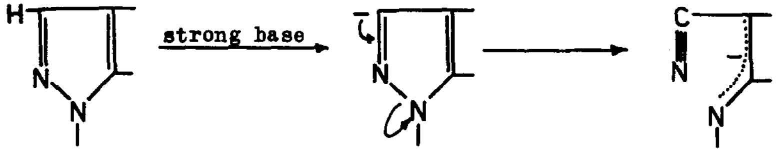
Tetrahedron Letters No.16, pp. 1739-1744, 1966. Pergamon Press Ltd.
Printed in Great Britain.

RING OPENING
OF 3-CARBOXY- AND 3-UNSUBSTITUTED PYRAZOLES.

R.Fusco, V.Rosnati and G.Pagani
Istituto di Chimica Industriale dell'Università di Milano

(Received 9 February 1966)

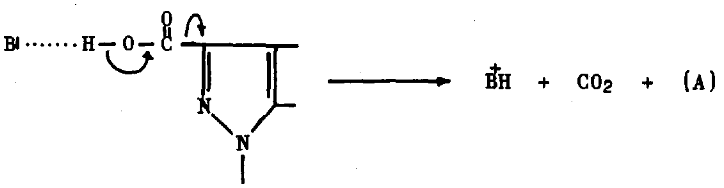
The pyrazole ring has been considered until recently to be resistant to alkaline treatments, independently of the substituents present at the different positions. Recently it has been reported that 3-unsubstituted-1-alkyl-indazoles are cleaved to the corresponding N-alkyl-anthranylamides by reaction with sodium amide and caustic soda in boiling xylene (1). Assuming that in such severe conditions the pyrazole ring opening might proceed through the formation of the carbanion (A), followed by the N-N bond cleavage (as indicated in the scheme), the following inferences seemed logical.



(A)

1) The above pyrazole ring cleavage should not be limited to

3-unsubstituted pyrazoles, but should also occur in the case of derivatives carrying in position 3 a proper substituent, capable of originating the incipient carbanion (A): 3-carboxy-pyrazoles, for instance, could originate (A) owing to the ability of the carboxyl group to undergo a thermal ionic decarboxylation, when hydrogen-bonded to a suitable base B:



2) The pyrazole ring cleavage, both in the case of 3-unsubstituted and 3-carboxy-derivatives, should be favored by the presence of electron-attracting substituents on the ring.

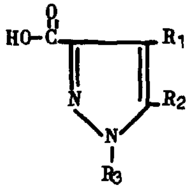
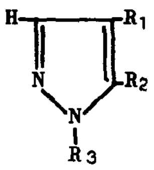
The experimental evaluation of the above hypothesis is still under extensive investigation. We now wish to report the results obtained with several pyrazole-3-carboxylic acids and 3-unsubstituted pyrazoles having in position 4 negative groups such as acetyl, benzoyl, cyano, nitro and p.tosyl. The compounds which have been considered are listed in the Table.(°)

The acids (I: b,c,d,e), not yet described, have been obtained by alkaline hydrolysis of their ethyl esters, which in turn have been synthetized through a known reaction (9), by condensing

---

(°) Satisfactory analyses were obtained for all new compounds. Melting points were not corrected.

TABLE

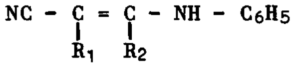
	N	R_1	R_2	R_3	Ref.
 (I)	Ia	H	H	C_6H_5	2
	Ib	CH_3CO	CH_3	C_6H_5	-
	Ic	C_6H_5CO	H	C_6H_5	-
	Id	C_6H_5CO	CH_3	C_6H_5	-
	Ie	CN	C_6H_5	C_6H_5	-
	If	p.$CH_3C_6H_4SO_2$	C_6H_5	C_6H_5	-
 (II)	IIa	H	H	C_6H_5	4
	IIb	CH_3CO	CH_3	C_6H_5	5
	IIc	C_6H_5CO	H	C_6H_5	6
	IId	NO_2	H	C_6H_5	7
	IIe	CN	C_6H_5	C_6H_5	-
	IIf	p.$CH_3C_6H_4SO_2$	C_6H_5	C_6H_5	8

ethyl phenylazo-chloroacetate respectively with: acetylacetone, 1-benzoyl-2-piperidino-ethylene, benzoylacetone, ω-cyano-acetophenone.

The 3-unsubstituted pyrazoles (II) were all described in the literature: however, we ascertained that 4-cyano-1,5-diphenylpyrazole (IIe) previously claimed to be obtained from anilino-methylene-benzoyl-acetonitrile and phenylhydrazine (8) actually is 5-amino-4-benzoyl-1-phenyl-pyrazole. This assignment is based on the chemical behaviour of the product, as well as on its spectroscopic data: in particular, its I.R. spectrum showed the absorption bands of NH and carbonyl group and no absorption in the region of the CN group.

The pyrazole (IIe, m.p.102-3°) could be obtained in high yields by thermal decarboxylation at 250° of the acid (Ie). This method was successfully applied also to a new synthesis of the pyrazoles (II: b,c,f), starting from the corresponding acids (I: b,c,f).

The ring opening, in the case of 3-carboxy-pyrazoles (I) was attempted by heating the acids in boiling quinoline for a standard period of time (90'): under these conditions all the acids (I) underwent a partial cleavage to the corresponding β-anilino-acrylonitriles (III).



$$NC - \underset{R_1}{C} = \underset{R_2}{C} - NH - C_6H_5$$

(III)

The results were the following.

The acid (Ia) gave as the major product 1-phenyl-pyrazole (isolated through vacuum distillation in mixture with quinoline and identified by gas-chromatographic analysis): a less volatile fraction, after chromatographic separation over Al_2O_3, gave a small quantity of an oily substance which showed in the I.R. spectrum a very intense band at 2215 cm^{-1}, (clearly indicating the presence of a CN group conjugated with a double bond). The full characterization of the above nitrile will be reported in a future paper.

The acid (Ib) gave 1-acetyl-2-anilino-1-cyano-2-methyl-ethylene (III: R_1=$COCH_3$, R_2=CH_3; m.p. 128°) and, as the major product, 4-acetyl-5-methyl-1-phenyl-pyrazole (m.p. 104-5°, lit.(5) 107-8°): the two products were separated by chromatography over Al_2O_3.

The acid (Ic) gave about 50% of 2-anilino-1-benzoyl-1-cyano-ethylene (III: R_1=COC_6H_5, R_2=H; m.p. 152°, lit.(8) 159°) and some 4-benzoyl-1-phenyl-pyrazole (m.p. 124, lit.(6) 122-3°).

The acid (Id) gave in 65% yield a mixture of 2-anilino-1-benzoyl-1-cyano-2-methyl-ethylene (III: R_1=COC_6H_5, R_2=CH_3) and 4-benzoyl-5-methyl-1-phenyl-pyrazole (IV): N.M.R. analysis showed that the two products were present in approximately 1:1 ratio. By chromatographic separation over Al_2O_3 the mixture gave pure pyrazole (IV) (m.p. 104-5°) identical with an authentic specimen of the pyrazole obtained from the acid (Id) by thermal decarboxylation, while the ethylene derivative was obtained in crystals (m.p. 88-90°, lit.(10) 98-99°) which by T.L.C. appeared to be still impure of pyrazole (IV).

The acid (Ie) gave about 40% of 2-anilino-1,1-dicyano-2-phenyl-ethylene (III: R_1=CN, R_2=C_6H_5; m.p. 182°,lit.(11) 182-4°).

The acid (If) gave about 10% of 2-anilino-1-cyano-2-phenyl-1-p.tosyl-ethylene (III: R_1=$SO_2C_6H_4CH_3$(p), R_2=C_6H_5; m.p. 188°) and about 50% of 1,5-diphenyl-4-p.tosyl-pyrazole (m.p. 164°, lit.(8) 164°).

The ring opening in the case of 3-unsubstituted pyrazoles (II) was attempted by heating the products with potassium tert-butoxide in tert-butyl alcohol for several hours.

The pyrazoles (II: a,b) were both resistant to the alkaline treatment; however, in the case of (IIb) a trace of the β-anilino acrylonitrile (III: R_1=$COCH_3$, R_2=CH_3) was detected by T.L.C.

The pyrazole (IIc) gave 2-anilino-1-benzoyl-1-cyano-ethylene (III: R_1=COC_6H_5, R_2=H;m.p. 152°,lit.(8) 159°) in 40% yields. (IIc) has been recently reported to undergo the same cleavage by reaction with sodium amide in boiling xylene (12).

The pyrazole (IId) gave 2-anilino-1-cyano-1-nitro-ethylene (III: R_1=NO_2, R_2=H; m.p. 213°,lit.(13) 215-6°) in 35% yields.

The pyrazole (IIe) gave 2-anilino-1,1-dicyano-2-phenyl-ethylene (III: R_1=CN, R_2=C_6H_5; m.p. 182°,lit.(11) 182-4°) in 81% yields.

The pyrazole (IIf) gave 2-anilino-1-cyano-2-phenyl-1-p.tosylethylene (III: $R_1=SO_2C_6H_4CH_3$(p), $R_2=C_6H_5$; m.p. 188°) in 59% yield.

These experimental data clearly support the above hypothesis about the reaction mechanism of the pyrazole ring cleavage.

ACKNOWLEDGMENT. This work was supported by the Italian Research Council (Consiglio Nazionale delle Ricerche)

REFERENCES

1) B.K.Martsokha and A.M.Simonov, Zh.Obshch.Khim. 133 (11),3777 (1963).
2) L.Balbiano and O.Severini, Gazz.Chim.Ital. 23 (I),354 (1893).
3) M.L.Panzeri, Rend.Ist.Lomb.Sc.Lett.Arti, 95, 437 (1961).
4) I.L.Finar and K.E.Godfrey, J.Chem.Soc. 2293 (1954).
5) L.Claisen, Ann. 295, 320 (1897).
6) L.Balbiano, Gazz.Chim.Ital. 19, 139 (1889).
7) D.Dal Monte,A.Mangini and P.Passerini, Gazz.Chim.Ital. 86, 797 (1956).
8) C.E.Grothaus and F.B.Dains, J.Am.Chem.Soc. 58, 1334 (1936).
9) R.Fusco and R.Justoni, Gazz.Chim.Ital. 67, 3 (1937).
10) J.Pascual and F.Serratosa, Ber. 85, 686 (1952).
11) B.C.Mc Kusick,R.E.Heckert,T.L.Cairns,D.D.Coffmann and H.F.Mower, J.Am.Chem.Soc. 80, 2806 (1958).
12) I.I.Grandberg and N.I.Bobrova, Khim.Geterot.Soed.(1965), 566. (See Index Chemicus, Dec. 19, 1965, ref.59589).
13) H.B.Hill and G.W.Hale, Am.Chem.J. 29, 270 (1883).