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BIS(METHOXYCARBONYL)[2.2](2,5)PYRIDINOPHANES AS NICOTINAMIDE COENZYME MODELS

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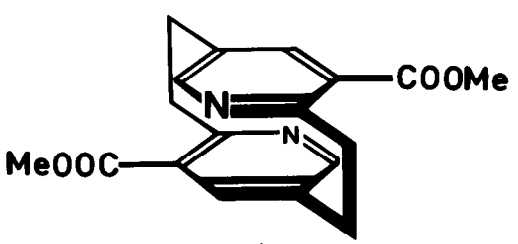
Abstract: [2.2](2,5)Pyridinophanes 1 - 4 consisting of two nicotinic ester units in the four different orientations possible were synthesized. Diquaternization to the corresponding pyridiniophanes 9 - 12 and partial reduction of 9 and 12 yielded the semi-reduced species 14 and 15; these isomers, due to their different mutual orientation of pyridinium and 1,4-dihydropyridine units, are of interest with regard to intramolecular redox reactions.

To mimic the direct hydrogen transfer between two nicotinamide units which occurs in transhydrogenases a number of model systems has been investigated in which, however, the sterical arrangements of the two interacting sites are not well defined [1]. Incorporation of the pyridinium and the 1,4-dihydropyridine units into cyclophane skeletons would allow to study intramolecular interactions as a function of precisely defined geometries of different isomers. This concept, successfully used before to study excimer and charge-transfer interactions [2], has recently been applied to other problems of biochemical interest like flavin interactions [3] and interactions of porphyrins with benzoquinones [4]. We now wish to report on nicotinamide coenzyme models of the [2.2]paracyclophane type; for the present work the nicotinamide units were, for synthetic reasons, replaced by nicotinic esters which, in general, show a very similar redox behaviour.



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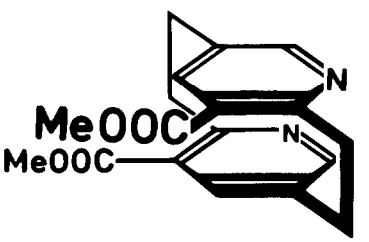

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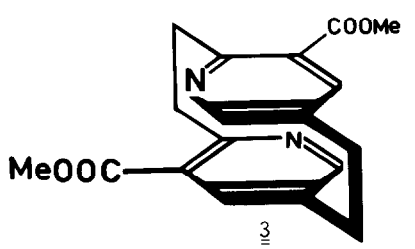

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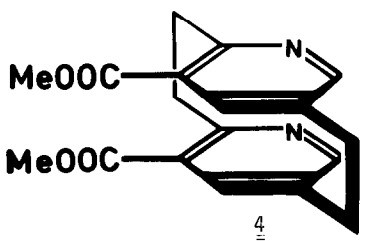

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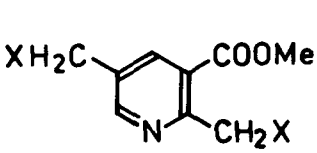
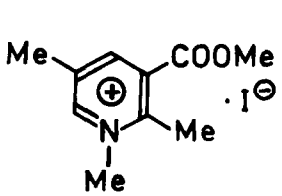
For the synthesis of 1 - 4, 2,5-bis(bromomethyl)-3-methoxycarbonylpyridine (5 [5], m. p. 79°C) was prepared from 3-methoxycarbonyl-2,5-dimethylpyridine by N-bromosuccinimide bromination, and 2,5-bis(isothiuroniomethyl)-3-methoxycarbonylpyridine dibromide (6 [5], m. p. 205°C, dec.) was obtained from 5 with thiourea. Cyclisation of 5 and 6 (boiling methanol/water (1%), potassium carbonate, high dilution) yielded bis(methoxycarbonyl)-2,11-dithia[3.3]pyridinophanes. By chromatography and fractionating crystallisation all four possible isomers (corresponding in structure to 1 - 4) were isolated [A [5]: 9%, m. p. 236 - 237°C; B [5]: 18%, m. p. 237 - 238°C; C [5]: 3%, m. p. 192°C; D [5]: 7%, m. p. 201 - 202°C]. The assignments of A and B to the 2,5';5,2'-bridged structures and of C and D to the 2,2';5,5'-bridged structures are clear from the results of the sulfur extrusion experiments to 1/2 and 3/4, respectively. Irradiation of A as well as B in trimethylphosphite yielded after chromatographic separation 1 [5] (27%, m. p. 174°C) and 2 [5] (14%, m. p. 152 - 153°C). By photolysis of C as well as D in trimethylphosphite 3 [5] (38%, m. p. 157 - 158°C) and 4 [5] (8%, m. p. 142 - 143°C) were obtained. The structural assignments of all four isomers are based on X-ray structure analyses which are valuable on their own for the comparison they allow with carbocyclic [2.2]paracyclophanes with regard to steric strain and deformation from planarity of the aromatic rings [6].



5: X = Br
6: X = SC(NH2)2]Br



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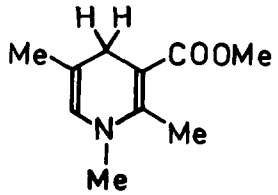

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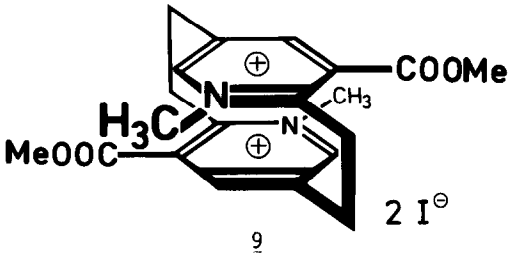
3-Methoxycarbonyl-2,5-dimethylpyridine, which has the same substitution pattern as present in 1 - 4, was easily quaternized by iodomethane in dimethylformamide (1 h, 50 - 60°; 64%) to the pyridinium iodide 7 [5] (m. p. 146°C). The diquaternization of 1 - 4 due to the steric hindrance and the building up of two neighbouring positive charges was expected to be more difficult. When 1 was reacted with iodomethane in dimethylformamide for 20 h at 50 - 60°C the double pyridinium salt 9 [5] (m. p. 238°C, dec.; 88% yield) was obtained. Although in 9 the electrostatic repulsion between the two positive ring charges must add considerably to the steric strain of the [2.2]paracyclophane system the molecular structure is only slightly different from that of the uncharged parent molecule 1 as shown by an X-ray analysis for the corresponding diperchlorate (derived from 9 by anion exchange) [7]. Under similar conditions as mentioned for 9 the isomers 10 [5] (m. p. 135°C, dec.), 11 [5] (m. p. 160°C, dec.) and 12 [5] (m. p. 175°C, dec.) were obtained from 2, 3 and 4, respectively.

Sodium dithionite reduction of N-alkylpyridinium salts normally leads to the 1,4-dihydropyridines as, for example, 7 was reduced with sodium dithionite to the 1,4-dihydro compound 8 [5] (m. p. 87 - 88°C; 32%). When 9 was reacted with sodium dithionite, however, UV and ^{1}H-NMR revealed that the product obtained was compound 13 with two 1,2-dihydropyridine units; accordingly 13 reacted in a Diels-Alder reaction with maleic anhydride to a 1 : 2 adduct [5]



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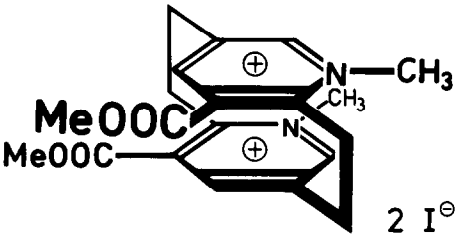

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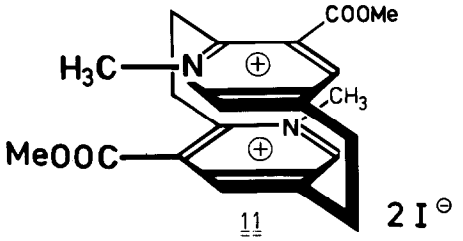

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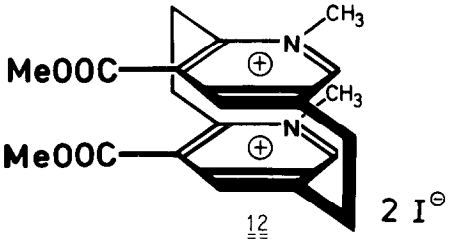
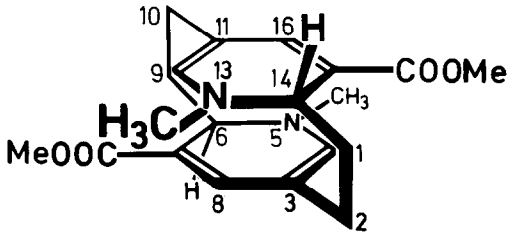


12

(m. p. 243°C). The irregular course of the reduction of 9 certainly has to do with the release of the [2.2]paracyclophane strain which favours the 1,2- over the 1,4-reduction under the conditions of the dithionite reduction.



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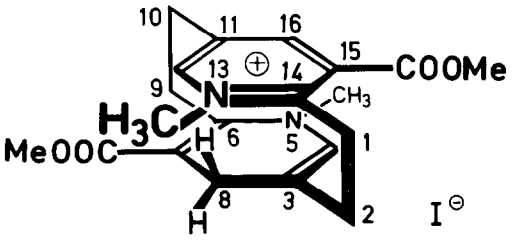
Surprisingly, when in water/methanol solution to 9 the 1,4-dihydropyridine 8 was added up to a molar ratio of 1 : 1 a fast and irreversible reduction of 9 occurred to a semi-reduced product which according to the UV/VIS spectrum should be the 1,4-dihydropyridine compound 14. This was indeed confirmed by an ^{1}H-NMR spectrum for which on the basis of structure 14 all signals (with the exception of the complex multiplets for the bridge protons) can be accounted for by reasonable assignments to the protons of either the oxidized ('ox') or the reduced



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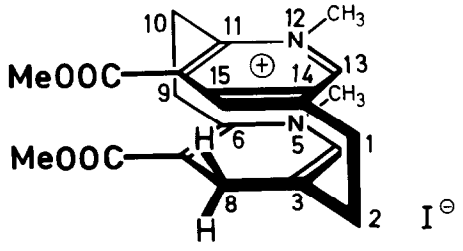

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('red') part of 14: δ = 2.43 and 2.66 (AB, J = 17.5 Hz, 2H; 8-H, red), 3.08 (s, 3H; 5-Me, red), 3.85 (s, 3H; 7-COOMe, red), 4.07 (s, 3H; 15-COOMe, ox), 4.31 (s, 3H; 13-Me, ox), 5.33 (br. s, 1H; 4-H, red), 8.50 (br. s, 1H; 12-H, ox), 8.53 (br. s, 1H; 16-H, ox) [360 MHz, D_2O]; of special significance is the appearance of an AB system for a pair of geminal protons (8-H) which was confirmed by decoupling.

In accordance with these results, starting from the pseudogeminal isomer 12 by adding 8 successively up to a ratio of 1 : 1 UV/VIS-spectral changes are observed, too, which indicate the formation of the semi-reduced 1,4-dihydro compound. The ^{1}H-NMR data (360 MHz, D_2O) of the reduction product of 12 are well in agreement with structure 15: δ = 1.94 and 2.45 (AB, J = 18.6 Hz, 2H; 8-H, red), 3.12 (s, 3H; 5-Me, red), 3.65 (s, 3H; 7-COOMe, red), 4.00 (s, 3H; 16-COOMe, ox), 4.20 (s, 3H; 12-Me, ox), 5.86 (br. s, 1H; 4-H, red), 8.52 (br. s, 1H; 15-H, ox), 8.65 (br. s, 1H; 13-H, ox).

For the semi-reduced isomers 14 and 15 due to their different mutual orientations of pyridinium and 1,4-dihydropyridine units a different behaviour with regard to intramolecular exchange of oxidation states might be expected: Whereas for 15 a direct hydrogen transfer from C(4) of the 1,4-dihydropyridine to C(4') of the pyridinium system seems likely to occur, this should be excluded for 14 because of the unfavourable geometry. Preliminary experiments on spin saturation transfer in ^{1}H-NMR [8] show indeed for 15 that on irradiation at δ = 4.20 (12-Me), besides a NOE to 13-H (a negative signal in the difference spectrum), a saturation transfer occurs to δ = 3.12 (5-Me; a positive signal in the same difference spectrum), and vice versa on irradiation at δ = 3.12 saturation transfer to δ = 4.20 (besides NOE to 4-H) is observed. For 14, on the other hand, on saturation at δ = 3.08 (5-Me) no saturation transfer can be detected under similar conditions.

This communication is dedicated to Harry Wasserman at the occasion of his 65th birthday remembering with great pleasure the many years of our joint Regional Editorship of Tetrahedron and Tetrahedron Letters (H. A. St.).

1) See, for example, J.-P. Behr and J.-M. Lehn, J. Chem. Soc. Chem. Commun. 1978, 143; O. Piepers and R. M. Kellogg, ibid. 1980, 1154; W. van Gerresheim, C. Kruk and J. W. Verhoeven, Tetrahedron Lett. 23, 565 (1982); Y. Murakami, Y. Aoyama, J. Kikuchi and K. Nishida, J. Am. Chem. Soc. 104, 5189 (1982).

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5) For these compounds elemental analyses and spectroscopic data are in accordance with the structures suggested.

6) H. A. Staab, H.-J. Hasselbach and C. Krieger, Chem. Ber., in press.

7) H.-J. Hasselbach, C. Krieger, M. Decker and H. A. Staab, Chem. Ber., in press.

8) J. Dabrowski, M. Decker and H. A. Staab, to be published.

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