FUSED [1]BENZAZEPINES. PENTACYCLIC [1]BENZAZEPINES BY REACTION OF 1*H*-[1]BENZAZEPINE-2,5(3*H*,4*H*)-DIONE WITH ALDEHYDES[1]

Conrad Kunick

Institut für Pharmazie, Universität Hamburg, 20146 Hamburg, Germany

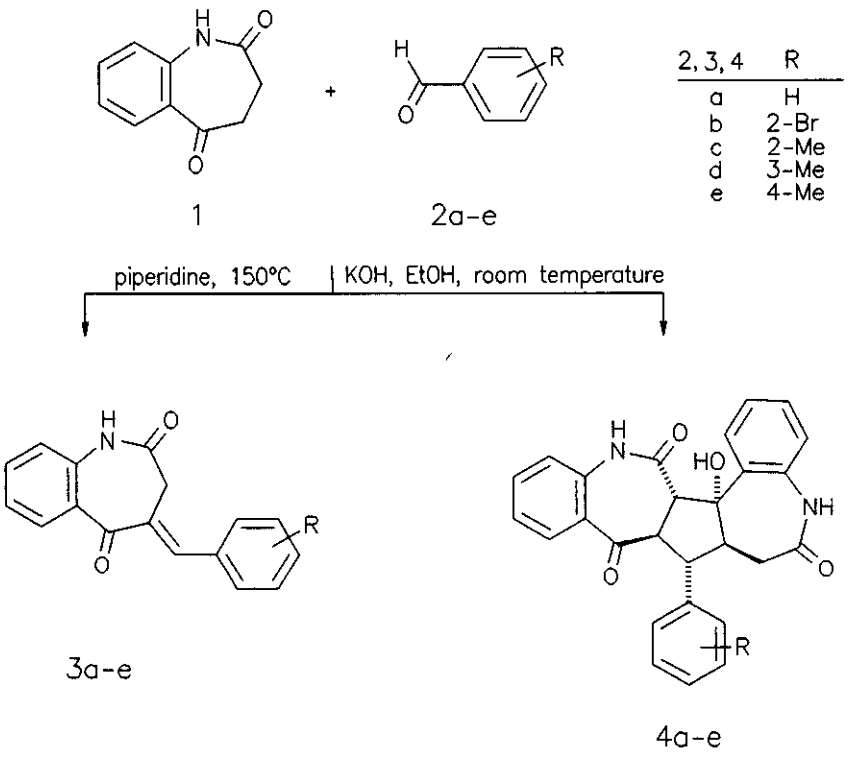
Dedicated to Prof. Paul Messinger on the occasion of his 60th birthday.

Abstract-Condensation reaction of 1*H*-[1]benzazepine-2,5(3*H*,4*H*)-dione (**1**) with the aromatic aldehydes (**2a-e**) in the presence of piperidine furnished 4-benzylidene-1*H*-[1]benzazepine-2,5(3*H*,4*H*)-diones (**3a-e**), whereas in the presence of potassium hydroxide the 7a,8,15a,15b-tetrahydro-15b-hydroxy-5*H*-[1]benzazepino[4',5':4,5]-cyclopenta[1,2-*c*][1]benzazepine-6,9,15(7*H*,8a*H*,14*H*)-triones (**4a-e**) were formed. The reaction of **1** with formaldehyde yielded the spiro compound (**7**) as the product of a Diels-Alder dimerization.

Like many natural occurring α-methylenesesquiterpene lactones, several synthetically prepared α-benzylidene-cycloalkanones exhibit cytotoxic activity.[2] One possible mode of action of these agents is accounted to be enzyme inhibition due to alkylation of thiol groups. In the course of studies on the chemistry of [1]benzazepines, it was intended to prepare 4-alkylidene substituted [1]benzazepine-2,5-diones with a view to gain derivatives with antitumor activity.

The 4-arylidene substituted compounds (**3a-e**) were synthesized by heating the 1*H*-[1]benzazepine-2,5(3*H*,4*H*)-dione (**1**) with a suitable aromatic aldehyde (**2a-e**) without solvent in the presence of a catalytic amount of piperidine, according to the method of Lévai and Szabó.[3] In all cases only one of the two possible diastereomers was isolated. Compound (**3a**) was shown to be *E*-configurated, because in an NOE experiment irradiation on the signal of the methylene protons resulted in a significant enhancement of the ortho phenyl proton signals, whereas the vinylic proton signal was not affected.

When **1** was reacted with the aromatic aldehydes (**2a-e**) in ethanolic solution containing potassium hydroxide, the pentacyclic compounds (**4a-e**) were isolated instead of the expected products (**3a-e**). The formation of **4**



may be the result of a Michael addition of the second molecule (**1**) to preformed **3** and subsequent intramolecular aldol reaction. The structure of **4a** was confirmed by the elemental analysis and the spectroscopic data (ir, ms, ^{1}H nmr, ^{13}C nmr, ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, ^{1}H-^{13}C COLOC). The relative configurations at the stereocenters of **4a** were assigned on the basis of NOE experiments, in which irradiation on the hydroxylic proton signal produced an enhancement of the signals of H(7a) and H(8a). On the other hand, an NOE relation between H(15a) and H(8) was observed. Furthermore, an NOE of the H(5) signal was detected when the signal of H(15a) was irradiated. This unexpected effect is accounted for a concave shape of the molecule resulting in a small distance through space between the two protons (Figure 1).

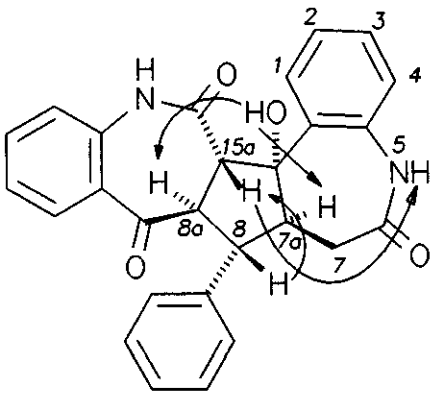
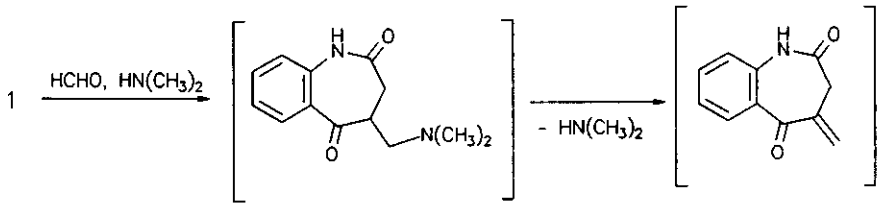
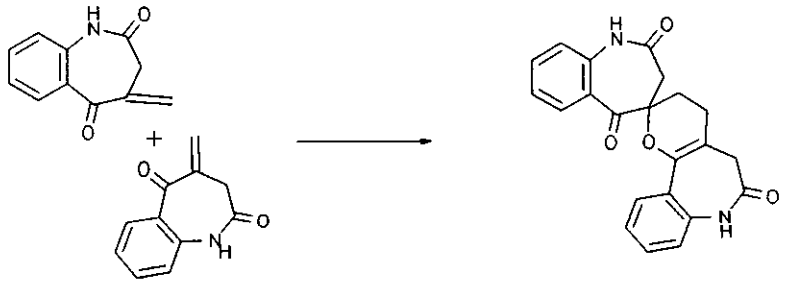


Figure 1: Nuclear Overhauser enhancements in **4a**

The attempted synthesis of 4-methylene-1*H*-[1]benzazepine-2,5(3*H*,4*H*)-dione (**6**) *via* aminomethylation of **1** and subsequent elimination of amine from the Mannich base (**5**) failed. Neither **5** nor **6** could be isolated, because amine elimination from **5** occurred spontaneously and the resulting *α*,ß-unsaturated ketone (**6**) underwent dimerization *via* a Diels-Alder reaction furnishing the spiroannulated dihydropyran (**7**). Similar reactions are known for other *α*-methylene ketones and methylenequinones.[4] The structural assignments of **7** were done on the basis of the elemental analysis and the spectral data (ir, ms, ^{1}H-nmr, ^{13}C-nmr, ^{1}H-^{1}H-COSY, ^{1}H-^{13}C-COSY). As expected, in the mass spectrum of **7** a prominent peak is caused by the ionized structure (**6**), being the product of a retro Diels-Alder reaction.



5 6



7

The compounds (**3a**), (**4a**), and (**7**) were screened by the National Cancer Institute for antitumor activity in different tumor cell lines. Only **3a** showed a moderate effect when it was submitted in relative high concentrations, with GI50-values (concentrations required for 50% growth inhibition of the tumor cells) ranging from 1.47 x 10^{-5} molar (colon cancer, HCT-116) to 8.17 x 10^{-5} molar (breast cancer, MCF7).

EXPERIMENTAL

Melting points were determined on an electric variable heater (Gallenkamp). Elemental analyses were performed on a Heraeus CHN-O-Rapid apparatus. Infrared spectra were recorded on a Pye Unicam SP1100 or a Pye

Unicam SP3-200S spectrophotometer, respectively, as KBr pellets. Nuclear magnetic resonance spectra were recorded on a Bruker AC 250P, a Bruker AMX 400 or a Varian XL 300 instrument, respectively. ^{13}C-Nmr spectra were recorded as ^{1}H-decoupled spectra and DEPT spectra. All nmr data are reported in ppm. Electron Impact mass spectra were recorded on a Kratos MS 50 (IE = 70 eV). Solvents were purified according to published methods.[5] Thus, ethanol was refluxed with sodium and subsequently with diethyl phthalate and then distilled. 1*H*-[1]Benzazepine-2,5(3*H*,4*H*)-dione (**1**) was prepared according to a method described previously.[6] Liquid aromatic aldehydes were distilled before use. All other commercial reagents were used as received.

(*E*)-4-Benzylidene-1*H*-[1]benzazepine-2,5(3*H*,4*H*)-dione (3a). A mixture of 350 mg of 1*H*-[1]benzazepine-2,5(3*H*,4*H*)-dione (**1**) (2.0 mmol), 212 mg of benzaldehyde (**2a**) (2.0 mmol) and 0.02 ml (0.2 mmol) of piperidine was stirred at 150°C for 1 h under nitrogen. After cooling, the resulting solid was recrystallized twice from ethanol to provide 267 mg (51%) as slightly greenish crystals, mp 190-191°C; ir: 3230 (NH), 1680, 1640 cm^{-1} (C=O); ^{1}H-nmr (250 MHz; DMSO-d_6): δ 3.62 (s, 2H, CH_2), 7.17 (d, 1H, J = 8 Hz, aromatic H), 7.26 (dd, 1H, J = 7.5/7.5 Hz, aromatic H), 7.40 - 7.63 (m, 4H, aromatic H), 7.76 - 7.87 (m, 4H, aromatic and vinylic H), 10.35 (s, 1H, NH); ^{13}C-nmr (62.9 MHz; DMSO-d_6): δ 34.68 (CH_2), 121.95, 124.28, 128.80, 129.73, 130.05, 131.30, 133.74, 139.08 (aromatic and vinylic tertiary C), 129.17, 131.47, 134.09, 138.17 (aromatic and vinylic quarternary C), 169.95 (C-2), 190.40 (C-5). Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.30; H, 5.12; N, 5.46.

(*E*)-4-(4-Bromobenzylidene)-1*H*-[1]benzazepine-2,5(3*H*,4*H*)-dione (3b). Prepared from **1** and 4-bromobenzaldehyde (**2b**) using the procedure for **3a**. Crystallization from ethanol yielded 227 mg (33%) brownish crystals, mp 234-236°C; ir: 3220 (NH), 1660 cm^{-1} (C=O); ^{1}H-nmr (400 MHz; DMSO-d_6): δ 3.62 (s, 2H, CH_2), 7.18 (d, 1H, J = 8 Hz, aromatic H), 7.28 (ddd, 1H, J = 1/7.5 /7.5 Hz, aromatic H), 7.60 (ddd, 1H, J = 1.5/7.5/7.5 Hz, aromatic H); 7.70 - 7.79 (m, 5H, aromatic and vinylic H), 7.85 (dd, 1H, J = 1.5/7.5 Hz, aromatic H), 10.35 (s, 1H, NH). Anal. Calcd for $C_{17}H_{12}NO_2Br$: C, 59.67; H, 3.53; N, 4.09; Br, 23.35. Found: C, 59.73; H, 3.61; N, 3.95; Br, 23.08.

(*E*)-4-(2-Methylbenzylidene)-1*H*-[1]benzazepine-2,5(3*H*,4*H*)-dione (3c). Prepared from **1** and 2-methylbenzaldehyde (**2c**) using the procedure for **3a**. Crystallization from ethanol yielded 187 mg (34%) yellowish crystals, mp 182-183°C; ir: 3210 (NH), 1675, 1655 cm^{-1} (C=O); ^{1}H-nmr (400 MHz; DMSO-d_6): δ 2.35 (s, 3H, CH_3), 3.52 (s, 2H, CH_2), 7.17 (d, 1H, J = 8 Hz, aromatic H), 7.25 - 7.40 (m, 4H, aromatic H), 7.59 (ddd, 1H, J = 1.5/7.5/7.5 Hz, aromatic H); 7.68 (d, 1H, J = 7.5 Hz, aromatic H), 7.88 (dd, 1H, J = 1.5/8 Hz, aromatic H), 7.95 (s, 1H, vinylic H), 10.30 (s, 1H, NH); ^{13}C-nmr (62.9 MHz; DMSO-d_6): δ 19.57 (CH_3), 34.79 (CH_2), 121.84, 124.21, 125.80, 128.85, 129.34, 130.24, 131.16, 133.61, 137.94 (aromatic and vinylic tertiary C), 129.49, 131.85, 133.12, 137.70, 137.96 (aromatic and vinylic quarternary C), 169.87

(C-2), 190.29 (C-5). Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.91; H, 5.48; N, 5.13.

(*E*)-4-(3-Methylbenzylidene)-1*H*-[1]benzazepine-2,5(3*H*,4*H*)-dione (3d). Prepared from **1** and 3-methylbenzaldehyde (**2d**) using the procedure for **3a**. Crystallization from ethanol yielded 281 mg (51%) yellowish crystals, mp 216-218°C; ir: 3205 (NH), 1665, 1655 cm^{-1} (C=O); ^{1}H-nmr (250 MHz; DMSO-d_6): δ 2.39 (s, 3H, CH_3), 3.65 (s, 2H, CH_2), 7.15 - 7.32 (m, 3H, aromatic H), 7.42 (t, 1H, J = 7.5 Hz, aromatic H), 7.55 - 7.68 (m, 3H, aromatic H); 7.76 (s, 1H, vinylic H), 7.85 (dd, 1H, J = 1.5/8 Hz, aromatic H), 10.35 (s, 1H, NH); ^{13}C-nmr (100.62 MHz; DMSO-d_6): δ 20.89 (CH_3), 34.63 (CH_2), 121.85, 124.15, 126.91, 128.57, 129.11, 130.28, 130.65, 131.16, 131.29, 133.60, 133.96, 137.93, 138.09, 139.13 (aromatic and vinylic C), 169.84 (C-2), 190.31 (C-5). Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.79; H, 5.62; N, 5.27.

(*E*)-4-(4-Methylbenzylidene)-1*H*-[1]benzazepine-2,5(3*H*,4*H*)-dione (3e). Prepared from **1** and 4-methylbenzaldehyde (**2e**) using the procedure for **3a**. Crystallization from ethanol yielded 353 mg (64%) pale yellow crystals, mp 232-233°C; ir: 3200 (NH), 1680, 1665 cm^{-1} (C=O); ^{1}H-nmr (400 MHz; DMSO-d_6): δ 2.38 (s, 3H, CH_3), 3.63 (s, 2H, CH_2), 7.18 (d, 1H, J = 8 Hz, aromatic H), 7.27 (ddd, 1H, J = 1.2/7.5/7.5 Hz, aromatic H), 7.33 (d, 2H, J = 8 Hz, aromatic H), 7.57 (ddd, 1H, J = 1.5/7.5/7.5 Hz, aromatic H), 7.73 (d, 2H, J = 8 Hz, aromatic H), 7.76 (s, 1H, vinylic H), 7.85 (dd, 1H, J = 1.5/8 Hz, aromatic H), 10.30 (s, 1H, NH); ^{13}C-nmr (62.9 MHz; DMSO-d_6): δ 20.94 (CH_3), 34.57 (CH_2), 121.83, 124.14, 129.34, 130.10, 131.15, 133.55, 139.07 (aromatic and vinylic tertiary C), 129.19, 130.57, 131.21, 138.08, 139.66 (aromatic and vinylic quarternary C), 169.91 (C-2), 190.30 (C-5). Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.82; H, 5.51; N, 5.04.

(±)-(7a*S*,8*S*,8a*R*,15a*S*,15b*R*)-7a,8,15a,15b-Tetrahydro-15b-hydroxy-8-phenyl-5*H*-[1]benzazepino[4′,5′:4,5]cyclopenta[1,2-*c*][1]benzazepine-6,9,15(7*H*,8a*H*,14*H*)-trione (4a). To a suspension of 350 mg of 1*H*-[1]benzazepine-2,5(3*H*,4*H*)-dione (**1**) (2.0 mmmol) in 6 ml of ethanol 212 mg of benzaldehyde (**2a**) (2.0 mmol) and 56 mg (1.0 mmol) of potasssium hydroxide were added. The mixture was stirred at room temperature for 24 h. A precipitate formed, which was filtered with suction, washed successively with ethanol, dilute acetic acid and water. Crystallization from ethanol gave 250 mg (57 %) colorless crystals, mp 307-309°C (decomp.); ir: 3390 (OH), 3200 (broad, NH), 1655 cm^{-1} (C=O); ^{1}H-nmr (300 MHz; DMSO-d_6): δ 1.92 (ddd, 1H, J = 2/3.5/13 Hz, H-7), 2.40 (dd, 1H, J = 5.5/13 Hz, H-7), 2.69 (m, 1H, H-7a), 3.48 (dd, 1H, J = 6/9 Hz, H-8), 3.74 (d, 1H, J = 13 Hz, H-15a), 3.88 (dd, 1H, J = 9/13 Hz, H-8a), 6.44 (d, 1H, J = 1 Hz, OH), 6.85 - 6.91 (m, 1H, aromatic H), 7.10 (dd, 1 H, J = 1/8 Hz, aromatic H), 7.19 - 7.36 (m, 6H, aromatic H), 7.49 - 7.58 (m, 3H, aromatic H), 7.77 (dd, 1H, J = 1.5/8 Hz, aromatic H), 7.83 - 7.88 (m, 1H, aromatic H),

9.65 (s, 1H, NH), 10.45 (s, 1H, NH); ^{13}C-nmr (75.43 MHz; DMSO-d_6): δ 36.96 (C-7), 48.28 (C-15a), 52.11 (C-8), 58.14 (C-8a), 62.00 (C-7a), 82.30 (C-15b), 122.17, 122.61, 124.23, 124.47, 126.23, 127.26, 127.46, 127.94, 127.99, 128.31, 130.09, 134.06, 135.26, 135.35, 136.97, 144.10 (aromatic C), 171.71, 172.55 (C-6 and C-15), 199.35 (C-9); ms (EI, m/z): 439 (18%), 438 (59%), 420 (24%), 403 (19%), 299 (14%), 265 (24%), 264 (100%), 263 (95%), 262 (18%), 259 (27%), 237 (20%). Anal. Calcd for $C_{27}H_{22}N_2O_4$: C, 73.96; H, 5.06; N, 6.39. Found: C, 73.95; H, 5.18; N, 6.57.

(±)-(7a*S*,8*S*,8a*R*,15a*S*,15b*R*)-8-(4-Bromophenyl)-7a,8,15a,15b-tetrahydro-15b-hydroxy-5*H*-[1]benzazepino-[4',5':4,5]cyclopenta[1,2-*c*][1]benzazepine-6,9,15(7*H*,8a*H*,14*H*)-trione (4b). Prepared from **1** and 4-bromobenzaldehyde (**2b**) using the procedure for **4a**. Crystallization from ethanol gave 280 mg (54%) colorless crystals, mp 295°C (decomp.); ir: 3420 (OH), 3210 (NH), 1675 cm^{-1} (C=O); ^{1}H-nmr (400 MHz; DMSO-d_6): δ 1.90 (d, 1H, J = 13 Hz, H-7), 2.40 (dd, 1H, J = 5/13 Hz, H-7), 2.66 (dd, 1H, J = 5/6 Hz, H-7a), 3.46 (dd, 1H, J = 6/9 Hz, H-8), 3.73 (d, 1H, J = 13.5 Hz, H-15a), 3.88 (dd, 1H, J = 9/13.5 Hz, H-8a), 6.44 (s, 1H, OH), 6.88 (dd, 1H, J = 1.5/7.5 Hz, aromatic H), 7.10 (d, 1 H, J = 8 Hz, aromatic H), 7.20 - 7.30 (m, 3H, aromatic H), 7.44 - 7.49 (m, 2H, aromatic H), 7.54 - 7.59 (m, 3H, aromatic H), 7.78 (dd, 1H, J = 1.5/8 Hz, aromatic H), 7.86 (dd, 1H, J = 2/7.5 Hz, aromatic H), 9.72 (s, 1H, NH), 10.50 (s, 1H, NH). Anal. Calcd for $C_{27}H_{21}N_2O_4Br$: C, 62.68; H, 4.09; N, 5.41; Br, 15.44. Found: C, 62.32; H, 4.17; N, 5.18; Br, 15.13.

(±)-(7a*S*,8*S*,8a*R*,15a*S*,15b*R*)-7a,8,15a,15b-Tetrahydro-15b-hydroxy-8-(2-methylphenyl)-5*H*-[1]benzazepino-[4',5':4,5]cyclopenta[1,2-*c*][1]benzazepine-6,9,15(7*H*,8a*H*,14*H*)-trione (4c). Prepared from **1** and 2-methylbenzaldehyde (**2c**) using the procedure for **4a**. Crystallization from ethanol gave 220 mg (49%) colorless crystals, mp 317-320°C (decomp.); ir: 3370 (OH), 3190 (NH), 1660 cm^{-1} (C=O); ^{1}H-nmr (400 MHz; DMSO-d_6): δ 1.87 (d, 1H, J = 13 Hz, H-7), 2.39 (dd, 1H, J = 5/13 Hz, H-7), 2.45 (s, 3H, CH_3), 2.67 (m, 1H, H-7a), 3.70 - 3.90 (m, 3H, H-8, H-8a, and H-15a), 6.42 (s, 1H, OH), 6.85 - 7.80 (m, 12H, aromatic H), 9.71 (s, 1H, NH), 10.43 (s, 1H, NH); ^{13}C-nmr (62.9 MHz; DMSO-d_6): δ 19.61 (CH_3), 36.94 (C-7), 46.49, 48.46 (C-15a, C-8), 59.60 (C-8a), 62.63 (C-7a), 82.17 (C-15b), 122.24, 122.64, 124.27, 124.66, 125.86, 126.58, 127.59, 127.68, 127.86, 127.00, 129.60, 130.07, 134.09, 135.29, 135.95, 136.88, 142.60 (aromatic C, one signal missing due to peak overlapping), 171.71, 172.40 (C-6 and C-15), 200.16 (C-9). Anal. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.35; N, 6.19. Found: C, 74.06; H, 5.60; N, 6.30.

(±)-(7a*S*,8*S*,8a*R*,15a*S*,15b*R*)-7a,8,15a,15b-Tetrahydro-15b-hydroxy-8-(3-methylphenyl)-5*H*-[1]benzazepino-[4',5':4,5]cyclopenta[1,2-*c*][1]benzazepine-6,9,15(7*H*,8a*H*,14*H*)-trione (4d). Prepared from **1** and 3-methylbenzaldehyde (**2d**) using the procedure for **4a**. Crystallization from ethanol/acetonitrile gave 307 mg (68%) colorless crystals, mp 325-328°C (decomp.); ir: 3410, 3380 (OH), 3200 (NH), 1665 cm^{-1} (C=O); ^{1}H-nmr (400 MHz; DMSO-d_6): δ 1.90 (d, 1H, J = 13 Hz, H-7), 2.33 (s, 3H, CH_3), 2.38 (dd, 1H, J = 5.5/13 Hz,

H-7), 2.66 (dd, 1H, J = 5.5/6 Hz, H-7a), 3.43 (dd, 1H, J = 6/9 Hz, H-8), 3.72 (d, 1H, J = 13.5 Hz, H-15a), 3.88 (dd, 1H, J = 9/13.5 Hz, H-8a), 6.42 (s, 1H, OH), 6.87 (dd, 1H, J = 1.5/7.5 Hz, aromatic H), 7.05 (d, 1H, J = 8 Hz, aromatic H), 7.10 (d, 1H, J = 8 Hz, aromatic H), 7.19 - 7.33 (m, 6H, aromatic H), 7.55 (ddd, 1H, J = 1.5/8/8 Hz, aromatic H), 7.76 (dd, 1H, J = 1.5/8 Hz, aromatic H), 7.85 (dd, 1H, J = 1.5/8 Hz, aromatic H), 9.71 (s, 1H, NH), 10.46 (s, 1H, NH); ^{13}C-nmr (100.62 MHz; DMSO-d_6): δ 21.06 (CH_3), 36.94 (C-7), 48.28, 52.06 (C-15a, C-8), 58.03 (C-8a), 62.04 (C-7a), 82.27 (C-15b), 122.19, 122.63, 124.28, 124.53, 125.13, 126.96, 127.36, 127.53, 127.99, 128.28, 128.58, 130.13, 134.12, 135.26, 135.38, 136.99, 137.33, 144.04 (aromatic C), 171.69, 172.57 (C-6 and C-15), 199.53 (C-9). Anal. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.35; N, 6.19. Found: C, 74.15; H, 5.46; N, 6.27.

(±)-(7a*S*,8*S*,8a*R*,15a*S*,15b*R*)-7a,8,15a,15b-Tetrahydro-15b-hydroxy-8-(4-methylphenyl)-5*H*-[1]benzazepino-[4',5':4,5]cyclopenta[1,2-*c*][1]benzazepine-6,9,15(7*H*,8a*H*,14*H*)-trione (4e). Prepared from **1** and 4-methylbenzaldehyde (**2e**) using the procedure for **4a**. Crystallization from ethanol gave 193 mg (43%) colorless crystals, mp 282-290°C (decomp.); ir: 3430 (OH), 3220 (NH), 1675, 1650 cm^{-1} (C=O); ^{1}H-nmr (400 MHz; DMSO-d_6): δ 1.88 (m, 1H, H-7), 2.30 (s, 3H, CH_3), 2.38 (dd, 1H, J = 5.2/12.8 Hz, H-7), 2.65 (m, 1H, H-7a), 3.41 (dd, 1H, J = 6.2/9.2 Hz, H-8), 3.71 (d, 1H, J = 13.6 Hz, H-15a), 3.84 (dd, 1H, J = 9.2/13.6 Hz, H-8a), 6.40 (s, 1H, OH), 6.82 - 7.85 (m, 12H, aromatic H), 9.73 (s, 1H, NH), 10.47 (s, 1H, NH); ^{13}C-nmr (62.90 MHz; DMSO-d_6): δ 20.55 (CH_3), 36.89 (C-7), 48.30, 51.78 (C-15a, C-8), 58.17 (C-8a), 62.07 (C-7a), 82.19 (C-15b), 122.19, 122.63, 124.26, 124.54, 127.53, 127.91, 127.99, 128.93, 130.10, 134.10 (aromatic tertiary C), 127.48, 135.26, 135.30, 135.37, 136.96, 141.02 (aromatic quarternary C), 171.69, 172.57 (C-6 and C-15), 199.57 (C-9). Anal. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.35; N, 6.19. Found: C, 74.05; H, 5.42; N, 6.32.

(±)4',7'-Dihydrospiro[1*H*-1-benzazepine-4(5*H*),2'(3'*H*)pyrano[3,2-*d*][1]benzazepine]-2(3*H*),5,6'(5'*H*)-trione(7). A suspension of 350 mg of 1*H*-[1]benzazepine-2,5(3*H*,4*H*)dione (**1**) (2.0 mmmol), 163 mg of dimethylammonium chloride (2.0 mmol) and 160 mg (5.3 mmol) of paraformaldehyde in 3 ml of ethanol was refluxed for 2 h. A precipitate formed, which after cooling was filtered with suction, washed with cold ethanol and then was crystallized from ethanol to yield 195 mg (52%) colorless crystals, mp 247-248°C (decomp.); ir: 3220 (NH), 1650 cm^{-1} (C=O); ^{1}H-nmr (300 MHz; DMSO-d_6): δ 1.84 - 2.38 (m, 4H, CH_2-CH_2), 2.45 (d, 1H, J = 13 Hz, CH_2), 2.52 (d, 1H, J = 13 Hz, CH_2), 3.08 (d, 1H, J = 16 Hz, CH_2), 3.23 (d, 1H, J = 16 Hz, CH_2), 6.96 (ddd, 1H, J = 1/7/8 Hz, aromatic H), 7.05 - 7.14 (m, 2H, aromatic H), 7.17 (dd, 1H, J = 1.5/8 Hz), 7.26 (ddd, 1H, J = 1.5/7/8.5 Hz, aromatic H), 7.29 (dd, 1H, J = 1/8 Hz, aromatic H, overlapped by the previous signal), 7.56 (ddd, 1H, J = 1.5/7.5/8 Hz, aromatic H), 7.67 (dd, 1H, J = 1.5/8 Hz, aromatic H), 10.05 (s, 1H, NH), 10.50 (s, 1H, NH); ^{13}C-nmr (75.43 MHz; DMSO-d_6): δ 23.88, 27.42 (C-3', C-4'), 37.40, 41.15 (C-3, C-5'), 78.25 (C-2'), 106.33 (C-4'a), 120.01, 120.86, 122.42, 122.81, 123.80, 125.23, 126.39, 128.42, 130.32, 134.02, 136.11, 138.24 (aromatic C), 143.26 (C-11'a), 168.25, 170.77 (C-2, C-6'), 197.3 (C-5); ms

(EI, m/z): 375 (22%), 374 (100%), 254 (14%), 201 (20%), 200 (23%), 199 (29%), 188 (22%), 187 (79%, product of the retro Diels-Alder Reaction). Anal. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.34; H, 5.04; N, 7.50.

ACKNOWLEDGEMENTS

My thanks are due to Prof. D. Geffken for generous support, to Dr. V. Sinnwell (Hamburg) and Mrs. M. Schneider (Bonn) for recording the nmr spectra and to the National Cancer Institute for performing the antitumor screening.

REFERENCES

1 Presented in part at the 14th International Congress of Heterocyclic Chemistry, Antwerp, 1993.

2 J. R. Dimmock, V. K. Arora, S. L. Wonko, N. W. Hamon, J. W. Quail, Z. Jia, R. C. Warrington, W. D. Fang, and J. S. Lee, *Drug Des. Delivery*, 1990, **6**, 183.

3 A. Lévai and Z. Szabó, *Pharmazie*, 1992, **47**, 56.

4 C. Mannich, *Ber.*, 1941, **74**, 557; D. S. Tarbell, H. F. Wilson, and E. Ott, *J. Am. Chem. Soc.*, 1952, **74**, 6263; H. Fiesselmann and J. Ribka, *Chem. Ber.*, 1956, **89**, 40; M. Protiva, V. Seidlová, E. Svátek, and F. Hradil, *Coll. Czech. Chem. Commun.*, 1972, **37**, 868; M. A. Chauncey and M. F. Grundon, *Synthesis*, **1990**, 1005; D. L. Boger and S. M. Weinreb, 'Hetero Diels-Alder Methodology in Organic Synthesis', Academic Press, New York, 1987, and references cited therein; A. S. Onishchenko, 'Diene Synthesis', Israel Program for Scientific Translations, Jerusalem 1964, and references cited therein.

5 D. D. Perrin and W. L. F. Armarego,'Purification of Laboratory Chemicals', 3rd ed., Pergamon Press, Oxford, England, 1988.

6 C. Kunick, *Arch. Pharm.*, 1991, **324**, 579.

Received, 1st June, 1995