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Preparation and Steric Structure of 3(2*H*)-Pyridazinones and 1,2-Oxazin-6-ones Fused with Three- to Six-membered Saturated Carbocycles or Norbornane Skeleton [1]

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Summary. Reactions of *cis*-2-(4-methylbenzoyl)-cyclopropane- (**1**) and -cyclobutanecarboxylic acids (**2**), the stereoisomeric cyclohexyl homologues (**3** and **4**), and di-*endo*-3-(4-methylbenzoyl)-bi-cyclo-[2.2.1]heptane-2-carboxylic acid (**5**) with hydrazines yield the cycloalkane-condensed (3(2*H*)-pyridazinones **6**–**9** and the norbornane di-*endo*-fused derivatives **10**. With hydroxylamine, compounds **1** and **3**–**5** were transformed to the cycloalkane- and norbornane-condensed 1,2-oxazin-6-ones **11**–**14**. Transformation of **3**–**5** led to the *trans*-hexahydroanthrone **17a** and its methylene-bridged analogue **24**. From the stereoisomeric hexahydro-1(3*H*)-isobenzofuranones **20** and **21**, the partly saturated anthrones were also prepared; the products (**16b** and **17b**) contain the methyl substituent in position 6. On reduction, **16b** yield the 2-methyloctahydroanthracene **22**. The structures of the compounds were proved by ^{1}H and ^{13}C NMR spectroscopy, making use of NOE, DEPT, and CH-COSY techniques.

Keywords. Cycloalkanes; Heterocycles; *Friedel–Crafts* acylation; Isomerization; Methyloctahydroanthracen-9-ones; Reduction; $LAH/AlCl_3$.

Synthese und räumliche Struktur von mit drei- bis sechsgliedrigen gesättigten Homocyclen oder Norbornan kondensierten 3(2*H*)-Pyridazinonen und 1,2-Oxazin-6-onen

Zusammenfassung. Die Reaktion von *cis*-2-(4-methylbenzoyl)-cyclopropan- (**1**) und -cyclobutancarbonsäuren (**2**), der stereoisomeren cyclohexyl-Homologen (**3** und **4**) und von di-*endo*-3-(4-methylbenzoyl)-bicyclo[2.2.1]heptan-2-carbonsäure (**5**) mit Hydrazinen ergibt die cycloalkankondensierten 3(2*H*)-Pyridazinone **6**–**9** und das methylenüberbrückte di-*endo*-Derivat **10**. Die Verbindungen **1** und **3**–**5** wurden mit Hydroxylamin zu den cycloalkan- und norbornankondensierten 1,2-Oxazin-6-onen **11**–**14** umgesetzt. **3**–**6** reagierten zum *trans*-Hexahydroanthron **17a** und seinem methylenüberbrückten Analogen **24**. Die teilweise gesättigten Anthrone wurden auch aus den stereoisomeren Hexahydro-1(3*H*)-isobenzofuranonen **20** und **21** hergestellt (**16b** und **17b**), wobei der Methylsubstituent jedoch in Position 6 lokalisiert ist. Reduktion von **16b** ergab das 2-Methyloctahydroanthracen **22**. Die Strukturen der Verbindungen wurden durch NMR-Spektroskopie abgesichert (^{1}H, ^{13}C, DEPT, CH-COSY, NOE).

Introduction

In recent years, one of our main topics has been the synthesis and conformational analysis of fused-skeleton saturated and partially saturated six-membered 1,3-heterocycles [2–4]. One aim of these investigations was to prepare potential pharmacons [5]; the stereochemical aspects which have proved to be of considerable interest [6, 7], must also be emphasized.

Our earlier work was mainly related to six-membered 1,3-heterocycles which were *cis*- or *trans*-fused with normal-ring carbocycles (*e.g.* cyclopentane, cyclohexane, cyclohexene and cycloheptane), or with norbornane or norbornene.

The present work describes the synthesis of several small ring (cyclopropane- and cyclobutane-fused) analogues of some of the earlier heterocycles. An important feature of the compounds described here and in further papers to be published [8] is that the synthons used are 2-aroyl-1-cycloalkanecarboxylic acids [9, 10] which yield fused-skeleton heterocycles containing an aroyl group in the neighbourhood or on a bridgehead carbon atom in the fused heterocycle. In our previous work, the starting materials were stereohomogeneous *cis*- and *trans*-1,2-disubstituted 1,3-difunctional alicyclic compounds or stereohomogeneous 1,2-di-*endo*- or 1,2-di-*exo*-substituted 1,3-difunctional norbornane derivatives: β-hydroxy acids, β-amino acids or stereoisomeric 1,3-aminoalcohols either with a secondary hydroxy group and aminomethyl group or a hydroxymethyl group and an amino group on the carbocycles. In comparison with our earlier investigations, the recent modification in the structure results in essential changes from both structural and pharmacological aspects. Our aim was the preparation of pharmacologically active compounds. The 2-aroylcyclohexanecarboxylic acids and their cyclic derivatives have been reported to have anorectic and hypotensive effects [11, 12].

Results and Discussion

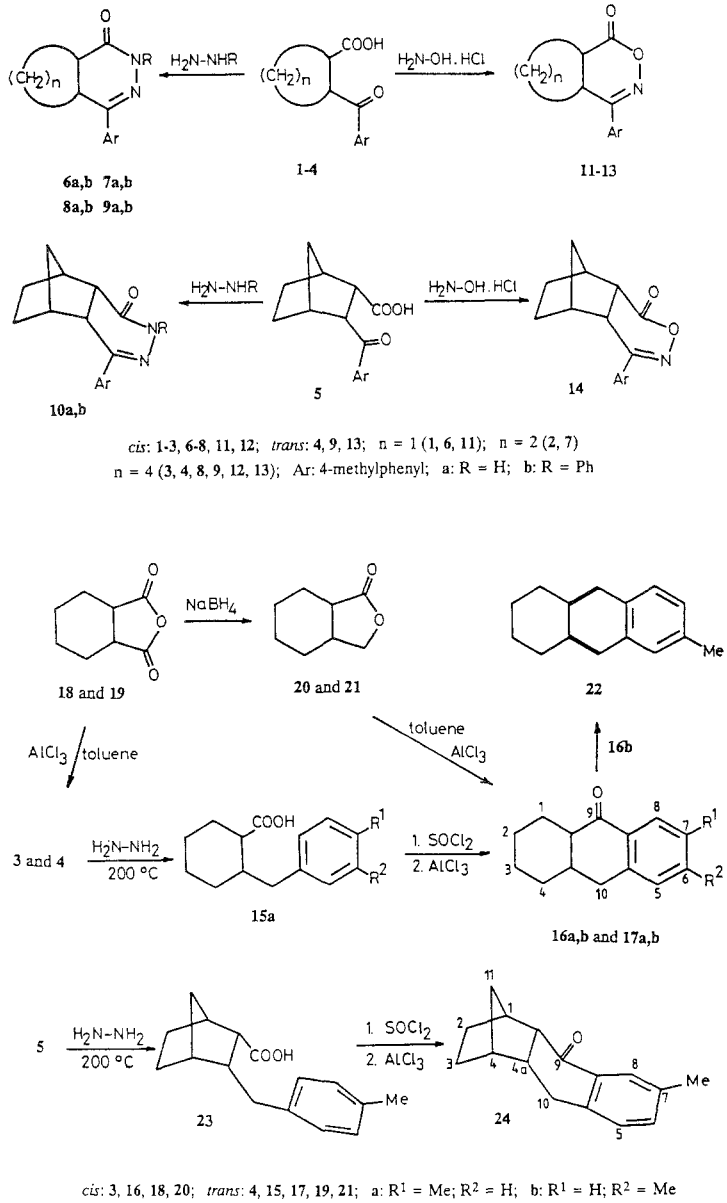
Syntheses

cis-2-(4-Methylbenzoyl)-cyclopropane-(**1**) and -cyclobutanecarboxylic acids (**2**), *cis*-(**3**) and *trans*-2-(4-methylbenzoyl)-cyclohexanecarboxylic acids (**4**) and di-*endo*-3-(4-methylbenzoyl)-bicyclo[2.2.1]heptane-2-carboxylic acid (**5**), prepared according to the literature or analogously from di-*endo*-norborane-2,3-carboxylic anhydride by *Friedel-Crafts* acylation, were cyclized with hydrazine hydrate and phenylhydrazine to the cyclopropane-, cyclobutane- and cyclohexane-*cis*-fused 4,5-dihydro-3-(2*H*)-pyridazinones (**6a**, **7a**, **8a**), the corresponding *trans* derivative (**9a**) and their 2-phenyl derivatives (**6b**–**9b**) (Scheme 1).

For pharmacological aims, the analogous norbornane-di-*endo*-condensed pyridazin-3(2*H*)-ones (**10a, b**) were also prepared. As potential drugs, the non-condensed or differently substituted derivatives of the 4-5-dihydropyridazinones have already been synthesized [10, 12, 13].

With hydroxylamine hydrochloride, synthons **1** and **3**–**5** yielded the cyclopropane-*cis*- (**11**), cyclohexane-*cis*- (**12**) and *trans*- (**13**), and norbornane-di-*endo*-condensed (**14**) 4,5-dihydro-1,2-6*H*-oxazin-6-ones.

As the aroylcyclohexanecarboxylic acids looked to be also suitable for the synthesis of partially saturated anthracene derivatives, synthons **3**–**5** were reduced



Scheme 2

by the *Wolff–Kishner* method. The product obtained from both **3** and **4** was the *trans*-2-(4-methylbenzyl)-cyclohexanecarboxylic acid [14–16] **15a** while the reduction of **5** led to the corresponding norbornane derivative (**23**) (Scheme 2).

The isomerization of the *cis* compound **3** persumably took place during the vigorous hydrazine reduction (200 °C, KOH). For dihydrouracils, *cis-trans* inversion on the action of acids, bases or heating is already known [17]. In the present case, the isomerization **3**→**15a** was proved by further reactions. Reduction and cyclization of the *cis* (**3**) and the *trans* synthon (**4**) gave the same *trans* compound (**17a**). The configuration of the fixed methylene-bridged di-*endo* analogue **5** was not changed by the reduction.

From *cis*-4-cyclohexene-1,2- and di-*endo*-5-norbornene-2,3-dicarboxylic anhydride, the preparation of the ketocarboxylic acids of types **3–5** under similar conditions was unsuccessful because of the saturation of the double bond in the *Friedel–Crafts* reaction. We will report this reaction later. Thus, for the synthesis of the *cis*-hexahydroanthrone, the *cis*-hexahydrophthalic anhydride (**18**) was reduced with $NaBH_4$ to the *cis*-lactone (**20**), which was then reacted with toluene in the presence of a large excess of $AlCl_3$. This reaction gave directly *cis*-6-methyl-1,2,3,4,4a,9a-hexahydroanthrone (**16b**) instead of the 7-methyl derivative (**16a**).

Starting from *trans*-hexahydrophthalic anhydride (**19**), *trans*-6-methyl-anthrone (**17b**) was formed in this way. Thus, acylation, *Wolff–Kishner* reduction and cyclization of the *trans* anhydride (**19**) yields the 7-methyl hexahydroanthrone (**17a**), whereas the route starting with reduction followed by simultaneous *Friedel–Crafts* acylation and cyclization furnishes the regioisomeric 6-methyl-hexahydroanthrone (**17b**).

On cyclization of **23** in the presence of $AlCl_3$, the tetracyclic 1,4-methylene-bridged hexahydroanthrone (**24**) containing the norbornane di-*endo*-fused structural moiety was formed.

On reduction with *LAH*/$AlCl_3$, the 6-methyl-*cis*-hexahydroanthrone (**16b**) gave the corresponding *cis*-octahydroanthracene (**22**). The synthesis of the *cis*- (**16a**) and *trans*-octahydroanthracen-9-one (**17a**) has already been described [14–16] and the preparation of 6-methyl-1,2,3,4,4a,9,9a,10-octahydroanthracene (**22**) by reduction of **16a** is also known [14]. *Mathur* and *Bhargava* applied the *Wolff–Kishner* method to reduce the derivative **16** obtained from **3** by reduction with hydrazine and subsequent cyclization, and reported the isolation of crystals of **22** with m.p. 126 °C in very good yield (90.3%) [14].

We repeated their work with **16b**, but this gave a colourless liquid (yield 64%). ^{1}H NMR indicated that the product contains starting **16b** (11%) besides **22**. Reduction of **16b** with *LAH* proved to be more convenient; for isolation, a HPLC method was applied, which resulted in **22** (35% of the distilled product), m.p. 77–80 °C. In addition, a heterogeneous fraction (53%) was obtained, which included derivatives partly saturated in the aromatic ring.

Structure

The spectral data of the new compounds are listed in Tables 1 and 2.

For **16b**, the *cis* anellation of the cyclohexane and cyclohexenone rings is proved by the broad ^{1}H NMR signal ($\sim$15 Hz) of the anellated methine hydrogen vicinal to the carbonyl group. It also shows that the carbonyl group is *axial* and that the methylene group in the cyclohexenone ring is *equatorial*, which is in accordance with the higher spatial requirements of the methylene group compared to those of the carbonyl group [18]. In the second relatively stable conformation with the cyclohexane ring in the chair conformation, the two functional groups adopt the reverse positions. The 15 Hz signal width excludes an *axial* methine hydrogen relative to the cyclohexane ring, because large *diaxial* splittings would cause a broader signal [19]. In accordance, the corresponding signal width of the *trans* analogues **17a, b** is $\sim$30 Hz (see Table 1). For **17a, b**, this signal appears 0.5 ppm upfield of that measured for **16b**, which is a consequence of the *equatorial* $\rightarrow$ *axial*

Table 1. IR and ^{1}H NMR data

Compd.	$\nu_{C=O}$ cm^{-1}	CH_3 *s*(3H)	CH(anellated)[a] 2 × m (2 × 1H)		CH_2 and CH[b] groups 1–5 m's (2/4/8/10/12H)[c]	ArH 1–4 m's (3/4/9H)[d]
6a	1657	2.37	2.15	2.45	0.80[e] 1.78[f]	7.20[g] 7.69[g]
6b	1659	2.36[h]	2.3[h]	2.6	1.0[e] 1.80[f]	~7.2[i] 7.40[j] 7.50[k] 7.73[g]
7a	1659	2.35[h]	3.38	3.88	2.35[h,l] ~2.6[i]	7.17[g] 7.52[g]
7b	1681	2.35[h]	3.52	3.90	2.35[h,l] ~2.6[i]	7.16[g] 7.25[l] 7.42[j] 7.55[m]
8a	1667	2.37	2.75	3.12	1.25–1.74[n] 1.80[l] 2.55[o]	7.20[g] 7.66[g]
8b	1677	2.37	~2.9	3.20	1.3–1.9[p] 2.60[o]	~7.2[i] 7.40[j] 7.60[k] 7.72[g]
9a	1674	2.36	~2.1[h]	2.60	1.0–1.4[m] ~1.85[q] ~2.1[h,l] 2.45[o]	7.18[g] 7.22[g]
9b	1688	2.35	2.25	2.72	1.0–1.5[m] 1.7–1.9[q] ~2.15[l] ~2.5[o]	~7.2[i] ~7.3[m] 7.55[k]
10a	1664	2.38	3.00	3.48[y]	1.2–1.8[n] 2.64[b,r] 2.91[b,o,r]	7.20[g] 7.60[g]
10b	1644	2.36	3.10	3.60[y]	1.2–1.8[n] 2.70[b,r] 3.01[b,o,r]	7.2–7.8[h] 7.26[g,h] 7.66[g,h]
11	1740	2.41[h]	~2.35[h]	2.55	1.30[e] 1.95[f]	7.27[g] 7.68[g]
12	1768	2.38	2.86	3.15	1.3–1.9[p] ~2.5[o]	7.23[g] 7.65[g]
13	1762	2.39	2.23	2.75	0.9–2.1[s]	7.24[m,r]
14	1751	2.39	3.10	3.50	1.2–1.7[n] 2.59[b,r] 2.94[b,o,r]	7.24[g] 7.58[g]
16b	1671	2.33[h]	~2.33[h]	2.62	~1.45[i] ~2.15[o] 2.85[t] 2.97[t]	7.00[u] 7.05[v] 7.92[w]
17a	1677	2.36[h]	~2.1	~2.4[h]	~1.3[m] 1.7–2.0[m] 2.70[t] 2.83[t]	7.10[w] 7.25[v] 7.82[u]
17b	1679	2.37[h]	~2.1	~2.4[h]	~1.3[m] 1.7–2.0[m] 2.70[t] 2.82[t]	7.00[u] 7.10[v] 7.91[w]
22	–	2.27	~2.0[h]		1.3–1.7[s] ~2.7[m]	6.95–7.00
24	1669	2.36[x]	2.6	~2.8[h,y]	~1.0[l] ~1.25[i] 1.38[z] 1.53[z] ~2.8[h,y] 3.00[t]	7.10[w] 7.25[v] 7.67[u]

Chemical shifts in ppm, $\delta_{TMS} = 0$ ppm, coupling constants in Hz, in $CDCl_3$ solution at 250 MHz. Further IR data (in KBr discs): ν_{NH} band: 3200 (**6a**), 3225 (**7a**), 3212 (**8a**), 3236 (**9a**), 3192 (**10a**). δ_{NH} signal (^{1}H NMR): 9.70 (**6a**), 9.20 (**7a**), 9.42 (**8a**), 9.05 (**9a**), 8.60 (**10a**). [a] In cyclohexenone (**24**), in hetero ring (**10a, b** and **14**). [b] Anellated hydrogens of the cyclopentane rings in **10**, **14** and **24**. [c] Total intensity: 10H (**16**, **17**, **24**), 12H (**22**), 8H (**8**, **9**, **10**, **12**–**14**), 2H (**6**, **11**), 4H (**7**). [d] Total intensity: 3H (**16b**, **17**, **22**, **24**), 4H (**6a**, **7a**, **8a**, **9a**, **11**–**14**), 9H (**6b**, **7b**, **8b**, **9b**, **10b**). [e] Quartet-like multiplet of the cyclopropyl methylene-H *trans* to the anellated hydrogens, $J \sim 5$ Hz. [f] *dt* signal of the *cis* cyclopropyl methylene-H, $J \sim 9$ and 5 Hz. [g] A or B part of AA′ BB′ spin system; 2 × ~s (2 × 2H), $J \sim 8$ Hz. The upfield signal originates from H-3,5, the downfield one from H-2,6. [h] Overlapping signals. [i,l,m,n,p,q,s] Overlapping signals with total intensity: 3/1/4/6/7/2/8. [j] H-3,5 (phenyl), ~*t*(2H). [k] H-2,6 (phenyl), ~d(2H), $J \sim 8.8$ Hz. [o] Signal of the hydrogen coplanar to the β-carbonyl group. [r] Singlet-like signal. [t] A or B part of ABX spin system, dd (1H), *J*: 16.7, 6.0 and 5.1 (**16b**), 16.2, 11.2, 4.2 (**17a, b**), 17.0, 8.8, ? (**24**). [u] Coalesced *d* ($j < 2$ Hz). [v] dd. [w] d ($J \sim 8$ Hz). [x] Overlapping signals of one of the anellated H's (norbornane, H-4) and the methyl group (4H). [y] Overlapping signals of H-1, 9a, 10_{ax} (3H). [z] AB spectrum (2 × d, 2 × H) of the bridging methylene hydrogens; $J = 9.5$ Hz

Table 2. ^{13}C NMR chemical shifts[a,b]

Compd.	CH_3	Cycloalkane ring		4-Methylphenyl and phenyl groups						CH_2[c]	
		CH_2	CH	C-1	C-2	C-6	C-3	C-5	C-4	C=N	C=O
6a	21.3	8.8	18.5 19.0	132.8	126.2		129.2		139.9	148.2	166.6
6b	21.1	9.6	19.1 20.1	132.8	126.2[d]		129.0[e]		126.2[d]	148.0	164.4
				141.9	124.8		128.2[e]		139.8		
7a	22.5	27.8 28.8	35.1 35.5	133.8	127.1		130.8		140.5	149.7	168.7
7b	21.0	26.4 27.4	34.5 35.1	131.6	125.8[e]		129.0[f]		139.5	149.2	165.3
				141.8	124.8[e]		128.1[f]		126.1		
8a	21.2	22.0 23.3 24.3 25.5	35.8 36.1	131.8	125.7		129.3		139.7	153.8	169.9
8b[g]	21.1	21.8 23.9 24.9 25.6	36.2 37.2	131.9	125.9[d]		129.2[e]		141.7	154.3	167.2
				139.8	124.6		128.1[e]		125.9[d]		
9a	21.3	25.1 25.4 25.8 30.1	38.7 40.3	133.2	127.6		128.8		138.7	157.9	170.1
9b	21.3	25.1 25.3 26.3 30.3	38.7 41.4	133.3	127.8		128.8[e]		138.8	158.7	167.9
				141.3	124.7		128.4[e]		126.2		
10a[g]	21.3	25.1 23.5 39.1[h]	41.2 41.3 43.1[d]	133.3	126.1		129.3		139.7	149.5	167.6
10b	21.4	23.7 25.2 39.5[h]	41.9 42.3	133.4	126.4[e]		129.3[f]		139.7	149.1	166.2
			43.4 44.3	141.9	125.3[e]		128.5[f]		126.6		
11	21.4	13.4	17.0 18.9	128.8	126.8		129.6		141.8	158.3	167.6
12	21.1[e]	21.2[e] 23.6 25.0 25.9	35.4 36.6	128.7	126.4		129.5		141.1	164.6	171.7
13	21.4	24.7 25.9 29.7	37.6 38.9		127.7[d]		129.2		140.1	168.0	172.1
14[g]	21.4	23.5 25.2 39.1[h]	39.8 41.3	130.0	126.7		129.6		141.2	158.5	169.7
			42.4 43.7								
16b[g]	21.1	23.1 23.6 25.1 28.5	35.6 47.8[i]	129.3	129.2	142.3	126.8[e]	127.0[e]	143.4	33.0	198.6
17a[g]	20.7	25.3 25.7 25.9 33.9	39.9 51.6[i]	131.8	127.0	135.7	140.3	128.2	133.8	36.6	199.2
17b	21.5	25.3 25.7 25.9 33.9	39.9 51.7[i]	129.9	128.9	143.3[e]	127.2[f]	127.4[f]	143.7[e]	37.1	192.2
22	21.0	23.5[d] 29.1[d]	33.8[d]	135.5	129.1[e]	134.7[f]	132.6[f]	129.7[e]	125.7	32.7[j]	32.2[j]
24[g]	21.0	22.9 24.8 40.0[h]	35.6 43.0[i]	134.2	126.5	136.2	140.1	128.2	134.6	28.1	203.1
			43.8 49.2[i]								

[a] Solvent: $CDCl_3$; *DMSO*-d_6 for **7a**, [b] Measuring frequency: 62.89 MHz; for **6b**, **7a**, **b**, **8b**, **11**, **12** and **16b**: 20.14 MHz. [c] CH_2 (Pos. 10) for **16b**, **17a**, **b**, **22** and **24**. [d] Two overlapping lines. [e,f,j] Interchangeable assignments. [g] Assignments were proved by DEPT measurement. [h] Bridging methylene in the norbornane moiety. [i] Vicinal to the carbonyl group

change [19, 20a]. Similarly, the 15 Hz signal width and the downfield shift of the hydrogen vicinal to the carbonyl group as compared to the signals for the *trans* isomers **9a, b** suggest a conformer containing an *axial* carbonyl group for the *cis*-anellated compounds **8a, b**.

This also holds for the former of the *cis-trans* pair **12–13**: the signal of the methine hydrogen vicinal to the carbonyl group is sharper (signal width ~8 Hz; ~30 Hz for **12**) and downfiend shifted (by 0.63 ppm). Thus the carbonyl group is *axial* to the cyclohexane chair ring in the preferred conformation.

Further proof of the *cis-trans* structures is that the sum of the cyclohexane carbon shifts is by 18.7 ppm smaller for *cis* **16b** with respect to *trans* **17b** [20b]. For **17a** and **17b**, the *trans*-anellated structure follows from the same magnitude of the carbon shifts (within measurement error, *cf.* Table 2).

For **6a, b** and **11**, the significantly different shielding and signal splitting of the two cyclopropane methylene hydrogens are noteworthy. The anisotropic effect of the hetero ring causes a strong upfield shift of the signal of the methylene hydrogen which is situated above the ring and *trans* to the vicinal hydrogens. The assignment based on the higher *cis* vicinal coupling [20c] is beyond any doubt.

For **10a, b** and **14**, the double doublet pattern of the signal of the heterocyclic anellated hydrogens [21] unambiguously proves the di-*endo* annelation of the hetero ring and the norbornane moiety.

The position of the methyl group in compounds **16b**, **17a, b** and **24** follows unambiguously from the ^{1}H NMR signals of the aromatic hydrogens. From the AMX system characteristic for 1,2,4-trisubstituted benzene derivatives, the assignment of the aromatic protons is obvious [20d]. The substituent effect [20e] (strong deshielding) of the *ortho* carbonyl group is decisive with regard to the *meta* or *para* position of the methyl group relative to the carbonyl group. As the coupling of the downfield H-8 signal in the ^{1}H NMR spectra of **16b** and **17b** is 8 Hz, the methyl group must be in position 6; this splitting is due to an *ortho* interaction with H-7. In **17a** and **24**, the coupling of the downfield H-8 doublet is <2 Hz, which indicates a methyl group in position 7; the coupling constant indicates a *meta* interaction of 6-H and 8-H.

For **16b**, the assignment of the H-9a signal was proved by combined DEPT and two-dimensional heteronuclear shift correlation (CH-COSY) methods. The signals of the two anellated carbons (C-4a,9a) at 35.6 and 47.8 ppm were identified by DEPT, and the ^{1}H NMR signal (2.62 ppm) corresponding to the downfield resonance (47.8 ppm) was located in the CH-COSY-spectrum. For the preferred conformation, the 15 Hz half-signal-width of 9a-H was decisive.

For **17b**, the 6-position of the methyl group was also proved by nuclear *Overhauser* effect (NOE) measurements. Saturation of the methyl signal causes enhancement of the two upfield signals of the three aromatic signals (the doublet with the small coupling constant and the double doublet) thus indicating their vicinity to the methyl group. This is in accordance with the downfield position of the signal originating from H-8, owing to the anisotropic effect of the carbonyl group [20e]. Accordingly, the upfield doublet (H-5) and the 10-methylene signal at ~2.75 ppm give mutual NOE (irradiation of one of the signals increases the intensity of the other).

For **22**, the signal width (~15 Hz) of the anellation hydrogens and cyclohexene

methylene hydrogens indicates the unaltered *cis* anellation. The C and H signal pairs point to the quasi-symmetry of the molecule as a consequence of the rapid inversion of its two conformers.

For the norbornane derivative **24**, the unaltered di-*endo* anellation can be deduced only indirectly, because the splittings due to the couplings $J_{1,9a}$ and $J_{4,4a}$, which would serve as a direct proof [21], cannot be observed owing to signal overlap. From a comparison of the H-4 and C-2,3,11 shifts with the corresponding data on the methylene-bridged di-*exo*- and di-*endo*-2-aryl-3,1-benzoxazines [22] it is obvious that the di-*endo* structure of the starting compound **5** or the intermediate **23** is not altered during the reduction and cyclization.

Experimental

IR spectra were run in KBr discs on a Bruker IFS-113v vacuum optic FT-spectrometer equipped with an Aspect 2000 computer.

The NMR spectra were recorded in $CDCl_3$ or *DMSO*-d_6 solution in 5 or 10 mm tubes at room temperature on Bruker WM-250 (^1H, ^{13}C) or WP-80-SY (^{13}C) FT-spectrometers controlled by an Aspect 2000 computer at 250.13 (^1H) and 62.89 or 20.14 MHz (^{13}C), with the deuterium signal of the solvent as the lock and *TMS* as internal standard. The most important measuring parameters were as follows: spectral width, 5 and 15 or 5 kHz; pulse width, 1 and 5 or 3.5 μs (~20° and ~30° flip angle); acquisition time, 1.64 and 1.02 or 1.64 s; number of scans 16 or 32 (^1H) and 500–5000 (17000 in the case of **10a**) (^{13}C); computer memory 16 K. Lorentzian exponential multiplication for signal-to-noise enhancement (line broadening: 0.7 and 1.0 or 2.0 Hz) was applied.

NOE difference experiments were performed with the Bruker microprogram 12.5 in the Aspect 2000 Pulse Programmer. Gated decoupling to generate NOE was used.

The CH-COSY spectra were obtained using the standard BRUKER pulse program "XHCORRD.AU". The number of data points was 4 K in the ^{13}C domain, and 64-256 increments were used to give better than 5 Hz/point digital resolution in the ^1H domain. 256 transients were obtained with a relaxation delay of 3 s. All C-H correlations were found by using $J_{C,H} = 135$ Hz for calculating of the delays.

DEPT spectra [23] were run in a standard way [24], using only the $\theta = 135°$ pulse to separate the CH/CH_3 and CH_2 lines phased up and down, respectively.

HPLC: ISCO system with two pumps, suitable for gradient elution, Chem. Research control system and data processing program. For the semipreparative separation, a BST Si-100-S 10-RP-18 column (250 × 16 mm) was used; eluent: MeOH–H_2O–CH_3CN (82 + 17 + 1 v/v%); flow rate: 9 ml/min. Injected sample: 500 μl of a 4% MeOH–THF (2 + 1) solution, detection at 270 nm.

cis-2-(4-Methylbenzoyl)-cyclopropanecarboxylic acid (**1**)

Prepared from 5.6 g (64 mmol) *cis*-cyclopropanedicarboxylic anhydride [25] according to Ref. [9]. Yield 9.7 g (89%), m.p. 105–107 °C. $C_{12}H_{12}O_3$ (204.2). Calcd.: C, 70.58; H, 5.92. Found: C, 70.71; H, 5.80.

cis-2-(4-Methylbenzoyl)-cyclobutane-1-carboxylic acid (**2**)

Prepared from 8.06 g (0.064 mol) *cis*-cyclobutane-1,2-dicarboxylic anhydride [26] according to Ref. [9]. Colourless crystals, m.p. 115–117 °C, yield 11.9 g (85%).

di-endo-Bicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride

To a solution of 16.4 g (0.1 mol) di-*endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride (Aldrich 24,763–4) in 250 ml dry *THF*, 16.3 g cyclohexene and 0.5 g 5% Pd on activated carbon were added. The mixture was refluxed for 15 h on a water bath. After cooling and filtration, the solution was evaporated and the residue was crystallized from benzene. Yield 15.0 g (90%), m.p. 170–172 °C. $C_9H_{10}O_3$ (166.2). Calcd.: C, 65.05; H, 6.07. Found: C, 65.14; H, 6.11.

di-endo-3-(4-Methylbenzoyl)-bicyclo[2.2.1]heptane-2-carboxylic acid (**5**)

Prepared from 8.31 g (0.05 mol) di-*endo*-bicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride according to Ref. [10]. Colourless crystals, yield 11.49 g (89%), m.p. 162–164 °C. $C_{16}H_{18}O_3$ (258.3). Calcd.: C, 74.4; H, 7.02. Found: C, 74.28; H, 7.14.

di-endo-3-(4-Methylbenzyl)-bicyclo[2.2.1]heptane-2-carboxylic acid (**23**)

Prepared from 12.92 g (0.05 mol) **5** according to the method of *Mathur* and *Bhargava* [14]. Colourless crystals, yield 9.40 g (77%), m.p. 232–234 °C.

(Bi)cycloalkane-condensed 4,5-dihydro-3(2H)-pyridazinones (**6a–10a**) *(general method)*

A mixture of 0.01 mol 2-(4-methylbenzoyl)-(bi)-cycloalkanecarboxylic acid (**1–5**) and 0.5 g (0.01 mol) hydrazine hydrate in 25 ml toluene was refluxed for 1–2 h. After evaporation of the mixture, the residue was crystallized. Data of **6a–10a** are listed in Table 3.

(Bi)cycloalkane-condensed 2-phenyl-4,5-dihydro-3(2H)-pyridazinones (**6b–10b**) *(general method)*

A mixture of 0.01 mol 2-(4-methylbenzoyl)-cycloalkanecarboxylic acid (**1–4**) or its methylene-bridged homologue (**5**) and 1.08 g (0.01 mol) phenylhydrazine in 25 ml toluene was refluxed for 1–2 h. After evaporation, the residue was crystallized. Data of **6b–10b** are listed in Table 3.

(Bi)cycloalkane-condensed 4,5-dihydro-6H-1,2-oxazin-6-ones (**11–14**) *(general method)*

A mixture of 0.01 mol ketoacid (**1–5**), 0.69 g (0.01 mol) hydroxylamine·HCl and 1.64 g (0.02 mol) CH_3COONa in 30 ml MeOH was refluxed for 2 h. After filtration, the solution was evaporated and the residue was crystallized. Data of **11–14** are listed in Table 3.

trans-7-Methyl-1,2,3,4,4a,9,9a,10-octahydroanthracen-9-one (**17a**)

To a mixture of 4.18 g (18 mmol) *trans*-2-(4-methylphenyl)-methylcyclohexanecarboxylic acid **15a** und 50 ml dry benzene, 0.6 ml thionyl chloride was added dropwise under stirring and cooling. The mixture was refluxed for 3 h and evaporated. To the residue, 48 ml CS_2 and 2.4 g (18 mmol) anhydrous $AlCl_3$ were added and, after refluxing for 3 h on a water bath, the mixture was left to stand overnight. After removal of the solvent, cooled 10 ml 10% HCl was added and the mixture was extracted with 3 × 30 ml $CHCl_3$. The combined extract was washed with 5% Na_2CO_3 solution, dried (Na_2SO_4) and evaporated. Data of **17a** are listed in Table 3.

cis- and trans-6-Methyl-1,2,3,4,4a,9,9a,10-octahydroanthracen-9-one (**16b** and **17b**)

To a solution of 16.9 g (0.12 mol) **20** or **21** [27] in 100 ml dry toluene 60.0 g (0.45 mol) anhydrous $AlCl_3$ was added during 2 h under stirring. The brown mixture was kept for 16 h at 80–90 °C and then poured into a mixture of 300 g ice and 50 ml conc HCl under stirring, and the mixture was extracted with 3 × 70 ml ether. After washing of the combined extract with 2 × 50 ml water and drying (Na_2SO_4), the

Table 3. Physical and analytical data of the compounds obtained

Compd.	M.p. °C	Yield %	Mol. formula	Mol. weight	Calcd. %			Found %		
					C	H	N	C	H	N
6a	169–171[a]	51	$C_{12}H_{12}N_2O$	200.2	71.97	6.04	13.99	71.25	6.10	14.05
6b	132–134[b]	29	$C_{18}H_{16}N_2O$	276.3	78.23	5.83	10.13	78.70	6.30	10.00
7a	166–168[a]	72	$C_{13}H_{14}N_2O$	214.3	72.87	6.58	13.07	73.01	7.02	13.60
7b	177–119[c]	45	$C_{19}H_{18}N_2O$	290.35	78.59	6.24	9.65	77.82	6.28	9.30
8a	176–178[a]	62	$C_{15}H_{18}N_2O$	242.6	74.34	7.48	11.56	74.60	7.20	11.30
8b	126–128[b]	62	$C_{21}H_{22}N_2O$	318.4	79.21	6.96	8.80	79.05	6.92	8.93
9a	201–203[a]	84	$C_{15}H_{18}N_2O$	242.6	74.34	7.48	11.56	74.40	7.66	11.30
9b	140–142[b]	46	$C_{21}H_{22}N_2O$	318.4	79.21	6.96	8.80	79.53	6.80	8.90
10a	254–256[c]	59	$C_{16}H_{18}N_2O$	254.3	75.56	7.13	11.01	75.26	7.11	10.70
10b	224–226[c]	66	$C_{22}H_{22}N_2O$	330.4	79.97	6.71	8.47	80.20	7.28	8.49
11	179–181[a]	35	$C_{12}H_{11}NO_2$	201.2	71.62	5.51	6.96	71.25	5.72	6.80
12	136–138[d]	41	$C_{15}H_{17}NO_2$	243.3	74.05	7.04	5.75	74.80	7.10	6.04
13	145–147[a]	29	$C_{15}H_{17}NO_2$	243.3	74.05	7.04	5.75	73.48	7.43	6.05
14	210–212[d]	47	$C_{16}H_{17}NO_2$	255.3	75.26	6.71	5.48	75.21	6.53	5.40
16b	84–86[e]	29	$C_{15}H_{18}O$	214.3	84.07	8.46	–	84.20	8.35	–
17a	97–99[d]	65	$C_{15}H_{18}O$	214.3	84.07	8.46	–	84.40	8.55	–
17b	101–103[d]	26	$C_{15}H_{18}O$	214.3	84.07	8.46	–	84.15	8.55	–
22	77–80[b]	25	$C_{15}H_{20}$	200.3	89.94	10.06	–	89.75	10.20	–
24	86–88[b]	20	$C_{16}H_{18}O$	226.3	84.91	8.01	–	85.20	8.10	–

Crystallized form: [a] EtOAC; [b] EtOH; [c] dioxane; [d] benzene; [e] Et_2O

solvent was removed by distillation and the residue was chromatographed on a silica gel column (Kieselgel 60, 0.060–0.20 mm, benzene). Data of **16b** and **17b** are listed in Table 3.

di-endo-7-Methyl-1,4-methano-1,2,3,4,4a,9,9a,10-octahydroanthracen-9-one (**24**)

24 was prepared from di-*endo*-3-(4-methylbenzyl)-bicyclo[2.2.1]heptane-2-carboxylic acid (**23**) as **17a**. Data of **24** are listed in Table 3.

cis-2-Methyl-1,2,3,4,4a,9,9a,10-octahydroanthracene (**22**)

To a suspension of 0.64 g (17 mmol) *LAH* in 10 ml dry ether, a mixture of 4.66 g (35 mmol) anhydrous $AlCl_3$ and 10 ml dry ether was added under stirring and cooling, and 2.14 g (10 mmol) **16b** in 10 ml ether was then added dropwise in 10 min. After refluxing for 30 min on a water bath, the excess of *LAH* was decomposed by adding 1 ml ethyl acetate and the mixture was poured into dilute 10 ml 20% H_2SO_4. The organic layer was separated and dried (Na_2SO_4), and the solvent was removed. The oily residue was fractionated, b.p. 100–104 °C/800 Pa.

The oily product obtained was purified by HPLC. Fraction A (11%), crystallized from MeOH–H_2O, gave **16b** as colourless crystals, m.p. 88–90 °C; B (53%), a yellowish oily product, which crystallized from MeOH–H_2O, gave almost colourless crystals, m.p. 76–80 °C; C (35%), an almost colourless oil, crystallized from EtOH, gave **22**, m.p. 77–80 °C.

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