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ENE REACTION OF 1-PYRAZOLINE DERIVATIVES WITH TETRACYANOETHYLENE

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Abstract.- 1-Pyrazoline derivatives 4 and 5 reacted with tetracyanoethylene to give, through a formal ene reaction followed by a loss of hydrogen cyanide, 1-tricyanovinyl-2-pyrazoline derivatives 6 and 7 as dominant products. By contrast, tetracyanoethylene played only a catalytic role in the reaction with 1-pyrazolines 11 promoting their tautomerization to 2-pyrazolines 13. The possible mechanisms of such reactions are discussed.

The ene reaction has recently grown into one of the most useful and interesting organic reactions due to its synthetic versatility and to its mechanistic problems.[1] Although a remarkable variety of aliphatic and alicyclic ene systems has been studied, rare examples of heteroatom analogs have been until now discovered.[1] In particular, no ene reactions involving a -CH-N=N- heteroene moiety have been, to our knowledge, reported. Thus, the facile reaction of 1-pyrazoline derivatives 4 and 5 with tetracyanoethylene (TCNE) provides the first example of such a heteroene system.

SYNTHESIS OF 1-PYRAZOLINE DERIVATIVES.

Excess cyclooctatetraene reacted smoothly at room temperature with diazomethane, diazoethane and phenyldiazomethane to give tricyclic adducts of type 2 [e.g. 2b, ν_{max}^{Nujol} 1538 (-N=N-) cm^{-1}; δ(CDCl$_3$) 1.20 (d, Me, $J_{5,Me}$ = 7.5 Hz), 2.18–2.62 (m, H-6 and H-7), 3.01 (ddd, H-1, $J_{1,7}$ = 10.5 Hz, $J_{1,2} \simeq J_{1,11}$ = 3.0 Hz), 4.74 (ddq, H-5, $J_{2,5}$ = 3.0 Hz, $J_{5,6}$ = 1.8 Hz), 5.23 (ddd, H-2, $J_{2,6}$ = 6.0 Hz), 5.45–6.00 (m, H-8, H-9, H-10 and H-11)] most seemingly through the not detected bicyclic adducts of type 1.[2] The trans relationship between H-5 and H-6 in compounds 2b and 2c is supported by their low coupling constants ($<$ 2.0 Hz).[3] The re -

action was found strongly selective giving, in the case of phenyldiazomethane, only the epimer 2c while in the crude adduct from the reaction with diazoethane traces ($\leq$ 5%) of the epimer of 2b were detected by ^{1}H n.m.r. analysis $\left[\delta\ 1.45\ (d,\ Me,\ J_{5,Me} = 7.3\ Hz)\right]$. Noteworthy, these findings are good evidence for steric hindrance to the achievement of a transition state 3, in sharp contrast with the results of the Diels - Alder reaction of dimethyl-diphenylcyclopentadienone with 1,3-cyclooctadiene where only the more crowded endo adduct was obtained.[4]

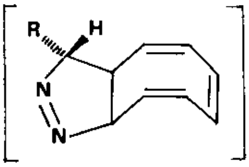
Dimethyl acetylendicarboxylate reacted easily with compounds 2 in ether under reflux to afford adducts 4 [e.g. 4b, ν_{max}^{Nujol} 1545 (-N=N-) and 1715 (COOMe) cm^{-1}; λ_{max}^{EtOH} 328 nm (log ε = 2.33); δ(CDCl$_3$) 1.18 (d, Me, $J_{6,Me}$ = 7.3 Hz), 1.40 (m, H-7), 1.70 - 2.40 (m, H-2 and H-8), 3.75 (s, two OMe), 4.00-4.80 (m, H-1, H-3 and H-9), 6.55 (m, H-12 and H-13)] while excess dimethyl maleate and 2b required heating under reflux in benzene to give 5b.[5a]

The attack of diazomethane to 10 resulted again highly selective and involved only the electron-poor tetrasubstituted double bond from the less hindered side, that is anti with respect to the cyclobutene moiety. In fact, the adduct 11a displayed the expected vinyl proton resonances [δ(CDCl$_3$) 2.97 (m, H-8 and H-11), 3.40 - - 3.90 (m, H-1 and H-7), 3.72 (s, two OMe), 4.51 and 4.92 (H-5, J=19.5, AB system), 5.65 (m, H-9, H-10, H-12 and H-13)] and the proposed anti-stereochemistry finds support in the upfield shift of H-12 and H-13 resonances, due to shielding by pyrazoline ring,[6] in comparison with H-8 and H-9 signals [δ(CDCl$_3$) 6.02, m] of the model compound 12.

Finally the cis relationship between the phenyl and methoxycarbonyl groups in 11c, isolated as dominant adduct from the reaction of phenyldiazomethane with 10, follows from the strong shielding experienced by one of the methoxycarboxyl groups [δ(CDCl$_3$) 3.00] compared to the other (δ 3.82).

REACTIONS OF 1-PYRAZOLINE DERIVATIVES WITH TCNE.

Pyrazolines 4 and 5 (1.0 mmol) reacted slowly (10 days) with TCNE (1.1 mmol) in acetonitrile (3 ml) at room *temperature to give 1-tricyanovinyl-2-pyrazolines 6 and 7. Minor amounts of azomethine imine derivatives* 8b and 9b were also isolated from the reactions of 4b and 5b, respectively, and compound 8c detected (traces, tlc analysis) but not isolated from the reaction of 4c. The structures of compounds 6 and 7 rest firmily on analytical and spectral data. Taking compound 6b as example it exhibits strong absorptions at 2220 and 1590 cm^{-1} in the IR spectrum and shows an UV maximum at 370 nm (EtOH, log ε = 4.34) in agreement with the presence of



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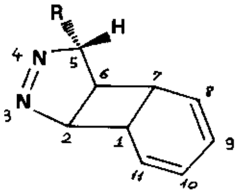

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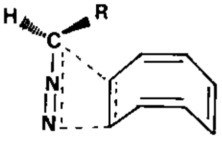

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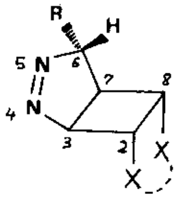

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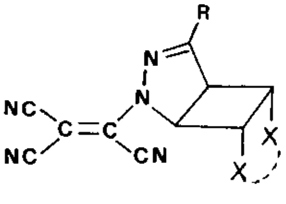

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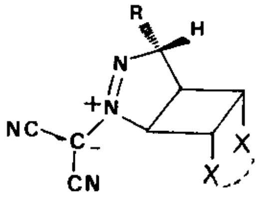

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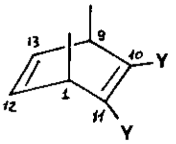

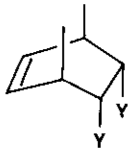

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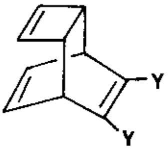

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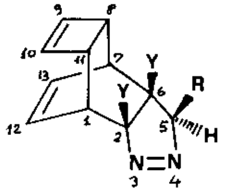

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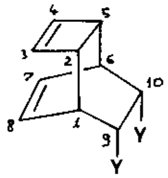

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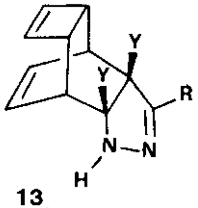

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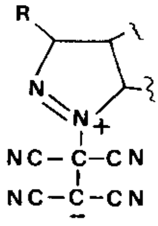
Y = COOMe

a : R = H , b : R = Me, c : R = Ph



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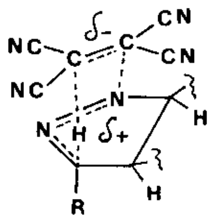

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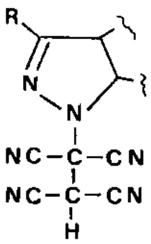

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Table

Comp.	Mp (°C)	Yield (%)[a]	Comp.	Mp (°C)	Yield (%)
2a	39–42	30	6c	207–209	78
2b	57–59	50	7b	254 dec	50
2c	95–98	60	8b[b]	157–158	8
4a	Oil	50	9b	198–203	5
4b	110–111	85	11a	132–133	85
4c	e	80	11c[c]	136–137	60[d]
5b	131–132	50	13a	103–107	50
6a	195–196	42	13c	180–186	90
6b	185–189	55			

[a] The yields are for pure products isolated by silica gel column chromatography. All compounds gave satisfactory microanalyses (C, ± 0.40; H, ± 0.30).

[b] ν_{max}^{Nujol} 2200, 2220 (CN) and 1485 (N=N) cm^{-1}

[c] δ 5.90 (m, H-9, H-10, H-12 and H-13), 5.44 (s, H-5).

[d] Tlc and ^{1}H n.m.r. analysis of the crude reaction product showed the presence of minor amounts of other adducts that we were not able to isolate in a pure state.

[e] Glassy solid

a N-C(CN)=C(CN)$_2$ group.[7] Moreover, its ^{1}H n.m.r. spectrum [δ ($CDCl_3$), 2.20 (s, Me), 2.55 (m, H-2 and H-8), 3.25 (m, H-7), 3.78 (s, two OMe), 4.1-4.9 (m, H-1, H-3 and H-9), 6.65 (m, H-12 and H-13)] clearly shows that the TCNE attack was localized at the heterocyclic ring leaving unaltered the carbocyclic moiety of the starting compound 4b. An X-ray analysis of compound 7b established beyond any doubt the correctness of the proposed structures.[8]

Compound 9b has been already reported as the dominant product of the reaction of 5b with TCNE oxide[5a] and 8b was isolated as the major product in a similar reaction between TCNE oxide and 4b.[5b]

In contrast with these results pyrazolines 11 rearranged slowly into 2-pyrazolines 13 in the presence of TCNE in acetonitrile [13a, ν_{max}^{Nujol} 3330 (NH) and 1735 (COOMe) cm^{-1}; δ($CDCl_3$) 3.2 (m, H-1, H-7, H-8 and H-11), 3.70 and 3.75 (two s, OMe), 5.85 (bs, H-9 and H-10), 5.92 (m, H-12 and H-13), 6.5 (s, H-5)]

Compounds 11 were found stable when alone in acetonitrile but they were also easily transformed into 13 upon treatment with concentrated aqueous hydrochloric acid.

Concerning the reactivity of 4 and 5 with TCNE, the zwitter ion 14 seems to be a necessary intermediate in the reaction path leading to 8 and 9[+], whereas two different mechanisms may be advanced to explain ene products 6 and 7: (a) an electrophilic attack of TCNE on a pyrazoline lone pair to give zwitter ion 14; (b) a concerted ene reaction involving the nitrogen-nitrogen double bond through the polar transition state 15 to give 16. In either cases the first step is followed by a loss of hydrogen cyanide.

We discarded for 4 and 5 a prior tautomerization from 1- to 2-pyrazoline derivatives and subsequent reaction with TCNE on the basis of the following i) attempted isomerization of 5b upon treatment with hydrochloric acid led only to decomposition products ii) 1-pyrazolines condensed with a cyclobutane ring are known to tautomerize with simultaneous breakdown of the carbon-carbon bond common to the two rings to give seven membered heterocyclic compounds.[9]

Competition reaction experiments of TCNE with an excess mixture of 4b/4c showed that 4c is ≃ 8 times more reactive than 4b in agreement with a C_6-H_6 bond breaking in the slowest reaction step. This result while reasonably expected for mechanism (b), is easily accomodated also for mechanism (a), if one consider that the formation of 14 is most seemingly fast and reversible. Inconclusive was also a qualitative study of solvent polarity effect in enhancing reaction rate of 4c with TCNE; the order found, acetonitrile > ethyl acetate > 1,2-dichloroethane > benzene did not exactly parallel (being 1,2-dichloroethane more polar than ethyl acetate)[10] the decrease in solvent polarity. A reasonable explanation of the above noted irregularity lies in the presence of a charge-transfer complex between 4c and TCNE, the association constant of which is probably very dependent on the nature of the solvent.[11] In fact a yellow colour developed at once when the reactants were mixed

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[+] We consider unlikely that compounds 8 and 9 could result from some TCNE oxide present in the reaction mixture; in fact TCNE oxide is reported to attack both the nitrogen atoms[5a] of the pyrazoline ring whereas only the nitrogen in position 4 was involved in the reactions studied. We are at present testing the hypothesis that oxygen may favour the process 14 ⟶ 8 or 9.

together and a yellow crystalline 1:1 complex (m.p. 124–125° dec., $\lambda_{max}^{CH_2Cl_2}$ 411 nm) was isolated from the reaction of TCNE with the adduct of 2-diazopropane to 12 (i.e. a pyrazoline of type 5 with two methyl groups in position 6). When this complex was dissolved in $CDCl_3$ it displayed a ^1H n.m.r. spectrum identical in all respect to that of the starting pyrazoline. In order to gain further data on the reaction mechanism we have at present undertaken an investigation (X-ray analysis and UV spectral study) on the nature and the role of this complex: in fact the pyrazoline can act either as a π or σ donor and the complex can be either a true intermediate or represent a side reaction product. A yellow-orange crystalline 1:1 adduct (m.p. 134–136°C, $\lambda_{max}^{CH_2Cl_2}$ 388 nm) precipitated in high yield when equimolar amounts of 11c and TCNE were dissolved in anhydrous ether and the mixture then cooled at −15°C; again its ^1H n.m.r. spectrum (CD_3CN) was identical to that of 11c. Consequently one may argue that the rearrangement $11 \rightarrow 13$ takes place in the 11•TCNE complex. Finally we suggest that the different reactivity of 4 and 5 in comparison to 11 originates from steric strain of the former compounds due to the presence of a condensed cyclobutane ring which in turn is condensed with a rigid carbocyclic moiety.

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