# TRANSFORMATION OF OXOMETHANOBENZOCYCLOOCTENECARBOXYLIC ACIDS TO PYRROLIDINONE-FUSED PENTA-, HEXA- AND HEPTACYCLIC HETERO COMPOUNDS[1]

Ferenc Miklós[a], Géza Stájer[a]*, Pál Sohár[b], Gábor Bernáth[a], and Reijo Sillanpää[c]

[a]Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, POB 121, H-6701 Szeged, Hungary, Telefax: 36-62/310-604, E-mail: Stajer@pharma.szote.u-szeged.hu; [b]Department of General and Inorganic Chemistry, Loránd Eötvös University, POB 32, H-1518 Budapest, Hungary; [c]Department of Chemistry, University of Turku, FIN-20014 Turku, Finland

**Abstract** – 10-Oxo-5*r*,6,7,8*c*,9*c*,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid (**1a**) or a C-8 epimeric mixture (**1a** and **1b**) reacted with 1,2-, 1,3- and 1,4-bifunctional reagents, 1,2- or 1,3-diaminopropane (**2, 3**), 1,2- or 1,3-propanolamine (**4**, **5**), 1,4-diaminobutane (**6**), *o*-aminothiophenol (**7**), *diexo*-3-aminobicyclo[2.2.1]heptane-2-methanol or *diendo*-3-aminobicyclo[2.2.1]hept-5-ene-2-methanol (**8**, **9**), to produce polycyclic compounds containing a pyrrolo-condensed pyrimidine (**10**), imidazole (**11**), 1,3-oxazine (**12, 16, 17**), oxazole (**13**), 1,3-diazepine (**14**), benzthiazole (**15**) moiety and one or two terminal aromatic rings by cyclization. The structures of **10-17** were established by $^1$H and $^{13}$C NMR spectroscopy and for **16** also by X-Ray analysis.

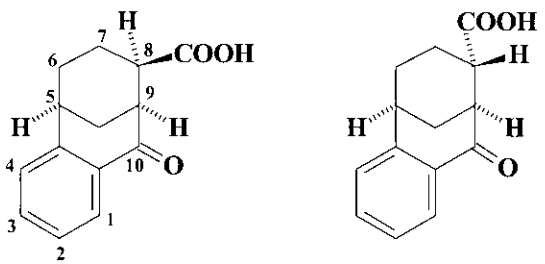
In our earlier studies, β- or γ-oxocarboxylic acids were used for the preparation of fused-skeleton saturated or partially saturated 1,3-heterocycles.[2-4] These derivatives were prepared with pharmacological aims, as the similar fused-skeleton methanocyclooctenes containing a benzene ring have promising analgetic,[5] neurotropic, psychotropic[6] or antispasmodic[7] effects. During cyclization with alicyclic bifunctional reagents, the stereohomogeneous starting compounds often isomerized and the reactions yielded isomeric mixtures. Consequently, structure elucidation of the fairly complex polycyclic systems, determination of the configuration and conformation and a comparative study of the closely related systems and the *cis*- and *trans*-fused isomers was a challenging task.

In our recent study, 10-oxo-5,7,8,9,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid (**1a**) was used as starting material of methanobenzocycloocta[9,8-*c,d*]pyridazinone.[4] For the preparation of **1a,b**, 4-*trans*-phenylcyclohexane-*cis*-1,2-dicarboxylate was cyclized with PPA, to give a mixture of the isomeric esters of **1a,b**. After hydrolysis, the isomeric acids were separated

by column chromatography.[4] In the present work, these acids were transformed to new poly-condensed ring systems.

## RESULTS

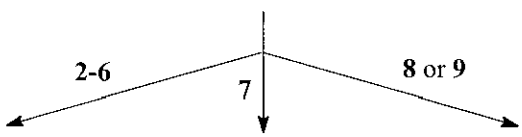
When the 10-oxo-5*r*,6,7,8*c*,9*c*,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid (**1a**)[4] was refluxed with 1,3- or 1,2-diaminopropane (**3**, **2**) in dry chlorobenzene in the presence of *p*-toluenesulfonic acid as catalyst for 6 h, benzo-9,13-diazatetracyclopentadecanone (**10**) (76%) or benzo-9,12-diazatetracyclotetradecanone (**11**) (42%) was formed (Scheme). On application of a 1:1 mixture of the isomeric acids (**1a**) and (**1b**),[4] the reaction with **3** gave the same product (**10**), in lower yield (56%), even under rigorous conditions (refluxing for 8 h). This proved a slow isomerization of **1b** to **1a** during the reaction. Cyclization requires an *equatorial* carboxyl group, and therefore **1b**, containing an *axial* carboxyl, isomerizes to **1a**.

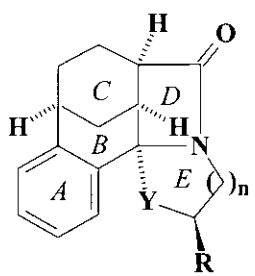



**1a**

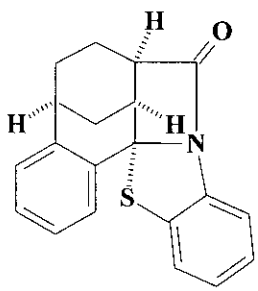



**1b**

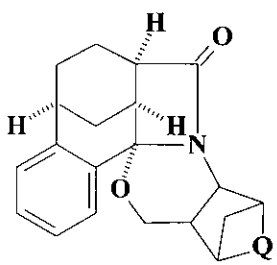



| | n | Y | R |
|---|---|---|---|
| **10**: | 2 | NH | H |
| **11**: | 1 | NH | Me |
| **12**: | 2 | O | H |
| **13**: | 1 | O | Me |
| **14**: | 3 | NH | H |




**15**



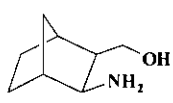

**16**: *diexo*, Q = $CH_2CH_2$

**17**: *diendo*, Q = CH=CH

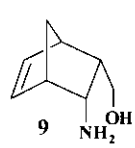
**2** (X = $NH_2$) and **4** (X = OH): $H_2NCH_2CH(CH_3)X$

**3** (m =3, X = $NH_2$), **5** (m = 3, X = OH) and **6** (m = 4, X = $NH_2$): $H_2N(CH_2)_mX$

**7**: $H_2NC_6H_4SH$-*o*




**8**




**9**

Scheme

In further experiments, only **1a** was used. In the reaction with 3-aminopropan-1-ol (**5**), benz-13-oxa-9-azatetracyclopentadecanone (**12**) was obtained, while **1a** and 3-aminopropan-2-ol (**4**) furnished benz-12-oxa-9-azatetracyclotetradecanone (**13**). The reaction of **1a** with 1,4-diaminobutane (**6**) yielded benzo-9,14-diazatetracyclohexadecanone (**14**).

While **10-14** are pentacyclic compounds containing a terminal aromatic ring and a condensed bicyclic hetero moiety at the other terminal, the reaction of **1a** with *o*-aminothiophenol (**7**) furnished dibenzo-12-thia-9-azatetracyclotetradecanone (**15**), which was a hexacyclic ring system with two terminal aromatic rings. *diexo*-2-Aminobicyclo[2.2.1]heptane-3-methanol (**8**) and *diendo*-2-aminobicyclo[2.2.1]hept-5-ene-3-methanol (**9**) reacted with **1a** to give heptacyclic derivatives: *diexo*-benz-2-oxa-10-azahexacyclopolyone (**16**) and the unsaturated *diendo* isomer (**17**).

The presence of the aromatic moiety in the ring system results in rather rigid condensed skeletons which are planar at the benzene terminal(s). These fused systems of 16-22 carbons and two hetero atoms display only limited conformational mobility. A few related rigid hetero compounds are known, e.g. pyrrolo-fused methanocyclooctane, formed from alkenes by acid-catalysed cyclization.[8] Further methods yield analogues with a benzo-fused skeleton by dehydration of cyclohexanecarbinols with phosphorus pentoxide,[9] oxidative cyclization of unsaturated enol silyl ethers,[10,11] conversion of benzylcyclohexanone to benzobicyclononanone[12] or carbocationic cyclization of unsaturated bromoimines.[13] However, these methods are not suitable for the preparation of similar benzocyclononane-condensed heterocycles, especially, containing two hetero rings, because the potential starting compounds have only one oxo and no other functional group.

## STRUCTURE

The IR, $^1$H and $^{13}$C NMR data (Tables 1-3) proved the expected structures of the new compounds; hence, only the stereostructures are discussed here.

The strained tetracyclic *A/B/C/D* rigid skeleton must contain the annelational CH-hydrogens, e.g. H-4,7,9* in **12**, in the all-*cis* position. The *cis* orientation of H-7 and H-9 with respect to the hetero atom Y in ring *E* (Y = N for **10**, Y = O in **12**) was proved by DNOE measurements (Figure 1) showing the interactions between the $NCH_2$ (**10**) or $OCH_2$ (**12**) groups and H-9. The analogous steric structure for **14** (Y = N) is plausible from the identical chemical shifts of H-9 in **10** or **14**.

For **11** (Y = N) and **13** (Y = N), NOE was observed between H-9 and the methine hydrogen in the C*H*$CH_3$ group. Hence, the heteroatom (N or O) must be in the α position (*cis* to H-9) and the methyl group in the β orientation (*trans* with H-9 relative to the imidazolidine or oxazoline rings). From the very high difference in the chemical shifts of H-9 in **11**, **13** and especially **15**, the α position of the S in **15** is straightforward.

For **12**, **16** and **17**, the very small shift differences of C-1 and H-9 indicate similar steric structures of rings *A*–*E* in these compounds: the oxygen is also in the α position (*cis* to H-9) in **16** and **17**.

---

*In the spectroscopic part and Tables 1-3, H-9 means the annelational H on the tertiary carbon at the *B/C/D* ring junction.

Table 1. Characteristic IR frequencies[a] and $^1$H-NMR data[b] on compounds (**10-17**) in $CDCl_3$ solution at 500 MHz[c]

| | νC=O band | $\gamma C_{Ar}H$ band | H-1 ~*d*(1H) | H-2,3 *m*(2H) | H-4 ~*d*(1H) | H-5 ~*s(1H)* | $CH_2$(6) *m*(2H) | $CH_2$(7) 2x*m*(2x1H) | | H-8[d] *td*(1H) | H-9[e] *td*(1H) | $CH_2$(11)[f] *td*+*d*(2x1H) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **10** | 1660 | 759 | 7.66 | ~7.3 | 7.14 | 3.07 | ~1.8[g] | 1.03 | ~1.8[g] | ~2.55[h] | ~2.55[h] | 1.8[g] | 2.20 |
| **11** | 1681 | 764 | 7.32 | ~7.25 | 7.10 | 3.10 | ~1.8[g] | 1.20 | ~1.8[g] | 2.52 | 2.49 | 1.91 | 2.21 |
| **12** | 1705[i] | 773 | 7.68 | ~7.3 | 7.14 | 3.05 | ~1.85[g] | 1.05 | 1.85[g] | 2.58 | 2.72 | 1.85[g] | 2.13 |
| **13** | 1709 | 763 | 7.42 | ~7.3 | 7.14 | 3.12 | ~1.8 | 1.32 | 1.88 | 2.61 | 2.65 | 1.92 | 2.18 |
| **14** | 1662 | 749 | 7.60 | ~7.25 | 7.10 | 3.02 | ~1.8[g] | 1.08 | ~1.8[g] | 2.55[h] | 2.55[h] | ~1.8[g] | 2.13 |
| **15** | 1706 | 749 | 7.47 | ~7.25[g] | 7.08 | 3.18 | ~1.8 | 1.32 | 2.00 | 2.75 | 3.44 | 2.08 | 2.20 |
| **16** | 1694 | | 7.70 | ~7.3 | 7.12 | 3.02 | ~1.8[g] | 1.15 | ~1.8[g] | 2.50 | 2.60 | ~1.8[g] | 2.06 |
| **17** | 1692 | 757 | 7.50 | ~7.2 | 7.02 | 2.93 | ~1.7[g] | 1.00 | ~1.7[g] | ~2.4[h] | ~2.4[h] | ~1.7[g] | 2.01 |

[a] In KBr discs, $cm^{-1}$. Further data: νNH band (sharp): 3305 (**10**), 3280 (**11**, **14**); [b] Chemical shifts in ppm ($\delta_{TMS}$ = 0 ppm) and coupling constants in Hz. Further signals: $CONCH_2$, 2x*m* (2x1H): 3.47 and 4.33 (**10**), 3.40 and 4.27 (**12**), 2x*dd* (*J* = 11.3, 10.0 and 5.3, **11** and **13**, ~13.5 and ~2.5, **14**): 2.82 and 4.12 (**11**), 3.03 and 4.20 (**13**), 3.25 and 4.07 (**14**); CONCH: 3.84, *d* (*J* = 7.3), **16**, 4.06 *dd* (*J* = 8.3 and 3.5), **17**; $(NH)CH_2$, (2x1H), 2x*m*: 2.92 and 3.16 (**10**), 2x*dd* for **14** (*J* = 14.5 and 11.5, upfield signal); (NH)CH: 3.23 *m* (**11**); $OCH_2$: 3.80 and 3.98, 2x*m* (**12**), *t* (*J* = 11.5) and *dd* (*J* = 11.5 and 6.3, **16**, 11.3 and 5.3, **17**): 3.44 and 3.84 (**16**), 3.20 and 3.86 (**17**); OCH, *m*: 4.10 (**13**), $CCH_2C$ heteroring): ~2.0 *m* (2H) for **10**, 1.99 and 2.26, 2x*m* (**12**), ~1.5 *m* (2H) and ~1.8 *m* (2H)[g] for **14**; $CH_3$, *d* (*J* = 6.1): 1.37 (**11**), 1.50 (**13**), CCHC (in oxazine ring): 2.35 *ddd* (*J* : 11.6, 6.3 and 6.3) for **16**, ~2.8 *m* (2H)[k] for **17**, CCHC (β to N in norbornane/ene): 4.14 *d* (*J* = 5.1) for **16**, 3.91 ~*s* (**17**), CCHC (γ to N in norbornane/ene): 1.94 ~*s* (**16**), ~2.8[k] (**17**); $CH_2$ (**16**, norbornane): 5x*m* (5x1H), 1.15, 1.35, 1.57, 1.68 and ~1.8[g] and 1.30 *d* (*J* = 10.4, *endo*-H of the bridging $CH_2$); $CH_2$ (**17**, norbornene), 2x*d* (2x1H): 1.29 (*endo*) and 1.56 (*J* = 8.8), CH (**17**, norbornene), 5.97 *dd* (*J* = 5.5 and 2.5) and 6.11 *dd* (*J* = 5.5 and 3.0), ArH-10-13 (for numbering, see the Scheme) for **15**: 7.69 *d*, ~7.15 *m* (2H), ~7.25[g]; NH: ~1.8[g] (**10**, **11**), 2.16 *s* (**14**); [c] Assignments were supported by DNOE (except for **14**), 2D-HSC and for **10**, **11**, **14** and **16** also by 2D-COSY measurements; [d] *J* = 11.0 and 7.5± 0.2 (**11-13**, **15**), 10.6 and 8.2 (**16**); [e] *J* = 7.2 and 3.6 (**12**), 6.7 and 3.4 (**15**), lines of *m* are coalesced (**13**, **16**); [f] *J* = 13.4 ± 0.1 and 3.0; [g,h,k] Overlapping signals; [i] Split band with the second maximum at 1684.

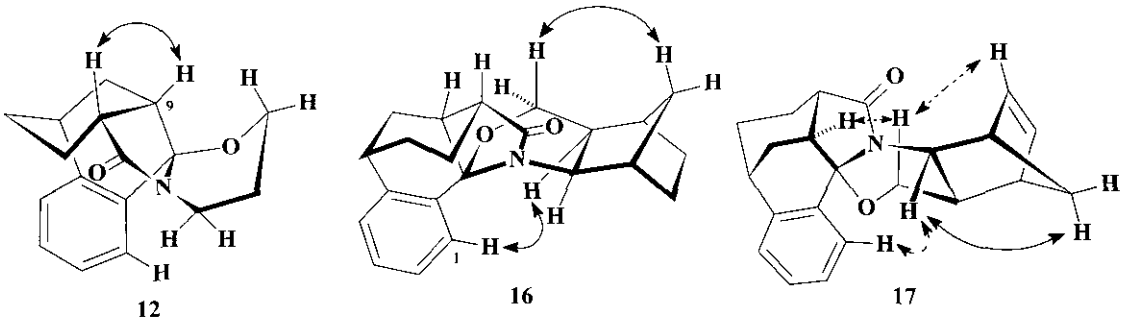



Figure 1. Stereostructures of **12**, **16** and **17** and the NOE's proving them

In accordance with our earlier experience,[14,15] the doublet splitting (by 7.3 Hz) of the NCH signal in **16** and the double doublet structure (splits 8.3 and 3.5 Hz) of the same signal in **17** confirm the *diexo* (**16**) and *diendo* (**17**) annelation, respectively, of the terminal bicycles to the skeleton. These structures were also proved independently by NOE measurements: interactions were observed between the *axial* $OCH_2$ hydrogen and the *endo*-H of the bridging $CH_2$ in **16** and between the latter atom and the NCH hydrogen in **17**.

Table 2. $^{13}$C-NMR chemical shifts ($\delta_{TMS}$ = 0 ppm) of compounds (**10-17**) in $CDCl_3$ solution at 125.7 MHz[a]

| | C-1 | C-2[b] | C-3[b] | C-4 | C-4a[c] | C-5 | C-6 | C-7 | C-8 | C-9 | C-10 | C-10a[c] | C-11 | C=O | NC[d] | XC[e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **10** | 126.2 | 128.7 | 127.4 | 129.4 | 140.3 | 34.8 | 32.0 | 21.0 | 40.7 | 42.7 | 75.6 | 141.9 | 26.2 | 177.0 | 34.4 | 38.1 |
| **11** | 126.5 | 129.0 | 127.8 | 128.8 | 141.7 | 34.3 | 31.5 | 20.7 | 44.4 | 45.5 | 84.8 | 142.5 | 27.3 | 181.3 | 52.8 | 55.0 |
| **12** | 127.3 | 129.0 | 127.1 | 129.1 | 139.0 | 34.6 | 31.2 | 21.3 | 40.5 | 40.4 | 89.9 | 140.5 | 26.3 | 176.7 | 32.8 | 59.3 |
| **13** | 127.8 | 129.2 | 127.5 | 128.5 | 139.9 | 34.2 | 30.9 | 21.2 | 44.4 | 44.3 | 97.5 | 141.1 | 27.3 | 180.9 | 50.3 | 74.8 |
| **14** | 125.0 | 128.1 | 126.8 | 128.7 | 140.3 | 34.5 | 31.4 | 21.2 | 40.2 | 37.8 | 78.9 | 141.9 | 25.7 | 176.4 | 40.3 | 42.5 |
| **15** | 127.0 | 129.1 | 127.6 | 127.8 | 141.7 | 33.3 | 29.9 | 20.0 | 43.3 | 45.9 | 80.2 | 136.9 | 27.6 | 176.9 | 135.3 | 132.9 |
| **16** | 127.5 | 128.5[f] | 126.5 | 128.4[f] | 138.7 | 34.2 | 30.4 | 20.9 | 40.0 | 38.3 | 90.1 | 140.3 | 25.9 | 176.0 | 58.2 | 61.7 |
| **17** | 127.8 | 128.9[g] | 127.1 | 128.9[g] | 139.5 | 34.6 | 31.2 | 21.0 | 39.5 | 39.0 | 90.4 | 140.4 | 26.5 | 175.9 | 52.6 | 65.0 |

[a] Assignments were supported by DEPT and 2D-HSC measurements; Further signals: $CH_3$: 17.4 (**11**), 18.0 (**13**), C-$CH_2$-C: 24.9 (**10**), 23.7 (**12**), 28.9 and 33.6 (**14**), 26.9, 29.3 and 34.2 (**16**, the line of the bridging methylene group at 34.2 is in overlap with the C-5 line), 47.7 (**17**); C-CH-C (ring *E*): 45.5 (**16**), 42.3 (**17**), C-**CH**-C (β to N): 37.7 (**16**), 47.6 (**17**), C-**CH**-C (γ to N): 37.5 (**16**), 44.4 (**17**); CH (**17**, olefinic): 135.1 and 137.1 (γ to N): CH (**15**, aryl; for numbering see the Scheme): C-10: 117.5, C-11,12: 125.2, 125.3, C-13: 121.4. [b,c,f] Probable assignments (may be interchanged); [d] Carbon bound to the amide nitrogen; [e] X: NH (**10, 11, 14**), O (**12, 13, 16, 17**), S (**15**); [g] Two very close-lying lines at 128.89 and 128.92 ppm.

The only question remaining is the relative position of the bridging $CH_2$-18 in **16** and **17**. NOE interactions were observed between the aromatic H-1 and the methine-H β to the heteroatoms (**16**) or the former and the NCH group (**17**). In **17**, NOE was also observed for H-9 and the *axial* $OCH_2$ hydrogen. These findings confirm the stereostructures depicted in Figure 1, *i.e.* the amide-carbonyl and the bridging-$CH_2$ are *cisoid* in **16** and *transoid* in **17** relative to the oxazine ring. The structure of **16** was confirmed by X-Ray measurements: Figure 2 clearly depicts the *cisoid* arrangement of the carbonyl and $CH_2$-18.

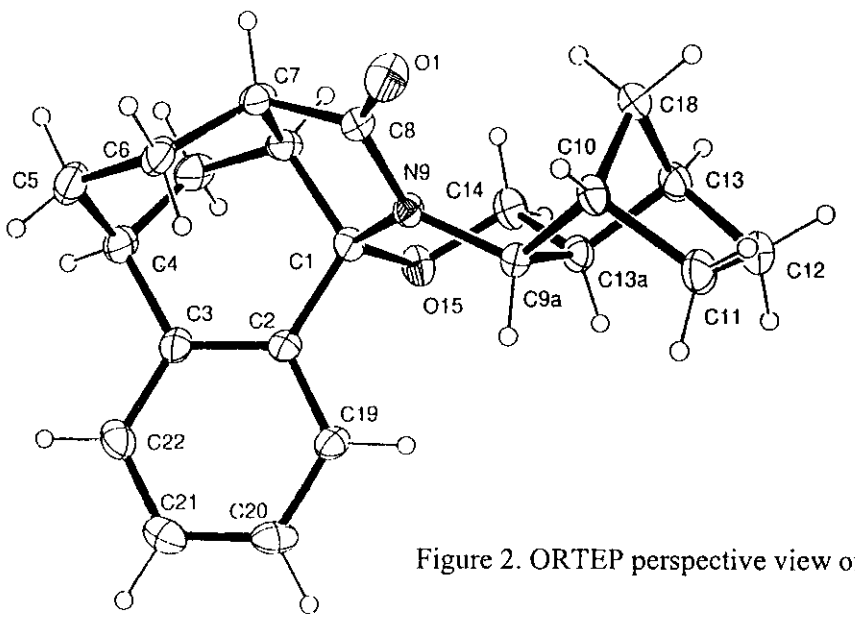



Figure 2. ORTEP perspective view of **16**

Table 3. Results of DNOE experiments with compounds (**10-13**, **16** and **17**)[a]

| Saturated signal | Responding signal H-1 | H-9 | $XCH_n$[b] | $(CO)NCH_n$[c] | $CCH_nC$[d] | $CH_3$ | H (*endo*)[e] |
|---|---|---|---|---|---|---|---|
| H-1 | | | **12, 16** | **10-12** | **12, 16** | **11** | |
| H-9 | | | **12, 13, 16** | | | | |
| $XCH_n$[b] | **10, 12, 16** | **10-12, 16, 17** | *10, 12, 16, 17* | *11* | *12, 16* | *11, 13* | *16*[f] |
| $(CO)NCH_n$[c] | **10-12, 17** | | | *10-12* | *10, 12, 17* | *11* | **17** |
| $CCH_nC$[d] | **16** | | *16* | *16* | | | |
| $CH_3$ | **13** | | *11, 13* | *11, 13* | | | |
| H(*endo*)[e] | | | | **17** | **17** | | |

[a] Interacting pairs (groups containing hydrogen) showing only trivial effects (NOE between geminal or vicinal hydrogens) are not included in this Table. Responses relevant for stereostructures are given with bold compound numbers. Italic compound numbers correspond to trivial effects; [b] X: NH (**10**, **11**) or O (**12**, **13**, **16**, **17**), $n = 2$ (**10**, **12**, **16**, **17**, $n = 1$ (**11**, **13**); [c] Methine-H (**16**, **17**) or methylene-H (**10-13**) vicinal to amide-N; [d] "Middle" $CH_2$ (**10**, **12**) or CH (**16**, **17**) in the diazine (**10**) and oxazine (**12**, **16**, **17**) ring, resp.; [e] In bridging methylene group (**16**, **17**); [f] NOE with both methylene-H atoms.

## EXPERIMENTAL

The $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature, on a Bruker DRX 500 spectrometer at 500.13 ($^1H$) and 125.76 ($^{13}C$) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The standard Bruker microprogram DNOEMULT.AU to generate NOE[16,17] was used with a selective pre-irradiation time. DEPT spectra[18] were run in a standard manner,[19] using only the $\theta = 135°$ pulse to separate the $CH/CH_3$ and $CH_2$ lines phased "up" and "down", respectively. The 2D-HSC spectra[20] were obtained by using the standard Bruker pulse program XHCO.AU. IR spectra were run in KBr discs on a Bruker IFS-55 FT-spectrophotometer controlled by Opus 2.0 software. Melting points are uncorrected. Physical and analytical data on the new compounds are listed in Table 4.

*Data collection and refinement.* A Rigaku AFC5S diffractometer was used at room temperature (21 °C) with graphite monochromated $MoK_\alpha$ radiation ($\lambda = 0.71069$ Å). The data were corrected for Lorentz and polarization effects. The structure was solved by a direct method, using SIR92[21] and DIRDIF[22] programs, and refined by full-matrix least-squares techniques. The hydrogens were kept in the calculated positions with the displacement parameter of 1.2 times $B_{eq}$ of the host atom. All calculations were performed with teXsan for Windows software.[23] The neutral atomic scattering and dispersion factors were those included in the program. Figures were drawn with ORTEP.[24]

*Crystal data and experimental details*: trigonal prisms, space group R-3 (No. 148, hexagonal axes), $a = 27.665(2)$, $b = 27.665(2)$, $c = 11.693(3)$ Å, $Z = 18$, $D_c = 1.293$ gcm$^{-3}$, $\mu = 0.82$ cm$^{-1}$, $F(000) = 3240$, $R_{int} = 0.01$. Measured refl. 3308, unique refl. 3040, obs. refl. 1741, no. of parameters 227, $R^b = 0.049$, $R_w^c = 0.042$. Other crystal data, anisotropic displacement parameters,

final atomic positional coordinates, temperature parameters, bond lengths and bond angles, have been deposited in the Cambridge Crystallographic Data Centre, Lensfield Rd., Cambridge, CB2 1EW, UK.

**2,3-Benzo-9,13-diazatetracyclo[7.4.1$^{1,7}$.1$^{4,14}$.0]pentadecan-8-one (10), 2,3-benzo-11-methyl-9,12-diazatetracyclo[7.1.1$^{1,7}$.1$^{4,13}$.0]tetradecan-8-one (11), 2,3-benz-13-oxa-9-azatetracyclo[7.4.1$^{1,7}$.1$^{4,14}$.0]pentadecan-8-one (12), 2,3-benz-12-oxa-9-azatetracyclo[7.3.1$^{1,7}$.1$^{4,13}$.0]tetradecan-8-one (13), 2,3-benzo-9,14-diazatetracyclo[7.5.1$^{1,7}$.1$^{4,15}$.0]hexadecan-8-one (14), (2,3)(10,11)-dibenzo-12-thia-9-azatetracyclo[7.3.1$^{1,7}$.1$^{4,13}$.0]dodecan-8-one (15), 3,8-diexo-16,17-benz-2-oxa-10-azahexacyclo[8.7.1$^{1,12}$.1$^{4,7}$.1$^{15,19}$.0$^{3,8}$.0]poly-11-one (16), 3,8-diendo-16,17-benz-2-oxa-10-azahexacyclo[8.7.1$^{1,12}$.1$^{4,7}$.1$^{15,19}$.0$^{3,8}$.0]poly-5-en-11-one (17). General method**

A mixture of **1a** (or **1b** or **1a,b**) (1.15 g, 5 mmol), **3-9** (6.5 mmol), *p*-toluenesulfonic acid (0.05 g) in chlorobenzene (15 mL) (for **2, 3** or **6**) or dry xylene (15 mL)was refluxed for 3-8 h (**10**: 8 h, **11**: 6 h, **12**: 8 h, **13**: 3 h, **14**: 8 h, **15**: 4 h, **16**: 5 h, **17**: 8 h). After evaporation, the residue was dissolved in $CHCl_3$ and transferred to an $Al_2O_3$ column [ACROS, Aluminium oxide, basic (for diamines) or neutral, 50-200 μ], then eluted with *n*-hexane–EtOAc (2:1 for diamines or 4:1). The residue of the eluates was crystallized. Data on compounds (**10-17**) are listed in Table 4.

Table 4. Physical and analytical data on compounds (**10-17**)

| Compd | mp (°C) | Yield (%) | Formula | Analysis Calcd % C | H | N | Found % C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| **10** | 180-181[a] | 76 | $C_{17}H_{20}N_2O$ | 76.09 | 7.51 | 10.44 | 76.25 | 7.58 | 10.28 |
| **11** | 183-185[a] | 42 | $C_{17}H_{20}N_2O$ | 76.09 | 7.51 | 10.44 | 76.18 | 7.47 | 10.33 |
| **12** | 171-172[b] | 55 | $C_{17}H_{19}NO_2$ | 75.81 | 7.11 | 5.20 | 75.69 | 7.18 | 5.15 |
| **13** | 121-123[a] | 58 | $C_{17}H_{19}NO_2$ | 75.81 | 7.11 | 5.20 | 75.65 | 7.08 | 5.14 |
| **14** | 140-141[b] | 23 | $C_{18}H_{22}N_2O$ | 76.56 | 7.85 | 9.92 | 76.42 | 7.69 | 9.81 |
| **15** | 206-207[c] | 60 | $C_{20}H_{17}NOS$ | 75.20 | 5.36 | 4.39 | 75.34 | 5.45 | 4.30 |
| **16** | 200-201[a] | 62 | $C_{22}H_{25}NO_2$ | 78.77 | 7.51 | 4.18 | 78.59 | 7.42 | 4.28 |
| **17** | 172-174[b] | 28 | $C_{22}H_{23}NO_2$ | 79.25 | 6.95 | 4.20 | 79.45 | 6.88 | 4.31 |

Crystallization solvent: [a] EtOAc; [b] $Et_2O$; [c] EtOH

ACKNOWLEDGEMENTS

The authors are indebted to Mrs. E. Csiszár-Makra and Mrs. A. Bőszin-Nagy for skilled technical assistance. They also express their thanks for Hungarian Research Foundation (OTKA) grants No 2693 and T 25415.

REFERENCES


1. Saturated Heterocycles, Part 259. Part 258: G. Stájer, A. E. Szabó, P. Sohár, J. Szúnyog, and G. Bernáth, *Synthesis*, in press.
2. G. Stájer, A. E. Szabó, G. Bernáth, and P. Sohár, *J. Mol. Struct.,* 1997, **415**, 29.
3. P. Tähtinen, R. Sillanpää, G. Stájer, A. E. Szabó, and K. Pihlaja, *J. Chem. Soc., Perkin Trans. 2,* 1997, 597.
4. F. Miklós, F. Csende, G. Stájer, P. Sohár, R. Sillanpää, J. Szúnyog, and G. Bernáth, *Acta Chem. Scand.*, 1998, **52**, 322.
5. M. E. Freed, J. R. Potoski, E. H. Freed, and G. L. Conklin, *J. Med. Chem.*, 1973, **15**, 595.
6. E. Adlerova and M. Protiva, *Collect. Czech. Chem. Commun.*, 1967, **32**, 3177.
7. M. Protiva and E. Adlerova, *Czech. P.* 130,736 1969 (*Chem. Abstr.*, 1970, **73**, 55880z).
8. E. Ciganek, A. S. Wright, and G. A. Nemeth, *J. Heterocycl. Chem.*, 1995, **32**, 1673.
9. J. W. Cook and C. L. Hewett, *J. Chem. Soc.*, 1936, 62.
10. B. B. Snider and T. Kwon, *J. Org. Chem.*, 1990, **55**, 4786.
11. B. B. Snider and T. Kwon, *J. Org. Chem.*, 1992, **57**, 2399.
12. M. T. Zoeckler and B. K. Carpenter, *J. Am. Chem. Soc.*, 1981, **103**, 7661.
13. J. P. Begue, D. Bonnet-Delpon, M. Charpentier-Morize, and A. Richard, *Tetrahedron Lett.*, 1985, **26**, 5681.
14. P. Sohár, G. Stájer, and G. Bernáth, *Org. Magn. Reson.*, 1983, **21**, 512.
15. P. Sohár, I. Pelczer, G. Stájer, and G. Bernáth, *Magn. Reson. Chem.*, 1987, **25**, 584.
16. P. Sohár, Nuclear Magnetic Resonance Spectroscopy, CRC Press, Boca Raton, Florida, 1983, Vol. 1, pp. 196, 197.
17. J. K. M. Sanders and J. D. Mersch, *Prog. Nucl. Magn. Reson.*, 1982, **15**, 353.
18. D. T. Pegg, D. M. Doddrell, and M. R. Bendall, *J. Chem. Phys.*, 1982, **77**, 2745.
19. M. R. Bendall, D. M. Doddrell, D. T. Pegg, and W. E. Hull, High Resolution Multipulse NMR Spectrum Editing and DEPT, Bruker, Karlsruhe, 1982.
20. R. R. Ernst, G. Bodenhausen, and A. Wokaun, Principles of Nuclear Magnetic Resonance in One and Two Dimensions, Clarendon Press, Oxford, U. K., 1987, pp. 471-479
21. A. Altomare, M. Cascarano, C. Giacovazzo, and A. Guagliardi, *J. Appl. Cryst.*, 1993, **26**, 343.
22. P. T. Beurskens, G. Admiraal, G. Beurskens, W. P. Bosman, R. de Gelder, R. Israel, and J. M. M. Smits, The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands, 1994.
23. teXsan for Windows: Crystal Structure Analysis Package, Molecular Structure Corporation, 1997.
24. C. K. Johnson, ORTEP II, A Fortran Thermal-ellipsoid Plot Program for Crystal Structure Illustrations. Report ORNL-5138, Oak Ridge National Laboratory, Tennessee, 1976.


Received, 19th March, 1998