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Isolation and Characterization of a Novel Tetrahydro-[2,2']bipyrrolyl Dimer as an Impurity from a Knorr Reaction

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Abstract

A novel dimer, tetraethyl 2,2',3,3'-tetramethyl-1,1',2,2'-tetrahydro-5H,5'H-2,2'-bipyrrolyl-5,5,5',5'-tetracarboxylate, has been isolated as an impurity (4% yield) from a Knorr reaction for the synthesis of ethyl 3,5-dimethylpyrrole-2-carboxylate from 2,4-pentanedione and diethyl oximinomalonate in a dissolving zinc reduction. The solid-state structure of this novel dimer was determined by X-ray crystallography. Knorr reactions typically rely upon the requisite pyrrole being the only water-insoluble crystalline material present in the reaction mixture, and so work-up and purification procedures for Knorr reactions should be monitored carefully given the water-insolubility of this dimer. Investigations regarding mechanistic implications and reductive dimerization are underway.

Key words: pyrrole synthesis, reductive dimerization, Knorr, Kleinspehn, Fisher-Fink

Introduction

The Knorr[1] reaction and derivatives thereof[2-4] represent the most efficient and economical synthetic methodology for the preparation of a wide variety of functionalized pyrroles. This procedure uses readily available 1,3-diketones, and oximes of either acetoesters or malonates, to give pyrroles functionalized with a variety of substituents *via* a dissolving zinc reduction. The basic mechanism of the Knorr reaction has long been established,[2,5,6] and yields are reliably in the range 30-60%, with perhaps 45% being considered average.[4] The starting materials are generally extremely cheap and the procedure is well suited for large-scale reactions (1-5 mole scales are routinely manageable in a laboratory environment).

Results and Discussion

Scheme 1 shows the Kleinspehn variation[7] of the Knorr reaction for the preparation of ethyl 3,5-dimethylpyrrole-2-carboxylate (**1**), whereby diethyl oximinomalonate (**2**) is reacted with 2,4-pentanedione (**3**) in the presence of zinc. This variation, involving the oximes of malonate esters, is often called the Fischer-Fink reaction, as Fischer and Fink isolated a small amount of ethyl 3,5-dimethylpyrrole-2-carboxylate from the Knorr reaction of 2,4-pentanedione and α-oximinoacetoacetate under dissolving zinc reduction conditions.[8] The reaction is conducted by first preparing the diethyl oximinomalonate by nitrosation of diethyl malonate with an aqueous solution of sodium nitrite. The crude oxime (**2**) is then added drop-wise to a vigourously stirring solution of 2,4-pentanedione in acetic acid, with concomitant slow addition of zinc dust. As such, the diethyl oximinomalonate is reduced to give diethyl aminomalonate (**4**) *in-situ*, which immediately reacts with the diketone (**3**); self-condensation of **4** is thus minimized. With slow addition of both the oxime and the zinc dust, the temperature of the exothermic

reaction is maintained at 60-80°C, a temperature range that gives maximized yields. Zinc acetate often precipitates as the reaction progresses, making stirring more difficult, although the yields are not generally affected.[4] Sodium (or ammonium) acetate (2.0 molar equivalents) is often added to the reaction mixture in order to keep the zinc acetate in solution and hence facilitate processing.

The work-up procedure for Knorr reactions is straightforward as the pyrrole is usually the only water-insoluble solid present in the reaction mixture.[4,9] Indeed, the work-up procedure merely involves adding 2-3 volumes of iced water to the crude reaction mixture once it has been decanted away from residual zinc solid. The precipitated crude pyrrole is then isolated by filtration, dissolved in a solvent such as dichloromethane and the layers are then separated; this removes the large amount of water trapped within the initial cake. The pure pyrrole product is then obtained by crystallization. The key purification step within this procedure involves separation, by filtration, of the crude precipitate and the aqueous acetic acid solution after addition of iced water to the reaction mixture. The success of this purification relies on the fact that the required pyrrole is the only water-insoluble crystalline material present.[4,9]

Following the Knorr procedure described above, we obtained a reasonable yield (44%) of ethyl 3,5-dimethylpyrrole-2-carboxylate (**1**) on a 1.0 mole scale, after two crystallizations from dichloromethane and hexane. Upon the third crystallization, it was noted that the crystals were different in appearance to those of the previous two crops: pyrrole **1** was obtained as fine white platelets in crops one and two, whilst the third crop of crystals was pale salmon-coloured, glassy and angular. Pyrroles are often isolated as coloured precipitates that are >98% pure by NMR spectroscopic analysis, and so the visual appearance of the crystals did not induce immediate concern or interest. However, the ^{1}H NMR spectrum of the salmon-coloured crystals indicated

the absence of a diagnostic pyrrole N-*H* signal (8-10 ppm). Instead, an amino N-*H* signal was observed (2.73 ppm), along with two ethyl ester signals. The presence of two ethyl esters in unique environments was confirmed by ^{13}C NMR spectroscopy; two electron-deficient alkene-type carbon environments were also evident (signals at 132.36 and 135.95 ppm). Mass spectrometry revealed a base peak of 240 (*m/z*) for the isolated impurity, and closer inspection revealed a molecular ion of low intensity at 480 (*m/z*). This led us to deduce the structure of the impurity to be that of the dimer **8** (Scheme 2), which may exist as either meso and chiral diastereoisomers. Attempted cleavage of the central C-C bond under thermal conditions, external of the mass spectrometer, was unsuccessful, and we were unable to convert **8** into **1**. X-ray crystallographic analysis[10] confirmed the dimeric structure of **8** (Figure 1). Selected bond lengths and angles are given in Table 1.

Analysis of the crystal structure shows that only one half of the dimeric structure is crystallographically unique. Within the five-membered ring, one of the bonds, C(2)-C(3) [1.321(4) Å], is significantly shorter than the others, confirming its assignment as a double bond. The ring itself is quite planar; the root mean square deviation of the atoms from the ring plane is 0.0594 Å. The two halves of the dimer are joined by the C(4)-C(4') single bond [1.563(6) Å], and the two rings adopt a twisted geometry relative to one another, with an angle of 61.22(8)° between the two ring planes. In the solid-state structure, long chains of molecules are aligned parallel to the *c* axis (Figure 2), and there are N-H…O hydrogen bonds between the molecules in adjacent chains (Figure 3). Indeed, the H(N) hydrogen atom adopts a bifurcated hydrogen bonding arrangement. There is the N(1)-H(1)…O(3') hydrogen bond that exists between the chains, as mentioned above [N(1)-H(1) 0.84(3) Å, H(1)…O(3') 2.43(3) Å, N(1)…O(3') 3.218(3) Å, and N(1)-H(1)…O(3') 156(3)°; the symmetry required to generate O(3') is 1-x, -y, 1-z]. The

second component of the hydrogen bond closes an internal five-membered ring involving N(1), H(1), O(3), C(8) and C(1) all in the same monomer unit, [N(1)-H(1) 0.84(3) Å, H(1)…O(3) 2.41(3) Å, N(1)…O(3) 2.797(3) Å, and N(1)-H(1)…O(3) 109(3)°].

The interesting observation that the dimer was isolated as the D,L-form, rather than the meso-form, is indicative of high diastereoselectivity in the dimerization process. An electronic search of Chemical Abstracts revealed no hits for the basic skeleton of compound **8**, and only a handful of reported 2,2'-bipyrrolidine[11-13] systems (reduced skeleton *c.f.* **8**) with C-substitution at the 2 and 2' positions accompanied by *bis*-substitution at the 5 and 5' positions. As such, we believe that dimer **8** represents a completely novel structural skeleton.

Analysis of the mechanism for the Knorr reaction,[4] reveals a number of intermediates, as shown in Scheme 1. The pyrrole is formed *via* nucleophilic attack on intermediate **7**, most probably by generated (and added, depending upon the experimental protocol) acetate, thus resulting in expulsion of the 5-membered ring that immediately achieves aromaticity and protonation of the anion on nitrogen. Presumably, compound **8** is formed *via* a reductive dimerization of an intermediate within the Knorr reaction (Scheme 2). It is likely that water is eliminated from the cyclized intermediate **6** such as to give the conjugated intermediate **7,** and that reductive dimerization of **7**, under buffered dissolving zinc conditions, gives the isolated dimer **8** *via* a radical anion. Presumably, the reduction is faster than nucleophilic attack in this case, and hence dimer is formed rather than pyrrole. This may have been due to the presence of a 'micro-environment' within the reaction mixture as, despite vigorous stirring, clumping of the zinc tends to occur.

Reaction conditions were then varied whereby different stoichiometries of the reductant zinc (0.5-5.0 eq.) were used, and the rates of stirring were varied whilst keeping within safe

limits, given the large exotherm of the reaction. The stoichiometry of sodium acetate was also varied (0-5.0 eq.), as reductive dimerization must compete with nucleophilic attack by acetate on **7**. Under these conditions, TLC analysis of the reaction mixture often and variably showed traces of the dimer, but we were unable to isolate any more material, no matter what scale we performed the Knorr reactions on (0.2-5.0 mol). Yields of **1** remained in the region of 40-50%, whatever the reaction conditions, as reported by others.[4] We are continuing to pursue the efficient synthesis of compound **8** since its skeleton is entirely unique, and these investigations will reveal more about the mechanism of the Knorr reaction itself.

In conclusion, a water-insoluble dimer with a novel tetrahydro-[2,2']bipyrrolyl-5,5,5',5'-tetracarboxylic acid skeleton has been isolated as an impurity (4% yield) from a Knorr reaction whilst synthesizing ethyl 3,5-dimethylpyrrole-2-carboxylate. Given the propensity of the Knorr reaction, it is remarkable that this dimer has not been previously isolated. The tetraethyl 2,2',3,3'-tetramethyl-1,1',2,2'-tetrahydro-5H,5'H-2,2'-bipyrrolyl-5,5,5',5'-tetracarboxylate (**8**) must arise from reductive dimerization of intermediates in the Knorr reaction. Given the reliance upon pyrroles being the only water-insoluble product of the Knorr reaction, the work-up and purification procedures for Knorr reactions should be monitored carefully, as it is likely that small amounts of dimers of this type are formed frequently. Further studies are underway in order to determine the factors influencing the formation of the dimer.

Acknowledgements

Experimental Section

General Procedures

Proton and carbon nuclear magnetic resonance (NMR) spectra were recorded at 250 and 63 MHz, respectively, in CDCl$_3$ on an AC 250 F NMR spectrometer in the Atlantic Region Magnetic Resonance Centre at Dalhousie University. Chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak, and all coupling constants are reported in hertz (Hz). Mass spectra (m/z) were obtained using a CEC 21-110B instrument (EI$^+$, 124°C probe temperature, 70.0 eV energy). Mass spectra are reported in units of mass over charge (m/z) for all values between 50 and the molecular ion, if over 10% of the base peak. Intensities are reported in parentheses as a percentage of the base peak. Melting points were collected on a hot-stage apparatus and are uncorrected. All reagents and solvents were used as received.

2,3,2',3'-Tetramethyl-1,2,1',2'-tetrahydro-[2,2']bipyrrolyl-5,5,5',5'-tetracarboxylic acid tetraethyl ester, 8

According to the general procedure for the synthesis of pyrroles *via* the Knorr reaction,[4] a saturated aqueous solution of NaNO$_2$ (207 g, 3.0 mol) was added drop-wise to a solution of diethyl malonate (152 mL, 1.0 mol) in acetic acid (200 mL). The solution was stirred overnight and the formed oil (crude oxime) separated. Water (500 mL) was added to the acetic acid solution, which was then extracted with diethyl ether (2 x 50 mL). The combined ethereal fractions were carefully concentrated *in vacuo* to give a further quantity of crude oxime. The two portions of oxime were combined and then added drop-wise to a solution of 2,4-pentanedione (103 mL, 1.0 mol) and NaOAc (272 g, 2.0 mol) in acetic acid (500 mL), in a 4-necked flask

equipped with an overhead stirrer, a dropping funnel, a powder funnel and a thermometer. During

the addition of the oxime, zinc dust (195 g, 3.0 mol) was added gradually to the reaction mixture.

The internal temperature was maintained at 65-80 °C with the aid of first a bath of hot water and

then an ice-bath. After the addition was complete, the reaction mixture was stirred for a further

hour and then the solution was decanted away from the solid zinc residue before iced water (2.0

L) was added. After standing overnight, the off-white precipitate was separated by filtration and

then dissolved in CH_2Cl_2 to enable removal of the water trapped within the cake. The CH_2Cl_2 was

then replaced with hexane, with the aid of a rotary evaporator, to effect

crystallization/precipitation. First and second crops of crystals yielded 68.3 g (41%) and 5.1 g

(3%), respectively, of ethyl 3,5-dimethylpyrrole-2-carboxylate (**1**) as a white powder,[14,15] R_f (1:4

EtOAc:hexane) 0.48. A further crystallization of the mother liquor at 4°C overnight gave the title

compound (**8**) as angular salmon-coloured glassy crystals (0.9 g, 0.4 %), m.p. 94-97°C; R_f (1:4

EtOAc:hexane) 0.40; δ_H 1.16 (6H, s, CH_3), 1.20-1.27 (12H, m, 2 x CH$_2$CH_3), 1.81 (6H, s, CH_3),

2.73 (2H, br s, NH), 4.10-4.25 (8H, m, 2 x CH_2CH$_3$), 5.54 (2H, s, CH); δ_C 13.64 (CH$_2$$CH_3$), 13.93

(CH$_3$), 13.95 (CH$_2$$CH_3$), 23.31 ($CH_3$), 60.98 ($CH_2CH_3$), 61.65 ($CH_2CH_3$), 73.52 (N$C$(CH$_3$)), 80.01

(C(CO$_2$Et)$_2$), 132.36 (CC(CO$_2$Et)$_2$), 135.95 (CH), 169.72 (CO$_2$Et), 171.09 (CO$_2$Et); *m/z* 480.2

(M$^+$, 5%), 240.1 (M$^+$/2, 100), 168.1 (11), 122 (11); $C_{12}H_{18}NO_4$ calc. 240.1236, actual 240.1287.

X-ray structure determination

Crystallographic data and details of the refinement are given in Table 1.[10] All

measurements were made on a Rigaku AFC5R diffractometer equipped with graphite

monochromated Mo-Kα radiation and a rotating anode generator. The data were collected at a

temperature of -60°C using the ω-2θ scan technique to a maximum 2θ value of 60.1°. Cell

constants and an orientation matrix for data collection were obtained from a least-squares refinement using the setting angles of 25 reflections in the range $38.52 < 2\theta < 39.99°$ and corresponded to a C-centered monoclinic cell. Based on the systematic absences, packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be *C2/c* (#15). The data were corrected for Lorentz and polarization effects. Data reduction was carried out using the teXsan software package.[16] The structure was solved by direct methods (SIR-92)[17] and expanded using Fourier techniques. Refinement was carried out on F^2 data using SHELXL-97.[18] The non-hydrogen atoms were refined anisotropically. The position of H(N) was located in the Fourier difference map after refinement of the heavy atoms; it was then allowed to refine with an isotropic temperature factor equal to 1.20 times the isotropic temperature factor of the bonded nitrogen atom. The remaining hydrogen atoms were placed in geometrically calculated positions. They were allowed to ride on the heavy atom to which they were bonded with isotropic temperature factors equal to 1.20 times the isotropic temperature of the heavy atom (1.50 times for methyl hydrogens). Neutral atom scattering factors and anomalous dispersion corrections were taken from the International Tables for X-ray crystallography.[19]

Crystal data for 8, $C_{24}H_{36}N_2O_8$, 480.56

Colourless needle, monoclinic, space group *C2/c* (no. 15), $a = 14.993(5)$ Å, $b = 13.789(4)$ Å, $c = 13.587(3)$ Å, $\alpha = 90°$, $\beta = 107.20(2)°$, $\gamma = 90°$, $V = 2683(1)$ Å^3, $Z = 4$, $T = 213(2)$ K, $2\theta_{max} = 60.1°$, Rigaku AFC5R diffractometer, Mo Kα ($\lambda = 0.7107$ Å), reflections collected = 4234, independent reflections = 3928 ($R_{int} = 0.0419$), final R ([$I > 2\sigma(I)$] R1 = 0.0679, wR2 = 0.2002), R indices (all data [R1 = 0.2046, wR2 = 0.2488]), gof (F^2) = 1.490. Data reduction was carried out using the teXsan software package.[16] The structure was solved by direct methods (SIR-92)[17] and

expanded using Fourier techniques. Refinement was carried out on F^2 data using SHELXL-97.[18]

The non-hydrogen atoms were refined anisotropically. The position of H(N) was located in the

Fourier difference map after refinement of the heavy atoms; it was then allowed to refine with an

isotropic temperature factor equal to 1.20 times the isotropic temperature factor of the bonded

nitrogen atom. The remaining hydrogen atoms were placed in geometrically calculated positions.

They were allowed to ride on the heavy atom to which they were bonded with isotropic

temperature factors equal to 1.20 times the isotropic temperature of the heavy atom (1.50 times

for methyl hydrogens).

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Scheme 1: Knorr reaction
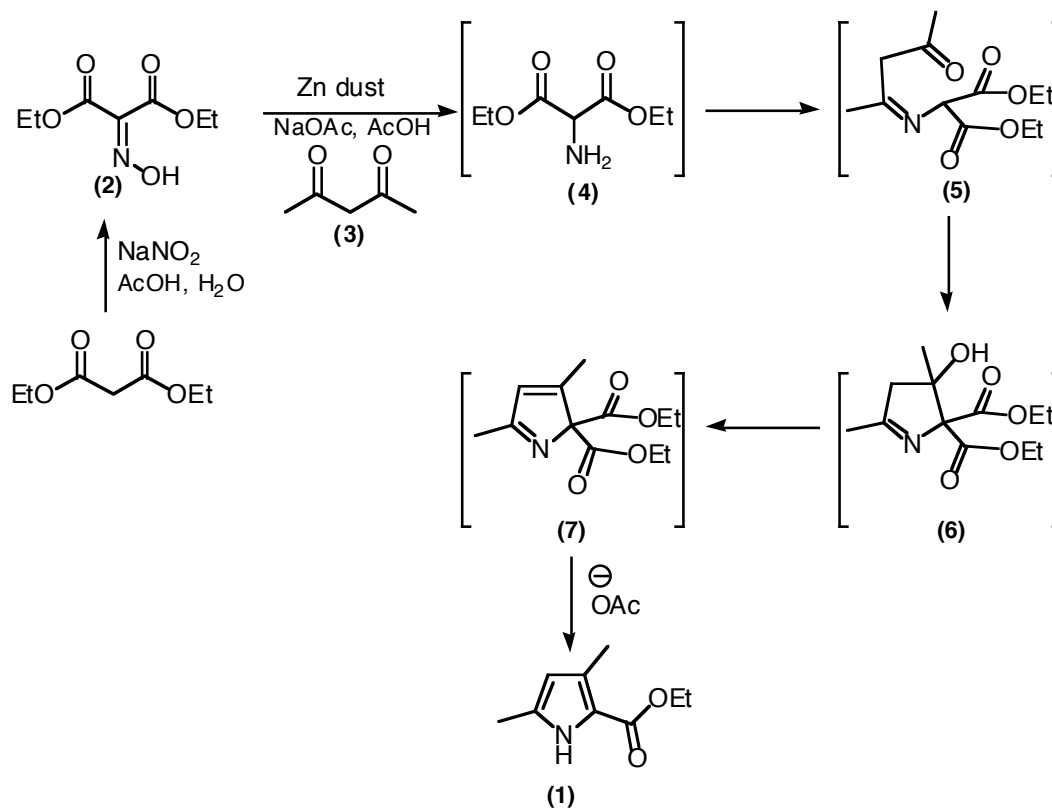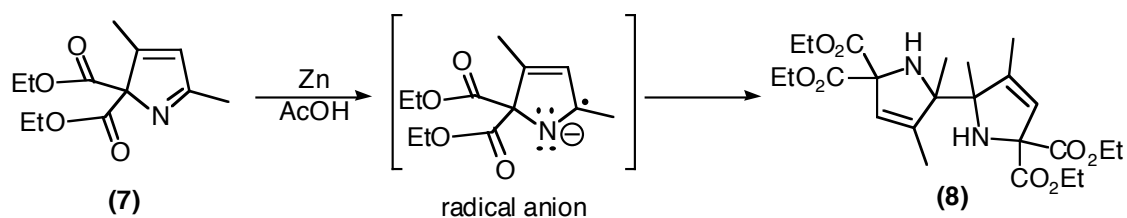

Scheme 2: Reductive dimerization

Table 1: Selected bond lengths (Å) and angles (°) for 8

Bond lengths

O(1)-C(5)	1.196(4)	O(2)-C(5)	1.319(4)
O(2)-C(6)	1.458(4)	O(3)-C(8)	1.198(4)
O(4)-C(8)	1.324(4)	O(4)-C(9)	1.470(4)
N(1)-C(1)	1.446(4)	N(1)-C(4)	1.497(3)
N(1)-H(1)	0.84(3)	C(1)-C(2)	1.514(4)
C(1)-C(5)	1.532(4)	C(1)-C(8)	1.550(4)
C(2)-C(3)	1.321(4)	C(2)-C(11)	1.501(4)
C(3)-C(4)	1.498(4)	C(4)-C(4)#1	1.563(6)
C(4)-C(12)	1.530(4)	C(9)-C(10)	1.467(6)
C(6)-C(7)	1.488(6)		

Bond angles

N(1)-C(1)-C(5)	107.0(2)	C(3)-C(2)-C(1)	108.3(2)
N(1)-C(1)-C(8)	112.1(2)	C(11)-C(2)-C(1)	124.2(3)
N(1)-C(1)-C(2)	104.9(2)	C(2)-C(3)-C(4)	113.9(3)
N(1)-C(4)-C(3)	101.4(2)	C(3)-C(4)-C(12)	112.6(2)
N(1)-C(4)-C(4)#1	108.7(3)	C(3)-C(4)-C(4)#1	110.33(17)
N(1)-C(4)-C(12)	111.2(2)	C(12)-C(4)-C(4)#1	112.1(2)
C(1)-N(1)-C(4)	109.6(2)	O(1)-C(5)-O(2)	124.3(3)
C(1)-N(1)-H(1)	110(2)	O(1)-C(5)-C(1)	123.6(3)
C(4)-N(1)-H(1)	115(2)	O(2)-C(5)-C(1)	111.9(3)
C(2)-C(1)-C(5)	116.2(3)	O(2)-C(6)-C(7)	106.5(3)
C(5)-O(2)-C(6)	116.2(3)	O(3)-C(8)-O(4)	124.2(3)
C(8)-O(4)-C(9)	116.8(3)	O(3)-C(8)-C(1)	124.7(3)
C(2)-C(1)-C(8)	110.8(2)	O(4)-C(8)-C(1)	111.0(3)
C(5)-C(1)-C(8)	106.0(2)	C(10)-C(9)-O(4)	108.2(3)
C(3)-C(2)-C(11)	127.5(3)		

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y,-z+3/2

Figure 1: ORTEP diagram of 8**; thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms, apart from H(1) have been omitted for clarity. Only half of the dimer is crystallographically unique.**
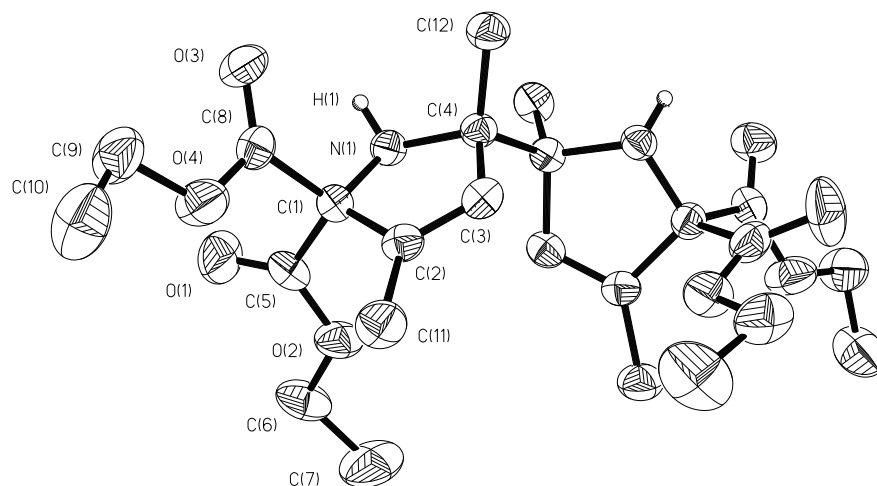
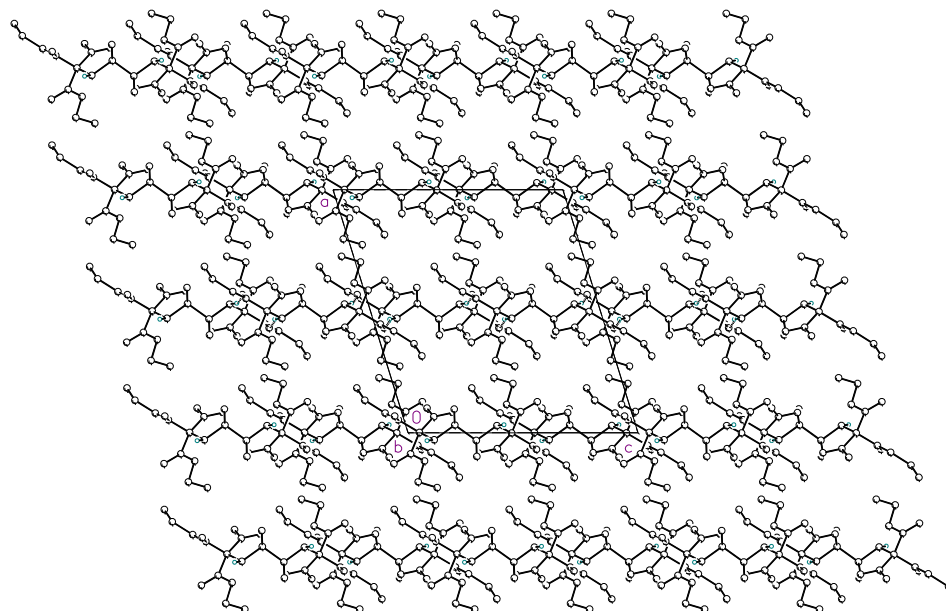**Figure 2: Crystal packing of 8 viewed down the *b* axis. Hydrogen atoms have been omitted for clarity.**

Figure 3: Hydrogen bonding within crystal packing of 8

List of Schemes, Figures and Tables

Scheme 1: Knorr reaction

Scheme 2: Reductive dimerization

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