CONDENSED 1,3,5-TRIAZEPINES – IV*
THE SYNTHESIS OF 2,3-DIHYDRO-1*H*-IMIDAZO-[1,2-a] [1,3,5] BENZOTRIAZEPINES

By

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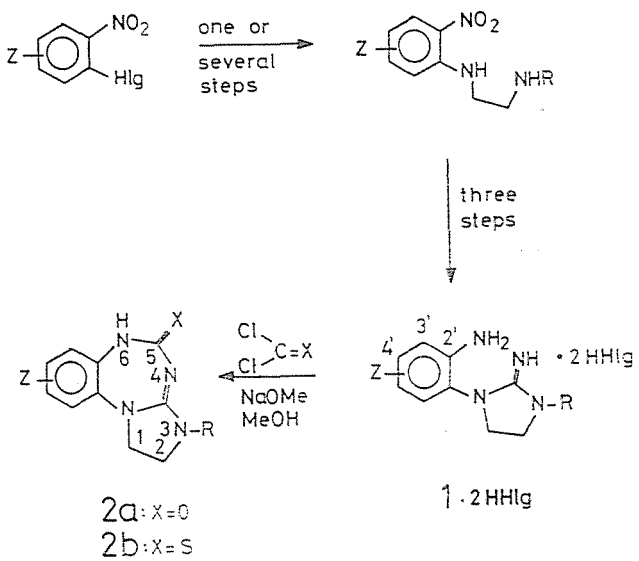
In Parts I [2] and II [3] of the present series the synthesis of 2,3-dihydro--1*H*-imidazo [1,2-*a*][1,3,5]benzotriazepin-5(6*H*)-ones (**2a**) and -thiones (**2b**) based on the ring closure with phosgen and thiophosgen (or their equivalents), respectively, of the appropriate 1-(2-aminophenyl)-2-iminoimidazolidines **1** has been described. The compounds **1**, themselves, were obtained in form of their dihydrobromides or dihydrochlorides starting with *o*-halonitrobenzenes as shown in Scheme 1; as a consequence, this method permitted only the synthesis of type **2** compounds carrying no substituents at N-6.

Here we wish to report on an alternative approach to the type **1** intermediates (Scheme 2), as well as on the synthesis of some compounds (**7**—**9**)



Scheme 1

* For Part III, see Ref. [1]

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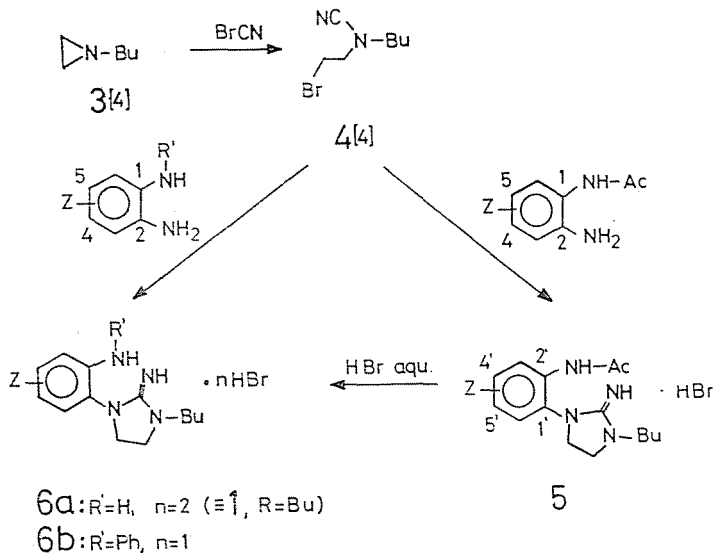
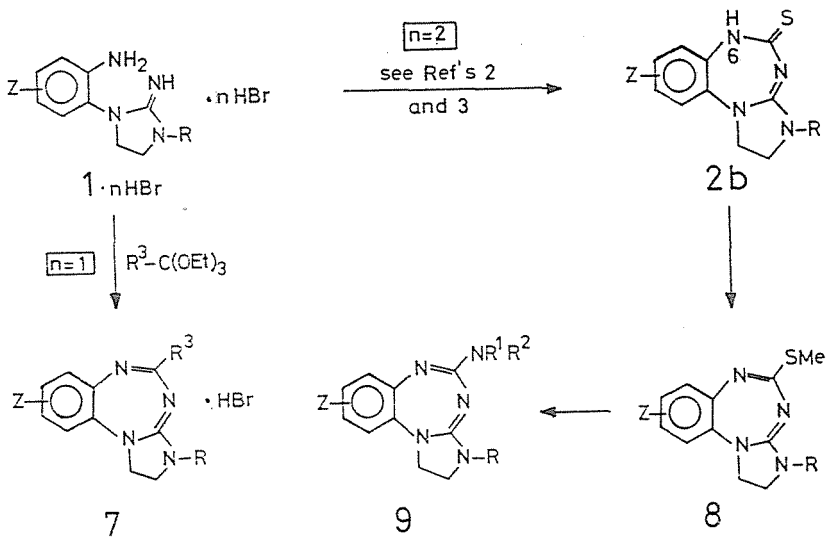


Scheme 2



Scheme 3

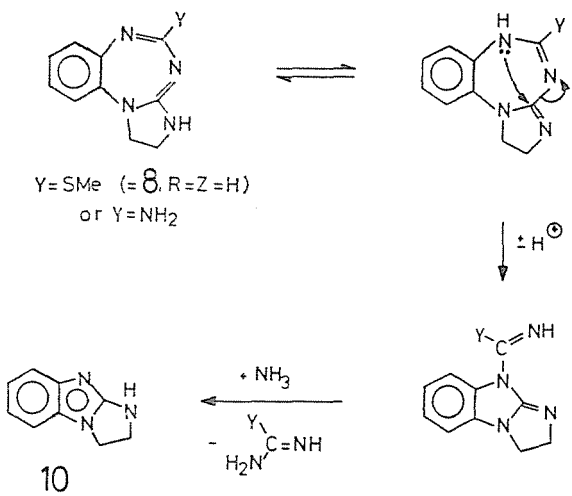
belonging to the class of the hitherto unknown 2,3-dihydro-1*H*-imidazo[1,2-*a*]-[1,3,5]benzotriazepines either by direct ring closure of the type **1** compounds or by modification of the thiourea moiety of type **2b** compounds (Scheme 3.)

Reaction of 1-butylaziridine (**3**) [4] with cyanogen bromide furnished *N*-butyl-*N*-cyano-(2-bromoethyl)amine (**4**) [4] which was condensed with

N-acetyl-*o*-phenylenediamines to furnish the 1-(2-acetylaminophenyl)-2-iminoimidazolidines in form of their monohydrobromides **5**. By acid catalyzed hydrolysis of the latter the deacetylated products **6a** (≡**1**, R=Bu) were obtained. Compound **4** can be condensed with the parent, *i.e.* non-acetylated *o*-phenylenediamines as well to yield the compounds **6a** directly, as demonstrated for the case Z=H. ((No attempt was made to isolate compound **6a**, Z=H, in pure form; the crude product was directly condensed with carbon disulfide to furnish compound **2b**, R=Bu, Z=H). This approach is clearly more general than that described previously [2, 3] because, in addition to the synthesis of the salts of 1-(2-aminophenyl)-2-iminoimidazolidines (**1**, **6a**), it permits the synthesis of their 1-(2-subst. aminophenyl) analogues as well, as demonstrated by the synthesis of the 1-(2-anilinophenyl) derivative **6b** (Z=4'-Cl, n=1).

Condensation of the type **1** compounds with thiophosgen (or its equivalents) [2, 3] and ortho esters furnished the desired type **2b** and **7** compounds, respectively. If the primary amino group of **1** carries a substituent (as in **6b**) the reaction with thiophosgen (or its equivalents) should furnish 2,3-dihydro-1*H*-imidazo[1,2-*a*][1,3,5]benzotriazepine-5(6*H*)-thiones **2b** substituted in position 6; this possibility has not been exploited yet.

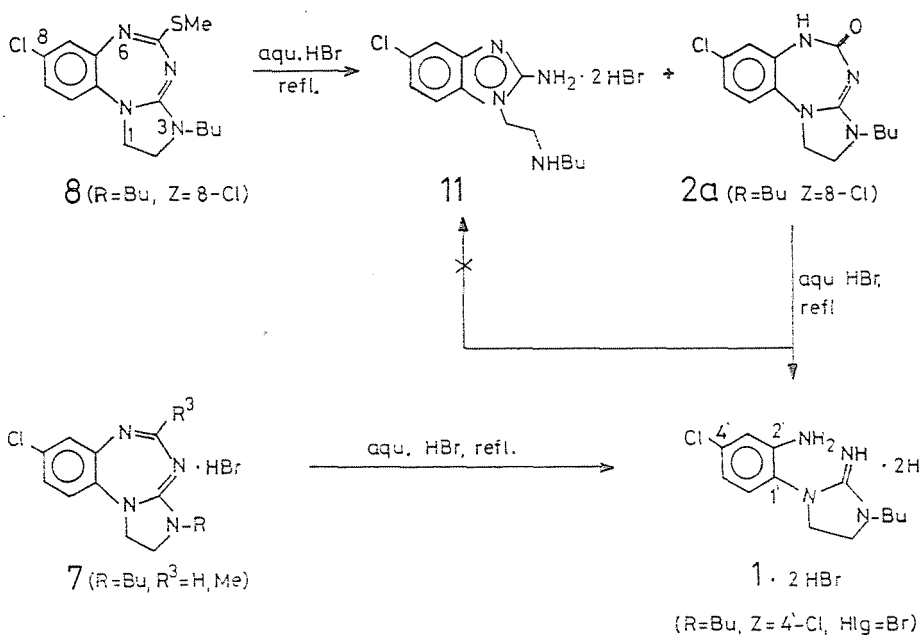
S-Methylation of the compounds **2b** furnished the corresponding compounds **8** which were aminolyzed with primary and secondary amines to obtain the amino derivatives **9**. Attempted ammonolysis of compound **8** (R=H=Z) under drastic conditions furnished the ring contracted product **10**. Formation of the latter probably takes place as shown in Scheme 4. Whether ammonolysis



Scheme 4

of the methylthio group precedes all other steps of the reaction sequence (Y=NH_2, throughout) or takes place in a later step is not known.

A different type of ring contraction with concomitant cleavage of the original five-membered ring took place when compound **8** (R=Bu, Z=8-Cl) was subjected to acid catalyzed hydrolysis, the main reaction product (65%) being the benzimidazole derivative **11**; the normal hydrolysis product **2a** (R=Bu, Z=8-Cl) was obtained as a co-product in 20% yield. Similar hydrolysis of compound **8** (R=Z=H) furnished the ring transformation product **11** (with the butyl group and Cl replaced by hydrogen) in 82% yield; the normal hydrolysis product **2a** (R=Z=H) was not isolated. Compound **2a** (R=Bu, Z=8-Cl), when separately subjected to hydrolysis with aqueous hydrogen bromide, furnished the known [3] dihydrobromide **1** (R=Bu, Z=4'-Cl, Hlg=Br) without ring contraction, *i.e.* **2a** (R=Bu, Z=8-Cl) is not an intermediate of the reaction **8** (R=Bu, Z=8-Cl) → **11**. (Scheme 5). The



Scheme 5

same product was obtained also from compounds **7** (R=Bu; R^3=H, Me) when subjected to hydrolysis with aqueous hydrogen bromide.

The novel compounds **7**—**9** as well as their type **1** intermediates and the corresponding 1-(2-nitrophenyl)-2-iminoimidazolidines [2, 3] were screened for CNS activities by Dr. L. Petőcz. The results will be published elsewhere.

Experimental

1-(2-Acetylaminophenyl)-3-butyl-2-iminoimidazolidine hydrobromides (**5**). *General procedure*

Mixtures of the *N*-acetyl-*o*-phenylenediamines and *N*-butyl-*N*-cyano-2--bromoethylamine (4 [4], 10 mmole, each) were heated for 0.5 h at 110 °C whereby the initially homogeneous melts gradually solidified. The resulting solids were ground by trituration with acetone, filtered off, washed with acetone and recrystallized from ethanol-ether to obtain the following products:

5 (Z=H), 92%, m.p.: 204 °C; found $Br^{\ominus}$, 22.79, N, 15.65; $C_{15}H_{23}BrN_4O$ (355.3) requires $Br^{\ominus}$, 22.49, N, 15.76%;

5 (Z=4'-Cl), 83%, m.p.: 237—238 °C, lit. [3] m.p.: 237—238 °C, identical (m.m.p., i.r.) with an authentic sample [3];

5 (Z=5'-MeO), 58%, m.p.; 243—244 °C; found $Br^{\ominus}$, 21.03, N, 14.58; $C_{16}H_{25}BrN_4O_2$ (385.3) requires $Br^{\ominus}$, 20.74, N, 14.54%.

5 (Z=5'-Cl) was similarly obtained; this product was deacetylated and subsequently cyclized without purification to obtain compound **2b** (R=Bu, Z=9-Cl), see below.

Deacetylation

The compounds **5** (Z=H and Z=4'-Cl; 10 mmol) were refluxed for 3 h with the mixture of ethanol (30 ml) and 48% aqueous hydrogen bromide (7 ml). The resulting solutions were evaporated to dryness *in vacuo* and the residues were recrystallized from methanol-ether to obtain the dihydrobromides **6a** (Z=H, 87%, m.p.: 291—292 °C) and **6a** (Z=4'-Cl, 92%, m.p.; 263—265 °C), respectively, identical (m.p., m.m.p., i.r.) with authentic samples [3].

Deacetylation of crude **5** (Z=5'-Cl) was carried out similarly and the crude deacetylation product was subsequently cyclized to obtain compound **2b** (R=Bu, Z=9-Cl), see Ref. [2].

1-(2-Anilino-4-chloro)-3-butyl-2-iminoimidazoline hydrobromide (**6b**, Z=4'-Cl, n=1).

The thoroughly ground mixture of 2-amino-5-chlorodiphenylamine [6] (2.2 g; 10 mmol) and compound 4 [4] (2.05 g; 10 mmol) was heated for 45 min in an oil-bath (bath temperature 110 °C). After about 30 min the initially clear melt started to turn crystalline. The mixture was allowed to cool and worked up as described above for the preparation of the compounds **5** to obtain 3.15 g (77%) of the title compound, colourless crystalline powder, m.p.: 224—225 °C (dec.; from ethanol-ether). Found C, 52.85, H, 5.85, N, 13.82. $C_{18}H_{24}BrClN_4$ (407.5) requires C, 53.05, H, 5.88, N, 13.74%.

*3-Butyl-2,3-dihydro-1*H*-imidazo[1,2-a][1,3,5]benzotriazepine-5(6*H*)-thione*) **2b**, R=Bu, Z=H).

The mixture of compound 4 [4] (2.05 g; 10 mmole) and *o*-phenylenediamine (1.08 g; 10 mmol) was heated for 0.5 h at 110 °C and allowed to cool. The resulting solid (compound **6a**, Z=H, n=1) was taken up in methanol (20 ml) in which metallic sodium (0.30 g; 13 mmol) had been dissolved. Carbon disulfide (2 ml) was added and the suspension was refluxed for 6 h. The residue, obtained on evaporation of the solvent *in vacuo* was triturated with dilute aqueous hydrogen chloride to obtain 0.92 g (34%) of the title compound, m.p.: 186 °C (from EtOH), identical (m.p., m.m.p., i.r.)with an authentic sample [3].

*2,3-Dihydro-1*H*-imidazo[1,2-a][1,3,5]benzotriazepine hydrobromides* (**7**)

(a) The monohydrobromides (10 mmol) of the appropriate 2-imino-1-(2-nitrophenyl)imidazolidines were catalytically reduced under the conditions described earlier [3] but without the addition of hydrogen bromide; the catalyst was filtered off and the filtrates were evaporated to dryness *in vacuo* to obtain the monohydrobromides of the corresponding 1-(2-aminophenyl) derivatives, **1** · HBr (R=Z=H; R=Bu, Z=4'-Cl; R=Bu, Z=4'-BuNHCO—) which, without purification, were allowed to react with ortho esters as described under (b)—(d).

(b) The crude compounds **1** · HBr (R=Z=H; R=Bu, Z=4'-Cl) were refluxed for 10 min with mixtures of triethyl formate (4 ml) and nitromethane (20 ml). The resulting mixtures were concentrated to about half of their original volumes to obtain, after chilling, the following products:

7 (R=R^3=Z=H), 74%, m.p.; 236—238 °C (dec.; from ethanol-ether); found C, 44.65, H, 4.32, $Br^{\ominus}$, 29.89; $C_{10}H_{11}BrN_4$ (267.1) requires C, 44.96, H, 4.15, $Br^{\ominus}$, 29.92%; and

7 (R=Bu, R^3=H, Z=8-Cl), 96%, m.p.: 247 °C (dec.; from ethanol-ether); found $Br^{\ominus}$, 22.13, N, 15.46; $C_{14}H_{18}BrClN_4$ (358.4) requires $Br^{\ominus}$, 22.30; N, 15.63%.

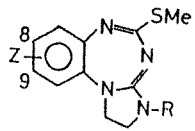
(c) The crude **1** · HBr (R=Bu, Z=4'-BuNHCO—) was refluxed for 2 h with the mixture of triethyl orthoformate (5.9 g; fourfold excess) and dry dioxane (15 ml) to obtain, after chilling, 51% of compound **7** (R=Bu, R^3=H, Z=8-BuNHCO—), colourless crystals, m.p.: 237—239 °C (dec.; from nitromethane); found C, 52.13; H, 7.14, N, 15.89; $C_{19}H_{28}BrN_5O \cdot H_2O$ (440.4) requires C, 51.82, H, 6.87, N, 15.90%.

(d) Replacing the orthoformate by triethyl orthoacetate but otherwise proceeding according to (b) and (c), respectively, the following compounds were obtained;

7 (R=Bu, R^3=Me, Z=8-Cl), 83%, m.p.: 232—235 °C (dec.; from ethanol-ether); found $Br^{\ominus}$, 21.62, N, 15.21; $C_{15}H_{20}BrClN_4$ (372.5) requires $Br^{\ominus}$, 21.46, N, 15.04%; and

7 (R=Bu, R^3=Me, Z=8-BuNHCO—), 54%, m.p.: 279—280 °C (dec.;

Table 1

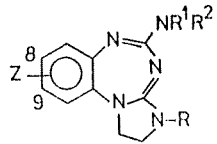


5-Methylthio-2,3-dihydro-1*H*-imidazo[1,2-*a*][1,3,5]benzotriazepines (**8**)

R	Z	Yield, %	M.p., °C Recryst. from	Formula Mol. wt.	Calc./Found			
					C, %	H, %	N, %	S, %
H	H	89[a] 77[b]	212 DMF	$C_{11}H_{12}N_4S$ 232.3	56.87 56.71	5.21 5.53		13.80 13.41
H	H[c]	86	276 MeOH — ether	$C_{11}H_{13}IN_4S$ 360.2			15.56 15.48	8.88 9.48
H	8-MeO	80	252 DMF	$C_{12}H_{14}N_4OS$ 262.3	54.94 54.64	5.38 5.24	21.36 21.33	12.23 12.29
H	8-MeOOC	92	226—227 DMF	$C_{13}H_{14}N_4O_2S$ 290.3			19.30 19.36	11.04 10.80
Bu	H	85	97 i-PrOH	$C_{15}H_{20}N_4S$ 288.4	62.46 62.30	6.99 7.05	19.43 19.13	11.12 11.08
Bu	8-Cl	86[a] 71[c]	113 EtOH—H_2O	$C_{15}H_{19}ClN_4S$ 322.9	55.79 55.73	5.93 5.92		9.93 9.54
Bu	8-Cl[c]	82	263—265 MeOH — ether	$C_{15}H_{20}ClIN_4S$ 450.8	39.96 40.21	4.47 4.50	12.43 12.89	
Bu	9-Cl	64	145 MeOH	$C_{15}H_{19}ClN_4S$ 322.9			17.35 17.10	9.93 10.32
Bu	8-BuNHCO—	86	168—170 aqu. MeOH	$C_{20}H_{29}N_5OS$ 387.6			18.08 18.25	8.27 7.96

[a] Yield of the conversion **8** · HI → **8** [b] Overall yield [c] Hydriodide

Table 2



5-(Subst. amino)-2,3-dihydro-1*H*-imidazo[1,2-*a*][1,3,5]benzotriazepines **9**

R	Z	—NR¹R²	Yield, %	M.p., °C Recryst. from	Formula Mol. wt.	Calc./Found		
						C, %	H, %	N, %
H	H	—NHBu	63	225—226 (dec.) DMF—H_2O	$C_{14}H_{19}N_5$ 257.3	65.34 65.06	7.44 7.63	27.22 26.90
H	H	morpholino	85	193 EtOH	$C_{14}H_{17}N_5O$ 271.3	61.98 61.90	6.32 6.11	25.81 25.55
H	8-MeO	morpholino	80	205—206 $MeNO_2$	$C_{15}H_{19}N_5O_2$ 301.3	59.78 59.53	6.36 6.29	23.34 23.14
Bu	H	morpholino	92	114—115 acetone — H_2O	$C_{18}H_{25}N_5O$ 327.4	66.03 65.89	7.70 7.43	21.39 21.35
Bu	8-Cl	—NHBu	60	115 light petrol.	$C_{18}H_{26}ClN_5$ 347.9	61.79 61.58	7.49 7.55	a
Bu	8-Cl	morpholino	89	161—162 acetone — H_2O	$C_{18}H_{24}ClN_5O$ 361.9	59.74 59.85	6.68 7.09	b
Bu	8-Cl	*N*-methyl-piperidino	45	114—115 light petrol.	$C_{19}H_{27}ClN_6$ 374.9	60.87 61.14	7.26 7.34	22.42 22.08
Bu	9-Cl	morpholino	83	145—146 EtOH	$C_{18}H_{24}ClN_5O$ 361.9	59.74 60.10	6.68 6.52	19.35 19.15
Bu	9-Cl	*N*-methyl-piperidino	54	85—87 light. petrol.	$C_{19}H_{27}ClN_6$ 374.9	60.87 60.58	7.26 6.93	22.42 22.14
Bu	BuNHCO—	morpholino	68	164—165 EtOH — H_2O	$C_{23}H_{31}N_6O_2$ 426.5	64.76 65.04	8.03 8.13	19.70 20.01
Bu	BuNHCO—	*N*-methyl-piperidino	68	180—182 CCl_4	$C_{24}H_{37}N_7O$ 439.6	65.57 65.78	8.48 8.53	22.30 22.04

[a] Cl, calc. 10.13, found 10.23%. [b] Cl, calc. 9.80, found 10.19%

from i-PrOH); found C, 55.04, H, 7.13, N, 16.33; $C_{20}H_{30}BrN_5O$ (436.4) requires C, 55.05, H, 6.93, N, 16.05%.

*5-Methylthio-2,3-dihydro-1*H-*imidazo[1,2-*a*][1,3,5]benzotriazepines* (**8**). *General procedure.*

Solutions or suspensions of the type **2b** thiones (10 mmol) in methanol (60—100 ml) were refluxed with methyl iodide (2 ml) for 8 h. The reaction mixtures were concentrated to about 30 ml and made slightly alkaline (pH 9) by the addition of 10% aqueous NaOH solution to obtain the title compounds listed in Table 1 as crystalline precipitates. Alternatively, the original reaction mixtures were treated with ether to precipitate the crystalline hydriodides which were recrystallized from methanol-ether. Treatment of the aqueous ethanolic solutions of the hydriodides with 1*N* NaOH furnished the bases **8**.

*5-(Subst. amino)-2,3-dihydro-1*H-*imidazo[1.2-*a*][1,3,5]benzotriazepines* (**9**)

The 5-methylthio compounds **8** (10 mmol) were refluxed with dry ethanol (15—20 parts) and the appropriate amine (100 mmol) until the evolution of methanethiol ceased (10—15 h). The mixtures were evaporated to dryness and the residues were triturated with water, filtered off and thoroughly washed with water. For the yields, physical and analytical data of the products, see Table 2.

*2,3-Dihydro-1*H-*imidazo[1,2-*a*]benzimidazole* (**10**)

Compound **8** (R=Z=H) (10 mmol) was heated with ethanol (100 ml) saturated at ambient temperature with ammonia, for 16 h at 170 °C. The resulting solution was evaporated to dryness *in vacuo*. The residue was worked up by preparative t.l.c. (Kieselgel, benzene–methanol, 2 : 1) to obtain 0.8 g (43%) of the title compound, m.p. 206—208 °C (from dioxane), lit. [5] m.p.: 204—206 °C (from dioxane) which proved identical (m.m.p., i.r.) with an authentic sample [5].

*Hydrolysis of the 5-methylthio-2,3-dihydro-1*H-*imidazo[1,2-*a*][1,3,5]benzotriazepines* **8** (R=Bu, Z=8-Cl) and **8** (R=Z=H)

(a) The mixture of compound **8** (R=Bu, Z=8-Cl) (800 mg; 2.5 mmol) in 20% aqueous ethanol (10 ml) and 48% aqueous hydrogen bromide (3 ml) was refluxed for 2.5 h and evaporated to dryness *in vacuo*. The dry residue was dissolved in water (30 ml) and the solution was made slightly alkaline (pH 9) by the addition of 1*N* NaOH to obtain a gummy product. The latter was thoroughly washed with water and crystallized from a small amount of ethanol to obtain 150 mg (20%) of compound **2a** (R=Bu, Z=4'-Cl), identical (m.p., m.m.p., i.r.) with an authentic sample [2].

The filtrate of this product was acidified with 48% aqueous hydrogen bromide (2 ml) and evaporated to dryness *in vacuo*. The residue was taken up in methanol (4 ml) and the insoluble inorganic salts were filtered off. The product, compound **11** (750 mg; 65%) was precipitated by the addition of ether and proved identical with an authentic sample [1].

(b) Similar treatment of compound **8** (R=Z=H) (210 mg; 0.9 mmol) furnished 2-amino-1-(2-aminoethyl)imidazolidine dihydrobromide (**11**, but the Bu group and Cl replaced by H; 251 mg, 82%), identical with an authentic sample [1]. No type **2a** product was isolated in this case.

*Hydrolysis of 3-butyl-8-chloro-2,3-dihydro-1*H*-imidazo[1,2-a][1,3,5]benzotriazepin-5(6*H*)-one* (**2a**, R=Bu, Z=8-Cl) *and of the 3-butyl-8-chloro-2,3-dihydro-1*H*-imidazo[1,2-a][1,3,5]-benzotriazepine hydrobromides* **7** (R=Bu, Z=9-Cl, R^3=H and Me)

(a) The mixture of compound **2a** (R=Bu, Z=8-Cl; 293 mg, 1 mmol), ethanol (1 ml) and 24% aqueous hydrogen bromide (4 ml) was refluxed for 8 h and evaporated to dryness to obtain 392 mg (92%) of compound **1** (R=Bu, Z=4'-Cl, Hlg=Br), identical (m.p., m.m.p., i.r.) with an authentic sample [3].

(b) The mixtures of the compounds **7** (R=Bu, Z=8-Cl, R^3=H and Me, respectively; 1 mmol), ethanol (1 ml) and 48% aqueous hydrogen bromide (1 ml) were refluxed for 1 h and evaporated to dryness to obtain 90% of compound **1** (R=Bu, Z=4'-Cl, Hlg=Br), identical (m.p., m.m.p., i.r.) with an authentic sample [3].

Acknowledgements

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Summary

A novel method is described for the synthesis of the key-intermediates **1** of derivatives (**2a**, **2b**, **7**—**9**) of the 2,3-dihydro-1*H*-imidazo[1,2-*a*] [1,3,5]benzotriazepine ring system. Reaction of the intermediates **1** with ortho esters furnishes the novel compounds **7**, while *S*-methylation of the previously described thiones **2b** and subsequent aminolysis furnishes the novel type **8** and **9** imidazobenzotriazepines, respectively. Some ring transformation reactions of the type **8** compounds are also described.

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