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THE REARRANGEMENT OF 2-CYANO-1-PHENYLPYRAZOLE DERIVATIVES

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Abstract—The thermal rearrangement of the N′-cyanoaryl hydrazine system, previously encountered with 1-aryl-2-cyanodiazetidin-4-ones, has now been observed with suitable 2-cyano-1-phenylpyrazol-5-one derivatives.

THE thermal rearrangement of diphenylketen–arenediazocyanide adducts, such as I, to derivatives of the previously unknown 1-*H*-imidazo[1,2a]benzimidazole ring system, e.g. II has been reported in previous papers.[1,2] Molecular rearrangements are a common feature of small ring compounds and usually depend on the relief of ring strain for their driving force. As a result, similar rearrangements are observed infrequently in larger ring compounds. The ease with which compounds such as I rearrange suggested the following work, to see if analogous transformations could be observed when the N′-cyano-phenylhydrazine system was incorporated into a five-membered ring.

The 2-cyano-3,3-dimethyl-1-phenylpyrazolid-5-one (IIIb) was readily prepared from the corresponding 3,3-dimethyl-1-phenylpyrazolid-5-one (IIIa) and cyanogen bromide. The geminal dimethyl group prevents the possible elimination of hydrogen cyanide yielding the pyrazolone. On heating to 270° the pyrazolidone (IIIb) was isomerized into the pyrimido[1,2a]benzimidazole derivative (IV). The product had the expected IR spectrum[1,2] with bands at 3,150 cm^{-1} (N–H), 1730 cm^{-1} (C=O) and 1650 cm^{-1} (C=N). In order to establish whether the carbonyl group at position 5 was necessary for the rearrangement, 2-cyano-1-phenylpyrazolidine was prepared. This compound was obtained as an oil with an appropriate IR spectrum (C≡N, 2240 cm^{-1}) which rapidly lost hydrogen cyanide on warming forming 1-phenyl-pyrazoline. A number of unsuccessful attempts were made to reduce the pyrazolidone (IIIa) with LAH to the corresponding pyrazolidine in which a similar elimination could not occur.

Attention was next directed to the possibility of rearranging 2-cyano-1-phenyl-pyrazol-5-ones. In view of a previous report[3] on the reaction of cyanogen bromide with pyrazolones, its reactions with the anions of 3-methyl-1-phenylpyrazol-5-one and 1,3,4-triphenylpyrazol-5-one were investigated, but in neither case was the desired 2-cyano derivative obtained. However, under similar conditions 2-phenyl-indazolone gave the desired 1-cyano compound (V), which rearranged on heating to the benzimidazo[2,1-b]quinazolone (VI). The IR spectrum showed absorption between 2,500 and 3,200 cm^{-1} characteristic of hydrogen bonded NH, as well as

[1] C. W. Bird, *Chem. & Ind.* 1556 (1963).
[2] C. W. Bird, *J. Chem. Soc.* 5284 (1964).
[3] T. Shimidzu, *J. Pharm. Soc. Japan* No **527**, 12 (1926); *Chem. Abstr.* **20**, 2857 (1926).

bands at 1700 cm^{-1} (C=O) and 1650 cm^{-1} (C=N). Compound VI was also obtained from the reaction of methyl anthranilate with 2-chlorobenzimidazole.

Two mechanisms have been considered[2] for the rearrangement of I into II. The first entailed an *ortho*-semidine rearrangement of compound I to VII, followed by either intramolecular cyclization to VIII and a subsequent N- to -N migration yielding II or, rearrangement of VII to the carbodiimide (IX) and subsequent intramolecular cyclization. An obvious test of this mechanism is to examine the thermal stability of the postulated intermediate corresponding to VII. The low reactivity of diphenylamine towards cyanogen chloride[4] appeared to exclude the preparation of Xb from Xa, the appropriate intermediate in the rearrangement of V, and we were unable to prepare an N-cyano derivative of the benzodiazepinone (XI). Eventually the N-cyanodihydroquinoxalone (XII) was prepared in low yield and found to be thermally stable at least to 350°. Although the direct synthesis of XIIIa by the addition of dimethylketen to phenyldiazocyanide has not been investigated, an attempt was made to synthesize it from the dimethylketen-ethyl phenylazocarboxylate adduct (XIIIb). This compound, in contrast to its diphenylketen analogue,[5] is quite stable to acid catalysed isomerization but acid hydrolysis resulted in ring opening, rather than removal of the carbethoxy group, to give XIIIc.

However, in view of the relative ease of rearrangement of IIIb it seems most unlikely that the diazetidinone (XIIIa) would not rearrange under these conditions. This observation supports a second mechanism which postulates[2] a novel Cope-type rearrangement of XIV to a carbodiimide intermediate (XV), followed by transannular cyclization to II.

The foregoing observations indicate that although relief of ring strain assists this type of rearrangement, it is still possible to effect such transformations in relatively strain-free cases and we are currently investigating appropriate acyclic systems.

EXPERIMENTAL

IR spectra were recorded for Nujol mulls on a Perkin-Elmer model 137E spectrophotometer.

2-Cyano-3,3-dimethyl-1-phenylpyrazolidin-5-one (IIIb)

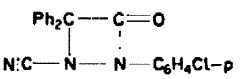
3,3-Dimethyl-1-phenylpyrazolidin-5-one[6] (2 g) and cyanogen bromide[7] (2·2 g) were dissolved in EtOH (20 ml) and the solution allowed to stand for 2 days. Dilution with water gave the *product* (IIIb; 1·9 g), which was recrystallized from cyclohexane, m.p. 105–106°. (Found: C, 66·8; H, 5·8; N, 19·6. $C_{12}H_{13}N_3O$ requires: C, 67·0; H, 6·0; N, 19·5%.) ν_{max} 2,240 and 1,730 cm^{-1}.

Isomerization of IIIb. The compound (IIIb; 1 g) was slowly heated to 270°, cooled and crystallized from benzene to give *2,2-dimethyl-4-oxo-1,2,3,4-tetrahydropyrimido*[1,2-a] *benzimidazole* (0·6 g), m.p. 222–224°. (Found: C, 66·8; H, 5·9; N, 19·4. $C_{12}H_{13}N_3O$ requires: C, 67·0; H, 6·0; N, 19·5%.)

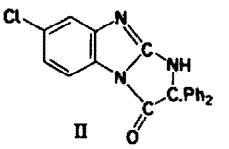
Reaction of 1-phenylpyrazolidine with cyanogen bromide

1-Phenylpyrazolidine[8] (18 g) in ether (50 ml) was added dropwise to a stirred, ice-cooled solution of cyanogen bromide[7] (6·5 g) in ether (100 ml). A white solid separated. The reaction mixture was stirred at room temp overnight, filtered and the filtrate washed with water and dried over Na_2SO_4. Evaporation of the ether in the cold gave an oil which rapidly evolved HCN on warming. Distillation

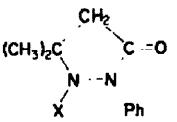
[4] W. Weith, *Ber. Chem. Dtsch. Ges.* **7**, 843 (1874).
[5] C. W. Bird, *J. Chem. Soc.* 674 (1963).
[6] B. Prentice, *Liebigs Ann.* **292**, 272 (1896).
[7] W. W. Hartman and E. E. Dreger, *Org. Syntheses* Vol. II; p. 150.
[8] A. Michaelis and O. Lampe, *Ber. Chem. Dtsch. Ges.* **24**, 3738 (1892); *Liebigs Ann* **274**, 316 (1893).



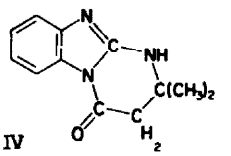
I



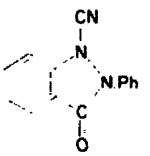
II



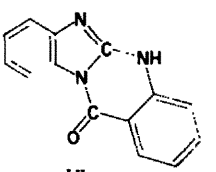
IIIa X = H
b X = C:N



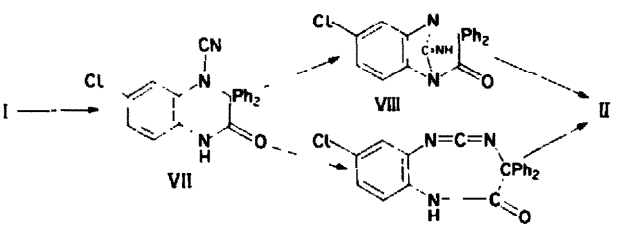
IV



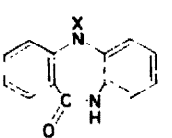
V



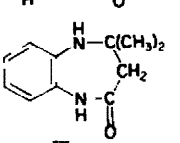
VI



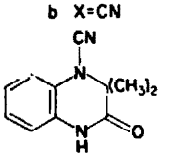
VII, VIII, IX



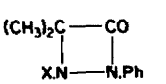
X a X = H
b X = CN



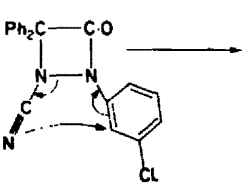
XI



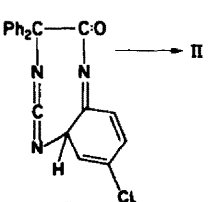
XII



XIII a X = CN
b X = CO_2Et
c X = H



XIV



XV

gave 1-phenyl-2-pyrazoline (5·2 g) b.p. 114–116° at 0·7 mm, m.p. 51–53° (from pet. ether) identical with an authentic sample.[8]

1-Cyano-2-phenylindazol-3-one (V)

2-Phenylindazol-3-one[9] (2·2 g) was dissolved in an ethanolic solution (30 ml) of EtONa (from Na 0·3 g). The solution was added slowly to a stirred solution of cyanogen bromide[7] (2·1 g) in EtOH (10 ml). A crystalline precipitate was rapidly formed. After stirring overnight the reaction mixture was diluted with water and the solid (1·8 g) filtered off. Recrystallization from MeOH gave *1-cyano-2-phenylindazol-3-one* m.p. 152–153° and slowly solidified on heating to ca. 250°. (Found: C, 72·0; H, 4·2; N, 17·8. $C_{14}H_9N_3O$ requires: C, 71·5; H, 3·9; N, 17·9%.) ν_{max} 2250, 1700 cm^{-1}.

Formation of benzimidazo[2,1-b]*quinazol-12(5H)-one*

(a) 1-Cyano-2-phenylindazol-3-one (0·5 g) was slowly heated to 270° and the resulting solid recrystallized from pyridine to give VI (0·27 g) m.p. 395–400°. (Found: C, 72·1; H, 4·3; N, 17·6. $C_{14}H_9N_3O$ requires: C, 71·5; H, 3·9; N, 17·9%.)

(b) Methyl anthranilate (3 g) and 2-chlorobenzimidazole[10] (1·5 g) were heated slowly to 150°. After 10 min the resulting solid was cooled and crystallized from pyridine to give VI (1·8 g) identical with the above sample.

1-Cyano-1,2,3,4-tetrahydro-2,2-dimethylquinoxalin-3-one (XII)

1,2,3,4-Tetrahydro-3,3-dimethylquinoxalin-2-one[11] (1·8 g) and cyanogen bromide[7] (2·0 g) were dissolved in EtOH (50 ml) and allowed to stand for 3 days. The solution was then poured into water and chloroform extracted. The extract was washed several times with 2 N H_2SO_4 to remove unreacted starting material before evaporation. The product (XII; 0·28 g) was obtained by crystallization of the residue from aqueous MeOH, m.p. 171–173°. (Found: C, 66·1; H, 5·9; N, 20·7. $C_{11}H_{11}N_3O$ requires: C, 65·7; H, 5·5; N, 20·9%.) ν_{max} 2230, 1675 cm^{-1}.

Ethyl 4,4-dimethyl-2-phenyl-3-oxo-2-phenyldiazetidine-1-carboxylate (XIIIb)

A stirred solution of ethyl phenylazocarboxylate[12] (17·8 g) and triethylamine (17 ml) in benzene (200 ml) was treated dropwise with isobutyryl chloride (24·6 g) and then allowed to stand overnight. Dil. H_2SO_4 was added to the reaction mixture, the benzene layer separated and washed with water. After drying over Na_2SO_4 the benzene was removed *in vacuo* and the residual oil distilled to give unreacted ethyl phenylazocarboxylate (8 g) b.p. 120° at 1·8 mm, and the XIIIb b.p. 145° at 1·8 mm as a pale orange viscous oil. (Found: C, 63·0; H, 6·6; N, 11·3. $C_{13}H_{16}N_2O_3$ requires: C, 62·9; H, 6·6; N, 11·3%.) ν_{max} 1800, 1745 cm^{-1}.

Acid treatment of (XIIIb). The diazetidinone (XIIIb) (6·0 g) was heated under reflux with EtOH (40 ml) and conc. HCl (20 ml) for 2 hr. The product was obtained by addition of water and ether extraction. Distillation gave *ethyl α-(N-carbethoxy-N'-phenylhydrazino)-isobutyrate* (3·4 g) b.p. 160° at 0·6 mm as a yellow viscous oil. (Found: C, 61·5; H, 7·3; N, 9·7. $C_{15}H_{22}N_2O_4$ requires: C, 61·2; H, 7·5; N, 9·5%.) ν_{max} 3300, 1730, 1700 cm^{-1}.

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[10] D. Harrison, J. T. Ralph and A. C. B. Smith, *J. Chem. Soc.* 2930 (1963).
[11] O. Hinsberg, *Liebigs. Ann.* **248**, 79 (1888).
[12] C. K. Ingold and S. D. Weaver, *J. Chem. Soc.* **127**, 378 (1925).