Synthesis and Thermochemical Behaviour of 1*H*-1,2-Benzodiazepine-3-carboxylic Acids

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The title carboxylic acids, prepared by alkaline hydrolysis of their ethyl esters, thermally decomposed to give *ortho*-aminocinnamonitriles and, in few cases, 3-unsubstituted 1*H*-1,2-benzodiazepines.

J. Heterocyclic Chem., 16, 1061 (1979).

Since we had developed a synthetic method for 3-carbethoxy-1*H*-1,2-benzodiazepines variously substituted in other positions (1), it was felt interesting to submit these substrates to hydrolysis in order to check whether the corresponding carboxylic acids might undergo decarboxylation giving 3-unsubstituted 1*H*-1,2-benzodiazepines. Actually, 1*H*-1,2-benzodiazepine-3-carboxylic acids are unknown in the chemical literature and few examples of 3-unsubstituted 1*H*-1,2-benzodiazepines have been reported (2,3).

Ethyl esters **1a-d** were hydrolized on reaction with sodium hydroxide in boiling 95% ethanol. In all cases, the corresponding carboxylic acids **2a-d** were obtained in high yield as crystalline compounds of analytical purity (see Table I).

Thermal decomposition of **2a-d** was done by heating at the melting temperatures for a few minutes; the chromatography of the resulting tarry mixture led to the products indicated in Table II (4). Aminocinnamonitriles **3a-c** were obtained as one isomer of undetermined stereochemistry. However, when starting from **2d**, the chromatographic separation of the crude reaction product gave, in addition to the pure *E* isomer of **3d**, a mixture containing 2-aminoquinoline (**5**) and another compound which may be suggested as the *Z* isomer of **3d** on the basis of the spectral evidence, *i.e.*, a band at 2220 cm^{-1} in the ir spectrum and a doublet at δ 5.35 with J = 12 Hz in the nmr spectrum. Unfortunately, isolation and characterization of the hitherto unknown *Z* isomer were precluded by its instability; in fact, a further work-up of the above mixture resulted exclusively in compound **5**, thus suggesting that (*Z*)-**3d** might readily cyclize to **5**.

The results now reported, which parallel the acquisition of 3-unsubstituted pyrazoles and β-aminoacrilonitriles from pyrazole-3-carboxylic acids (5), can be rationalized according to the step sequence outlined in the Scheme. As previously suggested for pyrazole (6) and isoxazole (7) 3-carboxylic acids, a zwitterionic form of **2** could be involved in the above decomposition process. Anionic intermediates such as **A** and **B** have been recently proposed for the base-promoted rearrangement of 3-unsubstituted 1*H*-1,2-benzodiazepines to 2-aminoquinolines (2).

Attempts to decompose acids **2** according to different decarboxylation techniques (8) were unsuccessful. In fact, the treatment of **2** with copper salts and quinoline resulted in untractable tarry mixtures; on the other hand, the sodium salts of **2** did not change in toluene suspension under reflux as well as in dimethylformamide solution at 110°.

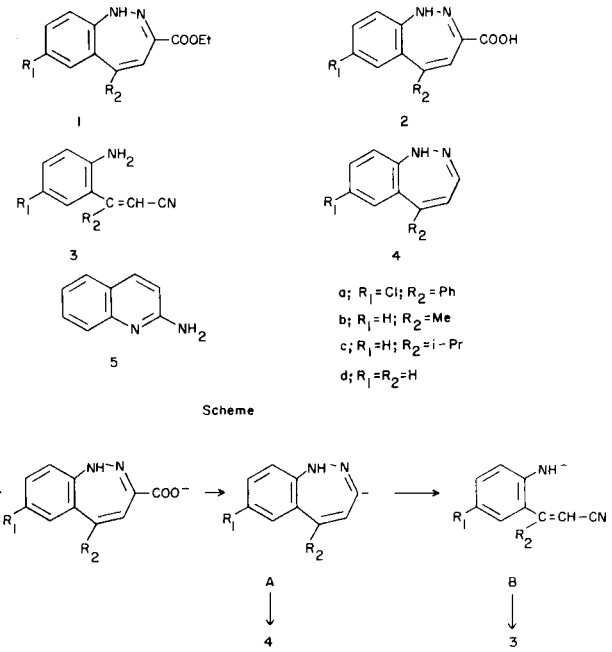

Table I

Preparation of Acids **2**

Compound No.	Yield %	M.p. °C	Ir, Cm^{-1} (Nujol)	*Anal.* Calcd.: C, H, N Found: C, H, N		
2a	90	126 (dec)	1690	64.33 64.55	3.71 3.80	9.38 9.21
2b	86	120 (dec)	1680	65.33 65.21	4.98 5.11	13.86 13.90
2c	87	130 (dec)	1690	67.80 68.03	6.13 6.15	12.17 12.01
2d	89	115 (dec)	1680	63.82 63.68	4.29 4.11	14.89 14.87

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Table II

Thermal Decomposition of Acids **2**

Compound No.	Products	Yield %	M.p. °C	Ir, Cm^{-1} (Nujol)	Nmr, δ (Deuteriochloroform)	*Anal.* Calcd.: C, H, N Found: C, H, N		
2a	**3a**	34	164	2220	3.5 (2H, broad s); 5.94 (1H, s); 6.69	70.73	4.35	10.99
	4a	6	(3)		(1H, d); 7.1-7.5 (7H, m)	70.98	4.47	10.83
2b	**3b**	15	74	2225	2.38 (3H, d, $J\sim1$ Hz); 3.7 (2H, broad s);	75.91	6.37	17.71
					5.51 (1H, m); 6.6-7.3 (4H, m)	75.77	6.52	17.59
	4b	10	(2)					
2c	**3c**	41	(145-150/ 0.1 mm)	2230	1.10 (6H, d); 2.6-3.0 (1H, m); 3.6 (2H,	77.38	7.58	15.04
					broad s); 5.47 (1H, d, $J\sim1$ Hz); 6.6-7.3 (4H, m)	77.60	7.57	15.17
2d	(*E*)-**3d**	6	(9)	2225	3.8 (2H, broad s); 5.75 (1H, d, J = 16 Hz); 6.6-7.6 (5H, m)			
	(*Z*)-**3d**							
	5	18						

EXPERIMENTAL

Ir spectra were taken on a Perkin-Elmer 377 spectrophotometer. Nmr spectra were recorded on a Varian HA-100 instrument with TMS as an internal standard. Melting points were determined on a Büchi apparatus and are uncorrected.

Compounds **1b,d** were prepared as previously described. Preparations of **1a,c** will be reported elsewhere.

General Procedure for the Preparation of 1*H*-1,2-Benzodiazepine-3-carboxylic Acids (**2**).

A solution of ester **1** (5 mmoles) and sodium hydroxide (5 mmoles) in 95% ethanol (150 ml.) was refluxed for 15 minutes. The solvent was removed under reduced pressure and the residue was taken up with water. The mixture was acidified by aqueous hydrochloric acid and extracted with ether; the organic solution was dried over sodium sulfate and evaporated. Recrystallization of the residue from methanol gave **2** (see Table I).

General Procedure for the Thermal Decomposition of 1*H*-1,2-Benzodiazepine-3-carboylic Acids (**2**).

Acid **2** (4 mmoles) was melted and kept at the melting temperature for 5 minutes. The resulting material was dissolved in ether and absorbed onto a silica gel column (120 g.). Elution with ether gave the products indicated in Table II. Compounds **4a** (3), **4b** (2), (**E**)-**3d** (9), and **5** (2) were recognized on comparison of their physical and spectral data with those reported in the literature.

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