SYNTHESIS OF 2,5-HEPTANO-1,2-DIHYDROPYRIDINE DERIVATIVES

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Abstract- The title compounds have been synthesized by reaction of the dihydro-methoxyoxepine (**1**) with hydrochlorides of amino esters (**2a - 2c**) or of hydrazides (**2d-2e**) in the presence of sulfuric acid.

Bridged oxepines can undergo various useful transformations.[1] In a previous communication we described the synthesis of alkano-1*H*-imidazo-azepines from 3,6-alkanomethoxyoxepines.[2] Here we report on the conversion of the 2,3-dihydro-2-methoxy-3,6-hexanooxepine (**1**) to the title compounds by changing the reaction conditions used earlier.[2]

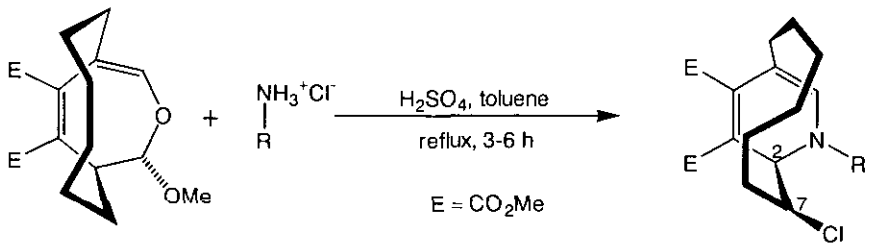
Compound (**1**) is readily available by addition of methanol to the corresponding oxepine in the presence of sodium methoxide.[3]

Heating of the dihydromethoxyoxepine (**1**) in toluene with a small excess of the amino compounds (**2a – 2e**) in the presence of catalytic amounts of conc. sulfuric acid for 3 – 6 h under reflux and under nitrogen led to the dihydropyridines (**3**), which were purified by column chromatography (silica gel, diethyl ether/pentane 1:1).[4]

In case of the hydrazine derivatives (**2d**) and (**2e**) the reaction mixture was first saturated with dry hydrogen chloride before refluxing in order to convert these compounds into the corresponding hydrochlorides.

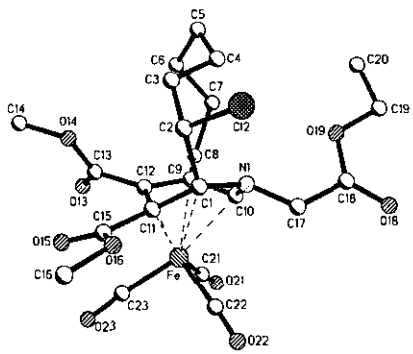
Under these reaction conditions no starting material and no by-products could be isolated. The structures of the new compounds were established by ^{1}H and ^{13}C NMR spectroscopy.[5]

All new compounds gave satisfactory MS and elemental analyses.The relative configuration on C-7 of **3a** was finally proved by X-Ray structural analysis of the corresponding iron tricarbonyl complex (**4**).[6]



1 **2** **3**

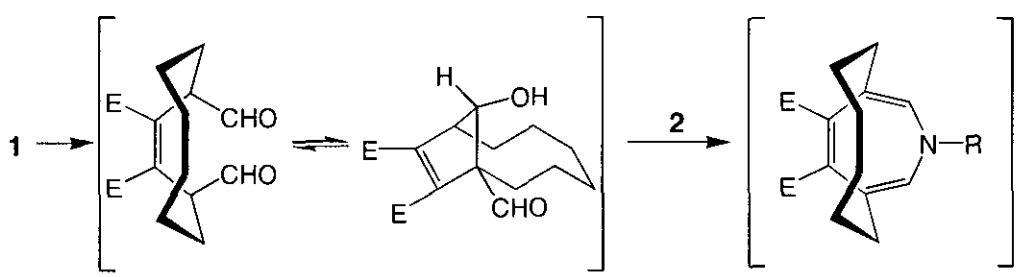
2-3	R	Yield (%)
a	CH_2CO_2Et	41
b	CH_2CO_2Me	62
c	$CH(CO_2Et)_2$	41
d	$NHCO_2Et$	12
e	NHTs	28



A molecule of **4** in the crystal; arbitrary numbering

Although the mechanism of this reaction is not known in detail the following tentative proposal is made at present.

We assume that in the first step a dialdehyde (**5**) or its aldol compound (**6**)[2,3b] is obtained by cleavage of the acetal structure of the methoxyoxepine (**1**). As reported earlier[2] an azepine (**7**) is formed in analogy to a Paal-Knorr synthesis.

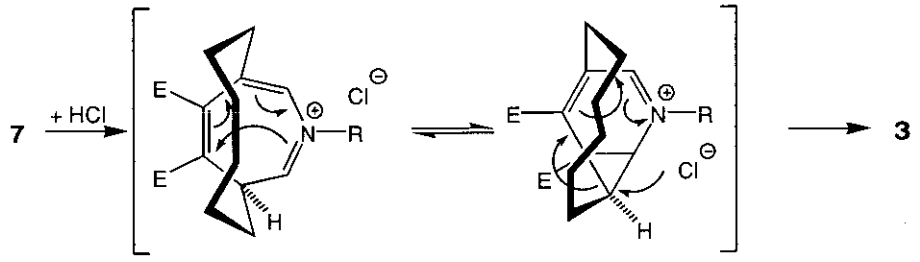


5 **6** E = CO_2Me **7**

In the highly acidic medium **7** can be protonated on a bridgehead atom to give the valence isomers (**8a**) and (**8b**). Stereoselective attack of a chloride on the bridgehead in β-position to the iminium group of **8b** may lead to the ring-opening of the cyclopropane yielding **3**.

The relief of strain in going from a hexano to a heptano bridge may provide the driving force for the conversion of **7** to **3**.

According to density functional theoretical calculations (B3LYP/6-31G*; gas phase)[7] the energy difference between cations (**8a**) and (**8b**) (R = CH_3) is negligibly small (E(**8a**) = -1017.64372 hartrees, E(**8b**) = -1017.64472 hartrees; ΔE = 0.63 kcal/mol).[8]



8a E = CO_2Me **8b**

In an independent experiment we have shown that the hydroxyaldehyde (**6**)[2,3b] and (**2a**) lead to **3a** under the above described conditions. The same holds for the tosyl hydrazone of **6** which is converted to **3e**.

In conclusion we have described a new one-pot transformation of the readily available dihydro-3,6-hexanooxepine (**1**)[3] to the title compounds.

REFERENCES AND NOTES

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2. B. Karl, and W. Tochtermann, *Heterocycles*, 1995, **40**, 555.
3. (a) W. Tochtermann, B. Popp, A. Mattauch, E.-M. Peters, K. Peters, and H. G. von Schnering, *Chem. Ber.*, 1993, **126**, 2547; (b) B. Popp, *Ph.D thesis*, Univ. Kiel, 1992.
4. Water was removed by molecular sieves (4Å) which were filled into a pressure equalized dropping funnel between the reaction vessel and the condenser.
5. Selected physical and spectroscopic data of new compounds:

   3a: yellow needles, mp 137-138 °C (CH_2Cl_2/pentane).– ^{1}H NMR (300 MHz, $CDCl_3$): 3.93 (ddd, $^3J_{7,2}$ = 1.6 Hz, $^3J_{7,8}$ = 1.6 Hz, $^3J_{7,8}$ = 11.1 Hz, 1H, 7-H), 5.03 (dt, $J_{2,6}$ = 1.6 Hz, $^3J_{2,7}$ = 1.6 Hz, 1H, 2-H), 6.56 (d, $J_{6,2}$ = 1.6 Hz, 1H, 6-H).– ^{13}C NMR (75 MHz, $CDCl_3$): 64.36 (d, C-2), 65.10 (d, C-7), 105.89 (s, C-3), 109.57 (s, C-5), 142.75 (d, C-6), 144.16 (s, C-4). The above assignments were derived from COSY, HMBC, NOESY and ^{13}C ^{1}H shift shift correlation spectra.

   3b: yellow needles, mp 127-128 °C (CH_2Cl_2/pentane).–^{1}H NMR (300 MHz, $CDCl_3$): 3.93 (dt,

$^3J_{7,2}$ = 1.6 Hz und 11.1 Hz, 1H, 7-H), 5.01 (dt, $^3J_{2,7}$ = 1.6 Hz, $J_{2,6}$ = 1.6 Hz, 1H, 2-H), 6.56 (d, $J_{6,2}$ = 1.6 Hz, 1H, 6-H).– ^{13}C NMR (75 MHz, $CDCl_3$): 64.35 (d, C-2), 65.10 (d, C-7), 105.96 (s, C-3), 109.49 (s, C-5), 142.75 (d, C-6), 144.12 (s, C-4).

3c: yellow needles, mp 106 – 107 °C, ^{1}H NMR (200 MHz, $CDCl_3$): 3.93 (dt, $^3J_{7,2}$ = 1.5 Hz, J = 11.3 Hz, 1H, 7-H), 4.96 (dt, $^3J_{2,7}$ = 1.5 Hz, $J_{2,6}$ = 1.5 Hz, 1H, 2-H), 6.95 (d, $J_{6,2}$= 1.5 Hz, 1H, 6-H).– ^{13}C NMR (50 MHz, $CDCl_3$): 65.19 (d, C-2), 66.37 (d, C-7), 110.37 (s, C-5), 140.65 (d, C-6), 144.21 (s, C-4).

3d: yellow needles, mp 127-128 °C (CH_2Cl_2/pentane).– ^{1}H NMR ($CDCl_3$, 500 MHz): 4.08 (dt, $^3J_{7,2}$ = 1.5 Hz, J = 11.0 Hz, 1H, 7-H), 5.01 (ddd, $^3J_{2,7}$ = 1.5 Hz, J = 1.5 Hz, $J_{2,6}$ = 1.6 Hz, 1H, 2-H), 6.58 (d, $J_{6,2}$ = 1.6 Hz, 1H, 6-H), 7.31 (s, 1H, NH).– ^{13}C NMR ($CDCl_3$, 125 MHz): 64.61 (d, C-2), 67.43 (d, C-7), 141.12 (d, C-3), 143.49 (d, C-4).

3e: yellow needles, mp 170-171 °C (CH_2Cl_2/pentane).– ^{1}H NMR ($CDCl_3$, 500 MHz): 3.84 (ddd, $^3J_{7,2}$ = 1.6 Hz, J = 1.8 Hz, J = 11.3 Hz, 1H, 7-H), 4.27 (ddd, $^3J_{2,7}$ = 1.6 Hz, J = 1.6 Hz, $J_{2,6}$ = 1.9 Hz, 1H, 2-H), 6.76 (d, $J_{6,2}$ = 1.9 Hz, 1H, 6-H), 7.56 (s, 1H, NH).– ^{13}C NMR ($CDCl_3$, 125 MHz): 64.91 (d, C-2), 65.41 (d, C-7), 109.54 (s, C-3), 109.91 (s, C-5),140.49 (d, C-6), 144.01 (d, C-4).

4: Heating a mixture of **3a** (385 mg, 0.93 mmol) and $Fe_2(CO)_9$ (387 mg, 1.07 mmol) in benzene (2.5 mL) for 2.5 h at 80 °C, removal of benzene *in vacuo* and purification by column chromatography (silica gel, ether/pentane 1:1) provided **4** in the first fraction (R_f = 0.52) in 17 % yield. In the second fraction (R_f = 0.31) starting material (**3a**) was recovered in 40 % yield.– **4**: red crystals, mp 119.5-120.5 °C (ethanol/pentane).– ^{1}H NMR (200 MHz, $CDCl_3$): 3.45 (d, $^3J_{2,7}$ = 2.5 Hz, 1H, 2-H), 4.43 (ddd, $^3J_{7,2}$ = 2.5 Hz, J = 2.7 Hz, J =5.6 Hz, 1H, 7-H), 5.14 (s, 1H, 6-H).– ^{13}C NMR (50 MHz, $CDCl_3$): 61.66 (s, C-3), 62.59 (d, C-2), 68.32 (d, C-7), 91.75 (s, C-4), 93.84 (d, C-6), 96.09 (s, C-5), 209.25 (s, CO). The above assignments were derived from COSY and HMBC spectra.

6. The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW. Any request should be accompanied by full literature citation for this communication and the deposition number CCDC 111585 for **4**.

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