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SYNTHESIS AND X-RAY ANALYSIS OF NEW 1,5-BENZO-DIAZEPINIUM PICRATES

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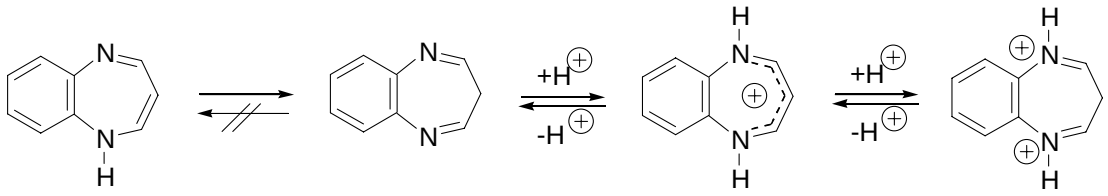
Abstract – 1,2-Diaminobenzenes react with pentane-2,4-dione in ethanol in the presence of picric acid to give 1,5-benzodiazepinium picrates. In the single crystal, the benzodiazepinium molecules form layers with overlapped 7-membered rings in head-to-tail arrangement. Hydrogen bonds to the picrate connect the 1,5-benzodiazepinium molecules of two layers.

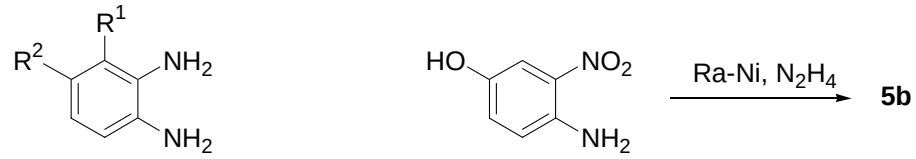
1,5-Benzodiazepines continue to be an interesting class of compounds both from a chemical and a biological point of view. Whereas nonprotonated 1,5-benzodiazepines form a diimine (**2**) to avoid an annular conjugation of 4n π-electrons around the diazepine (8 π-electrons) or benzodiazepine ring (12 π-electrons) as in **1**, protonation results in the formation of intensively colored salts (**3**) which possess a stabilizing vinamidinium chromophor. This chromophor causes stabilisation energies of the order of 20 $Kcalmol^{-1}$.[1] In stronger acids the colorless diprotonated species (**4**) are produced.[1] Depending on the substitution pattern 1,5-benzodiazepines display interesting physiological effects.[2]



1 **2** **3** **4**

Scheme 1

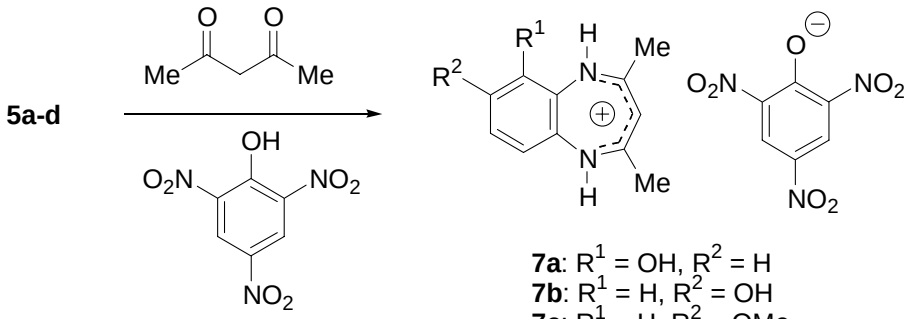
In continuation of our work on ionic heterocycles[3] and mesomeric betaines[4] we became interested in 1,5-benzodiazepinium salts. We describe here the syntheses of new compounds and the interesting results of an X-Ray structure analysis. We chose 2,3-diaminophenol (**5a**), 3,4-diaminophenol (**5b**), 4-methoxy-1,2-diaminobenzene dihydrochloride (**5c**), and 3,4-diaminobenzoic acid (**5d**) as starting materials. The new diamine (**5b**) was prepared by reduction of the readily available 4-amino-3-nitrophenol (**6**) with Raney-nickel in the presence of 98% hydrazine hydrate in quantitative yield (Scheme 2).



5a: R^1 = OH, R^2 = H
5b: R^1 = H, R^2 = OH
5c: R^1 = H, R^2 = OMe
5d: R^1 = H, R^2 = COOH

Scheme 2

Reaction of the 1,2-diaminobenzenes (**5a-d**) with pentane-2,4-dione in ethanol in the presence of picric acid gave the 1,5-benzodiazepinium picrates (**7a-d**) as intensely violet crystals. The presence of picric acid proved to be advantageous in comparison with other acids because the resulting salts readily precipitate from the reaction mixture and are analytically pure after washing with diethyl ether (Scheme 3). Not unexpected, the products are protonated due to the strong acidity of picric acid (pK_a 0.25).



7a: R^1 = OH, R^2 = H
7b: R^1 = H, R^2 = OH
7c: R^1 = H, R^2 = OMe
7d: R^1 = H, R^2 = COOH

Scheme 3

Single crystals of 1,5-diazepinium picrate (**7a**) suitable for an X-Ray analysis were obtained by slow evaporation from a concentrated solution in acetone.[5] The compound crystallizes triclinic with one molecule of acetone of crystallisation (Figure 1).

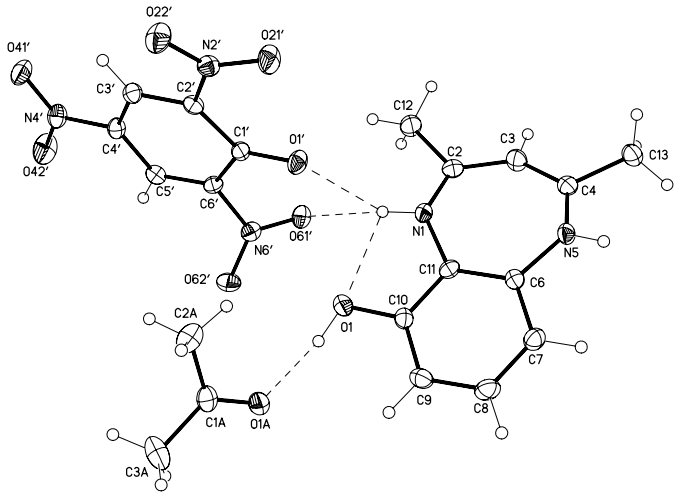


Figure 1: ORTEP plot of **7a**.

The dihedral angles C(3)-C(4)-N(5)-C(6) = 13(2)° and C(11)-N(1)-C(2)-C(3) = –10.3(2)° confirm the slightly helical structure of the diazepinium moiety which was also found in 2,3-dihydro-1,4-diazepines[8] and mixed crystals consisting of 2,4-dimethylbenzodiazepinium and benzene-1,2-diammonium cations and chloride anions.[9] 2,4-Dimethylbenzodiazepinium chloride[10] and hexafluorophosphate[11] as well as the hydrochloride of 2,4-dimethylnaphthodiazepine[12] are planar. As expected, the bond distances in the vinamidinium chromophor N(1)-C(2)-C(3)-C(4)-N(5) are in agreement with the extensive delocalisation of 6 π-electrons,[13] but they are slightly longer than reported in other systems mentioned above.[9-12] By contrast, the bond lengths N(1)-C(11) and N(5)-C(6) are 142.48(18) pm and 142.38(18) pm, respectively, and thus separate the benzene moiety from the 7-membered ring. Thus, the molecule avoids a conjugation of 4n π-electrons around the periphery of the rings by isolation of the two parts of the molecule. The bond angles in the 7-membered ring are larger than the 120° expected for sp^2-hybridized carbon atoms. Some selected bond lengths and dihedral angles of **7a** are given in Table 1.

Table 1. Atom Nos. / Selected bond lengths [pm], bond angles [°], and torsion angles [°] of **7a.**

N(1)-C(2)	133.07(18)	C(2)-N(1)-C(11)	129.86(13)	C(11)-N(1)-C(2)-C(3)	-10.3(2)
C(2)-C(3)	138.5(2)	N(1)-C(2)-C(3)	126.42(14)	C(11)-N(1)-C(2)-C(12)	170.71(13)
C(3)-C(4)	138.8(2)	C(2)-C(3)-C(4)	129.37(14)	N(1)-C(2)-C(3)-C(4)	-13.6(3)
C(4)-N(5)	132.58(18)	C(3)-C(4)-N(5)	127.10(13)	C(2)-C(3)-C(4)-N(5)	11.6(3)
C(2)-C(12)	149.8(2)	C(4)-N(5)-C(6)	130.07(12)	C(3)-C(4)-N(5)-C(6)	13.0(2)
C(4)-C(13)	150.0(2)	N(5)-C(6)-C(11)	125.10(13)	C(4)-C(5)-C(6)-C(11)	-19.7(2)
C(10)-O(1)	135.38(17)	C(6)-C(11)-N(1)	126.26(13)	C(4)-N(5)-C(6)-C(7)	160.18(14)
C(10)-C(11)	139.7(2)	N(1)-C(11)-C(10)	114.87(13)	C(6)-C(7)-C(8)-C(9)	-0.1(2)
C(9)-C(10)	139.4(2)	O(1)-C(10)-C(11)	116.49(13)	C(8)-C(9)-C(10)-O(1)	-179.64(12)
C(6)-C(11)	139.46(19)	C(9)-C(10)-C(11)	121.16(13)	O(1)-C(10)-C(11)-N(1)	1.47(17)

Several hydrogen bonds are formed between the three molecules. One intramolecular hydrogen bond is detected between N(1)-H and the oxygen atom of the 6-hydroxy group (Figure 1). The hydrogen atom of this group forms a hydrogen bond to the carbonyl oxygen atom of the acetone molecule of crystallisation. The hydrogen bonds between the acidic N(1)-H group of the diazepinium moiety and the olate group of the picrate anion on one hand, and between N(1)-H and one of the oxygen atom of one of the *ortho*-nitro groups of the picrate on the other stabilize the layers of 1,5-benzodiazepines (Figure 2). The individual molecules are in the layers head-to-tail orientated in such a way, that the 7-membered rings are overlapped (Figure 3). The olate group and two oxygen atoms of the *ortho*-nitro groups of the picrate combine two stacked 1,5-benzodiazepine molecules by hydrogen bonds through N(1)-H and N(5)-H.

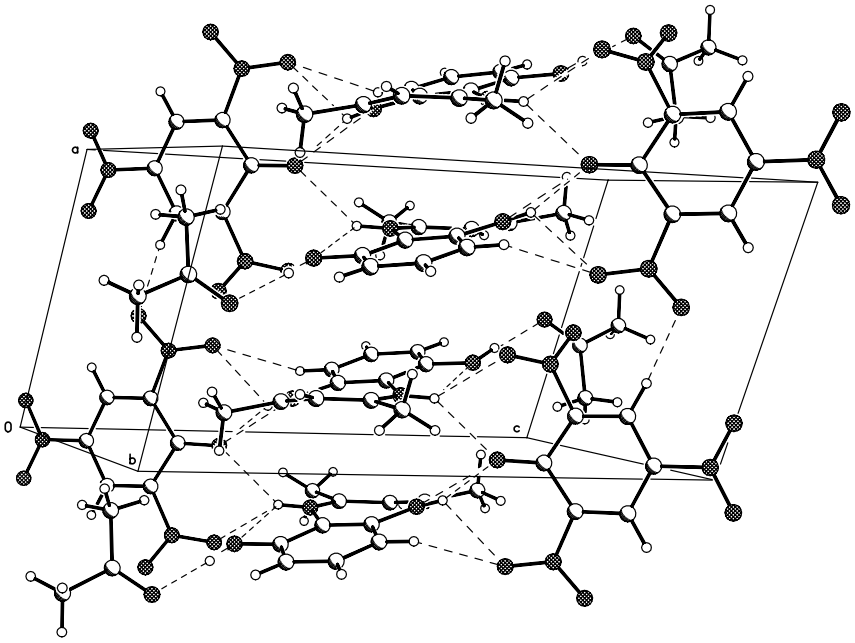


Figure 2.

Table 2. Hydrogen bonds of **7a**: Distances [pm] and angles [°].

D-H····A	d(D-H)	d(H····A)	d(D····A)	<(DHA)
N(1)-H(1N)····O(1´)	87.2(12)	224.2 (14)	296.71(16)	140.5(13)
N(1)-H(1N)····O(61´)	87.2(12)	243.9(14)	315.48(16)	139.7(12)
N(1)-H(1N)····O(1)	87.2(12)	217.4(16)	260.12(16)	109.7(13)
N(5)-H(5N)····O(1´)#1	86.1(13)	205.0(13)	287.73(15)	160.9(14)
N(5)-H(5N)····O(21´)#1	86.1(13)	253.4(15)	313.61(17)	127.7(13)
O(1)-H(10)····O(1A)	90.2(14)	180.2(14)	269.37(15)	169.7(17)

symmetry transformations used to generate equivalent atoms:
#1 -x+2, -y+1, -z+1

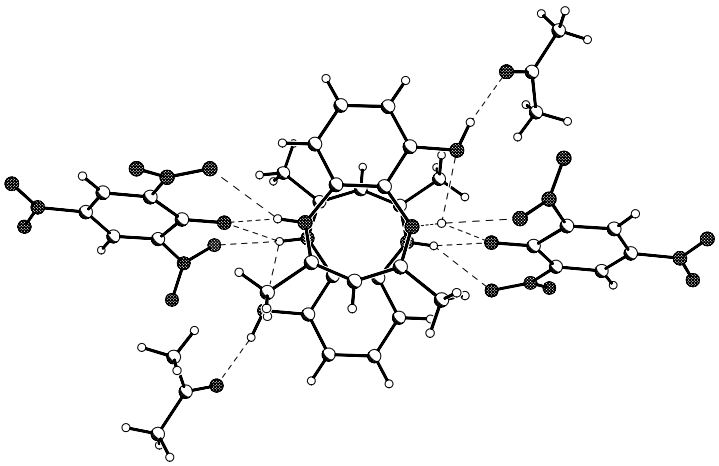


Figure 3

The distance between two molecules of 1,5-benzodiazepinium in two layers is 368 pm which is larger than the two-fold *van-der-Waals* radii of carbon [r_{vdW} = 165 –170 pm] and nitrogen [r_{vdW} = 155 pm], respectively (Figure 4).

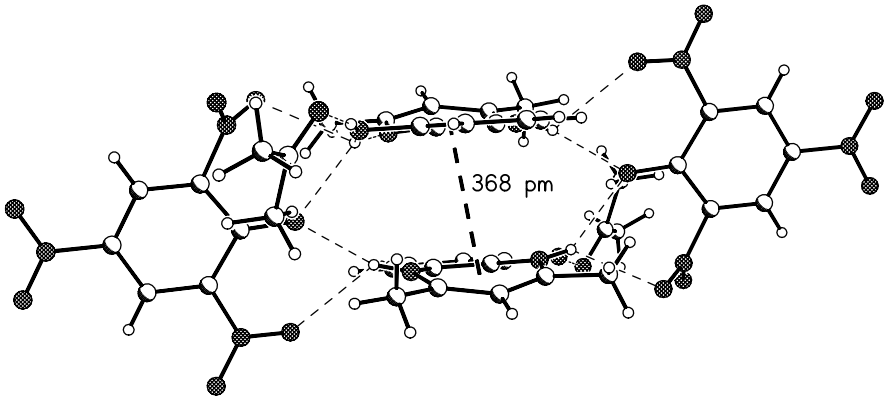


Figure 4

ACKNOWLEDGEMENTS

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EXPERIMENTAL

General methods: The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-400 and DPX-200 in DMSO-d_6 and $CDCl_3$ at 400 and 200 MHz, respectively. The chemical shifts are reported in ppm relative to internal tetramethylsilane (δ = 0.00 ppm). FT-IR spectra were obtained on a Bruker Vektor 22 in the range of 400 to 4000 cm^{-1} (2.5 % pellets in KBr). The GC-MS spectra were recorded on a GC Hewlett-Packard 5980, Serie II in combination with a MS Hewlett-Packard 5989 B and on a Varian GC3900 with SAT2100T mass spectrometer.

Synthesis of 3,4-Diaminophenol (5b).
To a suspension of activated Raney nickel (200 mg) and hydrazine hydrate (98%, 2 mL) in ethanol (40 mL) was cautiously added a solution of 1.54 g (10 mmol) of 4-amino-3-nitrophenol (**6**) in ethanol (10 mL) and the mixture was stirred for 30 min at rt. The catalyst was then removed by filtration through Celite and the solvent was distilled off under reduced pressure to give 3,4-diaminophenol (**5b**) as a light brown pure solid (1.19 g, 96%), mp 155 °C; ^{1}H NMR (DMSO-d_6) δ 8.12 (br s,1H), 6.31 (d, *J* = 8.14 Hz, 1H), 6.03 (d, *J* = 2.65 Hz, 1H), 5.81 (dd, *J* = 8.14/2.65 Hz, 1H), 4.21 (br s, 4H); ^{13}C NMR (DMSO-d_6) δ 102.2, 103.2, 115.8, 126.8, 136.7, 149.7; IR (KBr) 3398, 3353, 3272, 3024, 2931, 1621, 1606, 1510, 1486, 1382 cm^{-1}; UV λ_{max}(MeOH) 343 nm; MS *m/z* (rel. int.) 124 (M^{+}, 100), 96(28), 68(11), 52(12); Anal. Calcd for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 57.75; H, 6.32; N, 22.35.

General procedure for the preparation of the 1,5-benzodiazepinium picrates. Solutions of 1.0 mmol of the diaminobenzene derivatives in 20 mL of ethanol were treated with pentane-2,4-dione (0.1 g; 1.0 mmol), and 0.5 g of picric acid (50% water). The reactions started immediately whereupon the color changed to dark violet. The mixtures were stirred for 30 min at rt. By addition of ether the precipitation of the solids was completed. The compounds were filtered off and washed with ether to give intensely violet fine analytically pure solids.

6-Hydroxy-2,4-dimethyl-5*H*-benzo[*b*][1,4]diazepin-1-ium picrate (7a).
2,3-Diaminophenol (0.372 g, 3.0 mmol) was used, yield 0.75 g (61%), mp 198-200 °C; ^{1}H NMR (DMSO-d_6) δ = 10.70 (s, 1H), 9.55 (s, 1H), 9.07 (s, 1H), 8.60 (s, 2H), 6.78 (d, *J* = 8.15 Hz, 1H), 6.51 (dd, *J* = 8.15/7.83 Hz, 1H), 5.96 (d, *J* = 7.83 Hz, 1H), 4.30 (s, 1H), 1.89 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (DMSO-d_6): δ = 24.1, 24.2, 95.7, 113.8, 116.2 , 120.2, 124.1, 125.2, 129.8, 136.1, 141.8, 149.9, 160.8, 175.1, 176.5; IR (KBr) 3313, 3083, 1609, 1566, 1542, 1429 cm^{-1}; UV λ_{max}(H_2O) 218, 256, 358 nm; λ_{max}(MeOH) 356, 590 nm; λ_{max}(EtOH) 258, 360 nm; MS *m/z* (rel. int.) 188 (M^+-1, 100), 173(33), 148(29), 91(46), 77(29), 62(85), 52(64); Anal. Calcd for $C_{17}H_{15}N_5O_8$: C, 48.93; H, 3.62; N, 16.78. Found: C, 48.97; H, 3.53; N, 16.87.

7-Hydroxy-2,4-dimethyl-5*H*-benzo[*b*][1,4]diazepin-1-ium picrate (7b).
3,4-Diaminophenol (0.248 g, 2.0 mmol) was used, yield 0.59 g (71%), mp 228-230 °C; ^{1}H NMR (DMSO-d_6) δ = 9.97 (s, 1H), 9.78 (s, 1H), 9.09 (s, 1H), 8.60 (s, 2H), 6.29 (d, *J* = 8.59 Hz, 1H), 6.18 (dd, *J* = 8.59/2.40 Hz, 1H), 5.92 (d, *J* = 2.40 Hz, 1H), 4.06 (s, 1H), 1.73 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (DMSO-d_6): δ = 23.7, 23.8, 94.2, 110.7, 113.0, 123.5, 124.1, 125.2, 135.2, 141.8, 158.3, 160.7, 172.6, 173.6; IR (KBr) 3424, 3306, 3080, 1612, 1541, 1480, 1432 cm^{-1}; UV λ_{max}(H_2O) 204, 262, 352 nm; λ_{max}(MeOH) 284, 348 nm; λ_{max}(EtOH) 268, 286, 354 nm; MS *m/z* (rel. int.) 188 (M^+-1, 100), 173 (10), 146 (23), 106 (7), 77 (88), 5 (11); Anal. Calcd for $C_{17}H_{15}N_5O_8$: C, 48.93; H, 3.62; N, 16.78. Found: C, 48.65; H, 3.79; N, 16.78.

7-Methoxy-2,4-dimethyl-5*H*-benzo[*b*][1,4]diazepin-1-ium picrate (7c).
4-Methoxy-1,2-diaminobenzene dihydrochloride (1.056 g, 5.0 mmol) was used, yield : 1.83 g (86%), mp 210-212 °C; ^{1}H NMR (DMSO-d_6): δ = 9.83 (s, 1H), 9.20 (s, 1H), 8.61 (s, 2H), 6.39 (d, *J* = 1.26 Hz, 2H), 6.02 (m, 1H), 4.09 (s, 1H), 3.64 (s, 3H), 1.75 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (DMSO-d_6): δ = 24.5, 24.6, 56.2, 95.3, 110.8, 111.6 , 124.9, 125.7, 125.9, 126.0, 136.0, 142.5, 160.4, 161.5, 173.6, 174.7; IR (KBr) 3321, 1630, 1609, 1559, 1521, 1481, 1365 cm^{-1}; UV λ_{max}(H_2O) 214, 264, 350 nm; λ_{max}(MeOH) 350, 524 nm; λ_{max}(EtOH) 266, 284, 358 nm; MS *m/z* (rel. int.) 202(M^+-1, 100), 187(54), 159(10), 147(18), 118(11), 91(13), 77(7), 62(7); Anal. Calcd for $C_{18}H_{17}N_5O_8$: C, 50.12; H, 3.97; N, 16.24. Found: C, 50.15; H, 3.92; N, 15.93.

7-Carboxy-2,4-dimethyl-5*H*-benzo[*b*][1,4]diazepin-1-ium picrate (7d).
3,4-Diaminobenzoic acid (1.52 g, 10.0 mmol) was used, yield 3.87 g (88%), mp 205-207 °C; ^{1}H NMR (DMSO-d_6): δ = 13.15 (br s, 1H), 9.85 (s, 1H), 9.63 (s, 1H), 8.61 (s, 1H), 8.60 (s, 1H), 7.40 (d, *J* = 8.14 Hz, 1H), 6.99 (s, 1H), 6.48 (d, *J* = 8.14 Hz, 1H), 4.23 (s, 1H), 1.77 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (DMSO-d_6): δ = 24.1, 96.1, 96.2, 123.1, 124.0, 124.1, 125.2, 130.6, 133.5, 133.5, 138.2, 141.8, 165.1, 175.3, 176.5; IR (KBr) 3310, 3071, 3003, 1692, 1631, 1600, 1568, 1554, 1520, 1435 cm^{-1}; UV λ_{max}(H_2O) 268, 354 nm; λ_{max}(MeOH) 352, 524 nm; λ_{max}(EtOH) 242, 270, 360 nm; MS *m/z* (rel. int.) 216(M^+-1, 100), 199(16), 171(21), 159(13), 130(29), 103(13), 91(31), 77(28), 63(52), 53(29); Anal. Calcd for $C_{18}H_{15}N_5O_9$: C, 48.55; H, 3.39; N, 15.73. Found: C, 48.56; H, 3.40; N, 15.41.

REFERENCES AND NOTES

1 For reviews, see: D. Lloyd and H. McNab, *Adv. Heterocycl. Chem*., 1998, **71**, 1; G. V. Boyd, in *´Houben-Weyl: Six-membered and Larger Hetero-rings with Maximum Unsaturation*,´ ed. by E. Schaumann, Thieme Verlag, Stuttgart, New York, 1998, Vol. E9d, p. 299; A. Chimirri, R. Gitto, S. Grasso, A. M. Monforte, G. Omeo, and M. Zappalà, *Heterocycles*, 1993, **36**, 865; R. I. Fryer and A. Walser, *Chem. Heterocycl. Compd*., 1991, **50**, 209; D. Lloyd and H. P. Cleghorn, *Adv. Heterocycl. Chem.,* 1974, **17**, 27.

2 Tranquilizers: A. Tajana, R. Pennini, and D. Nardi, *Farmaco, Ed. Sci*., 1980, **35**, 181; antidepressant agents: K. C. Joshi, V. N. Pathak, P. Arya, and P. Chand, *Pharmazie*, 1979, **34**, 718; anticonvulsants or convulsants: C. Grieco, C. Silipo, and A. Vittoria, *Farmaco, Ed. Sci*., 1977, **32**, 909; cancerostatics: A. I. Kravchenko, *Farmakol. Toksikol. (Moscow)*, 1974, **37**, 474; herbicides: D. P. Clifford, D. Jackson, R. V. Edwards, and P. Jeffrey, *Pestic. Sci*., 1976, **7**, 453.

3 recent publications: A. Schmidt and N. Kobakhidze, *Heterocycles*, 2002, **57**, 2213; A. Schmidt, T. Mordhorst, and T. Habeck, *Org. Lett*., 2002, **4**, 1375; A. Schmidt, P. Vainiotalo, M. K. Kindermann, and M. Nieger, *Heterocycles*, 2002, **57**, 615.

4 recent publications: A. Schmidt, T. Habeck, M. K. Kindermann, and M. Nieger, *J. Org. Chem*., 2003, in press; A. Schmidt, *J. Heterocycl. Chem*., 2002, **39**, 949; A. Schmidt, N. Kobakhidze, and M. K. Kindermann, *J. Chem. Soc., Perkin Trans. 1*, 2002, **7**, 982; A. Schmidt and N. Kobakhidze, *Chem. Lett*., 2002, **2**, 222.

5 Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-215205. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Some crystal data of **3a**: $C_{11}H_{13}N_2O + C_6H_2N_3O_7 + C_3H_6O$; M = 475.42; space group P-1 (no. 2); dimensions 0.50 x 0.40 x 0.25 mm^3, a = 8.0073(2) Å, b = 9.6532(3) Å, c = 14.6882(5) Å; α = 81.282(2)°, β = 82.257(2) ° , γ = 71.068(2)°; V = 1057.06(6) $Å^3$, D_c = 1.494 MG m^{-3}, Z = 2; T = 123(2) K; F(000) = 496, 10292 reflections were collected in a Nonius KappaCCD diffractometer ($2\Theta_{max.}$ = 56.5 ° , -10 ≤ h ≤ 10, -12 ≤ k ≤ 12, -18≤ l ≤ 18), 4708 symmetry independent reflections (R_{int} = 0.0306) were used for the structure solution (direct methods)[6] and refinement (full-matrix least-squares on F^2,[7] 320 parameters, 3 restraints), non-hydrogen atoms were refined anisotropically, H atoms localized by difference electron density, aromatic and methyl hydrogen atoms were refined using a riding model, other free; wR2 (all data) = 0.1058 [R1 = 0.0393 for 3484 I>2σ(I)].

6 G. M. Sheldrick, SHELXS-97, *Acta Cryst*., 1990, A46, 467.

7 G. M. Sheldrick, SHELXL-97, University of Göttingen, 1997.

8 M. Brisander, S. G. Harris, D. Lloyd, H. McNab, and S. Parsons, *J. Chem. Res. (S)*, 1998, 72.

9 C. Svensson and L. Timby, *Cryst. Struct. Commun*., 1981, **10**, 429.

10 J. C. Speakman and F. B. Wilson, *Acta Crystallogr*., *Sect. B*, 1976, **B32**, 622.

11 A. J. Blake, M. Schröder, and R. J. Sorbie, *Z. Kristallogr*., 1991, **194**, 148.

12 N. Rodier, A. Agafonev, P. Dubois, M. Mariand, P. Levillain, and J. M. Sense, *Acta Crystallogr., Sect. C*, 1993, **C49**, 156.

13 D. Lloyd and D. R. Marshall, *Chem. Ind. (London)*, 1972, 335.

14 C. Glidewell and D. Lloyd, *Tetrahedron Lett*., 1982, **23**, 4379.