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THE SYNTHESIS AND SOME REACTIONS OF 3-(2-AMINOPHENYL)-2-IMINOTHIAZOLIDINES. RING CLOSURE OF N-(2-THIOCYANATOETHYL)-o-PHENYLENEDIAMINES: THIAZOLIDINE vs. 3,1,6-BENZOTHIADIAZOCINE FORMATION

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Abstract: When treated with strong acids, the N-(2-thiocyanatoethyl)-o-phenylenediamines (1g-1v) are cyclized exclusively to 3-(2-aminophenyl)-2-iminothiazolidines (6) while the related tertiary amines (1a-1f) gave, under the same conditions, benzothiadiazocines of types (2) or (3). Some of the type (6) compounds are highly active antidepressants of low toxicity. Thermal reactions of compound (6b) and its conversion into tricyclic compounds of types (23) and (24) are also reported.

The hydrogen chloride catalyzed ring closure of the N-methyl compounds (1a-e) and of the N-phenyl analogue (1f) has recently been found to afford 2-amino-3,1,6-benzothiadiazocine derivatives either as the mono- (2a-d) or the dihydrochlorides (3a, b), depending on whether the basicity of N-6 is sufficiently reduced by the substituents R, R^4, and R^5 or not.[1] Since compounds (2a-d) and (3a-b) had some effects on the central nervous system of rodents and their toxicity was low, the synthesis of 6-unsubstituted analogues [(2) or (3), R=H] was attempted. The thiocyanates (1g) and (1h), when treated with HCl gas in methanol-dichloromethane (1:1) solution at 0°C, gave products of the expected elemental composition. However, conspicuous differences were noticed (i) between the pharmacological properties of compound (3a) and the ring closure product of the thiocyanate (1g), and (ii) between the chemical shifts of the S-methylene group and the isothiourea moiety of compound (3b) (δ 31.0 and 170.6 ppm, respectively) and the cyc-

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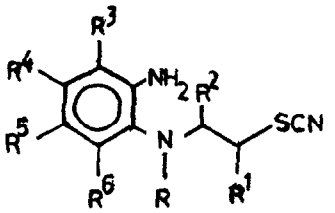
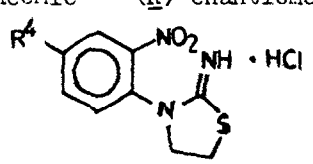


	R	R^1	R^2	R^3	R^4	R^5	R^6
1a:	Me	H	H	H	H	H	H
1b:	Me	H	H	H	Cl	H	H
1c:	Me	H	H	H	F_3C	H	H
1d:	Me	H	H	H	MeO_2C	H	H
1e:	Me	H	H	H	[illegible]	Cl	H
1f:	Ph	H	H	H	H	H	H
1g:	H	H	H	H	H	H	H
1h:	H	H	H	H	Cl	H	H
1i:	H	H	H	H	Br	H	H
1j:	H	H	H	H	I	H	H
1k:	H	H	H	H	F	H	H
1ℓ:	H	H	H	H	MeO	H	H
1m:	H	H	H	H	F_3C	H	H
1n:	H	H	H	H	MeO_2C	H	H
1o:	H	H	H	H	Me	H	H
1p:	H	H	H	Cl	H	H	H
1r:	H	H	H	H	H	Cl	H
1s:	H	H	H	H	H	H	Cl
1t:	H	Me	H	H	Cl	H	H[a]
1u:	H	H	Et	H	Cl	H	H[a]
1v:	H	H	Et	H	Cl	H	H[b]

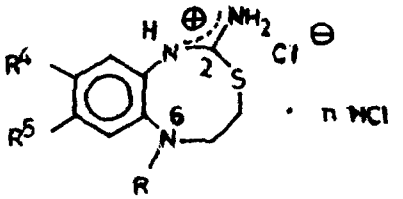
[a] racemic [b] (R) enantiomer



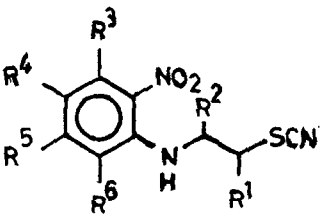
(5)

a: R=H, b: R=Cl, c: R=F_3C

The free bases are denoted by primed numbers

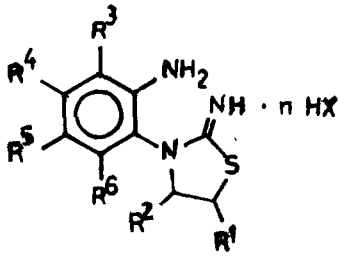


	R	R^4	R^5	n
2a:	Me	F_3C	H	0
2b:	Me	MeO_2C	H	0
2c:	Me	H	Cl	0
2d:	Ph	H	H	0
3a:	Me	H	H	1
3b:	Me	Cl	H	1
3c:	H	H	H	1
3d:	H	Cl	H	1



	R^1	R^2	R^3	R^4	R^5	R^6
4a:	H	H	H	H	H	H
4b:	H	H	H	Cl	H	H
4c:	H	H	H	Br	H	H
4d:	H	H	H	I	H	H
4e:	H	H	H	F	H	H
4f:	H	H	H	MeO	H	H
4g:	H	H	H	F_3C	H	H
4h:	H	H	H	MeO_2C	H	H
4i:	H	H	H	Me	H	H
4j:	H	H	Cl	H	H	H
4k:	H	H	H	H	Cl	H
4ℓ:	H	H	H	H	H	Cl
4m:	Me	H	H	Cl	H	H[a]
4n:	H	Et	H	Cl	H	H[a]
4o:	H	Et	H	Cl	H	H[b]

[a] racemic [b] (R) enantiomer



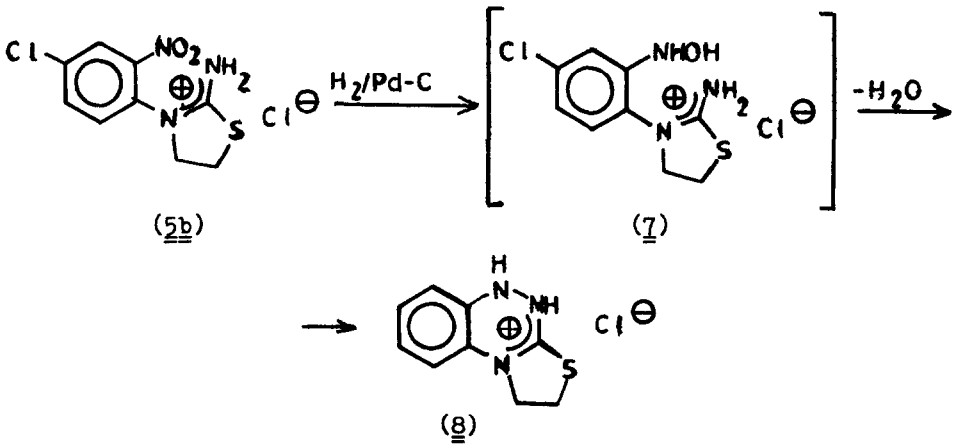
6

	R^1	R^2	R^3	R^4	R^5	R^6	n	X
6a:	H	H	H	H	H	H	2	Cl
6b:	H	H	H	Cl	H	H	2	Cl
6c:	H	H	H	Cl	H	H	2	O_3SEt
6d:	H	H	H	Cl	H	H	0	-
6e:	H	H	H	Br	H	H	2	O_3SEt
6f:	H	H	H	I	H	H	2	O_3SEt
6g:	H	H	H	F	H	H	2	O_3SEt
6h:	H	H	H	MeO	H	H	2	Cl
6i:	H	H	H	MeO	H	H	2	O_3SEt
6j:	H	H	H	F_3C	H	H	2	Cl
6k:	H	H	H	F_3C	H	H	2	O_3SEt
6l:	H	H	H	MeO_2C	H	H	2	Cl
6m:	H	H	H	Me	H	H	2	Cl
6n:	H	H	Cl	H	H	H	1	O_3SEt
6o:	H	H	H	H	Cl	H	2	Cl
6p:	H	H	H	H	H	Cl	1	O_3SEt
6q: [a]	Me	H	H	Cl	H	H	2	Cl
6r: [a]	Me	H	H	Cl	H	H	2	O_3SEt
6s: [a]	H	Et	H	Cl	H	H	1	Cl
6t: [a]	H	Et	H	Cl	H	H	1	O_3SEt
6u: [b]	H	Et	H	Cl	H	H	1	O_3SEt

[a] racemic [b] (R) enantiomer

lization product of thiocyanate (1h)(δ 29.4 and 174.8 ppm, respectively) in the ^{13}C n.m.r. spectra (both recorded in DMSO-d_6). These differences suggested that ring closure of the thiocyanates (1g) and (1h) may have afforded isomers of the expected 3,1,6-benzothiadiazocines (3c, d) rather than the benzothiadiazocines themselves. The cyclization product of thiocyanate (1h) was indeed found to be identical with an authentic sample of the 2-iminothiazolidine derivative (6b) obtained, in moderate yield, by acid catalyzed ring closure of the nitro compound (4b) and reduction of the resulting 2-imino-3-(2-nitrophenyl)thiazolidine salt (5b).

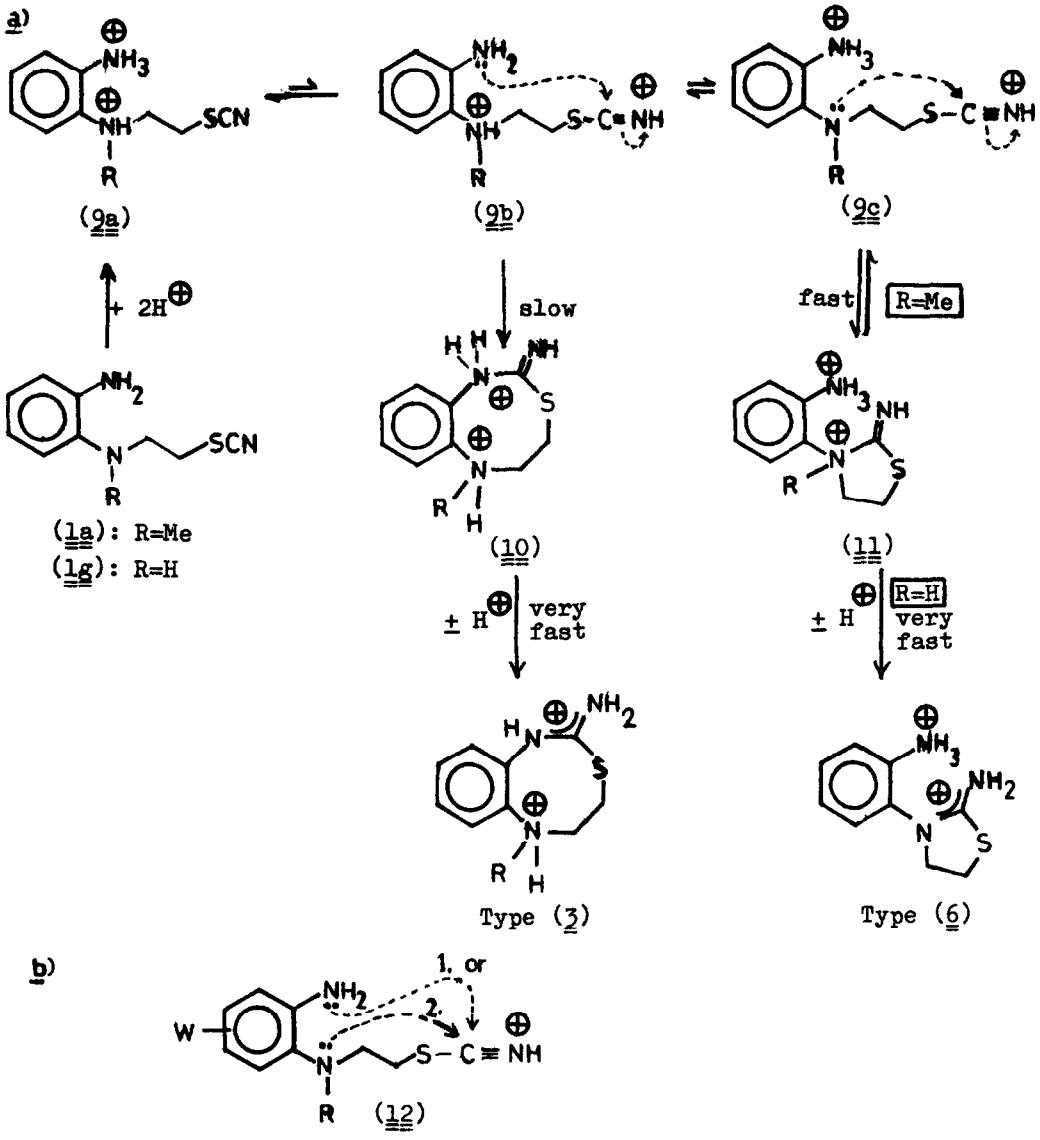
Appropriate choice of the reduction method ir the final step of this sequence is crucial. Thus, while the p-nitro isomer of compound (5a) was smoothly reduced catalytically to the corresponding amine, this reduction method proved unapplicable in the presence of o-nitro groups. E.g. attempted catalytic reduction of compound (5b) led, via hydroxylamine (7), to the formation of the tricyclic compound (8) whose N-N bond could not be reductively cleaved in spite of numerous attempts.



(5b) (7) (8)

Among the various reducing agents and reduction methods tested, stannous chloride was the only one with which compound (5b) could be reduced, in moderate yield (40%) to the corresponding amino derivative (6b). Thus, while the sequence (4) → (5) → (6) constitutes a structure proving synthesis of the final products, from a practical point of view the non-structure proving sequence (4) → (1) (R=H) → (6) is by far the more favorable.

The contrasting behaviour, in acid catalyzed ring closure, of the N-substituted (1a-f) and the N-unsubstituted thiocyanates (1g-h) may be rationalized as shown in Scheme 1 for the parent compounds (1a) and (1g). Both compounds are thought to be initially converted into their diprotonated dications which should be able to exist in three distinct prototropic forms, (9a) being the most stable and most abundant form but (9b) and (9c) being the more reactive. Ring closure of the latter two should lead to the 3,1,6-benzothiadiazocines (10) and iminothiazolidines (11), respectively, both for R=Me and R=H, the closure of the five-membered ring being faster in both cases. Due to the presence of the quaternary cationic nitrogen, the resulting compound (11) should be unstable for R=Me, revert to (9c) and finally be converted, via (9b) and (10), into the benzothiadiazocine of type (3). For the thiazolidine derivative (11) (R=H), on the other hand, an additional mode of stabilization is available, viz. rearrangement by protonation - deprotonation to afford the type (6) product. Since this prototropic rearrangement may be assumed to be rapid, no benzothiadiazocine formation takes place in this case. In the presence of electron withdrawing groups W attached to the benzene ring of the starting compound the basicity of one or the other amino group may be reduced to such an extent that dication formation becomes prohibited. In this case a monocation is formed whose reactive tautomeric form (12) then undergoes ring closure to afford



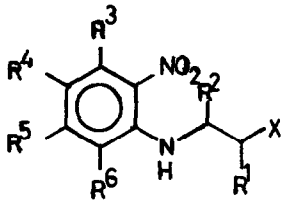
Scheme 1. (a) Acid catalyzed ring closure of type (1) compounds which are capable of forming diprotonated dications
(b) Reactive tautomer of the monoprotonated cation of type (1) compounds which, due to the presence of an electron withdrawing group W, fail to form diprotonated dications

ultimately a benzothiadiazocine or a thiazolidine dervative, again depending on whether R=Me or R=H.

The preliminary pharmacological screening results of compounds (6a) and (6b) were encouraging. Therefore and because no type (6) compounds had

been described previously, a series of type (6) compounds was synthesised in which (i) various substituents were attached to various positions of the benzene ring, (ii) in some cases simple alkyl groups were introduced into the thiazolidine ring in positions 4 or 5, and (iii) ethanesulphonic acid was used rather than hydrogen chloride for salt formation. The synthesis of all these compounds (6c-t)was carried out according to the sequence (4) → (1) → (6) which, although not structure proving, had been shown to be the more favourable one for the synthesis of compound (6b).

Most of the key intermediates (4)were obtained from the corresponding 2-(2-nitranilino)ethanols (13) via the mesylates (14). Many of the starting compounds (13) were known and even commercially available; the new compounds (13) were obtained by allowing to react the appropriate 2-chloronitrobenzenes with 2-aminoalcohols. Compounds (4d, e, and i) were obtained via the chlorides (15), while compound (4f) was obtained from N-(2-bromoethyl)-2-nitraniline (16f) (itself prepared by detosylation of its N-tosyl derivative[2]) by replacement of the bromine atom by a thiocyanato group.



(13): X = OH
(14): X = O_3SMe
(15): X = Cl
(16): X = Br

	R^1	R^2	R^3	R^4	R^5	R^6
a:	H	H	H	H	H	H
b:	H	H	H	Cl	H	H
c:	H	H	H	Br	H	H
d:	H	H	H	I	H	H
e:	H	H	H	F	H	H
f:	H	H	H	MeO	H	H
g:	H	H	H	F_3C	H	H
h:	H	H	H	MeO_2C	H	H
i:	H	H	H	Me	H	H
j:	H	H	Cl	H	H	H
k:	H	H	H	H	Cl	H
l:	H	H	H	H	H	Cl
m:[a]	Me	H	H	Cl	H	H
n:[a]	H	Et	H	Cl	H	H
o:[b]	H	Et	H	Cl	H	H

[a] Racemic [b] (R) enantiomer

Catalytic reduction (H_2/Pd-C) of the compounds (4) furnished the crude compounds (1) which, without purification, were cyclized to the desired compounds (6) by treatment with hydrogen chloride or ethanesulphonic acid. Alternatively, compound (6k) was obtained by hydrogen chloride induced cy-

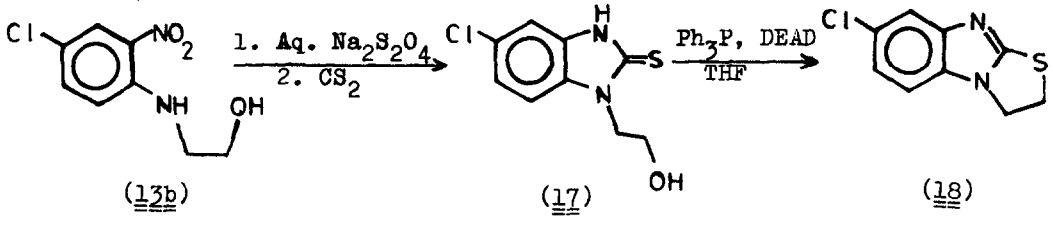
clization of compound (4g) and reduction of the resulting compound (5c) by stannous chloride.

The pK_a values (aqueous solution, 25°C), taken from literature, of anilinium, m-chloro-, p-chloro-, m-trifluoromethyl-, and p-trifluromethyl-anilinium ions are 4.57-4.60,[3-5] 3.52-3.67,[4,6] 4.00-4.15,[4,6] 3.49,[4] and 2.57,[4] respectively; i.e. the basicity of aniline (and, presumably, its nucleophilicity as well) are reduced by introduction of chlorine into the meta position to a greater extent than into the para position, while the opposite is true for the trifluoromethyl group. Therefore, the observation that acid catalyzed cyclization of both thiocyanates (4b) (see above) and (4g) affords type (6) iminothiazolidine rather than type (2) or (3) benzothiadiazocine derivatives appears to indicate that the preferred direction of cyclization of the thiocyanates (4) does not depend on the electronic nature of the substituents R^4. The same is, presumably, true also for substituents at other positions of the benzene ring.

The pharmacological studies (whose results will be published elsewhere, see also ref. 7) revealed the compounds (6) to possess considerable antidepressant, antiparkinson, anticonvulsant, and spasmolytic activities coupled with low toxicity and, in some cases, moderate analgetic activity. Encouraged by these results, we have selected compounds (6b) and (6c) for more detailed biological studies.

Meanwhile some reactions of compound (6b) were also studied.

When refluxed in anhydrous ethanolic solution, compound (6b) was converted into the hydrochloride of 2,3-dihydrothiazolo[3,2-a]benzimidazole (18) whose structure was established by an alternative synthesis starting with compound (13b) as shown in Chart 1.

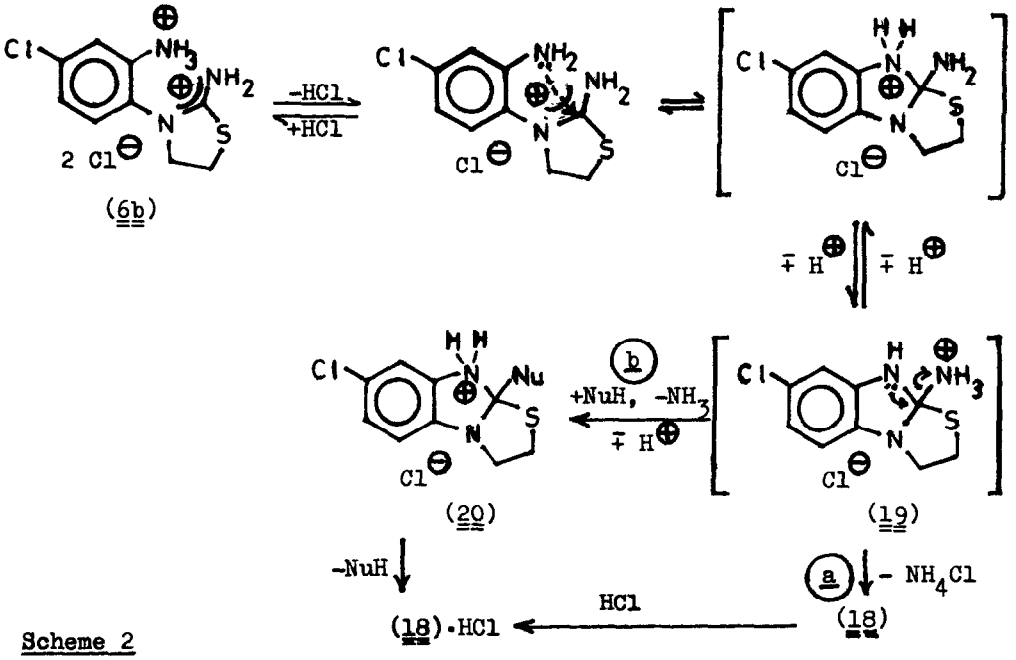


(13b) (17) (18)

Chart 1

The conversion of compound (6b) into (18)·HCl may be assumed to take place according to either of the two pathways a and b shown in Scheme 2. The tricyclic salt (19) is thought to be the common intermediate on both pathways. Loss of ammonium chloride and addition of hydrogen chloride would then lead to (18)·HCl (Path a). Alternatively, the salt could react with a

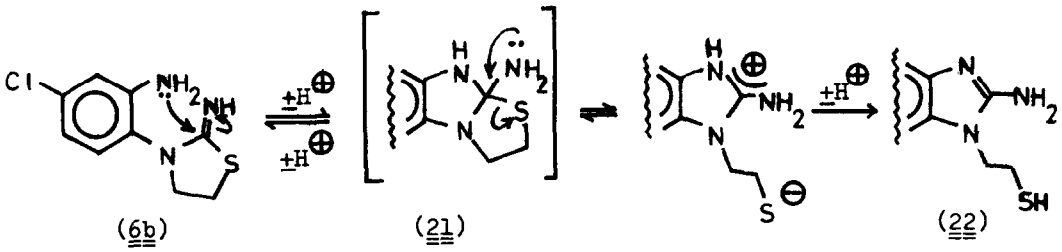
nucleophile NuH present in the reaction mixture (ethanol, traces of water) to yield the substitution product (20) which then would collapse to the final product by loss of the nucleophile (Path b). The latter path is substantiated by the formation of compound (20, Nu = OH) when compound (6b) is refluxed for 10 min. with 96% aqueous acetic acid. While (20, Nu = OH) is remarkably stable to refluxing acetic acid, it is converted into (18)·HCl



Scheme 2

by short refluxing in ethanolic solution as well as, gradually, when its crystals are allowed to stand at ambient temperature. When the free base corresponding to compound (6b) was refluxed for a short time with acetic acid, compound (18) was obtained and all our attempts to isolate an intermediate [the free base corresponding to the salt (20, Nu=OH)] failed.

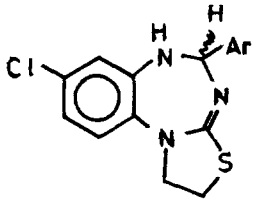
The reaction took a different course when the free base corresponding to compound (6b) was refluxed with ethanol or heated with benzylamine, the aminobenzimidazole (22) being the product in both cases. Formation of this product may be rationalized as shown in Scheme 3. The assumed intermediate is the free base (21) corresponding to intermediate (19) of Scheme 2. While in (19) the protonated amino group is the best leaving group among those attached to the tetrahedral carbon atom, in (21) the group attached to this carbon atom through sulphur becomes the best leaving group since the amino group is not protonated in this case.



(6b) (21) (22)

Scheme 3

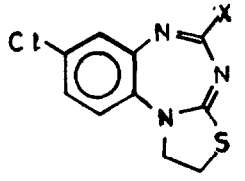
When treated with C_1 components (including aromatic aldehydes, cyanogen bromide, and triethyl orthoformate) the free base corresponding to compound (6b) gave the tricyclic derivatives (23) and (24), respectively.



(23)

a: Ar = Ph

b: Ar = C_6H_4OMe-p



(24)

a: X = NH_2 , hydrobromide

b: X = H

When refluxed with 20% aqueous HCl, compound (24b) gave the monohydrochloride - monohydrate of compound (22).

Experimental

M.p.'s are uncorrected. ^1H and ^{13}C n.m.r. spectra were recorded with a JEOL FX-100 spectrometer at 100 and 25 MHz, respectively, using TMS as internal reference. I.r. and mass spectra were obtained with a Spektromom 2000 (Hungarian Optical Works, Budapest) and a JEOL JMS-C 156-2 spectrometer, respectively.

The following starting 2-(2-nitranilino)ethanols were known from literature: (13a),[8] (13b),[9] (13c),[10] (13h),[8] (13i),[11] (13j),[9] (13k),[9] and (13ℓ).[9] Further type (13) compounds were obtained by allowing to react 1-chloro-2-nitrobenzenes with 2-aminoalcohols as described below.

(±)-2-(4-Chloro-2-nitranilino)butan-1-ol (13n)

A mixture of 1,4-dichloro-2-nitrobenzene (38.4 g, 0.2 mol), (±)-2-aminobutan-1-ol (20 ml, 0.22 mol), and pyridine (100 ml) was refluxed for 5 h and evaporated to dryness at reduced pressure. The oily residue, when triturated with water, gave the crystalline title compound (36 g, 73%),

orange-red needles, m.p. 45°C (from ether). Found C, 49.11; H, 5.32; N, 11.55. $C_{10}H_{13}ClN_2O_3$ (244.7) requires C, 49.07; H, 5.35; N, 11.44%. Similarly obtained were the following compounds:*

2-(4-Iodo-2-nitranilino)ethanol (13d), 66% yield, m.p. 110°C (from EtOH); found C, 30.92; H, 2.67; I 41.00; N, 8.82; $C_8H_9IN_3O_3$ (308.1) requires C, 31.19; H, 2.94; I, 41.19; N, 9.09%;

2-(4-Fluoro-2-nitranilino)ethanol (13e), 82% yield, an orange-red oil which was converted into its methanesulphonate in crude form;

2-(4-Trifluoromethyl-2-nitranilino)ethanol, (13g), 95% yield, yellow needles, m.p. 78-9°C (from benzene - light petroleum); found N, 11.35; $C_9H_9F_3N_2O_3$ (250.2) requires N, 11.19%;

(±)-2-(4-Chloro-2-nitranilino)-1-methylethanol (13m), 84% yield, orange-red crystalline powder, m.p. 98-100°C (from benzene); found C, 46.75; H, 4.63; Cl, 15.54; N, 11.83; $C_9H_{11}ClN_2O_3$ (230.7) requires C, 46.86; H, 4.80; Cl, 15.37; N, 12.15%;

(R)-(+)-2-(4-Chloro-2-nitranilino)butan-1-ol (13o), 80% yield, orange-red crystalline powder, m.p. 43°C (from ether), $[\alpha]_{20}^{D}$ +24.1 ($CHCl_3$, c = 1).

N-(2-Bromoethyl)-4-methoxy-2-nitraniline (16f)

N-(2-Bromoethyl)-N-tosyl-4-methoxy-2-nitraniline[2] (100 g, 0.23 mol) was added in small portions with ice-water cooling and continuous stirring to conc. H_2SO_4 (100 ml). The solution was allowed to stand for 24 h at room temperature and poured onto ice (300 g). The product was filtered off, thoroughly washed with water, dried in air, and recrystallized from MeOH to give the title compound (62 g, 97%) as a red crystalline powder, m.p. 53-5°C (from MeOH). Found Br, 29.19; N, 10.21. $C_9H_{11}BrN_2O_3$ requires Br, 29.05; N, 10.18%.

2-(2-Nitranilino)ethyl methanesulphonates (14a-c, 14g-i, and 14k-o)

Methanesulphonyl chloride (0.12 mol) was added dropwise to pyridine solutions (60 ml) of the 2-(2-nitranilino)ethanols (13a-c), (13g-i), and (13k-o) (0.1 mol) with continuous stirring and ice-water cooling at such a rate that the temperature of the mixtures did not exceed 5°C. The mixtures were stirred at ambient temperature until the starting compounds (13) were used up (t.l.c.) and poured into ice-water (ca. 300 ml). The resulting crystalline products were filtered off, washed with water, dried in air, and recrystallized to give, depending on the nature of the substituents R^3-R^6, yellow to brownish-red products. For the yields, m.p.'s, and analytical data, see Table 1.

* In some cases the solvent pyridine was replaced by ethanol or butan-1-ol and an additional 1-1.1 mol-equivalent of the 2-aminoalcohol was used.

Table 1: 2-(2-Nitranilino)ethyl methanesulphonates (14) by methanesulphonylation of 2-(2-nitranilino)ethanols (13)

	Yield %	M.p., °C (from)	Mol. formula (Mol. wt.)	Calc./found C%	H%	Cl%	N%	S%
14a	91	86-7 (EtOH)	$C_9H_{12}N_2O_5S$ (260.3)	41.53 41.76	4.65 4.41		10.76 10.63	12.32 12.54
14b	75	108-9 (MeOH)	$C_9H_{11}ClN_2O_5S$ (294.8)			12.04 12.34	9.50 9.30	10.88 10.52
14c	[a]							
14g	75	68-70 (EtOAc-l.p.[b])	$C_{10}H_{11}F_3N_2O_5S$ (328.3)				8.53 8.56	9.76 10.21
14h	65	109-11 (MeOH)	$C_{11}H_{14}N_2O_7S$ (318.3)	41.50 41.80	4.43 4.61		8.80 8.91	10.07 10.24
14i	93	65-7 (CH_2Cl_2-Et_2O)	$C_{10}H_{14}N_2O_5S$ (274.3)	43.79 43.78	5.14 5.20		10.21 9.88	11.69 11.62
14k	98	101-2 (MeOH)	$C_9H_{11}ClN_2O_5S$ (294.8)			12.04 11.71	9.50 9.45	10.88 11.00
14l	83	oil[c]	$C_9H_{11}ClN_2O_5S$ (294.8)				9.50 9.28	10.88 11.19
14m[d]	65	106-8 (MeOH)	$C_{10}H_{13}ClN_2O_5S$ (308.8)			11.49 11.52	9.07 9.25	10.40 10.52
14n[d]	63	91-3 (EtOH)	$C_{11}H_{15}ClN_2O_5S$ (322.8)			10.99 10.62	8.68 8.47	
14o[e]	60[f]	92-3 (MeOH)	$C_{11}H_{15}ClN_2O_5S$ (322.8)			10.99 10.80	8.68 8.72	

[a] The crude product was, without purification, allowed to react with KSCN to give the 2-thiocyanatoethyl derivative (4c) in 96% overall yield

[b] Light petroleum [c] Chemically pure (t.l.c.) [d] Racemic

[e] (R) enantiomer [f] $[\alpha]_{20}^{D}$ -62° (c=1, $CHCl_3$)

The non-crystalline products (14c) and (14l) were taken up in CH_2Cl_2, the aqueous supernatants were separated, and extracted with CH_2Cl_2 (2 x 30 ml). The combined CH_2Cl_2 solutions were washed with water, dried ($MgSO_4$), and evaporated to dryness. The crude compound (14c) was allowed to react with KSCN without purification while compound (14l) was purified by t.l.c. (Kieselgel 60 $PF_{254+366}$; benzene - acetone, 1:1; R_f 0.7).

N-(2-Thiocyanatoethyl)-o-nitranilines (4)

Method A: Mixtures of the 2-(2-nitranilino)ethyl methanesulphonates (14) (0.2 mol), KSCN (0.3-0.4 mol) and ethanol (30-300 ml, depending on the solubility of the starting methanesulphonate) [or, in some cases methanol, 2-propanol, or DMF (40-80 ml), respectively] were refluxed until the starting compound (14) was used up (t.l.c.; 8-50 h) and poured into water (ca. 500 ml). The crystalline products were filtered off, washed with water, dried in air, and recrystallized to give, depending on the nature of the substituents R^3-R^6, the yellow to orange-red title compounds. For the yields, m.p.'s, and analytical data, see Table 2.

Method B: $SOCl_2$ (30 mmol) was added dropwise to a $CHCl_3$ solution (30 ml) of the 2-(2-nitranilino)ethanol (13j) (10 mmol). The mixture was kept for 1 h at ambient temperature, refluxed for 6 h, and evaporated to dryness at reduced pressure. The residue was triturated with dil. aqu. ammonia until neutral, and taken up in ether. Conventional work-up furnished the crude chloride (15j) which was refluxed with a solution of KSCN (25 mmol) in acetonitrile (20 ml) for 50 h with continuous stirring. The mixture was evaporated to dryness and triturated with water and ether. The ethereal solution was dried ($MgSO_4$) and evaporated to dryness. Work-up of the residue by chromatography (Kieselgel 60; benzene - methanol, 4:1) gave the crude thiocyanate (4j) which was further purified by recrystallization.

The thiocyanates (4d) and (4e) were similarly obtained except that, for the preparation of compound (4d), benzene was used as the solvent in the first and ethanol in the second step. For yields, m.p.'s, and analytical data, see Table 2.

Method C: A mixture of the bromoethyl derivative (16f) (5.5 g, 20 mmol), KSCN (3 g, 30 mmol), and EtOH (50 ml) was refluxed for 8 h with continuous stirring and poured into water (200 ml) to obtain the crystalline product (4f).

The i.r. spectra of all thiocyanates (4a-o) exhibited the expected bands at ca. 2150 (νSCN), 1510, and 1350/cm (νNO$_2$).

3-(2-Aminophenyl)-2-iminothiazolidine salts (6)

Method A [by ring closure of N-(2-thiocyanatoethyl)-o-phenylenediamines with hydrogen chloride]: N-(2-Thiocyanatoethyl)-o-nitranilines (4) (10 mmol) were dissolved, depending on their solubilities, in dioxane (30-60 ml), methanol (50-150 ml), or CH_2Cl_2 - methanol, 1:1 (100-250 ml) and catalytically reduced (10% Pd-C) at room temperature and normal pressure. The catalyst was filtered off and the filtrates were saturated with dry HCl gas at 0°C, and evaporated to dryness at reduced pressure to give,

Table 2: N-(2-Thiocyanatoethyl)-o-nitranilines (4)

	Method[a]	Yield %	M.p., °C (from)	Mol.formula (Mol. wt.)	Calc/found C%	H%	Cl%	N%	S%
4a	A	85	112-3 (EtOH)	$C_9H_9N_3O_2S$ (223.3)	48.42 48.52	4.06 4.13		18.82 18.80	14.36 14.56
4b	A	97	154-5 (i-PrOH)	$C_9H_8ClN_3O_2S$ (257.7)	41.94 42.13	3.12 3.07	13.77 13.94	16.30 16.59	12.44 12.65
4c	A	96[b]	134-5 (i-PrOH)	$C_9H_8BrN_3O_2S$ (302.2)			[c]	13.91 13.82	10.61 10.63
4d	B	38[d]	115[e]	$C_9H_8IN_3O_2S$ (394.1)	30.96 30.83	2.31 2.03	[f]	12.03 11.90	
4e	B	10[g]	110 (aqu. EtOH)	$C_9H_8FN_3O_2S$ (241.2)				17.42 17.10	13.29 13.80
4f	C	89	116-8 (EtOH)	$C_{10}H_{11}N_3O_3S$ (253.3)	47.41 47.51	4.38 4.10		16.60 16.75	12.67 12.62
4g	A	85	115-7 (MeOH)	$C_{10}H_8F_3N_3O_2S$ (291.3)				14.42 14.38	11.01 11.46
4h	A	79	102-3 (MeOH)	$C_{11}H_{11}N_3O_4S$ (281.3)	46.97 46.72	3.94 4.24		14.94 14.92	11.40 11.36
4i	A	91	123-5 (CH_2Cl_2-Et_2O)	$C_{10}H_{11}N_3O_2S$ (237.3)	50.62 50.42	4.67 4.67		17.71 17.57	13.51 13.33
4j	B	21[h]	70 (aqu. MeOH)	$C_9H_8ClN_3O_2S$ (257.7)	41.94 42.30	3.13 3.40		16.41 16.60	
4k	A	92	115-6 (EtOH)	$C_9H_8ClN_3O_2S$ (257.7)			13.77 14.09	16.30 16.32	12.44 12.79
4l	A	80	92-4 (EtOH)	$C_9H_8ClN_3O_2S$ (257.7)			13.77 13.88	16.30 16.51	12.44 12.87
4m[i]	A	72	69-70 (MeOH)	$C_{10}H_{10}ClN_3O_2S$ (271.8)			13.06 12.96	15.46 15.61	11.80 11.73
4n[i]	A	84	126-8 (MeOH)	$C_{11}H_{12}ClN_3O_2S$ (285.8)			12.42 12.10	14.70 14.53	11.22 11.25
4o[j]	A	80[k]	124-5 (MeOH)	$C_{11}H_{12}ClN_3O_2S$ (285.8)			12.42 12.30	14.70 14.61	11.22 11.32

[a] Method A: from the methanesulphonates (14); Method B: from the chlorides (15); Method C: from the bromide (16f)

[b] Overall yield of the two-step sequence 13c → 14c → 4c

[c] Br, calc 26.45, found 26.19%

Continued on following page

in most cases, oily products which crystallized when triturated with small amounts of the appropriate solvents (EtOH, acetone, or EtOAc). For the yields, m.p.'s, and analytical data, see Table 3.

Method B [by ring closure of N-(2-thiocyanatoethyl)-o-phenylenediamines with ethanesulphonic acid]: N-(2-thiocyanatoethyl)-o- nitranilines (4) (10 mmol) were catalytically reduced (10% Pd-C) in CH_2Cl_2 (400 ml) or MeOH-CH_2Cl_2, 1:1 - 2:1 solutions (80-100 ml) at normal pressure and ambient temperature. The catalyst was filtered off and the filtrates were cooled to 0°C. $EtSO_3H$ (2-3 mol-equivalents) or ethereal solutions of $EtSO_3H$ were added. The mixtures were stirred for ca. 15 min at 0°C and evaporated to dryness at reduced pressure to give the desired products in most cases directly in crystalline form. In those cases where oily products were initially formed crystallization was induced by trituration with small amounts of acetone. For the yields, m.p.'s, and analytical data see Table 3.

Method C [by reduction of 2-imino-3-(2-nitrophenyl)thiazolidine salts (5)]:

(a) A mixture of compound (5b') [prepared from its hydrochloride (5b) as described for the related base (5a'), see below] (2.6 g, 10 mmol), $SnCl_2 \cdot 2\ H_2O$ (11.3 g, 50 mmol), and ethanol (120 ml) was stirred at 70°C under nitrogen or argon until, as indicated by the colour change of the mixture, the starting (5b') was used up (about 1/2 h). The mixture was poured into water (200 ml), the ethanol distilled off at reduced pressure, and the aqueous solution made slightly alkaline (pH 9) by adding 10% aqueous NaOH. The resulting product, (6d), was isolated by extraction with chloroform (3x50 ml) in the conventional manner and dissolved in methanolic hydrogen chloride. The resulting dihydrochloride (6b) was precipitated by adding ether to the solution, and proved identical (i.r., m.p.) with a sample obtained according to Method B.

(b) Similar treatment of compound (5c') (see below; 1.45 g, 5 mmol) in propan-1-ol gave the free base of the salt (6k) as a light yellow oil (0.73 g). Addition of ethanesulphonic acid (0.55 g, 5 mmol) to an ethanolic

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Footnotes to Table 2, continued

[d] Overall yield of the two-step sequence 13d → 15d → 4d

[e] Non-recrystallized material, purified by chromatography (Kieselgel 60; benzene - methanol, 1:1)

[f] I, calc 36.34; found 36.10%

[g] Overall yield of the two-step sequence 13e → 15e → 4e

[h] Overall yield of the two-step sequence 13j → 15j → 4j

[i] Racemic compound [j] (R) enantiomer

[k] $[\alpha]_{20}^{D}$ -249.4 (c=2, $CHCl_3$)

Table 3. 3-(2-Aminophenyl)-2-iminothiazolidine salts (6)

	Starting compound	Method	Yield, %	M.p., °C (from)	Mol. formula (Mol. wt.)	Calc/Found C%	H%	Cl%	N%	S%
6a	4a	A	81	178-9 (MeOH-Et_2O)	$C_9H_{13}Cl_2N_3S$ (266.2)			26.63 26.50	15.78 15.65	12.04 12.44
6b[a]	4b	A	76	185-6 (dec) (MeOH-Et_2O)	$C_9H_{12}Cl_3N_3S$ (300.6)			35.38 25.26	13.97 14.03	10.66 11.02
	5b	C	40	-"-						
6c	4b	B	78	162-4 (MeOH-Et_2O)	$C_{13}H_{22}ClN_3O_6S_3$ (449.0)			7.90 8.22	9.35 9.14	21.42 21.20
6d[b]	6b	c	88	108-10 (EtOH)						
6e	4c	B	57	207 (EtOH-Et_2O)	$C_{13}H_{22}BrN_3O_6S_3$ (492.4)				8.53 8.60	19.53 19.62
6f	4d	B	63	164 (EtOH-Et_2O)	$C_{13}H_{22}IN_3O_6S_3$ (539.4)	28.94 28.91	4.11 4.00	d	7.70 7.56	
6g	4e	B	36	135 (EtOH-Et_2O)	$C_{13}H_{22}FN_3O_6S_3$ (431.5)				9.73 9.79	22.29 22.87
6h	4f	A	61	198-200 (dec) (EtOH-Et_2O)	$C_{10}H_{15}Cl_2N_3OS$ (296.2)			23.94 24.38	14.18 14.10	10.83 11.04
6i	4f	B	70	187 (EtOH)	$C_{14}H_{25}N_3O_7S_3$ (443.6)				9.47 9.49	21.69 22.02
6j	4g	A	87	171-2 (dec) (MeOH-Et_2O)	$C_{10}H_{12}Cl_2F_3N_3S$ (334.2)			21.22 20.78	12.57 12.63	9.59 9.40
6k	4g	B	50	180-1 (MeCN)	$C_{14}H_{22}F_3N_3O_6S_3$ (481.6)				8.73 9.02	19.98 19.87
	5c	C	50	-"-						
6l	4h	A	74	163-4 (dec) (MeOH-Et_2O)	$C_{11}H_{15}Cl_2N_3O_2S$ (324.2)			21.87 21.91	12.96 12.77	9.89 10.24

Table 3, continued

	Starting compound	Method	Yield, %	M.p., °C (from)	Mol. formula (Mol. wt.)	Calc/Found C%	H%	Cl%	N%	S%
6m	4i	A	68	178 (MeOH-EtOAc)	$C_{10}H_{15}Cl_2N_3S$ (280.2)	42.86 42.52	5.40 5.77	25.30 24.78	15.00 14.90	11.44 11.21
6n	4j	B	55	160 (EtOH-Et_2O)	$C_{11}H_{16}ClN_3O_3S_2$ (337.5)			10.49 10.41	12.42 12.40	18.98 19.16
6o	4k	A	67	184-5 (dec) (MeOH-Et_2O)	$C_9H_{12}Cl_3N_3S$ (300.6)			35.38 35.31	13.97 13.75	10.66 10.82
6p	4l	B	63	168-70 (MeOH-Et_2O)	$C_{11}H_{18}N_3O_3S_2$ (339.0)			10.47 10.12	12.42 12.40	18.98 19.11
6q	4m	A	67	172-4 (dec) (MeOH-acetone)	$C_{10}H_{14}Cl_3N_3S$ (314.7)	38.17 38.52	4.48 4.19		13.35 13.53	10.19 9.71
6r	4m	B	35	141-3 (MeOH-Et_2O)	$C_{14}H_{24}ClN_3O_6S_3$ (462.0)	36.39 36.28	5.23 5.36	7.67 7.86		20.82 20.80
6s	4n	A	63	123-5 (dec) (MeOH-Et_2O)	$C_{11}H_{16}Cl_3N_3S$ (328.7)	40.19 39.94	4.90 4.71		12.78 13.03	9.76 10.13
6t	4n	B	65	169-71 (MeOH-Et_2O)	$C_{13}H_{22}ClN_3O_3S_2$			9.64 9.42	11.41 10.96	17.42 17.87
6u[e]	4o	B	41	160-1 (EtOH-Et_2O)	-"-			9.64 9.86	11.41 11.38	17.42 18.07

For the footnotes, see following page

(10 ml) solution of the base caused immediate precipitation of the crystalline salt (6k) (1.2 g, 50%), m.p. 180-181°C (from MeCN) which proved identical (m.p., mixed m.p., i.r.) with a sample obtained according to Method B.

All salts (6) prepared were colourless crystalline compounds.

2-Imino-3-(2-nitrophenyl)thiazolidines (5a'-5c') and their hydrochlorides (5a-c)

(a) Dry HCl gas was introduced into a refluxing ethanolic (50 ml) solution of compound (4a) (4.0 g, 18 mmol) for 30 min. The solution was allowed to cool and the crystalline product (3.9 g, 83%) filtered off. Recrystallization from ethanol-ether gave the yellow crystals of compound (5a), m.p. 286°C (dec.). Found Cl, 13.54; N, 16.23; S, 12.04. $C_9H_{10}ClN_3O_2S$ (259.8) requires Cl, 13.66; N, 16.17; S, 12.34%.

The free base (5a') was obtained in 90% yield by treating an aqueous (30 ml) solution of the hydrochloride (5a) (1.3 g, 5 mmol) with 40% aqueous NaOH (pH 9) and recrystallization from EtOAc - light petroleum. Yellow crystals, m.p. 127°C.

(b) A mixture of 2-aminothiazoline[12] (0.8 g, 8 mmol), o-fluoronitrobenzene (0.56 g, 4 mmol), and anhydrous DMSO (10 ml) was stirred for 3 h at 80°C, and poured into water (50 ml). The product, compound (5a') (0.4 g, 46%), was isolated by extraction with CH_2Cl_2 (3x20 ml) in a conventional manner and purified by recrystallization from EtOAc - light petroleum; it proved identical with the sample obtained as described in (a).

(c) Dry HCl gas was introduced into a refluxing suspension of 4-chloro-2-nitro-N-(2-thiocyanatoethyl)aniline (4b) (5.15 g, 20 mmol) for 1 h. The mixture remained heterogeneous throughout but its colour changed gradually from orange to light yellow. The mixture was allowed to cool and the

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Footnotes to Table 3

[a] δ_H (DMSO-d_6) 3.82t (2H; SCH_2), 4.30t (2H; NCH_2), 7.02-7.37 ppm, m (3H; ArH's). δ_C (DMSO-d_6) 29.4 (SCH_2), 58.1 (NCH_2), 120.3s,[f] 122.2d,[f] 122.5d,[f] 130.3s,[f] 138.3s,[f] and 143.0d[f] (aromatic C's), 174.8 (isothiourea carbon)

[b] Free base

[c] An aqueous solution (40 ml) of compound (6b) (1.5 g, 5 mmol) was made slightly alkaline (pH 8-9) by adding 40% aqueous NaOH. The free base, an oil which gradually crystallized, was isolated by extraction with CH_2Cl_2

[d] I, calc 23.52; found 24.07%

[e] $[\alpha]_{20}^{D}$ -3.7 (c=1, MeOH)

[f] Multiplicities in the off-resonance spectrum

resulting compound (5b) (5.5 g, 93%) filtered off, washed with ether, and recrystallized from EtOH. M.p. 295-6°C (dec). Found Cl, 24.08; N, 13.88; S, 10.61. $C_9H_9Cl_2N_3O_2S$ (295.0) requires Cl, 24.04; N, 14.24; S, 10.87%

(d) Similar treatment of 2-nitro-N-(2-thiocyanatoethyl)-4-trifluoromethylaniline (4g) (5 g, 17 mmol) gave the light yellow crystals of compound (5c) (4.5 g, 81%), m.p. 295°C (dec; from EtOH). Found Cl, 10.98; N, 12.78; S, 9.57. $C_{10}H_9ClF_3N_3O_2S$ (327.8) requires Cl, 10.83; N, 12.82; S, 9.78%.

(e) Treatment of 2-aminothiazoline[12] with 1-fluoro-2-nitro-4-trifluoromethylbenzene,[13] essentially as described in (b) for the preparation of compound (5a'), gave compound (5c') (35%; m.p. 153°C). Treatment of the free base with methanolic hydrogen chloride gave compound (5c) which proved identical (m.p., i.r., t.l.c.) with a sample obtained according to (d).

Catalytic reduction of compound (5b')

Compound (5b') (1.3 g, 5 mmol) was dissolved in a mixture of methanol (150 ml) and saturated ethanolic hydrogen chloride (18 ml), and reduced (H_2/10% Pd-C) to give, after conventional work-up, the colourless crystals (1.7 g, 65%) of 7-chloro-1,2-dihydro-5H-thiazolo[2,3-c][1,2,4]benzotriazinium chloride (8), m.p. 226-8°C (from MeOH). Found C, 41.33; H, 3.45; N, 15.74; S, 12.67. $C_9H_9Cl_2N_3S$ (262.2) requires C, 41.22; H, 3.46; N, 16.03; S, 12.23%.

7-Chloro-2,3-dihydrothiazolo[3,2-a]benzimidazole (18) and its hydrochloride

(i) A mixture of compound (6b) (1 g, 3.3 mmol) and ethanol (30 ml) was refluxed for 2 h and allowed to cool to give compound (18)·HCl (0.7 g, 85%) as a colourless crystalline powder, m.p. 144°C (from EtOH). Found C, 44.00; H, 3.12; Cl, 29.05; S, 13.15. $C_9H_8Cl_2N_2S$ (247.2) requires C, 43.72; H, 3.26; Cl, 28.68; S, 13.15%. m/z 210 $(M-HCl)^{+\cdot}$, 164 $(M-HCl-SCH_2)^{+\cdot}$.

(ii) An aqueous solution (5 ml) of the salt (18)·HCl (2 g) was treated with 5% aqueous NaOH (5 ml) and the resulting free base (18) isolated by extraction with CH_2Cl_2; colourless crystalline powder, 1.5 g (89%), m.p. 109-111°C.

(iii) A mixture of compound (6d) (0.9 g, 4 mmol) and 96% acetic acid (15 ml) was refluxed for 2 h and evaporated to dryness. The residue was dissolved in CH_2Cl_2 (30 ml), the solution washed with 5% aqueous $NaHCO_3$ and water, dried, and evaporated to dryness to give an oil which was crystallized from a small amount of ethanol. The product (0.4 g, 48%) proved identical (m.p., i.r., t.l.c.) with the sample obtained according to (ii).

(iv) (a) A methanolic (30 ml) solution of compound (13b)[9] (5.4 g, 25 mmol) was warmed to 60°C and added dropwise to an aqueous (100 ml) solution of $Na_2S_2O_4$ (17.5 g, 100 mmol) preheated to 60°C. The mixture was stirred for an additional 5 min at this temperature and made slightly alkaline (pH 8) by adding 40% aqueous NaOH. When the mixture was allowed to cool, the colourless crystals (4.2 g, 93%) of 2-(2-amino-4-chloroanilino)-ethanol, m.p. 123-5°C (from benzene) were deposited. Found C, 51.43; H, 5.82; Cl, 18.69; N, 14.97. $C_8H_{11}ClN_2O$ (186.6) requires C, 51.48; H, 5.94; Cl, 19.00; N, 15.01%.

(b) A mixture of the above product (1.8 g, 10 mmol), CS_2 (2 ml, 46 mmol), and ethanol (10 ml) was refluxed for 3 h and evaporated to dryness to give 5-chloro-1-(2-hydroxyethyl)benzimidazoline-2-thione (17) (1.2 g, 54%) as a colourless crystalline powder, m.p. 147-8°C (from water). Found N, 11.85; S, 13.98. $C_9H_9ClN_2OS$ (228.5) requires N, 12.25; S, 14.00%.

(c) A solution of diethyl azodicarboxylate (3 g, 16 mmol) in THF (10 ml) was added at ambient temperature with continuous stirring dropwise to a mixture of compound (17) (2.5 g, 11 mmol) Ph_3P (4.3 g, 16 mmol), and THF (40 ml). The mixture was stirred for 60 h at ambient temperature and evaporated to dryness to give a brown oil which gradually crystallized. This was worked up by t.l.c. (Kieselgel $PF_{254+366}$; cyclohexane - EtOAc, 2:3) to give compound (18) (0.6 g, 21%; R_f 0.3) which proved identical (m.p., i.r., t.l.c.) with the sample obtained according to (ii).

(v) An ethanolic (30 ml) solution of compound (20, Nu=OH) (see below) (1 g, 3.8 mmol) was refluxed for 2 h and allowed to cool. The resulting colourless crystals (0.8 g, 93%) of compound (18)·HCl proved identical (m.p., i.r.) with the sample obtained according to (i).

7-Chloro-9a-hydroxy-2,3,9,9a-tetrahydrothiazolo[3,2-a]benzimidazolium chloride (20, Nu=OH)

A solution of compound (6b) (1 g, 3.3 mmol) in 96% acetic acid (20 ml) was refluxed for 1/2 h and allowed to cool to give the colourless crystals (0.6 g, 68%) of the title compound which were filtered off and washed with ether; m.p. 230°C (from EtOH-Et_2O). Found C, 40.98; H, 4.01; Cl, 27.23; N, 10.39; S, 11.70. $C_9H_{10}Cl_2N_2OS$ (265.2) requires C, 40.76; H, 3.80; Cl, 26.74; N, 10.56; S, 12.09%. ν_{max} (KBr) 3420 (OH), 2500 cm^{-1} (N^+H_2).

2-Amino-5-chloro-1-(2-mercaptoethyl)benzimidazole (22) and its hydrochloride

(i) An anhydrous ethanolic (20 ml) solution of compound (6d) (1.1 g, 5 mmol), was refluxed for 18 h and evaporated to dryness to give a gradually crystallizing oil. Recrystallization from ethanol furnished the title

compound (0.6 *g*, 53%) as a colourless crystalline powder, m.p. 248-9°C. Found Cl, 15.46; N, 18.23; S, 14.31. $C_9H_{10}ClN_3S$ (227.7) requires Cl, 15.57; N, 18.45; S, 14.08. ν_{max} (KBr) 3430 (NH), 1650 cm^{-1} (C=N). m/z 227 ($M^{+\cdot}$), 180 $[(M-CH_2SH)^+]$, 167 $[(M-CH_2CH_2S)^{+\cdot}]$.

(ii) An identical (m.p., i.r.) product (0.4 *g*, 35%) was obtained when compound (6d) (1.1 *g*, 5 mmol) was stirred for 2 h at 80°C with benzylamine (2 ml) and the mixture worked up as described in (i).

(iii) A mixture of compound (24b) (see below) (1.1 *g*, 4.2 mmol) and 20% aqueous HCl (20 ml) was refluxed for 18 h (during which period a clear solution was gradually formed), treated with Norite, and allowed to cool. The resulting crystals were filtered off and washed with dioxan and ether to obtain the monohydrate of compound (22)·HCl (0.8 *g*, 67%) as a colurless crystalline powder, m.p. 124°C (methanol-ether). Found C, 38.33; H, 4.81; Cl, 24.83; N, 14.94; S, 10.97. $C_9H_{13}Cl_2N_3OS$ (282.5) requires C, 38.30; H, 4.64; Cl, 25.12; N, 14.89; S, 11.36%. δ_H (DMSO-d_6) 2.88q (2H; SCH_2), 3.12t (SH), 4.31t (2H; NCH_2), 7.2-7.6m (3H; ArH's). m/z 227 $[(M-HCl-H_2O)^{+\cdot}]$, 210 $[(M-HCl-H_2O-NH_3)^{+\cdot}]$, 167 $[(M-HCl-H_2O-CH_2CH_2S)^{+\cdot}]$.

(iv) The free base was liberated from this product by treating an aqueous (40 ml) solution of the salt (2.8 *g*, 10 mmol) with 10% aqueous NaOH until slightly alkaline (pH 9), neutralizing with acetic acid, and extracting the base with $CHCl_3$ (3x15 ml). The semicrystalline crude product was recrystallized from ethanol to give the pure base (1.7 *g*, 75%) which proved identical [m.p. (248-9°C), i.r.] with a sample obtained as described in (i).

5-Aryl-8-chloro-1,2,5,6-tetrahydrothiazolo[3,2-a][1,3,5]benzotriazepines (23a, b)

(i) A mixture of compound (6d) (1.1 *g*, 5 mmol), freshly distilled benzaldehyde (0.6 ml, 5.5 mmol), anhydrous ethanol (30 ml) and acetic acid (2.5 ml) was refluxed for 8 h. Concentration of the mixture to *ca.* 1/4 of its original volume afforded the 5-phenyl derivative (23a) (0.65 *g*, 41%) as a colourless crystalline powder which was filtered off, washed with ether and recrystallized from ethanol; m.p. 180-2°C. Found C, 60.60; H, 4.50; Cl, 10.73; N, 13.52; S, 10.23. $C_{16}H_{14}ClN_3S$ (315.8) requires C, 60.85; H, 4.47; Cl, 11.22; N, 13.30; S, 10.13%. ν_{max} (KBr) 3150 (NH), 1620 cm^{-1} (C=N). δ_H (DMSO-d_6) 2.5t (2H; SCH_2), 3.15t (2H; NCH_2), 6.0s (1H, CHPh), 7.0-7.7m (8H; ArH's). m/z 315 ($M^{+\cdot}$), 314 $[(M-H)^+]$, 254 $[(M-CH_2CH_2SH)^{+\cdot}]$, 210 $[(M-CH_2CH_2-Ph)^+]$.

(ii) A mixture of compound (6d) (1.1 *g*, 5 mmol), anhydrous ethanol (30 ml), 4-methoxybenzaldehyde (3 ml), and boron trifluoride diethyletherate (0.2 ml) was refluxed for 6 h and evaporated to dryness. The crystal-

line residue was recrystallized from EtOH to obtain the 5-(4-methoxyphenyl) derivative (23b) (0.8 g, 46%) as a light yellow crystalline powder, m.p. 141-2°C. Found C, 58.88; H, 4.96; Cl, 10.38; N, 11.88; S, 9.42. $C_{17}H_{16}ClN_3OS$ (345.8) requires C, 59.03; H, 4.66; Cl, 10.25; N, 12.15; S, 9.25%. ν_{max} (KBr) 3190 (NH), 1620 cm^{-1} (C=N).

5-Amino-8-chloro-1,2-dihydrothiazolo[3,2-a][1,3,5]benzotriazepinium bromide (24a)

A mixture of compound (6d) (1.1 g, 5 mmol), cyanogen bromide (0.72 g, 6.8 mmol), and anhydrous ethanol (30 ml) was refluxed for 1/2 h and evaporated to dryness. The resulting oil crystallized gradually; recrystallization from EtOH-Et_2O gave the title compound as a colourless crystalline powder, m.p. 282-3°C. Found C, 36.21; H, 3.25; N, 17.23. $C_{10}H_{10}BrClN_4S$ (333.7) requires C, 35.99; H, 3.02; N, 16.79%. ν_{max} (KBr) 3080 (νN^+H_3), 1650 cm^{-1} (δN^+H_3).

8-Chloro-1,2-dihydrothiazolo[3,2-a][1,3,5]benzotriazepine (24b)

A mixture of compound (6d) (1.1 g, 5 mmol), triethyl orthoformate (5 ml), and acetic acid (40 ml) was refluxed for 3 h and concentrated to ca. 1/4 of its original volume. The resulting crystals were filtered off and washed with ether to obtain the title compound (0.65 g, 55%) as a colourless crystalline powder, m.p. 298-9°C (from DMF). Found C, 50.40; H, 3.27; Cl, 14.53; N, 17.47; S, 13.51. $C_{10}H_8ClN_3S$ (237.6) requires C, 50.53; H, 3.39; Cl, 14.92; N, 17.68; S, 13.46%.

ν_{max} (KBr) 1620 cm^{-1} (C=N). m/z 237 ($M^{+\cdot}$), 236 $[(M-H)^+]$, 210 $[(M - CH=CH_2)^+]$, 209 $[(M - CH_2CH_2)^{+\cdot}]$.

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