A MESOMERIC BETAIN PYRAZOLO-OXYDOTRIAZINIUM RING SYSTEM. 6-ALKYL-2-METHYL-PYRAZOLO [1,5-d] [1,2,4] TRIAZIN-6-IUM-4-OLATES, SYNTHESIS AND RING CLEAVAGE

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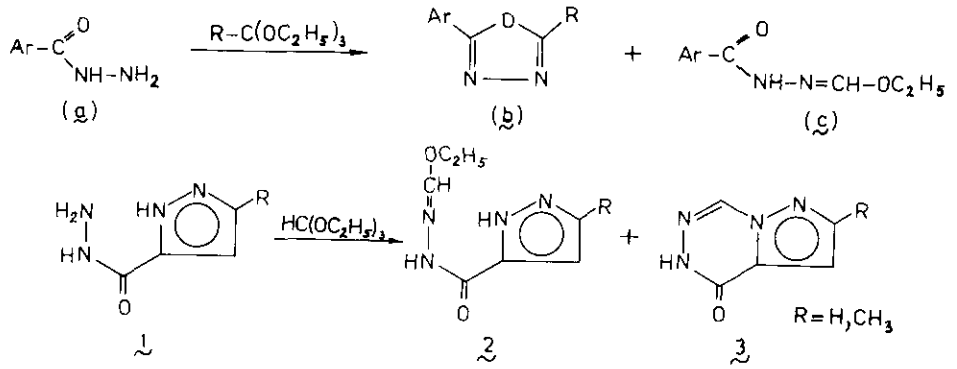
Abstract - A novel type of the mesomeric betain ring system was synthesized from pyrazolecarboxylic acid N'-alkyl-hydrazides by a simple method. The structure of the compounds was proved by spectroscopic methods and synthetic routes. The oxydotriazinium ring was opened with ethanol to yield the corresponding starting materials or with water to yield substituted pyrazolecarboxylic acid N'-acyl hydrazides.

In recent years a large number of mesoionic compounds[1] have been synthesized and examined, but only relatively few other types of mesomeric betain[2] heterocycles[3] have been reported.

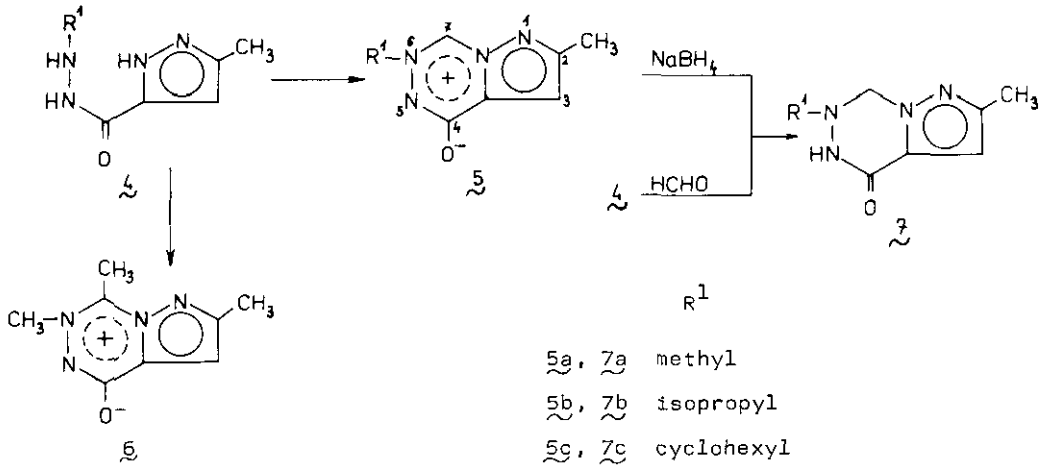
We have studied the reaction of aromatic carboxylic acid hydrazides /bearing an additional functionality besides their hydrazide group/ with carbonyl[4] and di-carbonyl[5] compounds and orthoesters to synthesize condensed rings. Condensation of the N'-unsubstituted hydrazides of homo- or heterocyclic carboxylic acids /a/ with orthoesters leads to substituted 1,3,4-oxadiazoles /b/ and in some cases a 1-acyl-2-ethoxymethylenehydrazine intermediate /c/ has been isolated[6]. Starting from 3/5/-pyrazolecarboxylic acid hydrazides 1, a pyrazolo-triazine ring system 3 was formed[6,7] besides intermediate 2.



(a) (b) (c)

1 2 3

On heating 3/5/-methyl-5/3/-pyrazolecarboxylic acid N'-alkyl hydrazides[8] 4 with an excess of ethyl orthoformate, we obtained crystalline, water soluble materials in good yields, which couldn't have structure 2 or 3 as indicated above because of N'-substitution of the hydrazide moiety. Thus, a mesomeric betain pyrazolo-oxydotriazinium structure 5 has been supposed. [5a, mp 217°C /decomp./; 88 % yield; δ /DMSO-d_6/ 2.45 s 3H, 3.90 s 3H, 6.7 s 1H, 10.20 s 1H; ν 1630, 1570 cm^{-1}; 5b, mp 202°C /decomp./; 61 % yield; δ /DMSO-d_6/ 1.55 d /7Hz/ 6H, 2.45 s 3H, 4.7 sp /7Hz/ 1H, 6.75 s 1H, 10.20 s 1H; ν 1610, 1570 cm^{-1}; 5c, mp 231°C /decomp./; 66 % yield; δ /DMSO-d_6/ 2.45 s 3H, 4.35 m 1H, 6.75 s 1H, 10.20 s 1H, m /60-140 Hz/ 10H; ν 1615 cm^{-1}.] The singlet at δ 10.20 was assigned to C_7-H. This signal was missing and a new methyl signal was identified at δ 2.25 in the ^{1}H NMR spectrum[9] of 6 [synthesized from 4 /R^1=methyl/ with an excess of ethyl orthoacetate; mp 225°C /decomp./; 88 % yield; δ /D_2O+TFA/ 2.25 s 3H, C_7-CH_3; 2.50 s 3H, C_2-CH_3; 3.35 s 3H, N-CH_3; 6.75 s 1H, C_3-H; ν 1600, 1565 cm^{-1}], rendering the expected mesomeric betain structure 6 probable[10]. The structure was unambiguously proved by the reduction of compounds 5 with $NaBH_4$ in methanol[11] yielding 7a [mp 177°C; 36 % yield; δ /DMSO-d_6/ 2.30 s 3H, C_2-CH_3; 2.60 s 3H, N-CH_3; 6.60 s 1H, C_3-H, 5.20 s 2H, C_7-H; 9.80 s 1H, NH; ν 3300-2700, 1670 cm^{-1}], 7b [mp 192°C; 62 % yield; δ /DMSO-d_6/ 0.95 d /7Hz/ 6H, CH/CH_3/$_2$; 2.25 s 3H, C_2-CH_3; 2.85 sp /7Hz/ 1H, N-CH; 6.50 s 1H, C_3-H; 5.30 s 2H, C_7-H; 9.85 s 1H, NH; ν 3300-2700, 1675 cm^{-1}] and 7c [mp 194°C; 87 % yield; δ /DMSO-d_6/ 2.25 s 3H, C_2-CH_3; 3.40 m 1H, N-CH; 6.50 s 1H, C_3-H; 5.25 s 2H, C_7-H; m /50-120 Hz/ 10H, CH_2; 9.80 s 1H, NH; ν 3300-2700, 1675 cm^{-1}], respectively, which were identical with the compounds synthesized from 4 and formaldehyde [7a, 31 %; 7b, 91 %; 7c, 85 % yield].



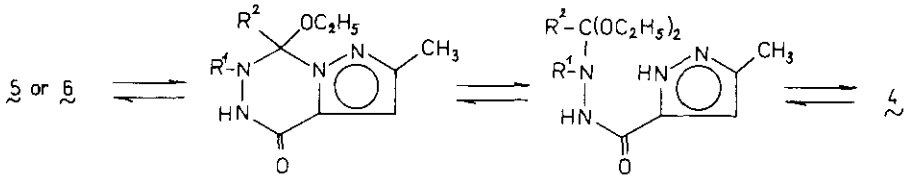
R^1

5a, 7a methyl

5b, 7b isopropyl

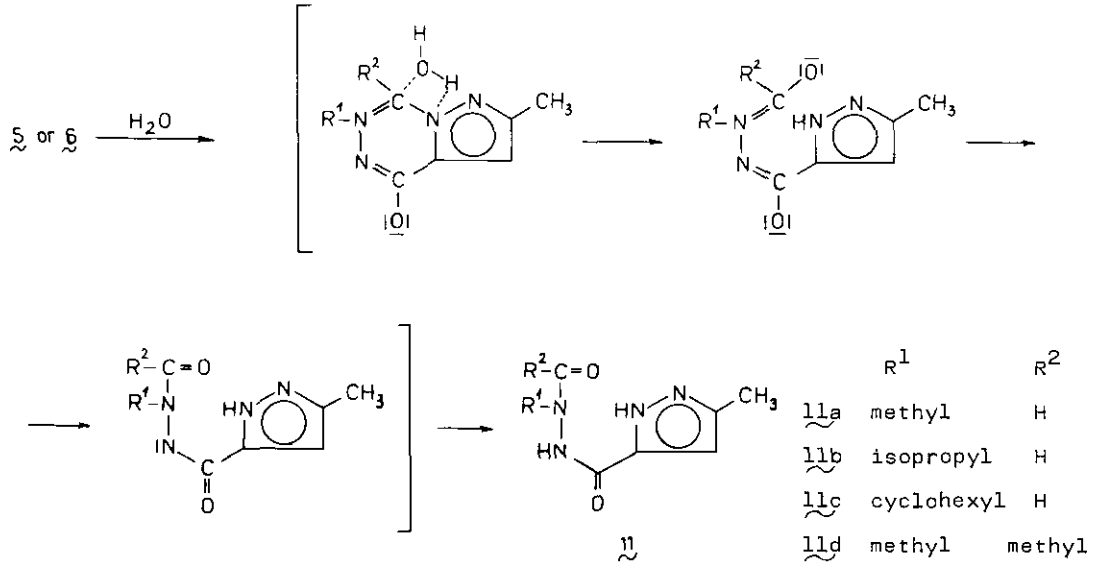
5c, 7c cyclohexyl

This new condensed mesomeric betain ring system is susceptible to ring cleavage, as 5 and 6 can be converted into 4 in boiling ethanol. The reaction proceeds most likely reversibly via intermediates 9 and 10, though the isolation of these intermediates has failed so far.



9 10

Further synthetic evidence for the structure was that the betain ring could be opened with water between the bridgehead N and C_7, yielding 11 [11a, mp 180°C; 73 % yield; δ/DMSO-d_6/ 2.33 s 3H, C_3-CH_3; 3.03 s 1.8H and 3.18 s 1.2H, N-CH_3; 6.53 s 1H, C_4-H; 8.06 s 0.6H and 8.18 s 0.4H, CHO; 10.7 and 13.1 s 1H, NH; ν3280, 1670, 1640 cm^{-1}; 11b, mp 175°C; 85 % yield; δ/DMSO-d_6/ 1.10 d /7Hz/ 4.2H and 1.17 d /7Hz/ 1.8H, CH/CH_3/$_2$; 2.32 s 3H, C_3-CH_3; 4.47 sp /7Hz/ 0.7H and 4.10 sp /7Hz/ 0.3H, N-CH; 6.50 s 1H, C_4-H; 7.91 s 0.7H and 8.21 s 0.3H, CHO; 10.4 s 0.7H, 9.7 s 0.3H and 13.0 s 1H, NH; ν 3280, 3240, 1690, 1630 cm^{-1}; 11c, mp 190°C; 81 % yield; δ/DMSO-d_6/ 2.31 s 3H, C_3-CH_3; 4.05 m 1H, N-CH; 6.52 s 1H, C_4-H; 7.93 s 0.8H and 8.22 s 0.2H, CHO; m /60-130 Hz/ 10H, 10.4 s 0.8H, 9.8 s 0.2H and 13.0 s 1H, NH; ν3300, 3260, 1700, 1640 cm^{-1}; 11d, mp 220°C; 69 % yield; δ/DMSO-d_6/ 1.94 s 3H, CO-CH_3; 2.32 s 3H, C_3-CH_3; 3.05 s 3H, N-CH_3; 6.52 s 1H, C_4-H; 11.6 s 1H and 13.9 s 1H, NH; ν 2800-3300, 1690, 1630 cm^{-1}].



	R^1	R^2
11a	methyl	H
11b	isopropyl	H
11c	cyclohexyl	H
11d	methyl	methyl

The reaction of 5a is completed at room temperature[12] in three days, whereas about seven days are needed for 5b and 5c. Under the same conditions 6 is much more stable and about one month is necessary for the complete cleavage[13]. In aqueous NaOH at room temperature 11 is immediately formed, indicating that a deprotonation is the rate determining step of the ring opening, so the cleavage proceeds presumably as the figure shows.

References and notes:

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2. The name "mesomeric betain" was proposed by W.D.Ollis and C.A.Ramsden, Adv. Heterocyclic Chem., 1976, 19, 1.
3. See ref. 2, p. 105 and e.g. A.R.Katritzky et al., '1,3-Dipolar Character of Six-Membered Aromatic Rings', part 1-51 /part 51: J. Chem. Soc., Perkin Trans. I, 1980, 362. /or T.Kappe et al., 'Mesoionic Six-Membered Heterocycles', part 1-11 /part 11: Chem. Ber., 1979, 112, 1585./
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5. M.Gál, Ö.Fehér, E.Tihanyi, Gy.Horváth, Gy.Jerkovich, Gy.Argay, A.Kálmán, Tetrahedron Lett., 1980, 1567.
6. C.Ainsworth, J.Amer.Chem.Soc., 1955, 77, 1148.
7. E.Ajello, C.Arnone, J. Heterocyclic Chem., 1973, 10, 103.
8. Synthesis of 4: R^1 = isopropyl, C.B.Torsi, M.Vuat, Gazz. Chim. Ital., 1961, 91, 1461; R^1 = methyl, cyclohexyl will be published in ref. 4.
9. ^1H NMR: 60 MHz, chemical shifts relative to $SiMe_4$ in ppm, at room temperature, IR: in KBr pellets.
10. The elementary analyses of all compounds were correct and the mass spectra proved the molecular weights.
11. Reduction of 6 gave the expected 8 [mp 142°C; 69 % yield; δ/$CDCl_3$/ 1.65 d /7Hz/ 3H, C_7-CH_3; 2.40 s 3H, C_2-CH_3; 2.70 s 3H, N-CH_3; 6.65 s 1H, C_3-H; 8.80 s 1H, NH; ν 3300-2700, 1675 cm^{-1}.], the C_7-methyl analog of 7a.
12. Checked by TLC and UV spectroscopy.
13. 11 could be synthesized in good yields from 4 by acylation. Our experiments to convert 11 back into 5 have not been successful so far.

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