Unexpected reactions of α,β-unsaturated esters with hydrazine hydrate

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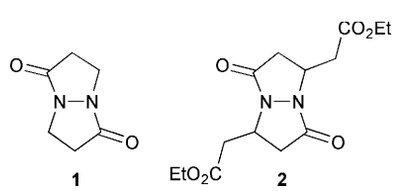
The reactions of hydrazine hydrate with methyl acrylate and ethyl acrylate do not result in the formation of 1,5-diazabicyclo[3.3.0]octane-2,6-dione **1** at reaction temperatures below 200 °C; 1,2-bis(alkoxycarbonylethyl)-pyrazolidin-3-one **8**, 1-(alkoxycarbonylethyl)pyrazolidin-3-one **6**, and 2-(alkoxycarbonylethyl)pyrazolidin-3-one **11** were isolated and identified. At 260–280 °C, however, **1** could be isolated in 20–28% yield; formation of **1** could also be observed by spectroscopic measurements when the reaction was carried out above 200 °C. It is concluded that the major pathway involves initial Michael addition to give a 1,1-disubstituted hydrazine that cannot yield **1** without undergoing unfavourable retro-Michael reactions. The apparently similar reaction of hydrazine with excess diethyl glutaconate to give 4,8-bis(ethoxycarbonylmethyl)-1,5-diazabicyclo[3.3.0]octane-2,6-dione **2** takes a quite different course. Initial Michael addition gives a 1,2-disubstituted adduct for steric reasons. Although double cyclisation of this adduct to **2** appears straightforward, retro-Michael reaction of the monocyclised adduct is very rapid and competes with the second cyclisation. The reaction of ethyl methacrylate and hydrazine hydrate at 80 °C results in a complex reaction mixture, which is transformed into 4-methylpyrazolidin-3-one **13** at 390 °C under reduced pressure.

Introduction

Since the first report on 1,8-bis(dimethylamino)naphthalene,[1] widely known as a "*proton sponge*", there has been continued interest in the synthesis and properties of compounds containing two nitrogen atoms which can trap a proton,[2] especially aromatic proton sponges[3] and intrabridgehead bicyclic systems.[4,5]

For the synthesis of bridgehead bicyclic amines, the preparation of 1,*k* + 2-diazabicyclo[*k*.1.0]alkanes is the most convenient method; they are then transformed into tricyclic intermediates by means of the dication[6] or the α-amino-ammonium ion routes,[7] which then give rise to diazabicycloalkanes by reductive cleavage.

In this paper we report unexpected reactions of α,β-unsaturated esters with hydrazine hydrate, which we observed during the synthesis of two bicyclic intermediates: 1,5-diazabicyclo[3.3.0]octane-2,6-dione[8,9] **1** and 4,8-bis(ethoxycarbonylmethyl)-1,5-diazabicyclo[3.3.0]octane-2,6-dione[10] **2**.



Results and discussion

In an attempt at Leuven to synthesise 1,5-diazabicyclo[3.3.0]-octane-2,6-dione **1**, an intermediate leading to the synthesis of 1,5-diazabicyclo[3.3.0]octane, by the reaction of hydrazine hydrate and ethyl acrylate in a 1:2 ratio in a sealed tube under vacuum at 140 °C during 3.5 hours, the expected reaction product could not be isolated, although Stetter and Findeisen reported an 80% yield of this compound.[8] Instead the condensation gave a complex reaction mixture that was separated by column chromatography on silica gel with ethyl acetate–ethanol (4:1, v/v). Three fractions were obtained in this way and were further analysed. The residue from the column, eluted with 95% ethanol, was still a mixture of products, but was not further characterised. Spectroscopic analyses (^{1}H NMR, ^{13}C NMR, FT-IR, CI-MS and EI-MS) allowed us to identify three main products: 1-(ethoxycarbonylethyl)pyrazolidin-3-one[9] **6b** (28%), 1,2-bis(ethoxycarbonylethyl)pyrazolidin-3-one **8b** (19%), and 2-(ethoxycarbonylethyl)pyrazolidin-3-one[9] **11b** (18%) (see Scheme 1).

As far as we are aware, the Stetter–Findeisen procedure has never been repeated successfully under the conditions originally described. The Bristol group reported previously that no bicyclic product **1** was formed (^{1}H NMR) after heating at 150 °C, and that the final cyclisation probably occurs during distillation of the reaction mixture; isolated yields, however, were low (20–28%).[6] In other work, the Bristol group made use of the related reaction of hydrazine with diethyl glutaconate,[10] which also requires elevated temperatures to form a mixture of *cis*- and *trans*-4,8-bis(ethoxycarbonylmethyl)-1,5-diazabicyclo[3.3.0]octane-2,6-dione **2**.

We were intrigued that these reactions to form five-membered rings, which are normally so rapid, were initially strongly exothermic, but then required such drastic conditions to go to completion and wondered if this was due to the necessity for 5-*endo-trig* cyclisations.[11] Indeed Baldwin and co-workers reported the failure of cinnamoyl hydrazide to cyclise to a pyrazolone below 200 °C.[12] Kemp *et al.*,[10] in their paper reporting the preparation of **2**, noted that the reaction to cyclise the adduct of hydrazine with methyl crotonate was completed by 2 hours' heating at 200 °C and suggested that this was due to unfavourable 5-*endo-trig* cyclisations.

We have studied these reactions by examining ^{1}H, ^{13}C, and ^{15}N NMR spectra at various stages during the heating process, and by the isolation of intermediates. We conclude that the

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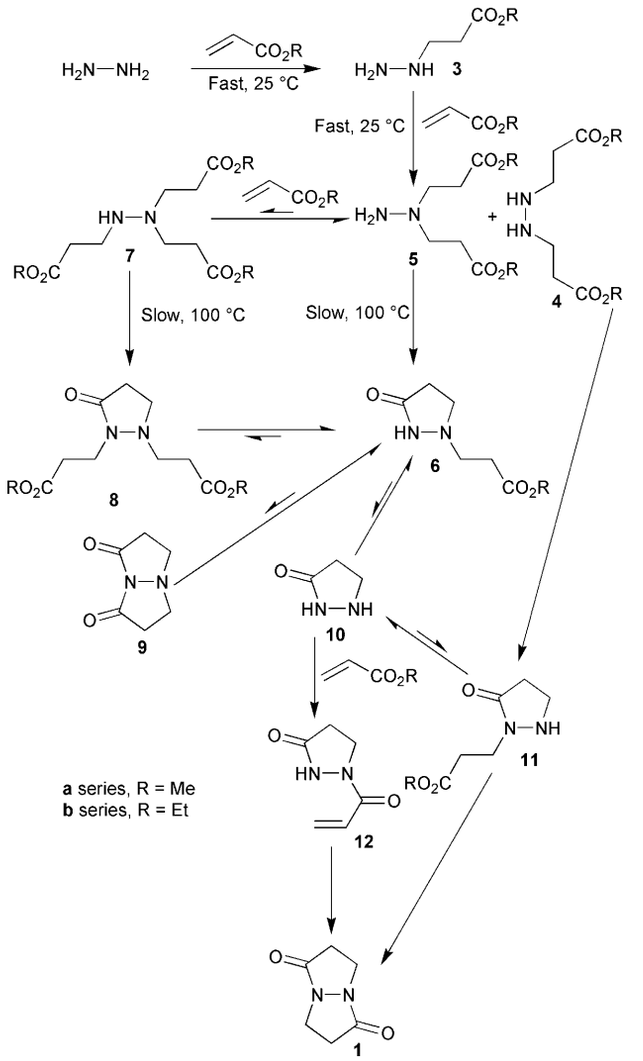


Scheme 1

need for vigorous heating is actually associated with the reversibility of Michael additions, and that 5-*endo-trig* cyclisations may not be involved. In detail, however, the reactions to form **1** and **2** are surprisingly different. Our proposed mechanistic sequences for reaction of hydrazine with methyl or ethyl acrylate and with diethyl glutaconate are shown in Schemes 1 and 3 respectively. They are based on the following principles:

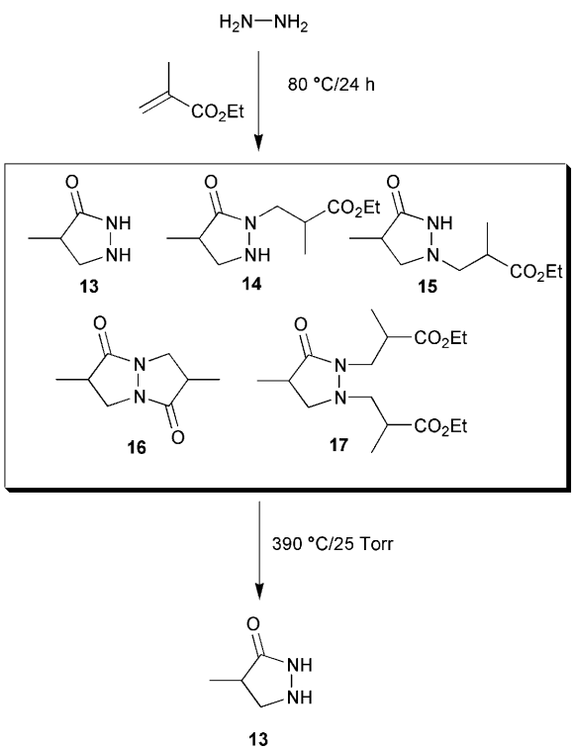
1. Michael additions are much faster than ester hydrazinolysis.

2. Mono-substituted hydrazines react more rapidly at the substituted position with unhindered electrophiles, giving 1,1- rather than 1,2-disubstituted products. However, this preference may be reversed with bulky electrophiles.

3. Compounds which are Michael adducts at amide nitrogen can undergo rapid reverse Michael reactions, especially if this relieves steric hindrance.

The major species formed when hydrazine reacts with excess acrylate at 25 °C is 1,1-bis(2-alkoxycarbonylethyl)hydrazine **5**, but some of the regioisomer **4** is observed,† and 1,1,2-tris(2-alkoxycarbonylethyl)hydrazine **7** is formed on further standing, together with a little cyclisation to 1-(alkoxycarbonylethyl)-pyrazolidin-3-one[9] **6**. There is no sign of any ester hydrazinolysis products, suggesting that Michael reactions are much faster. On heating to 100 °C for 2 hours, cyclisation of **5** to **6** is complete. Compound **6** is now quite stable, since cyclisation to 1,5-diazabicyclo[3.3.0]octane-2,8-dione **9** is probably thermodynamically unfavourable (**9** is an imide and should undergo rapid methanolysis). Further progress towards **1** now requires retro-Michael reaction to give dihydropyrazol-3-one[13,14] **10**, followed by unfavourable Michael addition to the amide nitrogen of **10** to give **11**, which should cyclise easily to **1** at these higher temperatures. Two alternative routes are (i) *via* the formation of **12** followed by 5-*endo-trig* cyclisation or (ii) *via* the cyclisation of the minor regioisomer 1,2-bis(2-alkoxycarbonylethyl)hydrazine **4** to **11**. While we have no direct evidence as to which of these pathways is followed, the general lack of evidence for the formation of α,β-unsaturated hydrazides, and the known difficulties with their cyclisation[12] make us favour the routes *via* **11**.

To confirm our assumptions, we performed some additional experiments. First, we heated an analytically-pure sample of 1,2-bis(ethoxycarbonylethyl)pyrazolidin-3-one **8b** in a sealed tube at 140 °C for 2 hours, then analysed the reaction products by means of TLC and CI-MS. In agreement with our proposals, we observed the formation of both 1- and 2-(ethoxycarbonylethyl)pyrazolidin-3-one **6b** and **11b** with the latter predominating (TLC). In a second experiment we refluxed a mixture of hydrazine hydrate and ethyl methacrylate in a 1:2 ratio in ethanol. After distillation of the reaction products (distillation temperature 107–111 °C/0.05–0.1 Torr) we could detect, by TLC and CI-MS, at least eight different reaction products that are mono- and bicyclic compounds (Scheme 2),

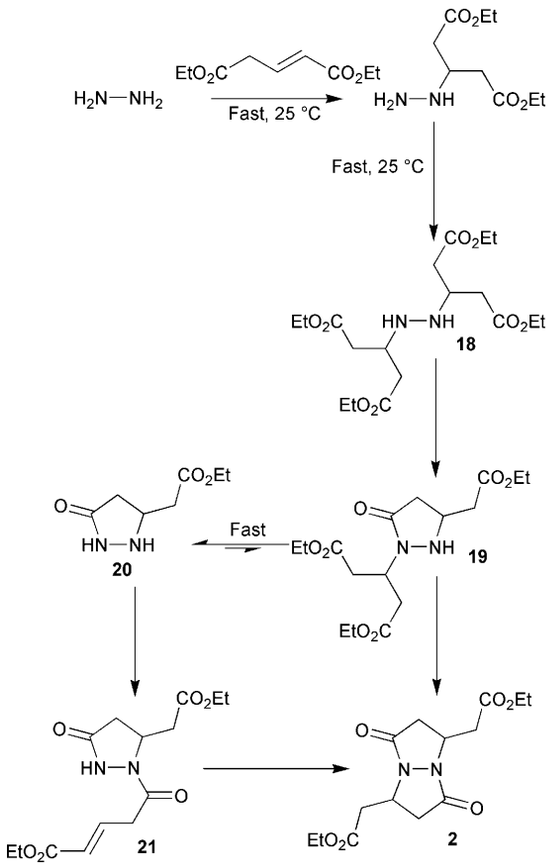


Scheme 2

two of them being 2-(2-ethoxycarbonylpropyl)-4-methylpyrazolidin-3-one **14** and 1-(2-ethoxycarbonylpropyl)-4-methylpyrazolidin-3-one **15**. Due to the presence of diasteroisomers of **13**–**17**, the analysis of this mixture is very complex. When we heated this mixture at 390 °C we could isolate 4-methylpyrazolidin-3-one[9,14,15] **13** in a very good yield (85%). From this, we conclude that at high temperatures, retro-Michael reactions play a major part in the formation of the reaction products.

The apparently similar reaction of hydrazine with excess diethyl glutaconate (Scheme 3) takes a quite different course. Kemp *et al.*[10] obtained a 20–25% yield of *cis*- and *trans*-4,8-bis(ethoxycarbonylmethyl)-1,5-diazabicyclo[3.3.0]octane-2,6-dione **2**. They recognised the stepwise nature of the reaction and proposed that the final step might be the 5-*exo-trig* cyclisation

† The **5**:**4** ratio is 85:15, according to ^{1}H NMR measurements.



Scheme 3

of **21**, but did not discuss the earlier stages of the process. It is immediately clear from the single line ^{15}N NMR spectrum, δ_N 75.4, that the second Michael addition of diethyl glutaconate gives 1,2-disubstituted adduct **18**, presumably for steric reasons, and that this is the major product at 25 °C. Lichter and Roberts[16] reported that MeNHNHMe has δ_N 75.3, while Me_2NNH_2 has δ_N 100.5 and 59.2 for N^1 and N^2 respectively. Although double cyclisation of this adduct to **2** now appears straightforward, retro-Michael reaction of the mono-cyclised adduct **19** to give ethyl 2-(5-oxotetrahydro-1*H*-pyrazol-3-yl)acetate[14,17] **20** is probably very rapid and in fact **20** can be identified as the major species in reaction mixtures heated to 100 °C (Kemp *et al.*[10] isolated a compound, mp 62–65 °C, to which they assigned structure **20**, but reported no spectroscopic data). It was also clear from ^{13}C NMR of these mixtures that diethyl glutaconate has been re-formed on heating from 25 to 100 °C. The details of the route from **20** to **2** are obscure, since we did not see any further intermediates by NMR. Attack of the amine nitrogen of **20** on the non-conjugated ester group of diethyl glutaconate could give **21**, which should cyclise rapidly (*5-exo-trig*), as suggested by Kemp, but the alternative route *via* low concentrations of **19** appears equally likely.

Conclusions

The unexpectedly severe conditions required to form bicyclic compounds **1** and **2** are not due to the necessity for 5-*endo-trig* cyclisations. The high temperatures are probably required to overcome unfavourable equilibria in Michael reactions. The routes to **1** and **2** are surprisingly different in detail however. The major pathway to **1** involves initial formation of 1,1-bis(2-alkoxycarbonylethyl)hydrazine **5** which cannot yield **1** without undergoing unfavourable retro-Michael reactions. On the other hand, hydrazine reacts with excess diethyl glutaconate to give 1,2-adduct **18** which can cyclise to **2** *via* the monocyclic **19**. However **19** undergoes rapid retro-Michael to 5-(ethoxycarbonylmethyl)pyrazolidin-3-one **20**, and this equilibrium provides the major obstruction to the formation of **2**.

Experimental

General

NMR spectra at Leuven were acquired on a Bruker WM-250 spectrometer operating at 250.1 MHz for ^1H and at 62.5 MHz for ^{13}C. NMR spectra at Bristol were acquired on a JEOL FX200 operating at 200 MHz for ^1H, 50 MHz for ^{13}C, and 20.3 MHz for ^{15}N; ^{15}N spectra were acquired using gated decoupling and are referenced to NH_3. All other spectra were determined in deuteriochloroform, with tetramethylsilane as internal standard. The abbreviations s, d, t, q, m, and br stand for singlet, doublet, triplet, quartet, multiplet and broad, respectively. Coupling constants *J* are expressed in hertz. Low resolution mass spectra, reported as *m*/*z* (relative intensity), were obtained using chemical ionisation (CI, CH_4) or electron impact ionisation (EI, 70 eV) on a HP 5989A MS Engine. Fourier-transform infrared spectra were recorded for CCl_4 solutions in 0.1 or 0.2 mm cells on a Bruker IFS66 spectrometer. Column chromatography was performed on Uetikon silica 60–200 micron using eluants specified.

Reaction of hydrazine hydrate with ethyl acrylate in a sealed tube

Hydrazine hydrate (10.0 g, 0.2 mol) and ethyl acrylate (40.0 g, 0.4 mol) were mixed at −60 °C (propan-2-ol–dry ice) in a glass tube equipped with a magnetic stirring bar, brought under vacuum, sealed, allowed to attain ambient temperature, then heated slowly to 140 °C (oil bath, *ca.* 90 min), and stirred at this temperature for 3.5 h. After cooling, the tube was carefully opened, the reaction mixture was diluted with ethanol (150 mL), then evaporated under reduced pressure to obtain 36.0 g of a yellowish oily residue. The following products were obtained after column chromatography (ethyl acetate–ethanol, 4 : 1 v/v).

1,2-Bis(ethoxycarbonylethyl)pyrazolidin-3-one (8b). (19%) Yellowish oil; δ_H 4.15 (4H, m), 3.40 (2H, t, *J* 7), 3.12–2.92 (2H, m), 2.65–2.40 (8H, m), 1.24 (6H, m); IR ν/cm^{-1} 2983, 2940, 2907, 1738s, 1700s, 1186s.

1-(Ethoxycarbonylethyl)pyrazolidin-3-one (6b). (28%) Pale yellow oil; δ_H 8.75 (1H, br s), 4.17 (2H, q, *J* 7.5), 3.30 (2H, t, *J* 7), 3.00 (2H, t, *J* 7.0), 2.52 (4H, m), 1.25 (3H, t, *J* 7.5); IR ν/cm^{-1} 3434, 3165, 3069, 2983, 2844, 1737s, 1696s, 1187s; EI-MS 187 (5), 186 (19), 140 (12), 112 (6), 99 (100), 73 (8), 71 (10), 55 (26), 42 (8).

2-(Ethoxycarbonylethyl)pyrazolidin-3-one (11b). (18%) Pale yellow oil; δ_H 4.50 (1H, br s), 4.15 (2H, q, *J* 7.1), 3.72 (2H, t, *J* 6.6), 3.35 (2H, t, *J* 7.7), 2.63 (2H, t, *J* 6.6), 2.45 (2H, t, *J* 7.7), 1.25 (3H, t, *J* 7.1); IR ν/cm^{-1} 3227, 2984, 2940, 1734s, 1698s, 1393, 1185s; EI-MS 187 (7), 186 (43), 140 (91), 112 (6), 99 (69), 86 (87), 84 (42), 55 (100).

Reaction of hydrazine hydrate with ethyl acrylate at 280 °C

This reaction was carried out according to the published procedure[6] to obtain 1,5-diazabicyclo[3.3.0]octane-2,6-dione **1** as pale yellow crystals in 20–28% yield. δ_H ($CDCl_3$) 3.90 (4H, t, *J* 6.0), 2.81 (4H, t, *J* 6.0); δ_C 170.8, 39.7, 32.9.

Reaction of ethyl methacrylate with hydrazine hydrate

A mixture of hydrazine hydrate (46.8 g, 0.94 mol) and ethyl methacrylate (213 g, 1.87 mol) in ethanol (350 mL) was stirred at 80 °C for 48 h. The volatile components were removed *in vacuo*, and the residue was distilled under reduced pressure (Vigreux column). The fraction of bp 107–111 °C/0.05–0.1

Torr was collected (151.6 g), and analysed after column chromatography (ethyl acetate–ethanol, 10 : 1 v/v) to obtain the following products.

1-(2-Ethoxycarbonylpropyl)-4-methylpyrazolidin-3-one (15). (29%) Colourless oil; δ_H 7.78 (1H, br s), 4.18 (2H, m), 3.43 (1H, m), 3.10–2.58 (5H, m), 1.27 (3H, m), 1.17 (3H, m).

2-(2-Ethoxycarbonylpropyl)-4-methylpyrazolidin-3-one (14). (15%) Colourless oil; δ_H 4.62 (1H, br s), 4.22 (2H, m), 3.49 (1H, m), 3.15–2.46 (5H, m), 1.25 (3H, m), 1.15 (3H, m).

The distilled mixture of products was heated at 390 °C/25 Torr for 4 h. The viscous residue obtained was dissolved in ethanol, evaporated *in vacuo* to give pure 4-methylpyrazolidin-3-one (**13**, 85%) as a yellowish liquid. δ_H 6.72 (2H, br s), 3.62 (1H, m), 2.99 (1H, t, *J* 11), 2.65 (1H, m), 1.17 (3H, d, *J* 7); δ_C 179.6, 54.1, 37.1, 14.1.

Reaction of methyl acrylate with hydrazine hydrate

1,1-Bis(methoxycarbonylethyl)hydrazine 5a. δ_H 3.65 (3H, CH_3), 2.8 (2H, m), 2.6 (2H, m); δ_C 173.2 (*C*O_2Me), 56.5 (*C*H_2N), 51.5 (*C*H_3), 32.6 (*C*H_2CO); δ_N 89.0 (NH_2), 70.3 (Me_2NNH_2 has δ_N 91.1 and 54.8 under the same conditions).

1,1,2-Tris(methoxycarbonylethyl)hydrazine 7a. δ_N 88.5, 76.5.

1-(Methoxycarbonylethyl)pyrazolidin-3-one 6a. δ_H 3.70 (3H, CH_3), 3.35 (2H, t, CH_2N), 3.08 (2H, t, CH_2N), 2.60 (4H, m, 2 × CH_2); δ_C 175.3 (*C*ONH), 172.4 (*C*O_2Me), 55.0, 52.4, 51.8, 32.4, 30.0; δ_N 153.8 (NHCO), 80.3.

1,2-Bis(methoxycarbonylethyl)pyrazolidin-3-one 8a. δ_N 154.7 (NHCO), 95.2.

Reaction of diethyl glutaconate with hydrazine hydrate

1,2-Bis[(1-(ethoxycarbonylmethyl)-2-ethoxycarbonylethyl]-hydrazine 18. δ_C 171.6 (*C*O_2Et), 60.0 (CH_3CH_2), 53.2 (*C*HN), 37.0 (*C*H_2CO), 13.7 (*C*H_3CH$_2$); δ_N 75.4 (MeNHNHMe has δ_N 68.2 under the same conditions).

5-(Ethoxycarbonylmethyl)pyrazolidin-3-one 20. δ_H 4.4 (1H), 4.1 (2H, q), 3.0 (4H, m), 1.3 (3H, t); δ_C 169.9, 166.4, 61.1, 49.1, 39.3, 38.7, 14.1.

4,8-Bis(ethoxycarbonylmethyl)-1,5-diazabicyclo[3.3.0]octane-2,6-dione, 2, *trans*-isomer. δ_H 4.55 (2H, ddd, *J* 10, 6, 6), 4.16 (4H, q, *J* 7), 3.20 (2H, dd, *J* 17, 10), 2.99 (4H, d, *J* 6), 2.69 (2H, dd, *J* 17, 6), 1.27 (6H, t, *J* 7); δ_C 169.7, 166.0, 61.1, 49.3, 40.3, 36.4, 14.2; the *cis*-isomer was not obtained pure: δ_C 169.5, 169.3, 61.1, 48.9, 39.3, 38.6, 14.2.

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