SYNTHESIS OF ALKANO-1*H*-IMIDAZO-AZEPINE DERIVATIVES FROM 3,6-ALKANO-OXEPINES

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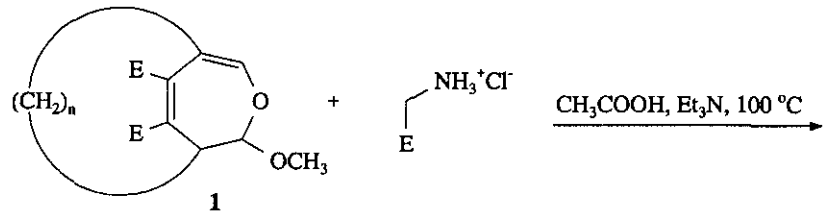
Abstract-The title compounds **(3a)** and **(3b)** have been synthesized by reaction of the dihydromethoxyoxepines **(1a)** and **(1b)** with glycine methyl ester hydrochloride.

Azepines and diazepines are important classes of heterocyclic compounds for theoretical, synthetic and therapeutic reasons.[1] Many investigations in this field were initiated by the classical work of Huisgen and coworkers in 1960.[2] The current literature shows that the development of new approaches to these heterocycles is still a topic of interest.[3] In previous papers we reported the convenient synthesis of 3,6-hexano- and heptano-oxepine-4,5-dicarboxylates[4] from oligo-methylene oxanorbornadienes by application of the method of Prinzbach and coworkers.[5] However attempts to use this reaction sequence[6] for the synthesis of the corresponding bridged 1*H*-azepines failed.[7] Recently, Hoffmann and Wenkert[8] have published a procedure for the conversion of 5-alkoxydihydrofurans into the corresponding pyrroles on treatment with β-alanine ethyl ester hydrochloride and other ammonium hydrochlorides in acetic acid and triethylamine

*) Dedicated with best wishes to Professor Rolf Huisgen on the occasion of his 75th birthday.

Here we report on the conversion of the 2,3-dihydro-2-methoxyoxepines **(1a)** and **(1b)** to the title compounds by extension of this reaction to seven-membered ring systems.



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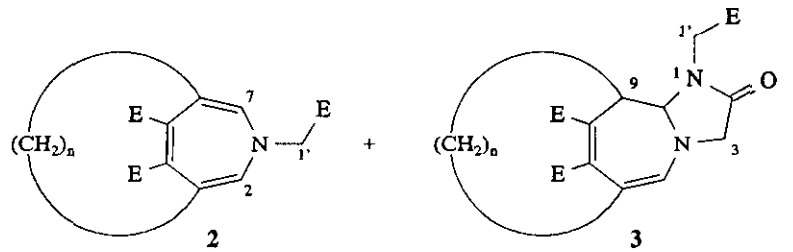
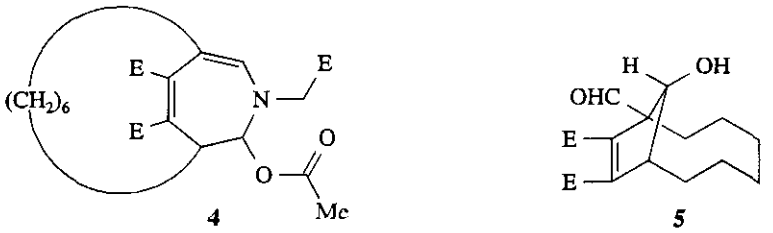


2 **3**

1-3	n	E
a	6	COOMe
b	7	COOMe



4 **5**

1a and **1b** are readily available by addition of methanol to the corresponding oxepines in the presence of sodium methoxide.[9]

Heating of the dihydromethoxyoxepine **(1a)** in acetic acid with a fourfold excess of glycine methyl ester hydrochloride and triethylamine in acetic acid for 3 h at 100 °C led to a mixture that was worked up as usual[8] and purified by column chromatography The second fraction (R_f=0 19, silica gel, ether) provided the crystalline imidazoazepine **(3a)** in 54% yield Less polar by-products were 1% **1a**, 2% acetoxyazepine **(4)** and 2% of a yet unidentified product

Similarly **1b** furnished 45% **3b**, 13% starting material **1b** and 8% 1*H*-azepine **(2b)** The yield of **2b** could be increased up to 20% using only a twofold excess of glycine methyl ester hydrochloride By-products in this experiment were 14% **3b** and 9% **1b**

The structures of all new compounds were established by ^{1}H and ^{13}C nmr spectroscopy [10,11] The symmetrical compound **(2b)** shows only 12 signals for 20 carbon atoms in the ^{13}C nmr spectrum

The formation of **2** and **3** can be explained by ring opening of the acetals **(1)**, reaction of the resulting aldehyde functionality with one or two moles of the glycine ester and ring closure in analogy to a Paal-Knorr synthesis Elimination of methanol leads to the additional formation of the imidazolone ring of **3** in the case of 1,2-addition compounds.

In agreement with these assumptions **1a** undergoes ring cleavage to the intramolecular aldol compound **(5)** by simple treatment with aqueous hydrochloric acid [9]

In conclusion we have shown that the reaction of **1** with glycine methyl ester hydrochloride yields bridged imidazo-1*H*-azepines in a one-pot reaction in attractive amounts

ACKNOWLEDGEMENT

Financial support of the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged

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10. Selected physical and spectroscopic data of new compounds·

3a. yellow needles, mp 116-117 °C (from dichloromethane/pentane); ^{1}H nmr (300 MHz, $CDCl_3$): δ=1 24-1.75 (m, 11H, CH_2), 2.31 (m, 1H, CH_2), 3 718 (d, ^2J=17 7 Hz, 1H, 1'-H), 3.723 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3 97 (m, 1H, 9-H), 3.98 (dd, ^2J=15.9, ^4J=1.6 Hz, 1H, 3-H), 4 26 (dd, ^2J=15 9, ^4J=1 5 Hz, 1H, 3-H'), 4 48 (d, ^2J=17 7 Hz, 1'-H'), 5 34 (ddd, ^3J=2.5, ^4J=1.6, ^4J=1.5 Hz, 1H, 9a-H), 6 29 (s, 1H, 5-H), ^{13}C nmr (75 MHz, $CDCl_3$) δ=15 20 (t, CH_2), 18 62 (t, CH_2), 19.82 (t, CH_2), 24 60 (t, CH_2), 27 62 (t, CH_2), 34 96 (t, CH_2), 36 62 (d, C-9), 41 60 (t, C-1'), 52 18 (q, OCH_3), 52.38 (q, OCH_3), 52.48 (q, OCH_3), 56.58 (t, C-3), 80 94 (d, C-9a), 104.12 (s, C-6), 124 36 (s, C-8), 140.59 (d, C-5), 146 84 (s, C-7), 166.13 (s, *C*OCH_3), 167 92 (s, *C*OCH_3), 168 76, 168 99 (2s, *C*OCH_3 and *C*ON)

2b· yellow crystals, mp 88-89 °C (from ether/pentane), ^{1}H nmr (300 MHz, $CDCl_3$). δ=1 26-1.66 (m, 10H, CH_2), 2 01 (dddd, ^2J=13.4, ^3J=8 4, ^3J=2 6, ^4J=0 8 Hz, 2H, 8-H/14-H), 2.22 (dddd, ^2J=13.4, ^3J=8.3, ^3J=2.8, ^4J=0 8 Hz, 2H, 8-H'/14-H'), 3 69 (s, 2H on C-1'), 3.76 (s, 3H, OCH_3), 3 78 (s, 6H, 2OCH_3), 5 92 (dd, ^4J=0.8 Hz, 2H, 2-H/7-H), ^{13}C nmr (75 MHz, $CDCl_3$). δ=22 72 (t, 2CH_2), 27.88 (t, C-11), 29 40 (t, 2CH_2), 30.54, 2CH_2), 51.87 (q, OCH_3), 52 13 (q, 2OCH_3), 53 17 (t, C-1'), 125 65 (s, C-3/C-6), 141 36 (s, C-4/C-5), 145.38 (d, C-2/C-7), 166 80 (s, 2*C*OCH_3), 170 24 (s, *C*OCH_3)

3b. yellow needles, mp 117-118 °C (from dichloromethane/pentane); **4**· yellow needles, mp 136-137 °C (from ether/pentane).

11. All new compounds gave satisfactory mass spectra and elemental analyses

Received, 29th July, 1994