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UNEXPECTED FORMATION OF REARRANGEMENT AND FRAGMENTATION PRODUCTS DURING THE THERMAL ACTIVATION OF PYRAZOLINO DIAZEPINES

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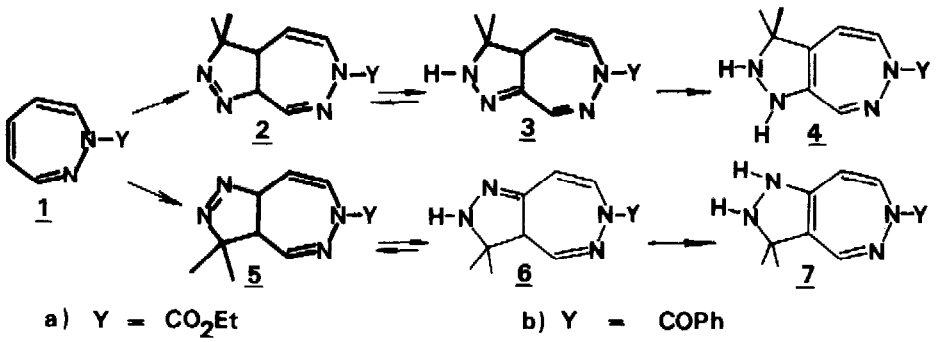
Abstract. Ionic and radical mechanistic steps are postulated in order to explain the formation of the rearrangement-, the isomerization- and the fragmentation-products isolated during the thermal treatment of pyrazolo-diazepines.

Diazepines 1 reacted in a site-specific way with diazoisopropane (DAP), whereby 1-pyrazoline adducts 2 were formed (1,2). These primary adducts showed a pronounced tendency to isomerize to the more stable 2-pyrazolines 3, the gain in stability being due to an increased double bond conjugation. As expected (3), these two types of pyrazoline adducts were in equilibrium in solution; the overall yields of 2 ⇌ 3 varying from 60% to 90%. The "inverse" cycloadducts 5 also formed (4), albeit in low yields (5 to 15%). This means that the DAP addition to the Δ^4 double bond of diazepines 1 is a regioselective but not a regiospecific process (5). In order to account for the formation of some of the rearrangement products, which stem from a thermal activation of the 2-pyrazoline adducts 3 and 6, we postulate a second type of prototropic equilibria 3 ⇌ 4 and 6 ⇌ 7 to occur, in which 3-pyrazolines are involved (Scheme 1). These latter and elusive compounds are actually (1-H)-1,2- diazepines.

Scheme 1



When the diazepine-DAP adducts were thermally activated, three sets of compounds could be isolated. In order to account for the formation of these

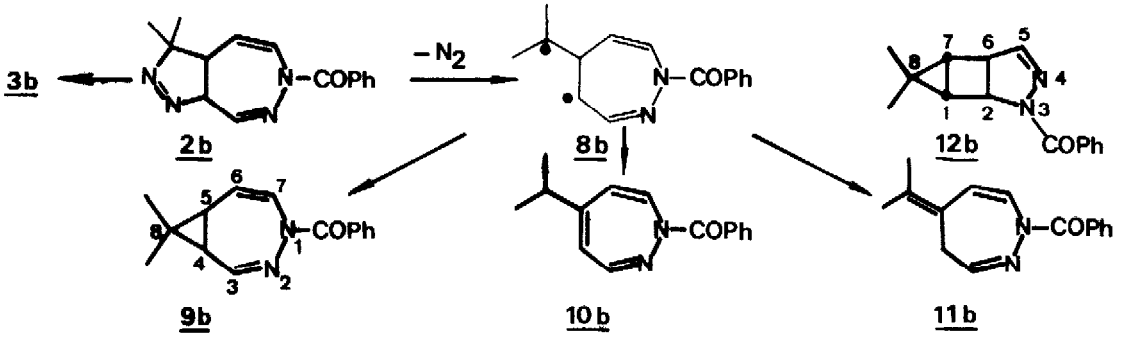
various reaction products, reasonable mechanistic pathways can be postulated, provided that one starts from 1-,2- and 3-pyrazolines respectively.

THERMAL ACTIVATION OF 1-PYRAZOLINES 2b (6) AND 5a. When 2b was heated to 105°, nitrogen evolved rapidly, whereby the colorless homodiazepine 9b was formed in 32% yield [mp 59°; ^{1}H nmr ($CDCl_3$) δ 7.8-7.23 (H arom. and H-7; m), 6.93 (H-3; t; J= 2Hz), 5.23 (H-6); ddd; J=10.0, 3.0 and 2.5 Hz), 1.76 (H-4 and H-5; m), 1.33 (CH_3) and 0.90 ppm (CH_3)]. A series of other products formed, three of which could be isolated in low yields : 5-isopropyl-1,2-diazepine 10b [yellow oil; ^{1}H nmr ($CDCl_3$) : δ 7-8 (H arom. and H-3; m), 6.5 (H-7; d; J= 8Hz), 6.1 (H-4; m), 5.8 (H-6; dd; J=8 and 2 Hz), 2.4 (H-8; septuplet; J=7 Hz) and 1.1 ppm (2 CH_3; d; J=7Hz)], its isopropenyl isomer 11b [mp 112°; ^{1}H nmr (C_6D_6) δ 7.7 (H-7; d; J=10 Hz), 6.8 (H-3; t; J=6 Hz), 5.8 (H-6; d; J=10 Hz), 2.9 (H-4; d; J=6 Hz), 1.5 (CH_3) and 1.4 ppm (CH_3)] and 3-benzoyl-3,4-diaza-8,8-dimethyl-[5,1,0,$0^{2,6}$]-tricyclo-4-octene 12b, m.p. 92°. The structure of this latter compound could easily be solved by an unambiguous correlation with a similar product described previously (7). The major product however which was formed during the thermal treatment of 2b was its 2-pyrazoline isomer 3b [mp 122°; yield : 50%] (2), a compound which proved to be stable at 105° (Scheme 2).

The formation of compounds 9b, 10b and 11b seems to be straightforward from a mechanistic standpoint, provided that the diradical intermediate 8b be postulated (Scheme 2). So far we do not have any satisfactory mechanistic explanation for the formation of 12b.

Only a small amount of the "inverse" adduct 5a was available; its thermal activation led to several products of which only two could be isolated : the homodiazepine 9a (1,2) and the pyrazolopyridine 24 (vide infra).

Scheme 2

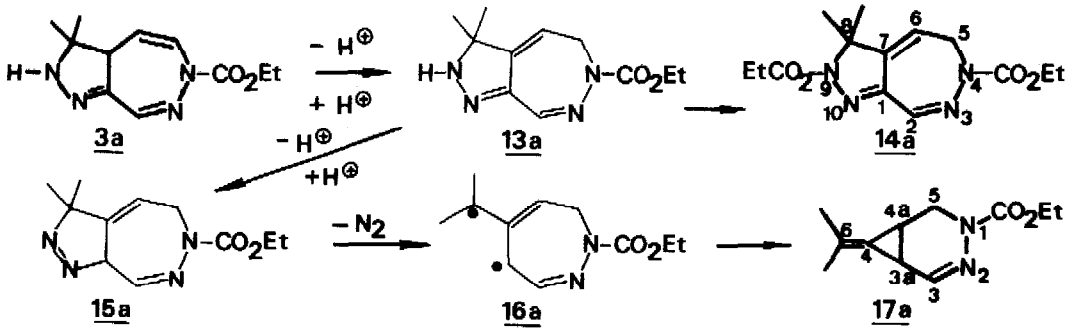


THERMAL ACTIVATION OF 2-PYRAZOLINE 3a. Thermal activation at 180-200° of 2-pyrazolines 3 led to an equilibrium with the 1-pyrazoline isomers 2 and, most likely, to a second equilibrium with the 3-pyrazolines 4. Consequently the reaction mixtures became very complex, since all three sets of compounds were present. We shall focus our attention on the fate of 3a whose thermal behaviour is characteristic. In addition to the reaction products, which

typically arouse from the 1-pyrazoline 2a and from the 3-pyrazoline 4a (see below), two compounds formed rather unexpectedly : the bis—ethoxycarbonyl 4-alkylidene-2-pyrazoline 14a [^{1}H nmr ($CDCl_3$) δ 7.78 (H-2; s), 5.95 (H-6; t; J=5 Hz), 4.58 (H-5; d; J=5 Hz), and 1.6 ppm ($2CH_3$)] and the dimethyl-methylene-cyclopropane derivative 17a [^{1}H nmr ($CDCl_3$) δ 7.5 (H-3; d; J=4 Hz), 4.5 (H-5; m), 2.85 (H-5; dd; J=12 and 2 Hz), 2.35 (H-3a and H-4a; m) and 1.90 ppm (2 CH_3; m)].

Ionic and radical mechanistic steps must be put forward, in order to explain the formation of compounds 14a and 17a (Scheme 3) : i) an intermolecular prototropy leads to isomer 13a, via a doubly allylic anion, and is followed by an ethoxycarbonyl transfer from a second molecule of 3a, whereby 14a is formed; ii) 13a undergoes a second prototropy whereby the 4-alkylidene 1-pyrazoline 15a is formed, nitrogen expulsion leads then to the trimethylene methane diradical 16a which ring-closes to the methylene-cyclopropane 17a (8)

Scheme 3

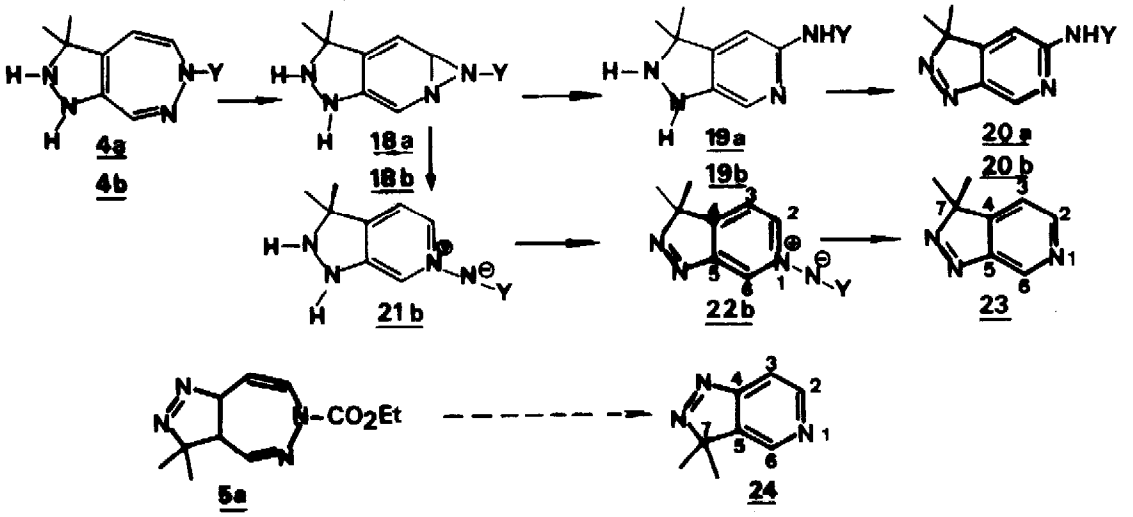


THERMAL ACTIVATION OF THE POSTULATED 3-PYRAZOLINES 4a, 4b and 7a. During the treatment at 180-200° of the 2-pyrazolines 3a and 3b, the pyrazolopyridines 20a, 20b, 22b and 23 were isolated, in addition to the products described above. The structure of 20b could be demonstrated unequivocally by X-ray (9). Physical data for the ylide 22b are as follows [mp 180-185° dec.; IR ($CHCl_3$) ν (C=O) 1550 cm^{-1}; UV (EtOH) λ_{max} 228 (16,800) and 335 nm (5,500); ^{1}H nmr ($CDCl_3$) δ 9.76 (H-6; s) 8.93 (H-2; dd; J=6.5 and 1.0 Hz), 7.66 (H-3; d; J=6.5 Hz) and 1.63 ppm (2 CH_3)]. Pyridine 23, mp 108°, showed physical data similar to the ones of 20.

It is know that 1,2-diazepines, when thermally activated, lead to ring contraction whereby the isomeric 2-amidopyridines (10) and the N-iminopyridinium ylides (11) are formed, both via the corresponding 1,7-diaza-norcaradiene intermediates. Furthermore these latter zwitterionic derivatives have been found to thermally fragment along the N-N bond to the corresponding pyridines (12). Scheme 4 represents our present views, concerning the mechanistic steps leading to the pyrazolo-pyridines; they are based on the above mentioned observations. Our interpretations are based on the intermediate occurrence of the 3-pyrazolines 4, and on easy air oxidation of cyclic

hydrazines (13).

Scheme 4



In a similar fashion thermal treatment of 5a led to the pyrazolopyridine 24 [mp 92°; ^{1}H nmr ($CDCl_3$) δ 8.90 (H-6; s) 8.83 (H-2; d; J=5 Hz), 8.01 (H-3; dd; J=1 Hz) and 1.63 ppm (2 CH_3; s)].

It is believed that the pyrazolo-pyridines 23 and 24 are good precursors for the formation of a common pyrido-cyclopropene.

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