OCTAHYDRO DERIVATIVES OF A NOVEL HETEROCYCLIC SYSTEM BENZO[f][1,2]DIAZEPINO[5,4,3-c,d]INDOLES

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Summary : The synthesis of benzo[f][1,2]diazepino[5,4,3-c,d]indol-11-ones **4** is described. The structure of the above mentioned compounds has been confirmed by X-ray crystallographic analysis. The influence of compounds **4a** and **3a** on mice behaviour was tested. The results obtained showed that compounds **4a** and **3a** tested at doses of 0.005 to 50.0 mg/kg exerted a slight sedative influence on the CNS.

Introduction

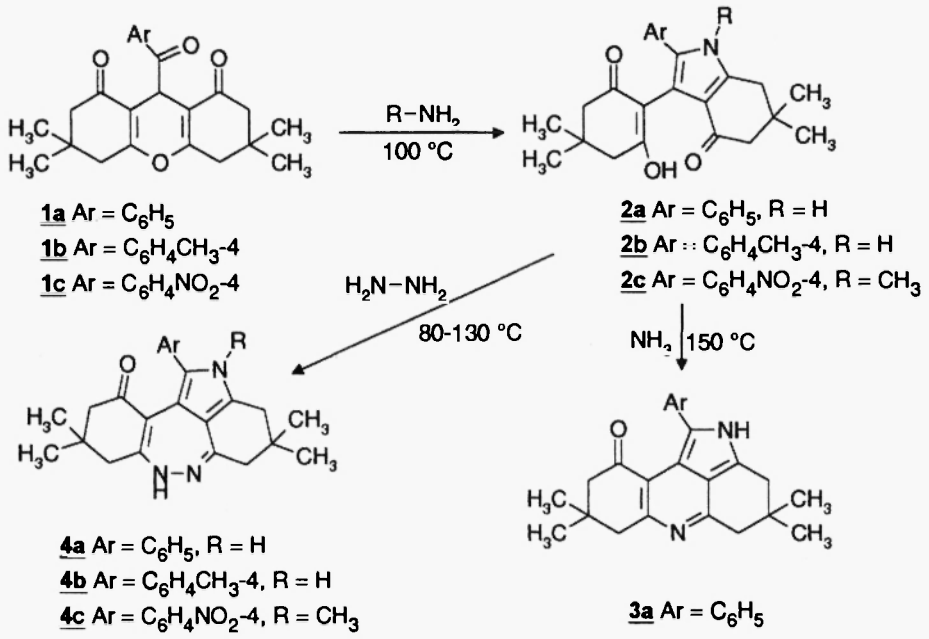
A lot of diazepine derivatives are known to have diverse and remarkable pharmacological activities. The most investigated group of diazepines is 1,4-diazepine derivatives – well-known tranquillizers and anticonvulsants (1,2). In contrast to 1,4-diazepines, data on pharmacological activity of 1,2-diazepines are very poor. There is a structure related to the title compounds described: pyrrolo[3,4-d][1,2]diazepines (3), however there are no pharmacological data on these compounds.

Our report includes data about synthesis of benzo[f][1,2]diazepino[5,4,3-c,d]indoles **4**, their effect on CNS functioning and its comparison with those of related six-membered analogue – pyrroloacridine **3**.

Results and discussion

Chemistry

In the previously investigated reaction of 9-aroyl-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanten-1,8-diones (**4**) with ammonia under heating 1-aryl-4,4,8,8-tetramethyl-3,4,5,6,7,8,9,10-octahydropyrrolo[4,3,2-m,n]acridin-10-ones **3** were obtained (5). The reaction proceeded via formation of 2-aryl-3-(4,4-dimethyl-2,6-dioxo-1-cyclohexyl)-6,6-dimethyl-4,5,6,7-tetrahydroindol-4-ones **2**, which were used in the further reactions with hydrazine (Scheme 1). These reactions proceed at 80-130 °C and lead to products **4** which represent a new class of heterocyclic compounds.



1a Ar = C_6H_5
1b Ar = $C_6H_4CH_3$-4
1c Ar = $C_6H_4NO_2$-4

2a Ar = C_6H_5, R = H
2b Ar = $C_6H_4CH_3$-4, R = H
2c Ar = $C_6H_4NO_2$-4, R = CH_3

4a Ar = C_6H_5, R = H
4b Ar = $C_6H_4CH_3$-4, R = H
4c Ar = $C_6H_4NO_2$-4, R = CH_3

3a Ar = C_6H_5

Scheme 1.

X-ray studies

X-ray studies of **4b** confirmed the structure proposed on the basis of ^{1}H-NMR spectral data. Two species of hydrogen bonds of an intermolecular nature are found in the crystal structure of **4b**. By shortest of them (N7-H7...N6) two molecules form the centrosymmetric associate in unit cell, the other (N2-H2...O29) bonded those associates parallel to *c* axis of the crystal. The structural fragment of condensed heterocycles is found to be rather planar (angle between plane C1N2C17C15C14 and C14C15C16N6C13C12 is 10°) (Fig.1). Planes of C=O group (O29C11C12) and

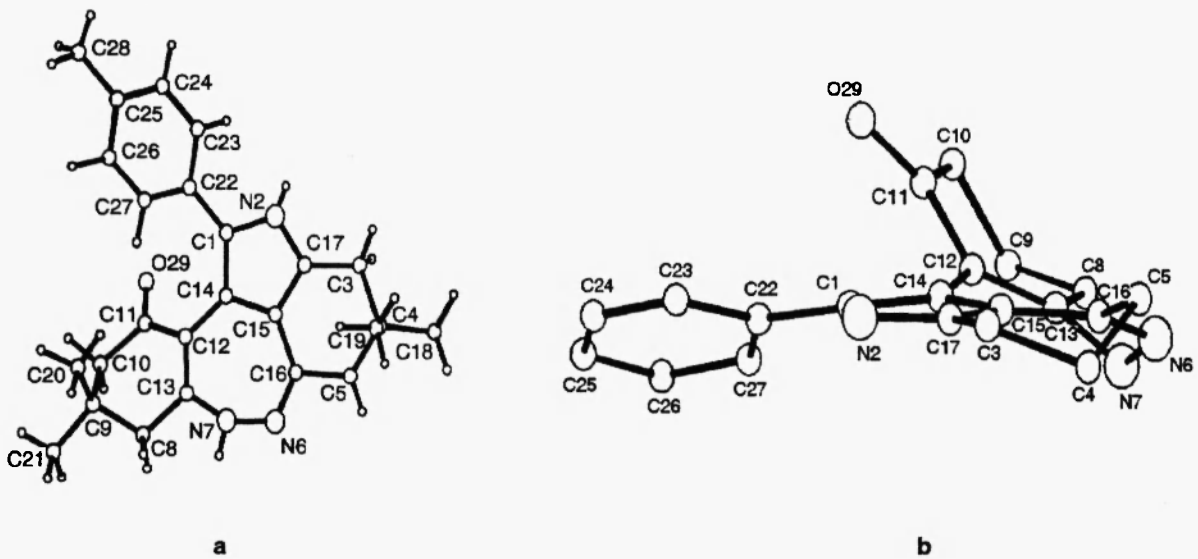


Fig.1. Structure of compound **4b**: frontal view (a); perspective view with omited methyl groups and hydrogen atoms (b)

NH group of diazepine ring (N6N7C13) appear out of common conjugated system and, in relation to this one, are oriented on diverse directions. Angles between these planes and plane C14C15C16N6C13C12 are 36° and 48° respectively, nevertheless conjugation of both groups may be assumed. The N2 atom is located at the plane of pyrrole ring. Apparently, NH-group of diazepine ring is unlikely to take part in common conjugation of the system due to considerable bending of these atoms from the plane of seven-membered ring.

Pharmacology

The compound 4a showed considerably lower toxicity in mice (LD_{50}>5000 mg/kg *i.p.*) than 3a (LD_{50}>300 mg/kg *i.p.*).

The compounds weakly influenced the mice behaviour (Table 1): only at high dose of 50 mg/kg 4a slightly increased the locomotor activity, 3a at the doses 5 mg/kg and 50 mg/kg induced slight but statistically significant depression of locomotion (actometria test). These compounds exhibited anticonvulsive action in pentylenetetrazole (PTZ) - seizure test at the doses from 0.05 mg/kg to 50 mg/kg, and lengthened the hexobarbital-sleeping time. Compounds 3a and 4a had no analgesic (hot plate test) and tranquilizing activity (rota rod test), however 3a was able to lower body temperature (by at least 3 °C) already from small doses (0.005 mg/kg) to 50 mg/kg. Both compounds (4a at the doses 0.5-50 mg/kg) slightly reduced amphetamine-induced hyperactivity indicating anti-dopamine component of their action. No considerable dose-response dependence was observed in tests used.

Experimental protocols

Chemistry

Melting points were determined on a HMR microscope apparatus. Elemental analyses (C,H,N) were within ±0.4% of the theoretical values. UV spectra were recorded on a Hitachi 557 spectrophotometer; peak positions λ_{max} are expressed in nm; log ε values are presented in parentheses. IR spectra were recorded on a Perkin Elmer 580B spectrometer, in Nujol; peak positions ν_{max} are expressed in cm^{-1}. ^{1}H-NMR spectra were recorded on a Bruker WH-90 spectrometer and chemical shifts are reported as δ values (ppm) relative to tetramethylsilane.

1-Phenyl-4,4,9,9-tetramethyl-2,3,4,5,8,9,10,11-octahydro-7H-benzo[f][1,2]diazepino[5,4,3-c,d]indol-11-one (4a)

A mixture of 5.3 g (0.014 mol) of 2a and 0.73 ml (0.015 mol) hydrazine monohydrate in 60 ml ethanol was heated in autoclave at 130 °C for 3 h. After cooling the orange crystalline precipitate was filtered and washed with ethanol. Yield - 3 g (57%) of 4a, m.p. 314-317 °C.

UV (C_2H_5OH): 206 (4.33), 230 (4.34), 277 (4.36), shoulder at 350 (3.70), plateau at 400-430 (3.44); IR: 3340, 3290, 3240, 3170, 3100, 3040, 1680, 1625, 1610, 1580; ^{1}H-NMR ($CDCl_3$): 1.05 (12H, s, 4-,9-C(CH_3)), 2.00 (2H, s, 3-CH_2), 2.05 (2H, s, 5-CH_2), 2.10 (2H, s, 8-CH_2), 2.35 (2H, s, 10-CH_2), 5.95 (1H, s, NH), 7,00-7.25 (5H, m, C_6H_5), 7.75 (1H, s, NNH).

Table 1. Neurotropic activity of compounds **4a** and **3a**, administered intraperitoneally in BALB/C mice 1 hr prior to test.

Compound	Dose (mg/kg)	Mean ± SEM						LD_{50} (mg/kg)
		Anticonvulsant activity, PTZ convulsions (mg/kg)		Sleeping time (min)	Locomotor activity (number of locomotor responses)		Body temperature °C	
		Clonic seizures	Lethality	Hexobarbital	Intact mice	Amphetamine treated mice		
Control	0	31.6±0.7	53.2± 7.7	46.6±1.5	389.5±16.5	485.6±30.3	39.2±0.25	
4a	0.005	30.6±3.3	74.1± 2.2	53.3±8.1	377.6±16.7	434.5±33.5	39.7±0.31	>5000
	0.05	31.2±2.9	96.3± 4.8[a]	56.5±2.5[a]	357.0±23.3	416.6±34.5	39.9±0.51	
	0.5	29.8±4.4	91.6± 8.6[a]	68.3±9.3[a]	445.3±17.8	338.5±25.6[a]	38.8±0.48	
	5.0	34.6±6.2	85.5± 4.5[a]	59.1±5.6	450.5±21.3	340.0±23.4[a]	38.6±0.38	
	50.0	30.2±1.0	79.4± 2.2[a]	33.3±3.1[a]	737.0±28.3[a]	142.5±18.3[a]	38.6±0.72	
Control	0	24.8±1.4	61.8± 3.1	44.1±1.1	336.1±15.5	1054.0±59.4	39.2±0.30	
3a	0.005	30.2±4.8	60.0± 4.8	45.1±3.4	488.2±24.4	495.6±42.3[a]	36.2±0.35[a]	564(342-814)
	0.05	28.6±3.9	85.1± 3.3[a]	47.0±2.2	365.0±18.9	478.8±38.8[a]	36.3±0.25[a]	
	0.5	38.0±2.1[a]	103.5± 9.4[a]	51.6±2.3[a]	358.5±20.0	320.8±23.4[a]	34.6±0.37[a]	
	5.0	41.6±3.8[a]	120.1± 6.4[a]	55.0±2.8[a]	272.5±13.2[a]	238.8±18.6[a]	33.8±0.53[a]	
	50.0	42.1±2.3[a]	134.0±12.5[a]	64.0±1.5[a]	224.6±15.4[a]	70.5± 8.5[a]	31.8±0.48[a]	

[a] $p<0.05$ *vs* control (Student's t-test)

1-(4-Tolyl)-4,4,9,9-tetramethyl-2,3,4,5,8,9,10,11-octahydro-7H-benzo[f][1,2]diazepino[5,4,3-c,d]indol-11-one (4b)

Compound 4b was prepared similar to 4a from 0.3 g (0.8 mmol) of **2b** and 0.04 ml (0.8 mmol) hydrazine monohydrate in 3 ml ethanol. Yield - 0.1 g (32%) of 4b, m.p. 308-311 °C (dec.).

UV (C_2H_5OH): 204 (4.35), 232 (4.33), 276 (4.37), 356 (3.69), plateau at 400-430 (3.47); IR: 3350, 3300, 3240, 3170, 3100, 3020, 1680, 1630, 1570; ^{1}H-NMR ($CDCl_3$): 1.10 (12H, s, 4-,9-C(CH_3)), 2.05 (2H, s, 3-CH_2), 2.10 (2H, s, 5-CH_2), 2.15 (2H, s, 8-CH_2), 2.35 (3H, s, 4'-CH_3), 2.40 (2H, s, 10-CH_2), 5.95 (1H, s, NH), 7.05 (4H, s, C_6H_4), 7.60 (1H, s, NNH).

1-(4-Nitrophenyl)-2,4,4,9,9-pentamethyl-2,3,4,5,8,9,10,11-octahydro-7H-benzo[f][1,2]diazepino[5,4,3-c,d]indol-11-one (4c)

A mixture of 1 g (2.3 mmol) of **2c** and 0.11 ml (2.3 mmol) hydrazine monohydrate in 15 ml ethanol was refluxed for 30 min and cooled. The red crystalline precipitate was filtered and washed with ethanol. Yield - 0.4 g (40%) of 4c; after crystallization from ethanol m.p. 325 °C (dec.).

UV (C_2H_5OH): 203 (4.35), 237 (4.39), shoulder at 272 (4.18), 373 (3.98); IR: 3370, 3300, 3280, 3230, 3170, 3120, 3080, 3040, 1680, 1650, 1620, 1600, 1570; ^{1}H-NMR ($CDCl_3$): 1.00 (6H, s, 4-C(CH_3)$_2$), 1.10 (6H, s, 9-C(CH_3)$_2$), 1.95 (2H, s, 3-CH_2), 2.10 (2H, s, 5-CH_2), 2.15 (2H, s, 8-CH_2), 2.40 (2H, s, 10-CH_2), 3.25 (3H, s, NCH_3), 6.05 (1H, br.s, NNH), 7.30 and 8.15 (total 4H, AA'BB'-type, m, 2',3',5',6'-H).

X-ray diffraction analysis

The well-shaped yellow crystal of compound 4b (molecular formula $C_{25}H_{29}N_3O$) with dimension 0.15x0.25x0.35 mm crystallized from ethanol in the triclinic space group P1 was used for X-ray measurement. The reflection intensities were collected by ω-scan technique at room temperature on the Syntex-P2$_1$ single-crystal diffractometer using graphite-monochromated Mo-K_α radiation (λ=0.71069 Å). The cell constants were obtained from a least-squares refinement on the setting angles of 18 reflections in the range of 23°<2θ>30°. The crystallographic data are *a*=7.045(1), *b*=11.314(2), *c*=14.152(2) Å, α=97.23(1), β=100.56(1), γ=103.31(1)°, V=1062.3(3) Å^3, Z=2, F(000)=416, D_x=1.21 g/cm^3, μ(MoK_α)= 0.5 cm^{-1}.

A total of 1984 reflections was collected, of which 1612 were used in calculations. The structure was solved by a direct method using program SHELX86 (6) and refined by full-matrix least squares procedure (program SHELX76 (7)) with the empirical absorbtion correction (program DIFABS (8)). The positions of hydrogen atoms were found from a difference Fourier map. Non-hydrogen atoms were refined in the anisotropic but hydrogens - in the isotropic approximations. The final reliability factor R was 0.0514 (unit weights). The highest peak in the final difference map was 0.20 e/Å^3.

Non-hydrogen atomic coordinates and isotrophic thermal parameters for atoms of 4b are given in Table 2 (9).

Acknowledgments

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References and Notes

(1) M.Negver, Organic-chemical drugs and their synonyms, Akademie-Verlag, Berlin, Pt. 1 and 2, 1987

(2) J.R.Prous, The Year's Drug News, Therapeutic Targets, Prous Science, Barcelona/Philadelphia, 1995

(3) D.Harris, S.Syren, J.Streith, *Tetrahedron Lett.* (42), 4093-4096 (1978)

(4) E.A.Bisenieks, M.F.Bundule, Y.R.Uldrikis, G.Y.Dubur, A.F.Mishnev, Y.Y.Bleidelis, *Chem. Het. Cpd.* 23, 89-92 (1987)

(5) E.A.Bisenieks, N.V.Makarova, Y.R.Uldrikis, G.Y.Dubur, *Chem. Het. Cpd.* 24, 417-423 (1988)

(6) G.M.Sheldrick, *Acta Crystallogr.* A46, 467-473 (1990)

(7) G.M.Sheldrick, SHELX-76, Program for Crystal Structure determination and Refinement, University of Cambrige, UK, 1976

(8) N.Walker, D.Stuart, *Acta Crystallogr.* A39, 158-166 (1983)

(9) **Table 2.** Non-hydrogen atomic coordinates ($x10^4$) and isotrophic thermal parameters (esd's in parentheses) for atoms of **4b**.

Atom	x/a	y/b	z/c	B_{eq} (Å^2)
C1	6566(6)	5921(4)	1223(3)	2.9(2)
N2	7516(6)	4993(4)	1049(3)	3.1(3)
C3	8223(10)	3149(6)	1770(4)	4.1(4)
C4	8461(7)	2841(4)	2810(3)	3.7(2)
C5	6592(8)	2913(5)	3186(4)	3.4(3)
N6	5750(6)	4632(4)	4004(3)	3.4(2)
N7	5522(7)	5849(4)	4119(3)	3.6(2)
C8	3262(9)	7127(5)	3962(4)	3.3(3)
C9	2536(8)	8058(4)	3397(3)	3.7(2)
C10	1580(8)	7377(5)	2356(4)	3.7(2)
C11	2830(7)	6663(4)	1878(4)	3.1(2)
C12	4456(6)	6326(4)	2489(3)	2.7(2)
C13	4450(7)	6393(4)	3458(3)	2.9(2)
C14	5801(6)	5723(4)	2047(3)	2.5(2)
C15	6428(6)	4708(4)	2372(3)	2.7(2)
C16	6190(6)	4175(4)	3218(3)	2.8(2)
C17	7427(7)	4260(4)	1730(3)	3.3(2)
C18	8744(12)	1532(6)	2788(5)	4.9(4)
C19	10273(11)	3742(7)	3475(6)	5.7(3)
C20	4286(11)	9144(5)	3419(5)	4.8(2)
C21	968(13)	8495(8)	3854(6)	5.4(4)
C22	6724(6)	6905(4)	645(3)	2.6(2)
C23	7161(7)	6753(5)	-276(3)	3.2(2)
C24	7415(7)	7709(5)	-788(4)	3.5(3)
C25	7261(7)	8865(5)	-420(3)	3.2(2)
C26	6848(7)	9024(5)	497(4)	3.7(2)
C27	6594(7)	8070(5)	1021(4)	3.5(3)
C28	7596(11)	9924(7)	-971(5)	4.3(3)
O29	2368(5)	6335(3)	990(2)	3.8(1)

$B_{eq}=8\pi^2 D_u^{1/3}$, where D_u is the determinant of the **U** matrix in orthogonal space

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