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UNUSUAL TRANSFORMATIONS OF THE CHRYSANTHEMIC NITRILE SKELETON BY SODIUM HYDRIDE IN N,N-DIMETHYLFORMAMIDE

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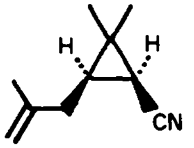
Abstract - It is shown that the title transformations occurred through base-catalyzed opening of the cyclopropane ring into the dienic nitrile 4 which then reacted with the in situ formed formaldehyde to yield the bicyclic compound 5.

In the course of a former work [1], we tried to equilibrate the iso-cis-chrysanthemic nitrile 1 into the corresponding trans isomer. When treated with a slight excess of sodium hydride in N,N-dimethylformamide at 110°C for 2 hr, it gave surprisingly a crystalline compound "X" as major product. As summarised in the table, the same new compound X (5) was also obtained by similar treatment of either the cis 2, the trans 3 chrysanthemic nitrile or the dienic nitrile 4.



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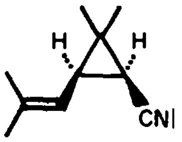

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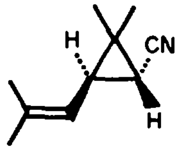

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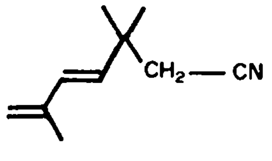

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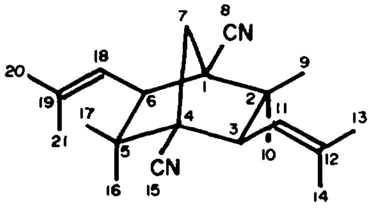

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Table

Substrate	Conditions in N,N-dimethylformamide	Yields of products %			
		<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>
<u>1</u>	1,3 equiv. NaH; 110°C; 2 hr	*	*	*	52
<u>2</u>	1,1 equiv. NaH; 115-120°C; 4 hr	9	9	25	8
<u>3</u>	1,1 equiv. NaH; 115-120°C; 4 hr	7	7	17	23
<u>3</u>	same conditions, but with N_2 bubbling	6	6	20	3
<u>4</u> **	1,1 equiv. NaH; 115-120°C; 4 hr	2.5	2.5	29	19

* not determined

** the starting material was a mixture of the compounds <u>4</u>, <u>3</u> and <u>2</u> (ratios = 72:14:14)

The new compound X has mp 191°C; IR (KBr) : 2240 (C≡N) and 1670 cm^{-1} (C=C); m/e (relative intensity): 310 (M^+, 10) and 110 (100) and gave acceptable analytical values for $C_{21}H_{30}N_2$. NMR parameters were as follows: ^1H ($CDCl_3$): 5.08 (1H; dxqxq; J = 10.25 Hz, 1.6 Hz, 1.6 Hz); 2.95 (1H; d, J = 10.25 Hz); 2.42 (1H, s); 1.81 (3H, d, J = 1.6 Hz); 1.66 (3H, d, J = 1.6 Hz); 1.26 (3H, s); 1.09 (3H, s); ^{13}C: 136.19 (s), 121.38 (s), 118.76 (s), 53.47 (s), 46.85 (d), 45.88 (s), 41.40 (t), 25.94 (q), 25.35 (q), 24.47 (q) and 18.19 (q).

The structural elucidation of compound <u>5</u> was based on two recently developped NMR techniques: INADEQUATE [2] and cross-relaxation chemical shift correlation spectroscopy (NOESY)[3]. Eleven carbons are present in the noise decoupled ^{13}C NMR spectrum and quantitative analysis demonstrates that the signal at 41.4 ppm integrates at half the value for the other signals. The molecule possesses either a center, an axis or a plane of symmetry, the isolated carbon being on the symmetry element.

The presence of an isobutylidene group * is easily recognized from the proton spectrum; that this group is attached to a tertiary carbon is evident from the coupling (J = 10.25 Hz) of the proton at 2.95 ppm and the vinylic proton.

The ^{13}C signal multiplicity was established by spin-echo experiments [4]. The carbon located on the symmetry element is shown to be secondary; the carbons at 18.2, 24.5, 25.4 and 25.9 ppm primary; the carbons at 121.4 and 46.8 tertiary and all others (136.2, 118.8, 53.5 and 45.9 ppm) quaternary.

The carbon skeleton could be established by an INADEQUATE experiment [2]. This technique allows the establishment and measurement of the homonuclear ^{13}C - ^{13}C scalar coupling constants. These couplings and singularly the one-bond couplings (^1J) are very sensitive to hybridisation and substitution, and allow the establishment of the nature and identity

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* Ozonolysis of compound <u>5</u> afforded the corresponding dialdehyde whose physical data are described in the experimental part.

of the various carbons. For exemple the carbon at 118.8 ppm has a single ^{13}C neighbour, with which it shows a large coupling constant (65 Hz), and is thus shown to be sp hybridised. The presence in the IR spectrum of an absorption at 2240 cm^{-1} indicates that this carbon is a nitrile.

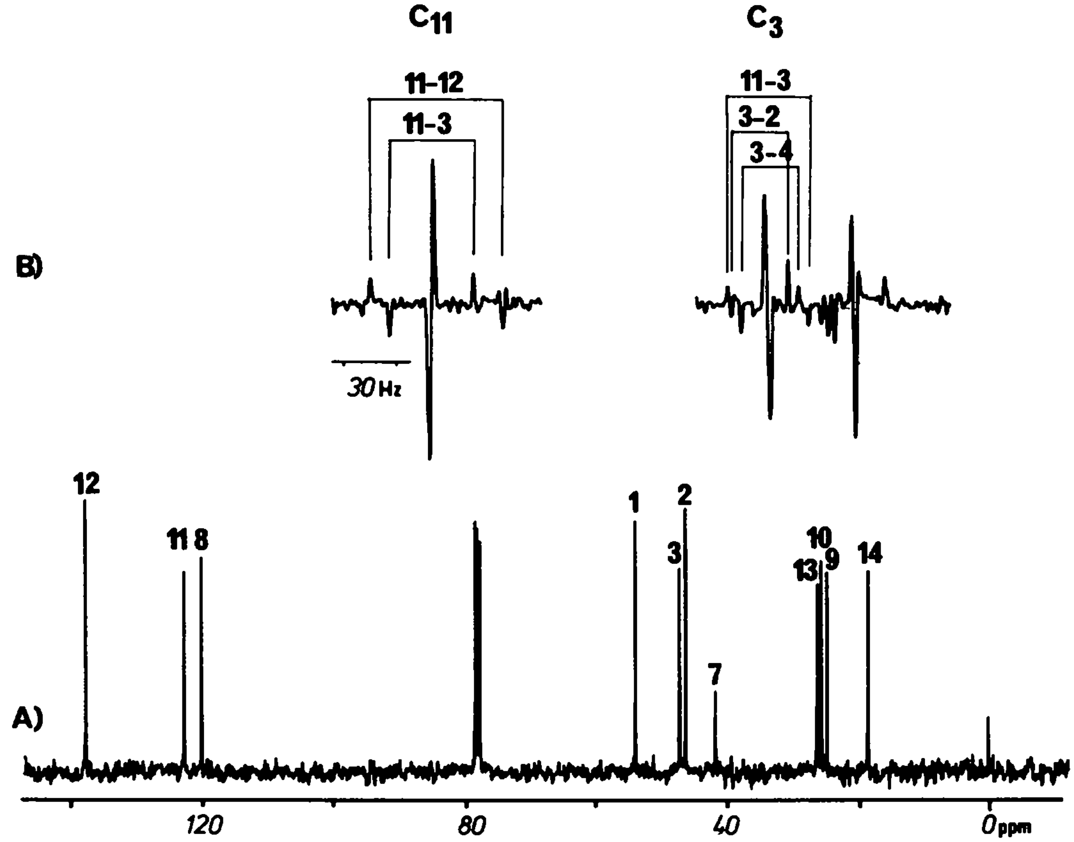
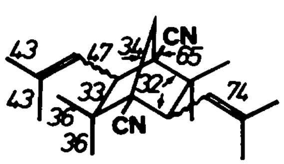
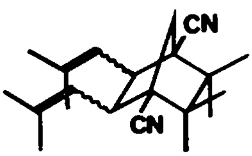


Figure 1. A) Quantitative 100 MHz ^{13}C spectrum (40 sec relaxation time between each scan without decoupling).
B) 50 MHz INADEQUATE spectrum showing carbons 3 and 11.

Another important advantage of the INADEQUATE technique is that it allows the identification of vicinal carbons by the measurement of their common ^{1}J coupling. In the present case this had a rather unusual application in that it made possible the determination of the symmetry element in the molecule (center, plane or axis) and hence the choice between two reasonable formulae 5a and 5b which were both compatible with the proton and carbon spectra.



5a



5b

In fact, carbon 3 (46.8 ppm) is shown (Fig. 1) to have three distinct (in the NMR sense) neighbours thus excluding structure 5b where due to the symmetry, it would have only two. The various one-bond homonuclear couplings (in Hz) are represented on the actual structure 5a. The last obstacle was the establishment of the stereochemistry at carbon 3 and this was overcome by demonstrating the existence of crossrelaxation mechanisms between spatially close protons.

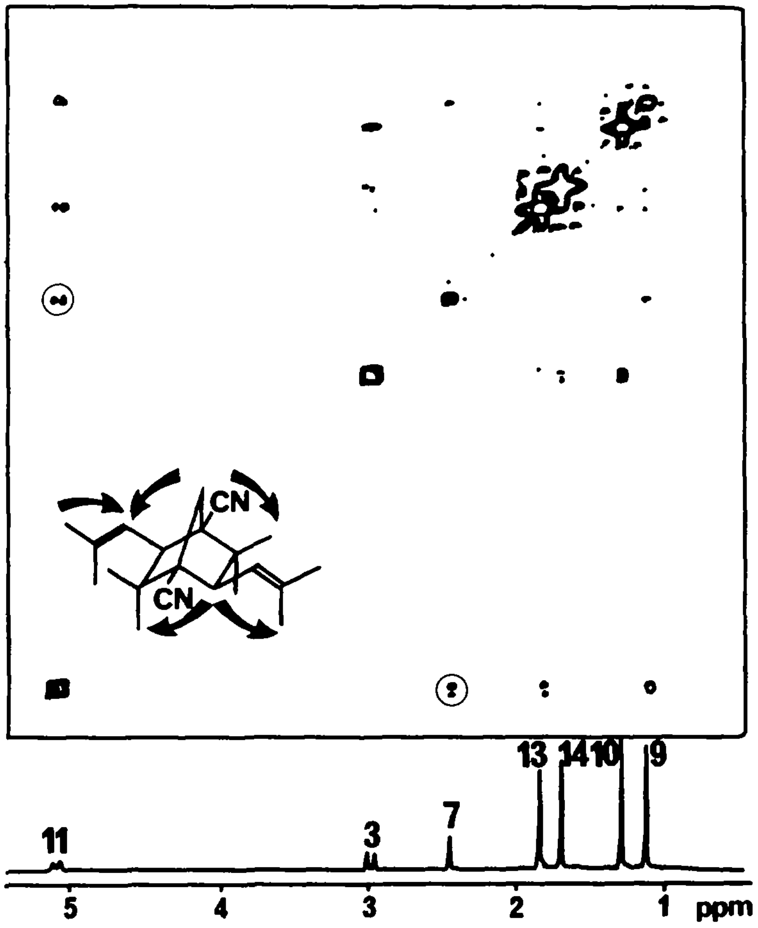
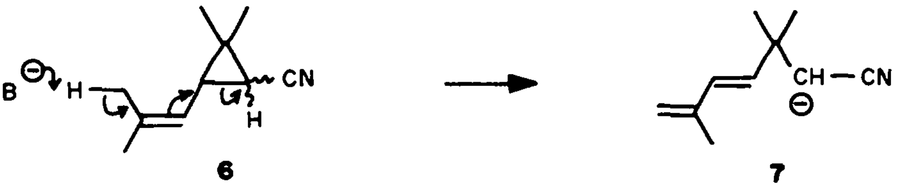


Figure 2. 200 MHz two-dimensionnal NOESY spectrum (1 sec mixing time)

Figure 2 represents a NOE chemical shift correlation map and establishes among others the spatial proximities (encircled spots) of the protons 7 and 11. Such a situation is only compatible with the stereochemistry indicated on formula 5. Besides identification of the various methyl groups is achieved and it allows by means of some selective heteronuclear decouplings the complete attribution of the ^{13}C spectrum. The γ effect supports the observed chemical shift difference of methyles 13 and 14. Finally the presence of a small but discernable ($J < 1$ Hz) W coupling between protons 7 and 3 supports 5 as the structure of the new compound.

The presence in this structure 5 of 21 carbons suggests that this compound originates from the reaction of two molecules of a precursor nitrile (10 carbons) with a single functionnal carbon. The second noticeable point is not only the formation of compound 5 from dienic nitrile 4 but also the formation in significant amounts of this same dienic nitrile from cyclopropane nitriles 2 or 3. This last transformation (2 or 3 $\longrightarrow$ 4) can easily be explained by an allylic deprotonation in the basic medium (6) that leads to carbanion 7. This represents a new case of carbon serving as the nucleofugal group in a Grob fragmentation [6].



This suggests that the final product 5 could arise from the reaction of two such carbanions 7 with a single carbon electrophile. Formaldehyde is the most reasonable electrophile in the medium. Indeed it has been reported [7] that when a suspension of sodium hydride in DMF was heated at 100°C for 1 hr, a decomposition took place according to the following equation:

$$(CH_3)_2N\text{-}CHO + NaH \longrightarrow (CH_3)_2N\text{-}CH_2O^{\ominus}Na^{\oplus} \rightleftharpoons (CH_3)_2N^{\ominus}Na^{\oplus} + H_2C{=}O$$

That formaldehyde is responsible for the formation of compound 5 is supported by the following two observations:

- bubbling of dry nitrogen through the heated mixture of chrysanthemic nitrile 3 and sodium hydride in DMF, eliminates most of the formaldehyde and leads to a very poor yield of compound 5, without any significant alteration of the final quantity of dienic nitrile 4;
- heating the trans chrysanthemic nitrile 3 with sodium hydride in 1,2-dimethoxy ethane for 3.5 hr gives a mixture of cis and trans (55 : 45) chrysanthemic nitriles, whereas compound 5 could not be detected in this experiment.

From those considerations it is reasonable to suggest that two molecules of carbanion 7 react with the formaldehyde [*] present in the reaction medium yielding dinitrile 8 [**]. This latter is then deprotonated by the base and the corresponding carbanion reacts through a nucleophilic addition of the 5-exo-trig type [9] onto one of the two isoprenic chromophores present in the molecule (formula 9) and leads to the monocyclic allylic carbanion 10 [**]. This cyclisation is similar to the known addition of the sodium salt of isobutyronitrile onto 1,3-dienes [10] and should reasonably lead to cyclopentane 10 whose ramified substituents are trans. Since the hydrogen α from the secondary nitrile in compound 10 is more acidic

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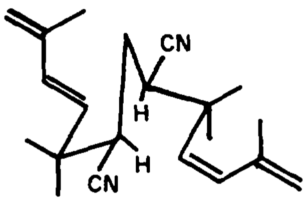
[*] This reaction is well known: for instance benzyl cyanide and trioxomethane (s-trioxane) lead when treated with methanolic potassium hydroxide during 1 hr at 84°C, to 1,3-diphenyl-propane-1,3-dicarbonitrile in 36 % yield [8]. Moreover, heating isovaleronitrile with sodium hydride in DMF for 3 hr gives a mixture of diastereoisomers $(CH_3)_2CH\text{-}CH(CN)\text{-}CH_2\text{-}CH(CN)\text{-}CH(CH_3)_2$ in 26 % yield (experimental part).

[**] No pure compound corresponding to any of the intermediates 8 or protonated 10 could be isolated by chromatographic analysis of the additional products obtained during the various preparations of dinitrile 5.

than an allylic hydrogen, a new carbanion 11 should form rapidly and lead to the allylic carbanion of final product 5 through a nucleophilic addition onto the last 1,3-dienic group present.



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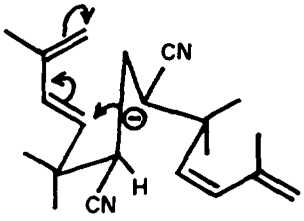

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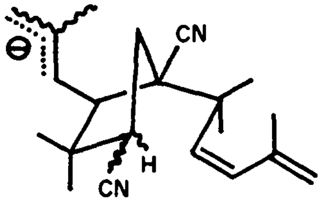

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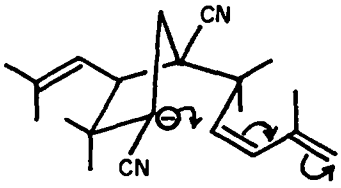

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EXPERIMENTAL

Melting and boiling points are uncorrected. Mass spectra were recorded on a Nermag R 10 - 10 B with Sidar reduction date (G.C. / M.S. or direct inlet; E.I. 70 eV).

NMR spectra were recorded on CAMECA 250 BRUKER WH-90 and SY-200 spectrometers. ^1H chemical shifts are given in δ (ppm) from internal TMS; ^{13}C chemical shifts are given in δ (ppm) from TMS with the solvent peaks as internal standard.

The IR spectra were recorded on a Perkin Elmer 457 spectrometer; frequencies are given in cm^{-1}.

3,6-Bis (2-methyl-1-propen)-yl-2,2,5,5-tetramethyl-bicyclo[2.2.1] heptane-1,4-dicarbonitrile - The trans chrysanthemic nitrile 3 [11] (2.1 g; 14 mmol) dissolved in N,N-dimethylformamide (25 ml) was treated with sodium hydride (0.360 g; 15 mmol from 0.720 g of a 50 % dispersion in mineral oil washed with anhydrous petroleum ether) at 115-120°C for 4 hr. Iced water was added and the mixture extracted three times with dichloromethane. The extracts were washed four times with water and dried over magnesium sulfate. Evaporation of the solvent left a crude product which afforded on distillation:

. a first fraction (0.660 g; 31%), b.p. 85-103°C/0.8 mm Hg which contains the three nitriles 2, 3 and 4 [12] (ratios : 2.2 : 2.3 : 5.5; g.l.c. carbowax 20 M, 2 m., programmed temperature);

. then a fraction (1.2 g) b.p. 110-140°C/0.002 mm Hg which became partially cristalline. Two crystallizations from ether:pentane afforded white crystals (0.370 g), m.p. 186 - 188°C. Evaporation of the mother liquors, a preparative silica gel TLC purification and a crystallization gave a further 0.137 g of the same compound 5 (total yield 23 %).

For analysis, it was sublimed at 90°C/0.02 mm Hg; m.p. 191°C; (Found: C, 80.76; H, 9.83; N, 9.28. $C_{21}H_{30}N_2$ Requires: C, 81.23; H, 9.74; N, 9.02 %); ν_{max}^{KBr}: 2240 and 1670; m/e (relative intensity): 310 (10) $[M^+]$, 295 (27), 216 (51), 199 (11), 185 (9), 174 (17), 160 (18), 148 (34), 132 (15), 128 (8), 110 (100), 95 (90).

- The cis iso chrysanthemic nitrile [1] 1 (0.664 g; 4.45 mmol) when treated with 0.140 g (6 mmol) of washed sodium hydride in DMF at 110°C for 2 hr gives, after the same work up as above, 0.360 g (52 %) of pure compound 5.
- The cis chrysanthemic nitrile 2 (0.670 g; 4.5 mmol) dissolved in DMF (7 ml) was treated with sodium hydride (0.120 g; 5 mmol) at 115-120°C for 4 hr. The same work up as above gave a first fraction (0.301 g) b.p. 80°C/0.8 mm Hg which contains the three nitriles 2, 3 and 4 in the ratios 2.15 : 2.15 : 5.7 (g.l.c.) and then a fraction (0.202 g) b.p. 130-140°C/ 0.002 mm Hg from which 0.052 g (8%) of pure compound 5 was crystallised out.
- A solution of the dienic nitrile 4 (containing 28% of the two nitriles 2 and 3; 0.150 g; 1 mmol) in DMF (1.8 ml) was treated with sodium hydride (1.1 mmol) at 115-120°C for 4 hr. The usual work up and a preparative silica gel TLC (petroleum ether:ether, 6:4) gave a fraction from which 0.029 g (19%) of compound 5 was crystallised. The mother liquor was evaporated to yield 0.051 g of a mixture of 2, 3 and 4 (ratios 7 : 7 : 86; g.l.c.).

3,6-Bis(formyl)-2,2,5,5-tetramethyl-bicyclo[2.2.1]heptane-1,4-dicarbonitrile

Ozonised oxygen was bubbled through a solution of compound 5 (0.31 g) in dichloromethane (50 ml) containing pyridine (0.3 ml) at - 70°C. After 30 min. reaction, the cooled ozonolysis solution was flushed with nitrogen during 10 min.; zinc dust (1 G) and acetic acid (10 ml) were added and the mixture was warmed to room temperature then at reflux for 15 min. Methylene chloride and water were added and the layers separated. The methylene chloride layer was washed with water and then dried over anhydrous sodium sulfate. Evaporation of the solvent left the crude dialdehyde (0.178 g; 69 %) which crystallized from methylene chloride:petroleum ether, m.p. 178-182°C; (Found: C, 69.53; H, 7.41; N, 11.01; O, 12.49. $C_{15}H_{18}N_2O_2$ Requires: C, 69.74; H, 7.02; N, 10.85; O, 12.39); ν_{max}^{KBr} : 2850, 2740, 2720, 2240 and 1727. m/e (relative intensity): 258 (30) $[M^+]$, 243 (23), 229 (13), 215 (18), 201 (13), 188 (30), 174 (47), 159 (30), 145 (31), 131 (39), 120 (31), 104 (30), 94 (51), 90 (61), 85 (100). δ ^{1}H ($CDCl_3$; 250 MHz): 1.31 (s, 6H); 1.42 (s, 6H); 2.85 (s, 2H); 2.98 (d, J=3 Hz, 2H); 9.80 (d, J = 3 Hz, 2H). δ ^{13}C ($CDCl_3$): 23.61 (q), 24.55 (q), 41.64 (t), 45.10 (s), 47.82 (s), 57.14 (d), 117.18 (s), 199.77 (d).

2,6-Dimethyl-heptane-3,5-dicarbonitrile

Isovaleronitrile (4.7 g; 56.5 mmol) dissolved in N,N-dimethylformamide (10 ml) was added to a suspension of washed sodium hydride (1.51 g; 62.7 mmol) in DMF (80 ml) and the mixture was heated to 115-120°C for 3 hr. The same work up as for compound 5 afforded a crude product (4.65 g) which was distilled; a fraction (1.32 g, 26%) b.p. 101-4°C/1 mm Hg became cristalline. Two crystallizations from pentane afforded 0.85 g of white crystals m.p. 48-52°C which were a mixture of diastereoisomers; ν_{max}^{KBr} : 2235. M.S. (direct introduction, electronic impact) m/e (relative intensity): 179 (1) $[M^+ +1]$, 163 (2), 149 (1), 109 (8), 96 (35), 83 (100), 68 (69), 54 (66). δ ^{1}H ($CDCl_3$, 250 mHz): 1.04-1.18 (4d, 2x2CH_3); 1.75-1.85(m, 2H); 1.85-2.10 (m, 2x1H); 2.66-2.69 (m, 1H); 2.69-2.82(m, 1H).

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