Synthesis of Crown Ethers Containing the 3,5-Di(alkoxycarbonyl)pyridine Ring System by Means of the Hantzsch Condensation

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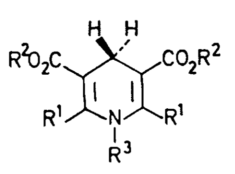
Summary The products obtained from reaction of ethyl acetoacetate with several (poly)ethyleneglycols undergo the Hantzsch condensation with ammonium carbonate and formaldehyde giving new crown ethers; transformations and properties of these new compounds are described.

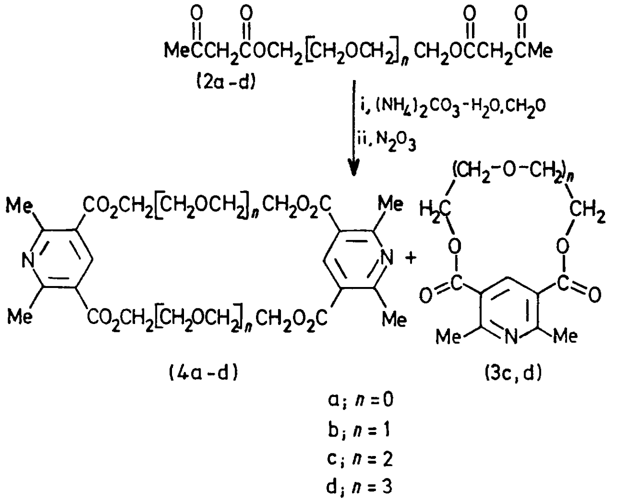
As a means of enhancing the hydride donating properties of 'Hantzsch esters' (**1**), used often as surrogates for NAD(P)H,[1] we have incorporated (**1**) and derivatives thereof into a 'crown ether' by the simple expedient of linking the carboxy-groups through a (poly)ethyleneglycol chain. The incentive to prepare such compounds lay in the knowledge that various positive ions (H^+, Zn^{2+}, Mg^{2+}, *etc.*) can catalyse hydride transfer from 1,4-dihydropyridines to, for example, fairly readily reducible carbonyl compounds;[2] were it possible to hold the positive ion in the vicinity of the donor, beneficial catalytic effects might be forthcoming. The remarkable complexing properties of crown ethers[3] seemed uniquely amenable to accomplishment of this end.



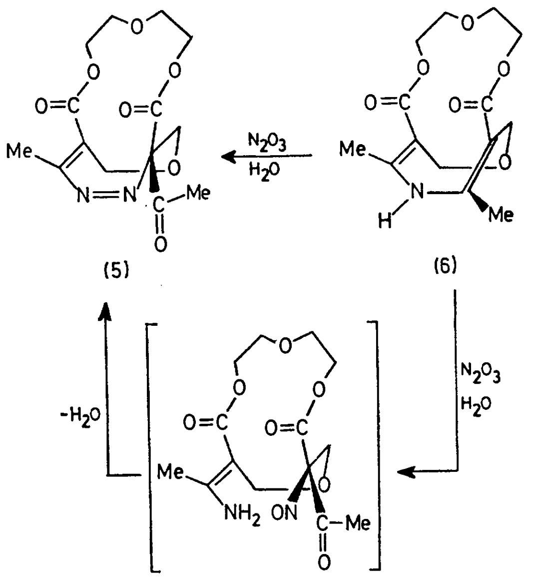
(1)

Syntheses of such compounds have not previously been described. To achieve ring-closure we relied not on the various modifications of the Williamson synthesis usually used in the syntheses of crown ethers[3c] but used instead the mechanistically complex Hantzsch condensation[4] as a means of simultaneously generating the heterocycle and closing the macrocyclic ring; the approach is to the best of our knowledge new to crown ether chemistry.

Transesterification of ethyl acetoacetate with the appropriate (poly)ethyleneglycol[5] gave (**2a**—**d**) (Scheme 1) in quantitative yield. With a large excess (*ca.* 40-fold) of ammonium carbonate in water these diesters react with aqueous formaldehyde solution to give 1,4-dihydropyridines as shown by the characteristic colour and fluorescence.[4] This mixture was dehydrogenated with N_2O_3[6] and then was chromatographed on silica gel to give the 'monomers' (**3c,d**) in 25 and 15% yields {(**3c**), m.p. 167—169 °C; u.v. λ_{max} (MeCN) 234 (ϵ, 12,400), 273 (3700), and 280 (3000) nm; ^{1}H n.m.r. ($CDCl_3$) δ 2·90 (6H, s, Me), 3·80 (4H, s, OCH_2), 3·85 (4H, m, OCH_2), 4·45 [4H, m, (CO)OCH_2], and 9·67 (1H, s, ArH); (**3d**) m.p. 90—92 °C; comparable spectral data} and the 'dimers' (**4a**—**d**) in 13—32% yields [(**4a**), m.p. 196—198 °C, u.v. λ_{max} (MeCN) 234 (ϵ, 13,200), 273 (4400), and 282 (3500) nm; ^{1}H n.m.r. ($CDCl_3$) δ 3·00 (12H, s, Me), 4·82 (8H, s, OCH_2), and 9·82 (2H, s, ArH)].† No systematic effort to improve yields or separation procedures has been made. Preliminary experiments indicate that other aldehydes such as benzaldehyde or acetaldehyde may be substituted for formaldehyde and that other glycols can be used.[7] We consider it possible that the excess of ammonium ion acts as a template in the condensation to bring the acetoacetate units into closer proximity to enhance intramolecular ring closure.‡



SCHEME 1



SCHEME 2

No isolable quantities of (**3a,b**) were formed owing perhaps to the smallness of the rings. The condensation with (**2b**) proceeded abnormally in that it provided in 18% yield a crystalline compound identified as having the remarkable structure (**5**) {m.p. 124—126 °C; i.r. (KBr) 1750, 1730, 1720 (C=O), and 1630 (N=N) cm^{-1}; u.v. λ_{max} (MeCN) 236 (ϵ, 4200) and 294 (11,300) nm; ^{1}H n.m.r. ($CDCl_3$) δ 2·32 (3H, s, COMe), 2·88 (3H, d, *J* 2 Hz, Me), 2·38 [1H, dd, *J*(Me–H^a) 2, *J*(H^a–H^b) 15 Hz, C=C–C–H^a], 3·63 [1H, dd, *J*(H^b–H^c) 3, *J*(H^a–H^b) 15 Hz, C=C–C–H^b], 4·53 [1H, dd,

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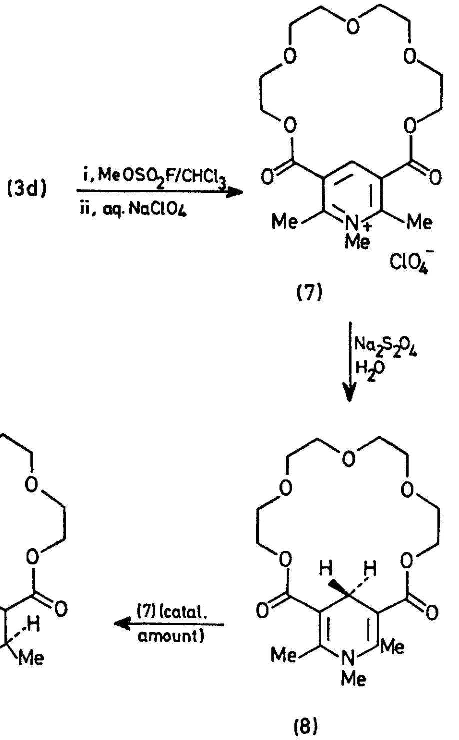
† Satisfactory elemental analyses or mass spectra with parent peaks at the calculated *m/e* values were obtained for all new compounds with the exception of (**4b**—**d**). We feel that the spectral data and chromatographic behaviour for (**4b**—**d**) are in accord with the suggested structures; the ^{1}H n.m.r. spectra for these compounds are temperature dependent.

‡ The reaction of (**2d**) is representative. In H_2O (2 l) were dissolved (**2d**) (10·86 g) and $(NH_4)_2CO_3$ (90 g). To this vigorously stirred solution was added over 16 h formaldehyde (2·6 g of 35% solution) dissolved in H_2O (250 ml). The crude product was extracted with CH_2Cl_2, the organic layer was dried, and thereafter a vigorous stream of N_2O_3 was passed through the solution until t.l.c. revealed no longer the characteristic fluorescence of a 1,4-dihydropyridine. Chromatography over a silica gel column using 1 : 1 ether–CH_2Cl_2 as eluent allowed isolation of (**3d**) (fastest moving fraction).

$J(\mathrm{H^b}$–$\mathrm{H^c})$ 3, $J(\mathrm{H^c}$–$\mathrm{H^d})$ 15 Hz, OCH^c–C–], 3·38 [1H, d, $J(\mathrm{H^c}$–$\mathrm{H^d})$ 15 Hz, OCH^d–C–], 3·65—4·00 (5H, m, CH_2O), and 4·22—4·75 (3H, m, CH_2O); ^{13}C n.m.r. ($CDCl_3$) p.p.m. from Me_4Si 16·4 and 26·9 (*J* 135 Hz, Me), 28·9, 47·8, 59·3, and 70·2 (*J* 150 Hz, OCH_2), 63·1 and 65·7 (*J* 150 Hz, CH_2), and 70·5, 109·0, 148·2, 166·7, 168·8, and 206·5 (quaternary C)}. This appears to be formed in the indicated fashion (Scheme 2) from (**6**) [m.p. 141—145 °C; the spin–spin coupling pattern for the $-CH_2OCH_2-$segment of the ring closely resembles that found in (**5**)] isolated when the dehydrogenation step of Scheme 1 is deleted. Formation of (**6**) involves a variation of the Hantzsch condensation wherein 2 mol of formaldehyde are incorporated; nitrosation of the enamine, hydrolysis by traces of water, and dehydration leads to (**5**).



SCHEME 3

To obtain compounds required for the investigation of potential catalysis of hydride transfer, (**3d**) was modified to (**7**) {m.p. 190—193 °C; u.v. λ_{max} (MeCN) 228 (ϵ, 8800), 280 (6500), 288 (6300), and 310 (900) nm; ^1H n.m.r. (C_3D_6O) δ 3·15 (6H, s, 2-and 6-Me), 3·60 (8H, s, 2 × C_2H_4), 3·71 (4H, m, OCH_2), 4·38 (3H, s, NMe), 4·50 [4H, m, (CO)OCH_2], and 9·08 (1H, s, ArH)} and (**8**) [m.p. 110—113 °C; spectral data comparable to those for (**7**)], by the straight forward procedures indicated (Scheme 3). The potential of compounds like (**8**) as NAD(P)H models is illustrated by its ready conversion into (**9**) (m.p. 131·5—133 °C) in the presence of a catalytic amount of (**7**).[1a] Details of this and other transhydrogenations as well as complexation reactions of these new crown ethers will be described elsewhere.§

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§ Crown ethers containing the 2,6-di(methylene)pyridine unit (not Hantzsch esters) have been made and studied chiefly by the group of Cram (M. Newcombe, G. W. Gokel, and D. J. Cram, *J. Amer. Chem. Soc.*, 1974, **96**, 6811). Bridged pyridine derivatives have been reported also by D. C. Dittmer and B. B. Blinder, *J. Org. Chem.*, 1973, **38**, 2873. Demonstrations of the ability of properly designed crown ethers to act as catalysts of reactions (and not exclusively as complexing agents) have also been provided by the Cram group. For an example of transacylation, see Y. Chao and D. J. Cram, *J. Amer. Chem. Soc.*, 1976, **98**, 1015.

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[2] See, for example: (a) U.K. Pandit and F. R. MasCabré, *Chem. Comm.*, 1971, 552; (b) D. J. Creighton, J. Haydn, G. Mooser, and D. S. Sigman, *J. Amer. Chem. Soc.*, 1973, **95**, 6855; (c) Y. Ohnishi, M. Kagami, and A. Ohno, *J. Amer. Chem. Soc.*, 1975, **97**, 4766.

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[4] For discussions of the Hantzsch condensation, see: (a) F. Brody and P. R. Ruby in 'Pyridine and Its Derivatives,' Part I, ed. E. Klingsberg, Interscience, New York, 1960, p. 500; (b) U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1.

[5] Procedure of (a) A. R. Bader, L. D. Cummings, and H. A. Vogel, *J. Amer. Chem. Soc.*, 1951, **73**, 4195; (b) G. P. Toney and W. V. McConnell, Eastman Kodak Co., Fr. P. 1,401,130, Appl. 1964; (*Chem. Abs.*, 1966, **64**, 11,435g).

[6] A. Singer and S. M. McElvain, *Org. synth.*, 1934, **14**, 30.

[7] H. van Doren and J. Kooi, work in progress.