselgel 40; benzene–acetone, 4:1) to obtain 0.4 g (16%) of **14a**, m.p.: 144–145° from EtOH–acetone, 4:1.

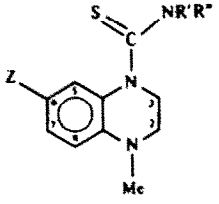
6 - Chloro - 1 - methyl - 4 - phenyl(thiocarbamoyl) - 1,2,3,4 - tetrahydroquinoxaline (**14b**)

Compound **9b** (0.35 g, 10 mmol) was refluxed for 0.5 hr with the freshly prepared ethanolic (10 ml) soln of NaOEt (10 mmol). The NaCl was filtered off, the filtrate was evaporated to dryness *in vacuo* and the residue was triturated with 2-propanol (1 ml) to obtain 0.25 g (79%) of the title compound, cream-coloured crystalline powder, m.p.: 137–138° from MeOH. (Calc for $C_{16}H_{16}ClN_3S$ (317.9): Cl, 11.17; N, 13.21; S, 10.38%. Found: Cl, 10.97; N, 13.21; S, 10.30%.) For the ^{1}H- and ^{13}C-NMR spectra, see Tables 1 and 2, respectively.

Methyl 1 - methyl - 4 - phenyl(thiocarbamoyl) - 1,2,3,4 - tetrahydroquinoxaline - 6 - carboxylate (**14c**) *(without isolation of the intermediate* **9c**)

The mixture of methyl 4-[N-(2-chloroethyl)-N-methyl-

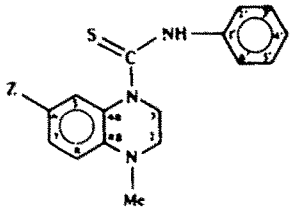
Table 1. ^{1}H-NMR spectra of some 1-methyl-4-thiocarbamoyl-1,2,3,4-tetrahydroquinoxalines **14** (δ values)



Compound	**14a**	**14b**	**14c**	**14e**
Z	H	Cl	MeOOC	H
—NR'R"	—NHPh	—NHPh	—NHPh	morpholino
Solvent	$CDCl_3$	DMSO-d_6	$CDCl_3$	DMSO-d_6
N-Me	3.01 s	2.92 s	3.07 s	2.89 s
2-H_2	3.50 t	3.40 t	3.58 t	3.39 t
3-H_2	4.51 t	4.19 t	4.53 t	3.80 t
6-H	6.68 t			
8-H	6.78 d	6.69 d[a]	6.77 d[a]	[c]
7-H	7.05–7.50 m (7H)	6.97 dd[a,b]	7.86 dd[a,b]	6.92 dd[a,b]
5-H		7.11 d[b]	7.96 d[b]	[c]
Ph		7.0–7.4 m (5H)	7.15–7.75 m (5H)	—
NH	8.01 s	9.78 s	8.02 s	
Other			3.82 s (OMe)	3.5–3.8 m (morpholine)

[a] J_o = 8.5 Hz.
[b] J_m = 2 Hz.
[c] 5-H + 8-H: 6.6–6.7 m (2H).

Table 2. ^{13}C-NMR spectra of some 1-methyl-4-thiocarbamoyl-1,2,3,4-tetrahydroquinoxalines **14** (δ values)[a]



Compound	**14a**	**14b**	**14c**
Z	H	Cl	MeOOC
Solvent	$CDCl_3$	DMSO-d_6	$CDCl_3$
N-Me	37.8	37.7	37.7
C-3	45.5	45.6	44.9
C-2	50.3	49.8	50.1
C-8	112.5 d	112.7 d	111.1 d
C-6	116.0 d	118.4 s	117.1 s
C-5	123.8 d	121.9 d	126.0 d
C-2′ + C-6′	124.6 d	123.8 d	125.1 d
C-4′	125.6 d	125.1 d	125.3 d
C-7	127.8 d	124.3 d	129.6 d
C-4a	128.6 s	126.4 s	122.7 s
C-3′ + C-5′	128.6 d	128.0 d	128.6 d
C-8a	139.3 s[b]	138.2 s	143.6 s
C-1′	140.6 s[b]	140.3 s	139.0 s
C=S	180.4 s	181.1 s	180.6 s
Other			51.7 (OMe) 166.3 s (C=O)

[a] The symbols s and d refer to the off-resonance spectra.
[b] The assignments may be interchanged.

amino]-2-isothiocyanatobenzoate (7.3 g, 26 mmol), aniline (2.6 ml, 29 mmol) and ether (50 ml) was allowed to stand for 2 days at room temp to obtain 2.0 g (20%) of the title compound as a crystalline ppt, m.p.: 165–166° from acetone. (Calc for $C_{18}H_{19}N_3O_2S$ (341.4): C, 63.32; H, 5.61; N, 12.30%. Found: C, 63.99; H, 6.20; N, 12.59%.) For the ^{1}H- and ^{13}C-NMR spectra, Tables 1 and 2.

1 - *Methyl* - 4 - *morpholino(thiocarbonyl)* - 1,2,3,4 - *tetrahydroquinoxalin* - 1 - *ium chloride* (**14d** · HCl)

Compound **10a** (1.0 g, 3 mmol) was stirred with the freshly prepared ethanolic (25 ml) soln of NaOEt (3 mmol) for 1 hr at 50°. The mixture was evaporated to dryness *in vacuo* and the residue was taken up in CH_2Cl_2 (50 ml) and water (15 ml) to obtain, after conventional work-up of the organic layer, the free base **14d** as an oil. The latter was dissolved in saturated ethanolic HCl, the soln was evaporated to dryness *in vacuo* and the residue was triturated with ether to obtain 0.7 g (70%) of the title compound as a colourless crystalline powder, m.p.: 190–192° dec; from EtOH. (Calc for $C_{14}H_{20}ClN_3OS$ (313.9): C, 53.37; H, 6.42; Cl, 11.29; N, 13.39%. Found: C, 53.76; H, 7.06; Cl, 11.62; N, 13.23%.)

6 - *Chloro* - 1 - *methyl* - 4 - *morpholino(thiocarbonyl)* - 1,2,3,4 - *tetrahydroquinoxaline* (**14e**)

Compound **10b** (3.5 g, 10 mmol) was refluxed with the freshly prepared ethanolic (40 ml) soln of NaOEt (10 mmol) for 1 hr. The hot mixture was filtered to remove the NaCl formed, and allowed to cool to obtain 2.8 g (90%) of the title compound as a yellowish crystalline powder, m.p.: 150–151° from EtOH. (Calc for $C_{14}H_{18}ClN_3OS$ (310.9): Cl, 11.41; N, 13.51; S, 10.31%. Found: Cl, 11.41; N, 13.41; S, 10.48%.) For the ^{1}H-NMR spectrum, Table 1.

2-*Anilino*-1-*methylbenzimidazole* (**16**)

(a) The mixture of **9a** (1.0 g, 3.5 mmol), acetone (20 ml) and NaI (2.3 g, 16 mmol) was refluxed for 11 hr and evaporated to dryness *in vacuo*. The residue was taken up in CH_2Cl_2 (30 ml) and water (50 ml) to obtain, after conventional work-up of the organic layer, the title compound in form of an oil which turned into 0.15 g (19%) of colourless crystals, m.p.: 162–163° from EtOH, when triturated with 2-propanol, and which proved identical with an authentic sample prepared as described below.

(b) The mixture of **17** (4.3 g, 16 mmol) (obtained as described below), MeI (1.2 ml, 19.5 mmol) and MeOH (40 ml) was refluxed for 4 hr and evaporated to dryness to obtain **16** · HI as a crystalline product which was washed with ether and dissolved in the mixture of EtOH (20 ml) and water (10 ml). 10% NaOH aq (10 ml) was added. The mixture was refluxed for 10 min and allowed to cool to obtain 2.9 g (80%) of the title compound, m.p.: 162–163° from EtOH. (Calc for $C_{14}H_{13}N_3$ (223.3): C, 75.30; H, 5.87; N, 18.82%. Found: C, 75.58; H, 5.59; N, 18.70%.)

1-(2-*Aminophenyl*)-1-*methyl*-3-*phenylthiourea* (**17**)

The mixture of N-methyl-*o*-phenylenediamine[b] (3.66 g, 30 mmol), phenyl isothiocyanate (3.6 ml, 30 mmol) and $CHCl_3$ (50 ml) was allowed to stand overnight and evaporated to dryness *in vacuo*. The residue was crystallised from EtOH to obtain 7.1 g (92%) of the title compound as colourless crystals, m.p.: 144–145°. (Calc for $C_{14}H_{15}N_3S$ (257.4): N, 16.33; S, 12.46%. Found: N, 16.50; S, 12.59%.) ^{1}H-NMR ($CDCl_3$): δ 3.65 s (N-Me), 3.85 bs (NH_2), 6.6–7.45 m (10H; ArH's + NH).

1 - {2 - [N - (2 - *Hydroxyethyl*) - N - *methylamino*]*phenyl*} - 1 - *methyl* - 3 - *phenylthiourea* (**18**)

Compound **7a** (5.0 g, 26 mmol) was catalytically reduced as described above. The mixture of the resulting 2-(2-amino-N-methylanilino)ethanol, MeOH (25 ml), Et_3N (3.6 ml, 26 mmol) and MeI (5 ml, 80 mmol) was refluxed for 20 hr and evaporated to dryness *in vacuo*. The residue was taken up in $CHCl_3$ (50 ml) and 1 N NaOH (26 ml) to obtain, after conventional work-up, 2-(N-methyl-2-methylaminoanilino)ethanol as an oil. The methanolic (20 ml) soln of the latter was saturated with dry HCl at 0° to obtain 5.2 g (81%) of the dihydrochloride as a colourless crystalline powder, m.p.: 161–164° dec; from MeOH–ether. (Calc for $C_{10}H_{18}Cl_2N_2O$ (253.3): C, 47.44; H, 7.16%. Found: C, 47.27; H, 6.78%.)

The mixture of the dihydrochloride (2.5 g, 10 mmol), $CHCl_3$ (25 ml), Et_3N (2.0 g, 20 mmol) and phenyl isothiocyanate (1.2 ml, 10 mmol) was refluxed for 1 hr and evaporated to dryness *in vacuo*. The residue was taken up in CH_2Cl_2 (50 ml) and water (10 ml) to obtain, after conventional work-up, 0.8 g (25%) of the title compound as a colourless oil which slowly turned crystalline when allowed to stand for some days; m.p.: 79–80° from cyclohexane. (Calc for $C_{17}H_{21}N_3OS$ (315.4): C, 64.72; H, 6.71; S, 10.16%. Found: C, 64.37; H, 6.83; S, 10.60%.) ^{1}H-NMR ($CDCl_3$): δ 2.1 (exchangeable, OH), 2.86 s + 3.65 s (two N-Me's), 3.20 q + 3.77 m (both collapsing to t's on addition of D_2O; N—CH_2—CH_2—O), 6.9–7.4 m (9H, ArH's), 7.55 (exchangeable, NH).

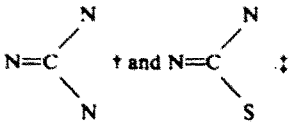
Reaction of 1 - {2 - [N - (2 - *hydroxyethyl*) - N - *methylamino*] - *phenyl*} - 1 - *methyl* - 3 - *phenylthiourea* (**18**) *with triphenylphosphine DEAD*

DEAD (0.6 g, 3.3 mmol), dissolved in THF (5 ml) was added at 0° to a mixture of **18** (0.6 g, 2.2 mmol), triphenylphosphine (0.87 g, 3.3 mmol) and THF (30 ml). The mixture was stirred for 48 hr at ambient temp and evaporated to dryness *in vacuo*. The residue was worked up by column chromatography (Kieselgel 60; cyclohexane–ethyl acetate, 2:3) to obtain a colourless oil (0.15 g, 23%).† ^{1}H-NMR ($CDCl_3$): δ 2.75 s (0.75H, N_o-Me),‡

† Yield calculated by assuming the product to be pure tetrahydrobenzothiadiazocine **20**.

‡ Signal arising from compound **20**.

3.2 s (4.5H, 2 × N-Me),† 3.55 s (0.75H, N_1-Me),‡ 3.6 m (0.5H, S-CH_2),‡ 4.2 m (0.5H, N-CH_2),‡ 6.7–7.5 m (9H, ArH's). ^{13}C-NMR ($CDCl_3$): δ 29.7 (S-CH_2),‡ 30.4 (2 × N-Me),† 39.8 (N_1-Me),‡ 41.0 (N_6-Me),‡ 57.0 (N-CH_2),‡ 149.3 and 149.4



Mass spectrum: *m/z* 237 ($M^{+\cdot}$), 236, 222 (M − Me), 207 (M − 2Me), 160 (M − Ph), 146 (M − NPh).

Note added in proof. We have noted, that some slight errors have slipped into the ^{1}H-NMR data of compound 3 (Z = MeO, R = 4-MeC_6H_4, R' = H) published in Part II§ of the present series where this compound was designated as 7 (Y = MeO, R = H, V + W = S). The correct data may be found in Part III[1] where the same compound was designated **12A**. In the Experimental of the latter paper this compound has been erroneously named a 1,3,6-benzotriazine-2(1H)-thione rather than a 1,3,6-benzotriazocine-2(1H)-thione.

Acknowledgements- The authors are grateful to Mrs I. Balogh-Batta and staff for the microanalyses, to Mrs M. Székely-Csirke for the IR spectra, to Mrs A. Gergely for the mass spectrum and to EGyT Pharmaceutical Works, Budapest, for financial assistance.

REFERENCES

[1] F. Bertha, Gy. Hornyák, K. Zauer, K. Lempert, E. Pjeczka and G. Tóth, *Tetrahedron* **39**, 1203 (1983).
[2] H. Nagasawa and O. Mitsunobo, *Bull. Chem. Soc. Japan* **54**, 2223 (1981).
[3] For the role of alkoxytriphenylphosphonium salts in reactions of alcohols brought about with the aid of the DEAD–triphenylphosphine reagent, see O. Mitsunobo and M. Eguchi, *Bull. Chem. Soc. Japan* **44**, 3427 (1971).
[4] A. P. Montague, *Rec. Trav. Chim. Pays-Bas* **19**, 46 (1900).
[5] J. S. Morley, *J. Chem. Soc.* 4002 (1952).
[6] A. P. Montague, *J. Chem. Soc.* 2820 (1929).

† Signal arising from compound **22**.
‡ Signal arising from compound **20**.
§ F. Bertha, Gy. Hornyák, K. Zauer and K. Lempert, *Tetrahedron* **39**, 1199 (1983).