CONDENSED 1,3,5-TRIAZEPINES – V*
THE SYNTHESIS OF PYRAZOLO [1,5-a] [1,3,5]-BENZOTRIAZEPINES

By

B. Ágai,** Gy. Hornyák and K. Lempert

Department of Organic Chemistry, Technical University and
Research Group for Alkaloid Chemistry of the Hungarian Academy of Sciences,
H-1111, Gellért tér 4, Budapest, Hungary

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1,3,5-Benzotriazepines and their derivatives are members of a scarcely known class of compounds [1—7]. This is partly the result of the existence of alternative cyclization modes suppressing the desired ring closure to 1,3,5--benzotriazepines in reactions devised for the synthesis of the latter, see *e.g.* Chart 1 [8]. Moreover, ring contraction of the eventually formed 1,3,5-benzo-

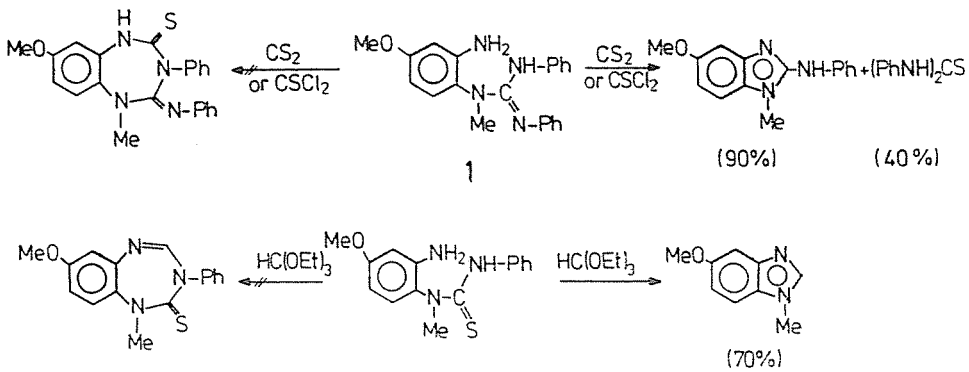
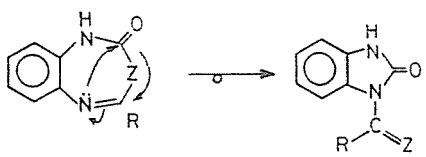


Chart 1 [8]

triazepine derivatives, *e.g.* **2** (Z=NH) to the corresponding benzimidazoles **3** (Z=NH) may be anticipated to take place easily;*** as a result, not all com-



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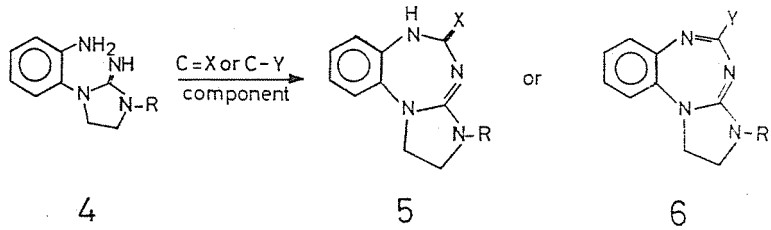
* For Part IV, see preceding paper

** Present address: Department of Organic Chemical Technology, Technical University, Budapest

*** Similar thermal ring contractions have been observed in the related 1,5-benzodiazepin-2(3*H*)-one (**2**, Z=CH_2) series [9, 10].

pounds described in literature as 1,3,5-benzotriazepine derivatives really belong into this class of compounds.

In earlier papers [11a, 11b] of the present series a method has been described for the synthesis of authentical condensed derivatives of the 1,3,5--benzotriazepine system (Chart 2). The basic idea of this method was the



4 5 6

Chart 2

incorporation of the guanidine moiety of type **1** compounds into an imidazole ring (**4**) whereby both the direct formation of the benzimidazole ring system and subsequent ring contraction of the once formed imidazobenzotriazepines (**5**, **6**) could be avoided.

Here we wish to report on the application of the same principle to the synthesis of derivatives of the hitherto unknown pyrazolo[1,5-*a*][1,3,5]benzotriazepine system. The method of synthesis of the 5-amino-1-(2-aminophenyl)--3-methylpyrazole hydrochlorides **12**, the key intermediates of the synthesis, their ring closures and some reactions of the products **13**, **16** and **17** are outlined in Chart 3.

The well-documented [12] general method for the synthesis of 5-aminopyrazoles was applied for the preparation of compounds **11a—d**. The intermediates **9** ⇌ **10** were shown by their ^1H n.m.r. spectra to exist in $CDCl_3$ solution in the hydrazone (**9**) rather than the ene-hydrazine form (**10**). Cyclization of the hydrazones **9** was accomplished with ethanolic hydrogen chloride. Treatment of the resulting hydrochlorides with aqueous sodium acetate furnished the free bases **11a—d**. When, in the **a** series, the sodium acetate was replaced by sodium or potassium hydroxide, the resulting **11a** was contaminated by the *N*-oxide **18**; at elevated temperatures the latter became the only product. For the related ring closure of 2-nitrophenylguanidine to 3-amino--1,2,4-benzotriazine-1-oxide, see Ref. [13]. Sodium dithionite reduction of compound **18** furnished compound **19**.

By catalytic reduction of the nitro compounds **11a—d** · HCl the diamino derivatives were obtained in form of their monohydrochlorides **12a—c**; in the **d** series the product was isolated as the *di*hydrochloride. Refluxing compounds **12a** and **b** with triethyl orthoformate furnished the pyrazolobenzo-

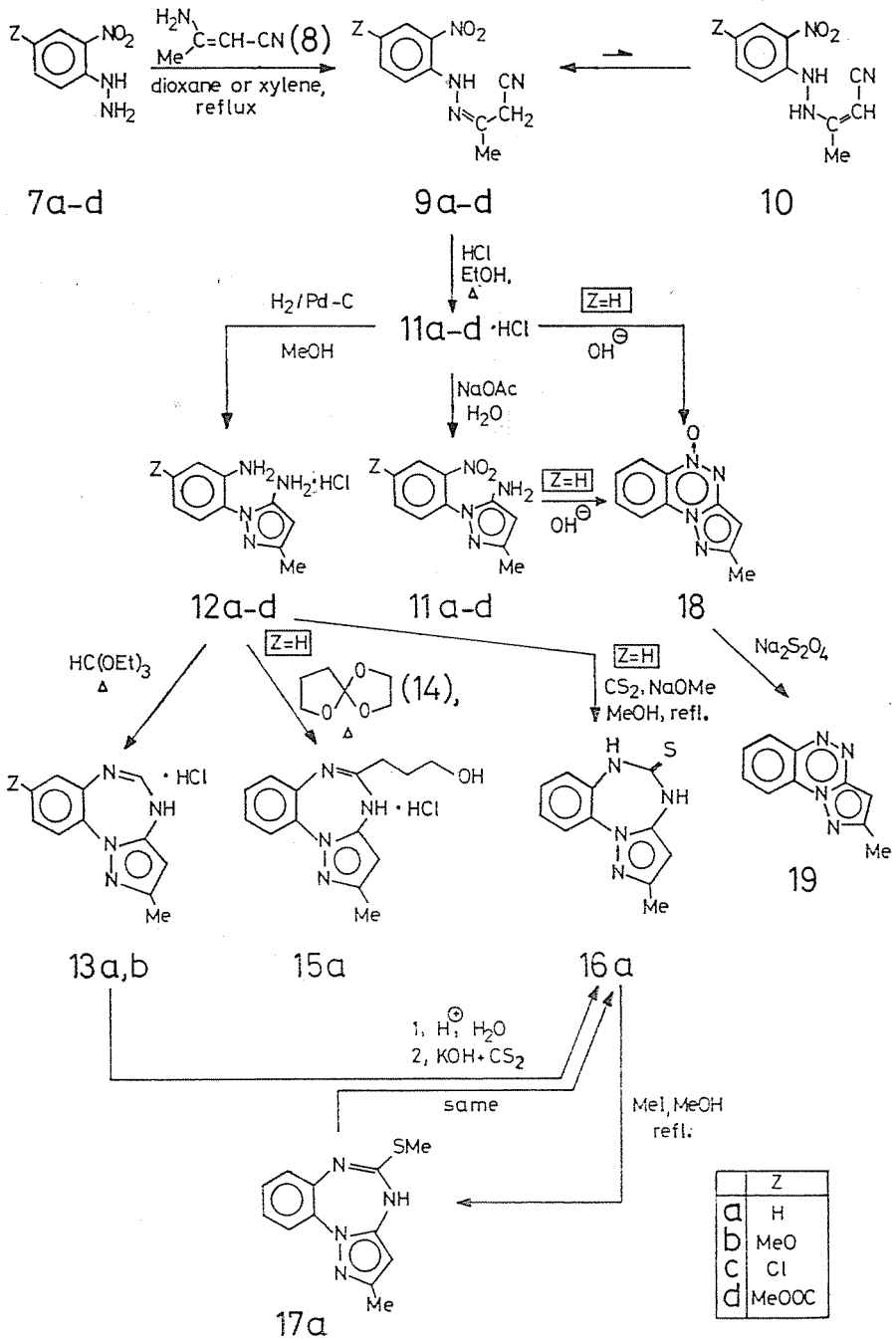
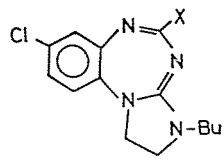

dioxane or xylene, reflux
7a-d
9a-d
10
HCl EtOH, Δ
H2/Pd-C
MeOH
11a-d ·HCl
Z=H
OH⊖
NaOAc H2O
12a-d
11a-d
18
HC(OEt)3 Δ
(14), Δ
CS2, NaOMe MeOH, refl.
Na2S2O4
19
13a,b
15a
16a
1, H⊕, H2O
2, KOH+CS2
same
MeI, MeOH refl.
17a
Z
a H
b MeO
c Cl
d MeOOC

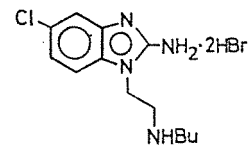
Chart 3

triazepines **13a** and **13b**, respectively, in high yield. Similarly obtained was compound **15a** by replacing the orthoformate by the spirocyclic orthoester **14** [14]. Ring closure of compound **12a** with carbon disulfide in the presence of methanolic sodium methoxide furnished the tricyclic thione **16a** which was subsequently methylated to obtain compound **17a**. The site of methylation was clearly shown by the evolution of methanethiol upon refluxing with dilute hydrochloric acid.

The 2,3-dihydro-1*H*-imidazo[1,2-*a*][1,3,5]benzotriazepine **20a** described in Part IV [15] of the present series, when subjected to acid catalyzed hydrolysis, suffered partial ring transformation to yield compound **21**; the related compound **20b** [15], in contrast, furnished the normal hydrolysis product **22**



20a: X=SMe
b: X=H



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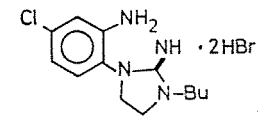

22

upon similar treatment. It was therefore of interest to compare the behaviour of the pyrazolobenzotriazepine analogues **13a** and **17a** under the conditions of acid catalyzed hydrolysis. In both cases the normal hydrolysis product **12a**, isolated after treatment with carbon disulfide in the presence of alkali in form of the cyclization product **16a**, was obtained. This of course reflects the enhanced stability of the aromatic pyrazole ring of **17a** as compared to the non-aromatic dihydroimidazole ring of **20a**.

The pyrazolo[1,5-*a*][1,3,5]benzotriazepine derivatives described in this paper were screened for CNS activatives by Dr. L. Petőcz; no useful activities were found.

Experimental

^{1}H n.m.r. spectra were obtained at 60 MHz in $CDCl_3$ solutions with a Perkin-Elmer R-12 spectrometer.

N-(2-Cyano-1-methylethylidene)-N'-(2-nitrophenyl)hydrazines (**9a—d**)

(a) Mixtures of the 2-nitrophenylhydrazines **7a—c** (0.1 mol), 3-aminocrotononitrile (**8**; 9.5 g, 116 mmol) and dioxane (40 ml) were refluxed for 2 h. Water (200 ml) was added to the warm solutions to obtain the title compounds **9a—c** on cooling as crystalline precipitates.

Compound **9a**: yield 85%, m.p.: 147 °C (from EtOH); found C, 55.25; H, 4.75; N, 25.77; calc. for $C_{10}H_{10}N_4O_2$ (218.2): C, 55.06; H, 4.62; N, 25.69%. ^{1}H n.m.r.: δ 2.10s (*C*-Me), 3.48s (CH_2), 6.75—8.35m (4H, ArH's).

Compound **9b**: yield 87%, m.p.: 136 °C (from toluene-gasoline); found C, 53.54; H, 5.08; N, 22.31; calc. for $C_{11}H_{12}N_4O_3$ (248.3): C, 53.22; H, 4.87; N, 22.57%. ^{1}H n.m.r.: δ 2.11s (*C*-Me), 3.50s (CH_2), 3.85s (MeO); 7.40dd + 7.65d (J = 3 Hz) + 7.80d (J = 9 Hz) (ArH's).

Compound **9c**: yield 95%, m.p.: 142 °C (from EtOH); found Cl, 14.21; N, 22.11; calc. for $C_{10}H_9ClN_4O_2$ (252.7): Cl, 14.03; N, 22.18%. ^{1}H n.m.r.: δ 2.14s (*C*-Me), 3.54s (CH_2), 7.55dd + 7.95d (J = 8.5 Hz) + 8.23d (J = 3 Hz) (ArH's).

(b) The mixture of compound **7d** (0.1 mol), **8** (9.5 g; 116 mmol) and xylene (80 ml) was refluxed for 2 h to obtain, on cooling, the crystals of compound **9d**, m.p.: 138 °C (from MeOH), in 57% yield.

Found C, 52.07; H, 4.38; N, 20.63; calc. for $C_{12}H_{12}N_4O_4$ (276.3): C, 52.17; H, 4.38; N, 20.28%. ^{1}H n.m.r.: δ 2.15s (*C*-Me), 3.50s (CH_2), 4.35 (COOMe), 7.62dd + 8.05d (J = 9 Hz) + 8.47d (J = 3 Hz) (ArH's).

5-Amino-3-methyl-1-(2-nitrophenyl)pyrazoles (**11a—d**) *and their hydrochlorides*

Dry hydrogen chloride was introduced into the refluxing ethanolic (150 ml) suspensions of compounds **9a—d** (0.1 mol) until they became saturated (10—15 min). The solvent was distilled off *in vacuo* and the residues were triturated with ether to obtain the crystalline hydrochlorides **11a—d** · HCl. The free bases were liberated from their salts (10 mmol) by stirring them for 10 min with 30% aqueous sodium acetate solution (20 ml); the orange coloured bases were thoroughly washed with water.

Compound **11a** · HCl: yield 94%, m.p.: 216 °C (from MeOH-ether); found C 47.01; H, 4.35; N, 21.65; calc. for $C_{10}H_{11}ClN_4O_2$ (254.7): C, 47.16; H, 4.35; N, 22.00%.

Compound **11a**: yield 82%, m.p.: 118 °C (from toluene); found C, 54.91 H, 4.61; N, 25.49; calc. for $C_{10}H_{10}N_4O_2$ (218.2): C, 55.06; H, 4.62; N, 25.69%. ^{1}H n.m.r.: δ 2.15s (Me), 3.63bs (NH_2), 5.45s (4-H), 7.3—8.1m (ArH's).

Compound **11b** · HCl: yield 87%, m.p.: 220 °C (from i-PrOH-ether); found Cl, 11.92; N, 19.56; calc. for $C_{11}H_{13}ClN_4O_3$ (284.7); Cl, 12.45; N, 19.68%.

Compound **11b**: m.p.: 128 °C (from aqueous MeOH); found C, 53.06; H, 4.80; N, 22.48; calc. for $C_{11}H_{12}N_4O_3$ (248.2): C, 53.22; H, 4.87; N, 22.57%. ^{1}H n.m.r.: δ 2.17s (Me), 3.67 bs (NH_2), 3.95s (MeO), 5.45s (4-H), 7.25dd + 7.50d (J = 2.5 Hz) + 7.60d (J = 7 Hz) (ArH's).

Compound **11c** · HCl: yield 92%, m.p.: 211 °C (from EtOH-ether); found C, 41.64; H, 3.74; Cl, 24.16; N, 19.33; calc. for $C_{10}H_{10}Cl_2N_4O_2$ (289.1): C, 41.54; H, 3.57; Cl, 24.53; N, 19.38%.

Compound **11c**: m.p.: 152 °C (from toluene); found Cl, 14.01; N, 22.26;

calc. for $C_{10}H_9ClN_4O_2$ (257.7): Cl, 14.33; N, 22.18%. ^1H n.m.r.: δ 2.19s (Me), 3.63bs (NH_2), 5.53s (4-H), 7.7m (2) + 8.0m (1) (ArH's).

Compound **11d**:* yield 57%, m.p.: 147 °C (from MeOH); found C, 52.49; H, 4.43; N, 20.31; calc. for $C_{12}H_{12}N_4O_4$ (276.3): C, 52.17; H, 4.38; N, 20.28%. ^1H n.m.r.: δ 2.18s (Me), 3.60bs (NH_2), 4.00 s (COOMe), 5.52s (4-H), 7.85d (J = 7.5 Hz) + 8.43dd + 8.65d (J = 2.5 Hz) (ArH's).

Pyrazolo[5,1-c][1,2,4]benzotriazine-5-oxide (**18**)

(a) The mixture of compound **11a** · HCl (2.54 g; 10 mmol), ethanol (20 ml) and 40% aqueous potassium hydroxide solution (2 ml) was refluxed for 2 h. The mixture was allowed to cool to obtain 1.85 g (93%) of the title compound, yellow crystals, m.p.: 176 °C (from MeOH).

Found C, 60.24; H, 4.15; N, 27.55; calc. for $C_{10}H_8N_4O$ (200.2): C, 59.99; H, 4.03; N, 27.98%. IR (KBr): *no* NH bands.

(b) The mixture of compound **11a** (1.09 g; 5 mmol), methanol (20 ml) and 25% aqueous potassium hydroxide solution (4 ml) was refluxed for 30 min to obtain 0.89 g (89%) of the title compound, identical by m.p., m.m.p. and i.r. with the product obtained according to (a).

Pyrazolo[5,1-c][1,2,4]benzotriazine (**19**)

$Na_2S_2O_4$ (5.7 g; 40 mmol) was added within 10 min to the aqueous (50 ml) suspension of compound **18** (2.0 g; 10 mmol) at 70—80 °C with continuous stirring. A clear colourless solution was obtained which was made alkaline by adding 10% aqueous sodium hydroxide solution to obtain 1.68 g (93%) of the title compound, m.p.: 140 °C (from MeOH or gasoline).

Found C, 65.30; H, 4.47; N, 30.05; calc. for $C_{10}H_8N_4$ (184.2): C, 65.20; H, 4.38; N, 30.42%.

5-Amino-1-(2-aminophenyl)-3-methylpyrazole hydrochlorides (**12a—d**)

Methanolic (300 ml) solutions of the hydrochlorides **11a—d** · HCl (0.1 mol) were reduced in the presence of Pd/C catalysts at normal pressure and ambient temperatures. The catalyst was filtered off, the filtrates were evaporated to dryness and the residues were recrystallized to obtain the following compounds:

12a, 80% yield m.p.: 175 °C (from MeOH-ether); found Cl, 15.94; N, 25.08; calc for $C_{10}H_{13}ClN_4$ (224.5): Cl, 15.78; N, 24.94%.

12b, 84% yield, m.p.: 182 °C (from MeOH-ether); found Cl, 14.08; N, 21.87; calc. for $C_{11}H_{15}ClN_4O$ (254.7): Cl, 13.92; N, 22.00%;

12c, 92% yield, m.p.: 187 °C (from MeOH-ether); found Cl, 27.43; N, 21.81; calc. for $C_{10}H_{12}Cl_2N_4$ (259.1): Cl, 27.36; N, 21.62%;

12d, dihydrochloride,** 62% yield, m.p.: 193 °C (from MeOH-ether); found Cl, 22.37; N, 17.05; calc. for $C_{12}H_{16}Cl_2N_4O_2$ (319.2): Cl, 22.22; N, 17.55%.

* The crude hydrochloride was, without purification, converted into the free base.

** Obtained by adding cc aqueous hydrogen chloride (10 ml) to the filtrate obtained after removing the catalyst.

*2-Methyl-4*H*(6*H*)-pyrazolo[1,5-a]]1,3,5]benzotriazepine hydrochlorides* (**13a, b**)

Compounds **12a** and **12b** (20 mmol) were refluxed for 10 min with triethyl orthoformate (40 ml) to obtain the title compounds as yellow crystalline products (95%) which were washed with acetone and ether, respectively, and recrystallized from MeOH-ether.

Compound **13a**: m.p.: 255 °C (dec.); found C, 56.45; H, 4.68; Cl, 15.06; N, 23.78; calc. for $C_{11}H_{11}ClN_4$ (234.6); C, 56.32; H, 4.73; Cl, 15.12; N, 23.89%.

Compound **13b**: m.p.: 243 (dec.); found Cl, 13.26; N, 21.17; calc. for $C_{12}H_{13}ClN_4O$ (265.7); Cl, 13.35; N, 21.09%.

*5-(3-Hydroxypropyl)-2-methyl-4*H*(6*H*)-pyrazolo[1,5-a][1,3,5]benzotriazepine hydrochloride* (**15a**)

The mixture of compound **12a** (2.25 g; 10 mmol), 1,4,6-trioxaspiro[4,4]-nonane (**14** [14]; 2.0 g, 15 mmol) and dry dioxane (10 ml) was refluxed for 10 min. The initial suspension turned first into a clear solution from which the product soon started to precipitate. The mixture was allowed to cool, the crystalline product was filtered off and washed with dioxane and ether to obtain 2.1 g (73%) of the title compound, m.p.: 200 °C (from EtOH); found Cl, 12.03; N, 19.29; calc. for $C_{14}H_{17}ClN_4O$ (292.8): Cl, 12.11; N, 19.14%.

*2-Methyl-4*H*-pyrazolo[1,5-a][1,3,5]benzotriazepine-5(6*H*)-thione* (**16a**)

The mixture of compound **12a** (4.5 g; 20 mmol), carbon disulfide (10 ml), sodium methoxide (1.1 g; 20 mmol) and methanol (30 ml) was refluxed for 6 h. The solvent was distilled off *in vacuo* and the residue was triturated with water to obtain 3.4 g (74%) of the title compound, m.p.: 282 °C (from 1-butanol), which was washed with water until free of chloride ions.

Found N, 24.26; S, 13.78; calc. for $C_{11}H_{10}N_4S$ (230.3); N, 24.33; S, 13.92%.

*2-Methyl-5-methylthio-4*H*(6*H*)-pyrazolo[1,5-a][1,3,5]benzotriazepine* (**17a**)

The mixture of compound **16a** (2.3 g; 10 mmol), methyl iodide (2 ml) and methanol (10 ml) was refluxed for 30 min whereby the initial suspension turned into a clear solution which was allowed to cool and treated with 10% aqueous sodium hydroxide solution to obtain 2.0 g (83%) of the title compound m.p.; 201 °C (from toluene); m.m.p. with the starting substance: 184 °C; found N, 22.81; S, 12.96; calc. for $C_{12}H_{12}N_4S$ (244.3): N, 22.93; S, 13.13% which was washed with water until neutral.

Acid catatyzed hydrolysis of compounds **13a** *and* **17a**

Compounds **13a** and **17a** (10 mmol) were refluxed with 20% hydrochloric acid (20 ml) for 2 h. The resulting mixtures were evaporated to dryness *in vacuo* and this operation was repeated once more after taking up the dry residues in water (20 ml). The residues were dissolved in methanol or ethanol (30 ml); carbon disulfide (2 ml) and potassium hydroxide (1.4 g) were added, and the mixtures were refluxed for 6 h and subsequently evaporated to dryness

in vacuo. The residues were triturated with water (20 ml) and the resulting suspensions were slightly acidified (pH 5) with 5% aqueous hydrogen chloride to obtain 1.85 g (85%) of compound **16a**, identical (m.p., m.m.p., i.r., t.l.c.) with an authentic sample.

Acknowledgements

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Summary

The method developed earlier in these laboratories for the synthesis of 2,3-dihydro-1*H*-imidazo[1,2-*a*][1,3,5]benzotriazepines has been extended to the synthesis of derivatives of the novel pyrazolo[1,5-*a*][1,3,5]benzotriazepine ring system. No useful central nervous system activities were exhibited by these compounds.

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Béla ÁGAI
Dr. Gyula HORNYÁK
Prof. Dr. Károly LEMPERT
H-1521 Budapest