ANTIINFLAMMATORY 2,3-DIHYDRO-1H-PYRROLIZINES. II: ADDITION OF 6,7-DIPHENYL-2,3-DIHYDRO-1H-PYRROLIZINE TO DIMETHYL ACETYLENEDICARBOXYLATE AND DIETHYL AZODICARBOXYLATE

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Abstract - The addition of the litle compound to the acetylene and the azo derivative,resp., leads to C5 functionalized dihydropyrrolizines. Competitive 1 : 1 and 1 : 2 adduct formation is observed using the diethyl azodicarboxylate. A significant antiinflammatory activity is shown for the 5-hydrazopyrrolizine derivative (1 : 1-adduct).

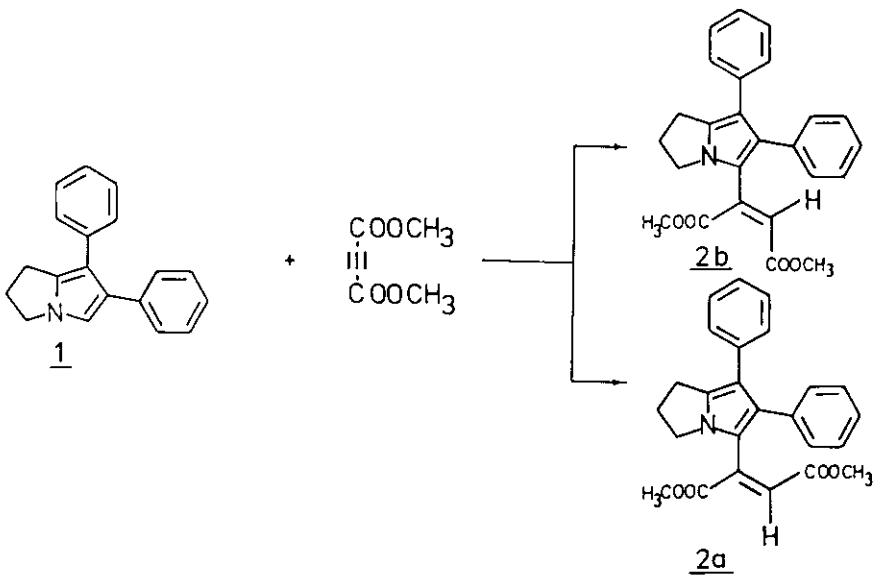
The pyrrolizine skeleton is an essential part of the biological active pyrrolizidine alkaloids[1], mitomycin antibiotics[2] and ant venom alkaloids[3]. 2,3-Dihydro-1H-pyrrolizine derivatives are potent antineoplastic[4] and antiinflammatory[5,6] agents, respectively.

According to their chemical behaviour and spectral data, 6,7-diphenyl-2,3-dihydro-1H-pyrrolizines (DADHP) have to be considered as 1,2-brigded pyrroles[7], therefore allowing structural variations at position 5 by electrophilic substitution.

After stirring a mixture of 1 and dimethyl acetylendicarboxylate (1 : 2 equiv.) at room temperature for 20 h, two compounds, 2a and 2b, were separated by column chromatography. Mass spectral data and elemental analyses indicate that both are 1 : 1 adducts. The NMR spectra represent the intact dihydropyrrolizine skeleton and two carbomethoxy singlets for each adduct; the H5 signal of starting 1 has disappeared.

The stereochemistry was determined by the chemical shift of the vinylic protons, because it is known[8], that the proton resonance signal of analogous substituted fumaric esters (2a, δ = 6.74 ppm) appears at lower field than the proton of the corresponding maleic compounds (2b), δ = 5.78). Moreover, the strong absorption of the E-isomer 2a at 412 nm is hypsochromically shifted to 369 nm in the Z-isomer 2b,

a result, which is found for comparable pyrrole derivatives[9], too. The ms of 2a and 2b is characterized by successive elimination of two carbomethoxy groups and ring opening with loss of HCN.

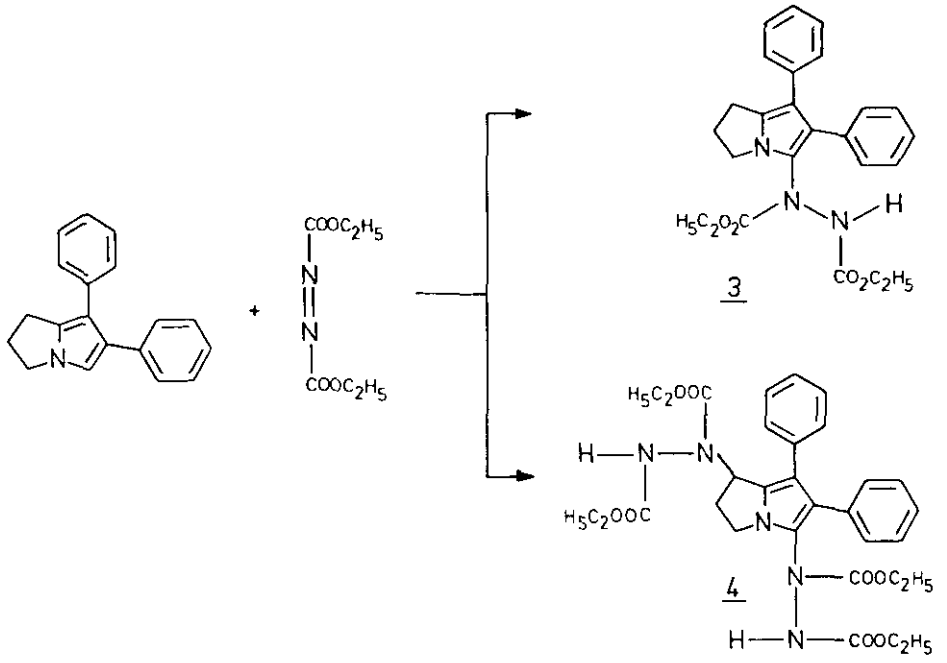


1 2b 2a

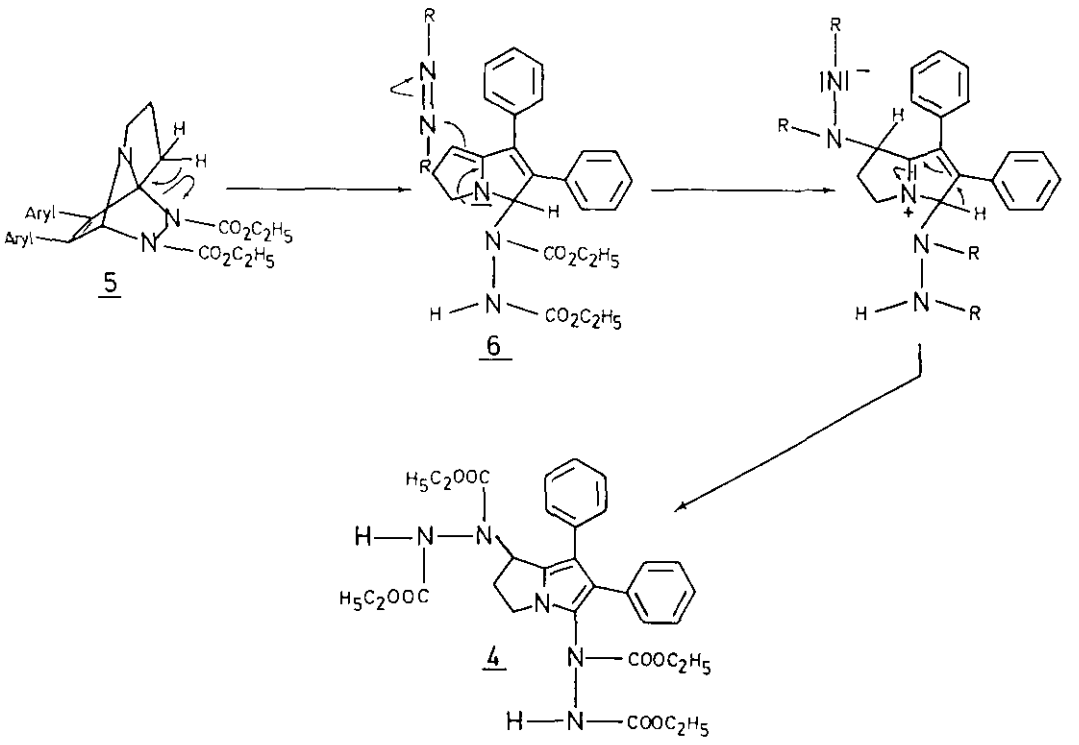
The E/Z ratio 3 : 2 indicates that the addition is not stereospecific. The intermediate zwitterion is possibly transfered to the Z-isomer 2b by an intramolecular H-shift and to the E-isomer 2a by intermolecular protonation, respectively, as already described for analogous systems[8]. An acid catalyzed isomerisation could not be observed under the conditions (CD_3COOH, 25°C, NMR control) described. We suppose that the basicity of the ß-carbon atom in the double vinylogous enamine carbocylic esters 2 is decreased by the vicinal carbomethoxy groups and the diphenyl dihydropyrrolizine system, thus, the necessary sp^3 centre in the vinyl substituent could not be created by protonation.

The electrophilicity of diethyl azodicarboxylate in substitution[10] and addition[11,12] reactions is well known. Heating 1 and the azo compound (1 : 1 equiv) in boiling toluene afforded the expected adduct 3 and a second product with the molecular formula $C_{31}H_{37}N_5O_8$ (elemental analysis, FD-MS: m/z = 607), which correspond to the 1 : 2-adduct 4. The IR spectrum of 3 shows a sharp NH signal at 3270 cm^{-1} and two C=O signal at 1735 and 1700 cm^{-1}. The NMR data (see exp. section) agree with

structure 3, too. Elimination of a $^{\cdot}NH\text{-}CO_2C_2H_5$ and carbomethoxy radical, respectively, from the molecular ion is observed in the MS of 3. ^{13}C-NMR investigations on 4 pointed out that in 4 compared to 1 carbon C1 is paramagnetically shifted (27.34 ppm in 1[7], 56.84 ppm in 4) and splits off as doublet in the off-resonance spectrum; therefore the position of the second hydrazo substituent was clear. All other spectroscopic data (exp. section) are in agreement with the shown 1 : 2 - structure 4. 1 : 2-Adducts are also produced by reaction of azo dicarboxylate with 1,4-dihydrobenzene and 9,10-dihydroanthracene[12].



We suppose, that 1,4-addition to 5 is followed by ring opening of the tricyclic system to the enamine 6, which then adds to a second molecule diethyl azodicarboxylate. Thus, competitive electrophilic substitution at C5 and 1,4-addition between 1 and the azo compounds leads to 3 (44 %) and 4 (22 %).
Inhibition (53.8 % and 41.7 %) of the carrageenin induced edema of the rat paw[13] is observed using 25 mg/kg and 2.5 mg/kg 4, respectively, with p. o. application. A detailed study of pharmacologically active DADHP derivatives will be published elsewhere[6].



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EXPERIMENTAL

Apparatus: Mp (Tottoli apparatus, uncorr.); IR spectra: Beckman Acculab III; UV spectra: Kontron 810; NMR spectra: ^{1}H-NMR spectra: Varian EM 390 (90 MHz). ^{13}C-NMR measurements were performed with a sweep of 4800 Hz at 36°C in the PFT mode on a Bruker WH 90 spectrometer under noise and off-resonance decoupling, operating at 22.63 MHz. Chemical shifts in all cases are reported in δ units from the internal standard TMS in $CDCl_3$. Mass spectra: Varian MAT CH 5 and 311 A, 70 eV, direkt insertion-probe. Microanalyses: Microanalytical laboratory, University Regensburg.

(6,7-Diphenyl-2,3-dihydro-1H-pyrrolizin-5-yl)-dimethyl fumarate 2a and (6,7-Diphenyl-2,3-dihydro-1H-pyrrolizin-5-yl)-dimethyl maleate 2b: To a solution of 2.59 g (10 mmol) 1 in 50 ml of benzene/dimethoxyethane (1/1) was added 2.84 g (20 mmol) of

dimethyl acetylenedicarboxylate in 10 ml of dimethoxyethane. The mixture afterwards was stirred for 20 h at room temperature, and then the solvens was distilled off. From the red residue 2a and 2b were separated by column chromatography (SiO_2, CH_2Cl_2).

2a (Rf = 0.8): Yield 0.85 g (21 %), vermilion crystals, mp 147° C (ethanol). $C_{25}H_{23}NO_4$ (401.4) Calc. C, 74.8; H, 5.77; N 3.4. Found: C, 74.1; H, 5.71; N, 3.3. IR 1725, 1620, 1610 cm^{-1}. UV λmax (logε) 412 (3.61), 272 (4.12), 242 (4.36), 205 nm (4.50). ^{1}H-NMR δ(ppm) 2.21 - 2.62 (m, 2H, C2), 3.05 (t, 2H, J = 7.0 Hz, C1), 3.42, 3.55 (2s, 6H, 2 x CO_2CH_3), 3.81 (t, 2H, J = 7.0 Hz, C3), 6.74 (s, 1H, vinyl-H), 6.90 - 7.29 (m, 10 H arom.). MS: m/z = 401 (70 % $M^{+\cdot}$), 341 (90 %), 342 (100 % M-CO_2CH_3), 311 (66 %, 342-OCH_3), 283 (50 %, 311-CO), 255 (17 %, 283-HCN).

2b (Rf =0.5): yield 0.52 g (13 %), yellow crystals, mp 142° C (ethanol). IR 1740, 1710, 1600 cm^{-1}. UV λmax (logε) 369 (4.09), 265 (sh), 235 (4.31), 205 nm (4.56). ^{1}H-NMR δ(ppm) 2.28 - 2.68 (m, 2H, C2), 2.99 (t, 2H, J = 7.0 Hz, C1), 3.41 and 3.60 (2s, 6H, 2 x CO_2CH_3), 4.08 (t, 2H, J = 7.0 Hz, C3), 5.78 (s, 1H, vinyl-H), 6.85 - 7.39 (m, 10 H arom.)

(6,7-Diphenyl-2,3-dihydro-1H-pyrrolizin-5-yl)-diethyl hydrazodicarboxylate 3 and 1,5-Di(diethyl hydrazodicarboxylate)-6,7-diphenyl-2,3-dihydro-1H-pyrrolizine 4

1.73 g (10 mmol) of diethyl azodicarboxylate in 20 ml of abs. toluene is added at 0° to a solution of 2.59 g (10 mmol) of 1 in 30 ml of abs. toluene; after the temperature had increased to room conditions the mixture was refluxed for 4 h. Evaporation of the solvent yields a brown residue. Separation of 3 and 4 was achieved by column chromatography (SiO_2, CH_2Cl_2/ethyl acetate = 9 : 1).

3 (Rf = 0.8): yield 1.90 g (44 %), mp 143° C (ethanol). $C_{25}H_{27}N_3O_4$ (433.2). MS (high resolution): Calc.: 433.20015. Found: 433.19900. IR 3270, 1735, 1700, 1595 cm^{-1}. UV: λmax (logε) = 269 (sh), 240 (4.34), 206 nm (4.53). ^{1}H-NMR: δ(ppm) 1.11 - 1.49 (m, 6H, 2 x $CO_2CH_2\underline{CH_3}$), 2.41 - 2.71 (m, 2H, C2), 3.63 (t, 2H, J = 7.0 Hz C1), 4.00 - 4.50 (m, 6H, C3 and 2 x $CO_2\underline{CH_2}CH_3$), 6.59 (s, 1H, NH), 7.01 - 7.41 (m, 10 H, arom.). MS: m/z = 433 (100 % $M^{+\cdot}$), 360 (60 % M-$CO_2C_2H_5$), 345 (98 % M-$NHCO_2C_2H_5$), 301 (19 %, 345 - C_2H_4O), 286 (25 %, 360 - $HCO_2C_2H_5$), 273 (80 %, 301-CO), 258 (55 %, 345 - $NCO_2C_2H_5$), 245 (23 %, 273 - C_2H_4), 230 (27 % , 258 - C_2H_4).

4 (Rf = 0.2): yield 1.35 g (22 %), mp 160°C(ether, -20°C). $C_{31}H_{37}N_5O_8$ (607.6) Calc.: C,61.2, H,6.14; N,11.5. Found : C,61.0; H,5.90; N,11.6. IR 3300, 1760, 1710, 1610 cm^{-1}. ^{1}H-NMR δ(ppm) 0.90 - 1.45 (m, 12H, 4 x $CO_2CH_2CH_2\underline{CH_3}$), 2.60 - 3.00 (m, 2H, C2), 3.88 - 4.50 (m, 10H, C3 and 4 x $CO_2\underline{CH_2}CH_3$),

5.80 - 6.20 (m, 2H, C1 and NH), 6.60 (s, 1H, NH), 6.90 - 7.40 (m, 10H arom.). ^{13}C-NMR δ(ppm) 14.36 (q, 4 x $CO_2\underline{CH_2}\underline{CH_3}$), 32.63 (t, C2), 44.63 (t, C3), 56.84 (d, C1), 62.08, 62.50, 63.12, 63.27 (4 x $CO_2\underline{CH_2}CH_3$), 115.63 (s, C7), 122.19, 122.84, 125.74, 126.42, 127.07, 127.43, 128.08, 128.46, 128.57, 129.09, 129.35 (C arom.), 134.12 134.25 (s, C7a, C6), 155.16, 155.58, 155.92, 156.49 (s, 4 x C=O). FD-MS (toluene): m/z = 607 (100 % $M^{+\cdot}$).

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