Synthesis and Reactions of 7-Oxonorbornane-2,3-dicarboximides

Pelayo Camps*[a], Xavier Farrés[a], Mercè Font-Bardia[b], Diana Marina Görbig[a], Francesc Pérez[a], and Xavier Solans[b]

Laboratori de Química Farmacèutica, Facultat de Farmàcia, Universitat de Barcelona[a],
Av. Diagonal s/n; E-08028 Barcelona, Spain

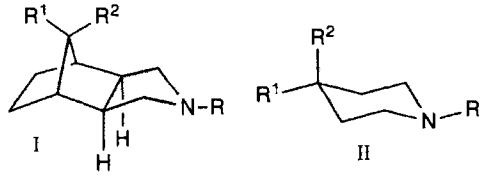
Serveis Científico-Tècnics, Universitat de Barcelona[b],
Av. Martí Franqués, E-08028 Barcelona, Spain

Received March 7, 1994

Key Words: 7-Oxonorbornane-2,3-dicarboximides / Reductive amination / 4,7-Methanoisoindoles

Ozonizations of several 7-isopropylidenenorbornane-2,3-dicarboximides (**2**, **10**) yield 7,7-dihydroxynorbornane-2,3-dicarboximides (**3**, **11**) and/or 7-oxonorbornane-2,3-dicarboximides (**4**, **12**). Dehydration of the dihydroxy derivatives to the corresponding carbonyl compounds can be carried out by reaction with P_2O_5 in an aprotic solvent. Reaction of hydrates **3** with methanol gives mixtures of the stereoisomeric hemiacetals **13** and **14**, whereas reaction with other nucleophiles give only the stereoisomer derived from attack by the less hindered carbonyl face. Thus $NaBH_4$ or $Al(iPrO)_3$ reduction of **3** or **4** yields alcohols **15** and $LiAlH_4$ reduction of **3** or **4** amino alcohols **16**. Reaction of **4b** with phenylmagnesium bromide gives alcohol **22** and a direaction product (*rac*-**26**) that easily dehydrates to a tetracyclic compound (*rac*-**30**). Reductive aminations of **3** or **4** lead to amines **19** directly or via imines *rac*-**20** and amines **23**. $LiAlH_4$ reduction of amine **23b** affords tricyclic compounds (*rac*-**27**) and (*rac*-**28**). The last one was converted to diamine **24** by reduction with $NaBH_3CN$. Similarly, amine **21** was converted into diamine **25**, partially via aminal **29** as intermediate. The structures of compounds **3b**, **19a**, *rac*-**27**, and *rac*-**30** have been established by X-ray diffraction analysis.

In connection with the synthesis of compounds with potential analgesic activity containing the perhydro-4,7-methanoisoindole skeleton (**I**), structurally related to piperidine analgesics of general structure **II**, such as anilidopiperidines [**II**, R^1 = H, R^2 = $N(C_6H_5)COCH_2CH_3$] and prodines (**II**, R^1 = $OCOCH_2CH_3$, R^2 = C_6H_5)[1] (Figure 1), we needed several 7-oxonorbornane-*exo*-2,*exo*-3-dicarboximides as synthetic intermediates.



R = Alkyl or Arylalkyl (i.e.: CH_3, $CH_2CH_2C_6H_5$)
R^1 = Aryl and R^2 = OH, OCO-Alkyl, or
R^1 = H and R^2 = OCO-Aryl [or N(Aryl)CO-Alkyl]

Figure 1. General structures of potential (**I**) and known (**II**) analgesic compounds

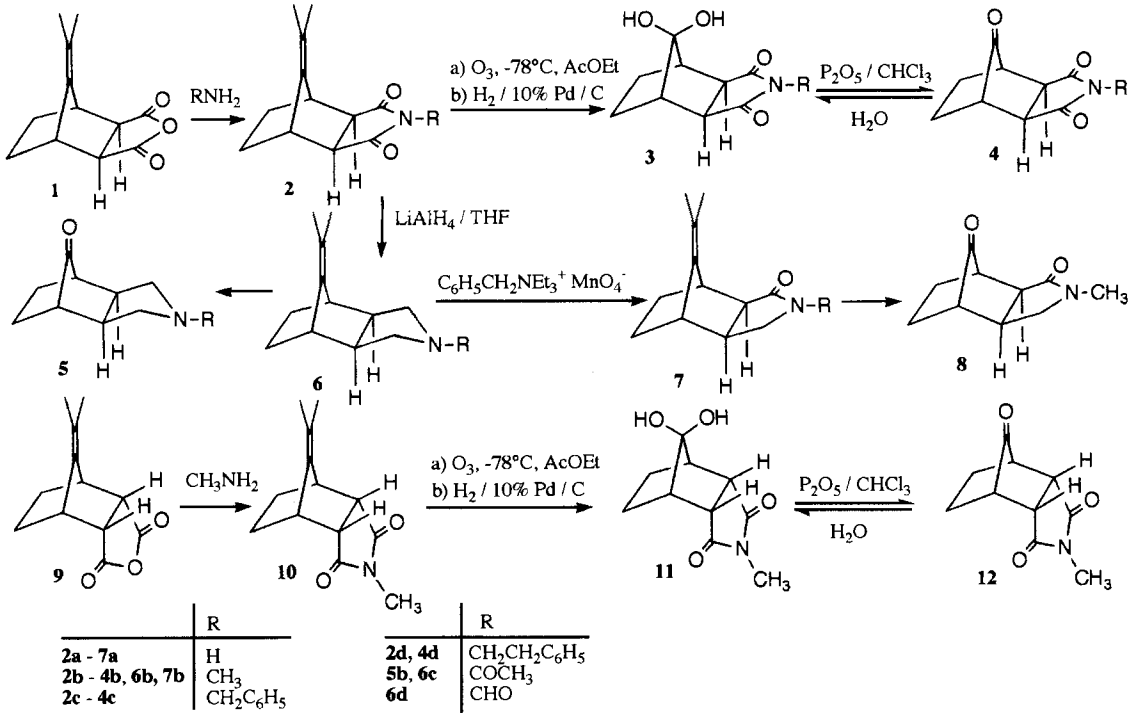
According to previous work from our group[2], these compounds could be obtained from anhydride **1** by standard manipulations of functional groups, with the ozonization of the carbon-carbon double bond as key step.

As shown in Scheme 1, reaction of anhydride **1** with ammonia, methylamine, benzylamine, or (2-phenylethyl)amine gave in good yields the corresponding cyclic imides **2a**, **2b**, **2c**, and **2d**, respectively. Ozonization of imide **2a** in ethyl acetate at −78°C followed by hydrogenation of the ozonide using 10% Pd on charcoal as catalyst afforded an almost insoluble product in very good yield. The analytical data (Tables 1, 4, 6 and 7) of this compound were in accordance with the hydrate **3a** of the anticipated ketone **4a**. Especially significant was the ^{13}C-NMR spectrum in which a signal of a carbonyl carbon atom was absent while an absorption at δ = 105.2 indicated a carbon atom with two oxygen functionalities. As a proof of the structure, treatment of **3a** with phosphorus pentoxide in chloroform gave a solution of the corresponding ketone **4a**, from which hydrate **3a** slowly precipitated on standing. Concentration of the above solution led to an oily residue, the elemental analysis of which was in accordance with a mixture of hydrate **3a** and ketone **4a**.

Similarly, ozonization of imide **2b** followed by catalytic hydrogenation of the ozonide gave in good yield hydrate **3b**. Treatment of **3b** with phosphorus pentoxide in chloroform afforded the corresponding ketone **4b**. However, the best elemental analysis obtained fitted for a mixture of hydrate **3b** (85%) and ketone **4b** (15%). Hydrate **3b** was also obtained, although in lower yield, by methylation of **3a** with dimethyl sulfate. The identity of hydrate **3b** was confirmed by X-ray diffraction analysis (Figure 2). The distances between atoms of different molecules in the unit cell show the existence of intermolecular hydrogen bonds between the hydroxy hydrogen atoms of one molecule and the carbonyl oxygen atoms of other molecules with significant in-

  0009−2940/94/1010−1933 $ 10.00+.25/0

Scheme 1. Synthesis of 7-oxonorbornane and 7,7-dihydroxynorbornane derivatives



teratomic distances C-8–O*syn*-H···O=C-1′ 2.24(6) and C-8–O*anti*-H···O=C-3″ 2.26(6) Å. In Table 8 further crystallographic data of this compound are compiled[3].

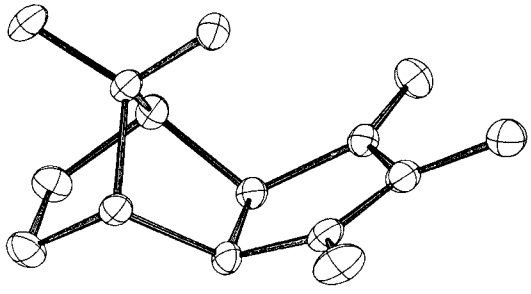


Figure 2. Perspective drawing (ORTEP) of hydrate **3b**. Significant bond lengths [Å] and angles [°]: C-8–O*syn* = 1.401(1), C-8–O*anti* = 1.409(2); O*syn*–C-8–O*anti* = 110.4(1), O*syn*–C-8–C-4 = 114.5(1), O*anti*–C-8–C-4 = 111.0(1), C-4–C-8–C-7 = 95.6(1)

Benzylation of **3a** under different conditions gave either hydrate **3c** or ketone **4c**. Moreover, ketone **4c** was obtained by ozonization of **2c** followed by catalytic hydrogenation of the ozonide.

Since the aromatic ring of **2c** was stable under the ozonization conditions, the *N*-(2-phenylethyl)imide **2d** was submitted to the ozonization/hydrogenation sequence, which furnished ketone **4d** as a solid compound stable to hydration.

In order to obtain more information about the hydration of these compounds, we prepared other derivatives containing the same skeleton but exhibiting different functionalities or configuration. Thus, imide **2a** was reduced with $LiAlH_4$ to the corresponding amine (**6a**), characterized as its hydrochloride. Similarly, amine **6b** was obtained by reduction of **2b**. Ozonization of **6a**·HCl in methanol gave, after hydrogenation of the ozonide, the corresponding ketone **5a**·HCl. Since this compound proved to be unstable, crude **5a**·HCl was transformed to acetamide **5b**, which could be fully characterized and does not show any tendency to undergo hydration (Tables 2, 3, 5, 6, and 7). To improve the preparation of **5b**, amine **6a** was acetylated. However, the resulting **6c** failed to give **5b** in the ozonization/hydrogenation sequence. Also, ozonization of **6b**·HCl did not give defined products.

On the other hand, amine **6b** was transformed to lactame *rac*-**7b** by oxidation with benzyltriethylammonium permanganate[4]. The crude reaction mixture contained a by-product that was characterized as the formyl derivative **6d** by a comparison with an authentic sample prepared by formylation of **6a**. The isolation of *rac*-**7b** was achieved by selective alkaline hydrolysis of **6d**. In a similar manner, amine **6a** was oxidized to lactame *rac*-**7a**, although in low yield. Ozonization of *rac*-**7b** under standard conditions gave in good yield the rather unstable keto lactame *rac*-**8**.

Moreover, the *endo* isomer **10** of **2b** was prepared by reaction of the *endo* anhydride **9**[5] with methylamine. This compound was also obtained from a mixture of anhydrides **1** and **9** by reaction with methylamine, followed by controlled sublimation of the product with **10** being the less volatile imide. Ozonization of **10** followed by hydrogenation of the ozonide under the standard conditions gave a crude product containing a 2:1 mixture of hydrate **11** and ketone **12**, that on crystallization from ether gave a solid consisting of **11** and water in the ratio 4:1. Reaction of **11** with P_2O_5 in chloroform led to ketone **12**, that was characterized spec-

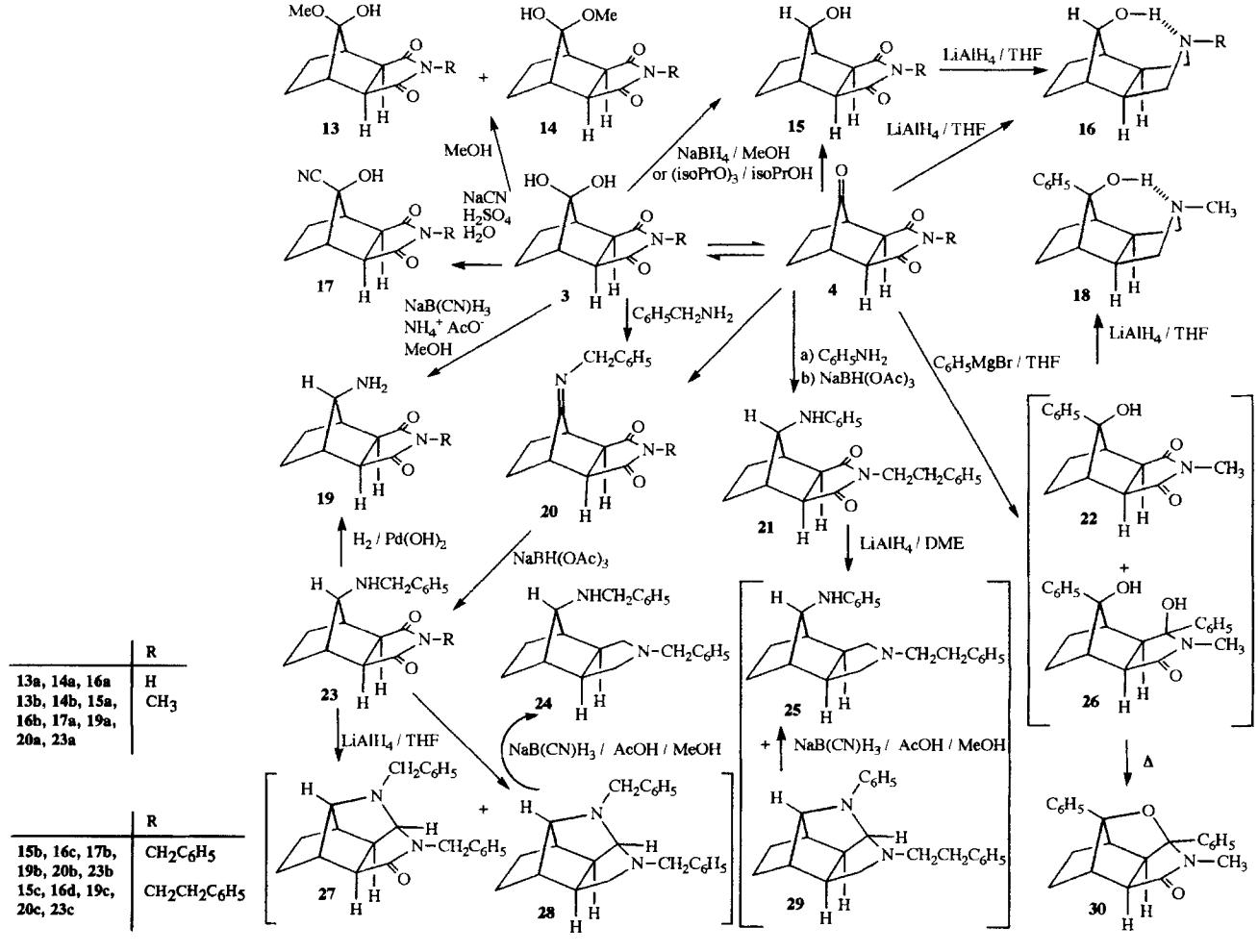
troscopically, but the elemental analysis indicated complete reversion to **11**.

The easy hydration of ketones **4a**, **4b**, and **12** is in striking contrast with the behaviour of **4c**, **4d**, **5b** and many other 7-norbornanone derivatives[6] such as *endo*-7-oxonorborn-5-ene-2,3-dicarboximide and its *N*-ethyl and *N*-phenyl derivatives[6i] that have been described as ketones without mention of the hydrated form. At first, we considered two points that could favor the hydrates: (a) The strain release associated with the change in the hybridization on conversion of the ketone into its hydrate, that could be partially modified by the functionality of the pyrrolidine ring, and (b) the possibility of establishing an intramolecular hydrogen bond between the 8-*syn*-hydroxy group and the nitrogen atom. The strain release hypothesis does not explain why so many norbornan-7-one derivatives exist as carbonyl compounds. The intramolecular hydrogen bond hypothesis is ruled out by the easy hydration of ketone **12**. The X-ray diffraction analysis of **3b** confirmed the absence of an intramolecular hydrogen bond in the solid state and showed the existence of intermolecular hydrogen bonds. Probably, the stabilization due to these intermolecular hydrogen bonds and the low solubility in organic solvents of the hydrates **3a**, **3b**, and **11**, which are readily soluble in water, shift the hydration equilibrium towards the hydrate. The hydrate of **4d** has not been observed, whereas **4c** was easily obtained from its hydrate **3c** by heating in ether. In these cases, the *N*-alkyl substituents increase the lipophilicity and, consequently, the solubility of the hydrates in organic solvents. On the other hand, these substituents may hamper the packing of the hydrates in a crystal lattice with intermolecular hydrogen bonds[7].

Reactions of these hydrates and/or ketones with nucleophiles are represented in Scheme 2. On heating of **3a** and **3b** in methanol, stereoisomeric hemiacetals **13a/14a** and **13b/14b**, respectively, were formed as mixtures with ratios close to 1:1. As to their structure, the ^{13}C-NMR spectra are of special significance, since they contain two closely related sets of absorptions in the expected regions (Table 4). Relative to the carbon atoms of position 8 of the corresponding hydrates, those of the hemiacetals are deshielded by about 4 ppm, whereas the other absorptions of the tricyclic skeleton experience only slight changes.

Hydrate **3b** and ketones **4c** and **4d** were reduced by two different reagents, i.e. $NaBH_4$ in methanol and aluminium triisopropoxide in 2-propanol. In all cases, only one alcohol

Scheme 2.



(**15a**, **15b** and **15c**, respectively) was obtained. These alcohols show very similar resonances of C-1, 3a,4,5,8 in the ^{13}C-NMR spectrum (Table 4), which is indicative of the same configuration at C-8. The *syn* position of the hydroxy group at C-8 is expected to be due to the nucleophilic attack to the carbonyl group of the corresponding ketone from the less hindered *anti* face. To confirm this configuration, the alcohol from **3b** was reduced with $LiAlH_4$ to the amino alcohol which was obtained by direct reduction of hydrate **3c** under similar conditions as well. Similarly, reduction of ketone **4d** and alcohol **15c** with $LiAlH_4$ gave amino alcohol **16d**. Also, the hydrates **3a** and **3b** were converted into the amino alcohols **16a** and **16b**, respectively, which turned out to be rather labile. The ^{1}H-NMR spectrum of amino alcohol **16d** (Table 1) shows a doublet at $\delta = 8.52$ ($J = 7.0$ Hz) which is indicative of the hydroxylic proton exhibiting an intramolecular hydrogen bond and being coupled to 8-H. Also, its IR spectrum shows the existence of an intramolecular hydrogen bond with hydroxy absorptions in $CHCl_3$ solution at 3625 and 3475 cm^{-1} that remain essentially unchanged in changing the concentration from 0.1 to 0.001 M. These facts lead us to propose structure **16d** which has the hydroxy group oriented *syn* to the pyrrolidine ring. Consequently, the corresponding imide should be the *syn* stereoisomer **15c**. Since amino alcohols **16** show very similar resonances of C-3a, 4,5,8 in the ^{13}C-NMR spectrum (Table 4), which is indicative of the same configuration at C-8, alcohols **15** and amino alcohols **16** all must have the same configuration at C-8, i.e. must be the *syn* stereoisomers.

Reaction of hydrates **3b** and **3c** with hydrogen cyanide gave in each case only one of the two possible cyanohydrines. They must have the same configuration at C-8 on the basis of the small differences in the ^{13}C-NMR chemical shifts (Table 4) of the tricyclic skeleton. A comparison of these values with those of related compounds (**3b** and **3c**, **15a**, **15b**) points to the 8-*anti* position of the cyano groups as shown for cyanohydrines **17a,b** (Scheme 2). Thus, in passing from hydrate **3b** to alcohol **15a**, the chemical shift of C-3a(7a) ($\delta = 47.4$ and 47.6, respectively) remains essentially unchanged, while that of C-5(6) ($\delta = 26.3$ and 24.9, respectively) moves upfield by 1.4 ppm due to the absence of the *anti*-OH group in the last mentioned compound. The same situation is found on comparison of **3c** and **15b**. Also, in passing from hydrates **3b** and **3c** to the cyanohydrines **17a** and **17b**, the chemical shifts of C-3a(7a) remain essentially unchanged, whereas those of C-5(6) move upfield by about 1.5 ppm, a fact pointing to the *anti* arrangement of the cyano groups. Since the formation of these cyanohydrines should take place by cyanide addition to the ketones **4b** and **4c**, being in equilibrium with the hydrates, the steric course of this reaction is in accord with the expected addition of the cyanide ion from the less hindered carbonyl *anti* face.

To study the steric course of the Grignard addition with these compounds, we treated **4b** with phenylmagnesium bromide. Two products were obtained. The major product was reduced with $LiAlH_4$ to an amino alcohol, for which an intramolecular hydrogen bond was evident from the ^{1}H-NMR spectrum (Table 1) and the IR spectrum (Table 7). Thus the hydroxy group should occupy the *syn* position, and the structures of the amino alcohol and its precursor should be **18** and **22**, respectively. Obviously, as for the $NaBH_4$ and $LiAlH_4$ reductions, the addition of phenylmagnesium bromide to the ketone functionality of **4b** takes place stereoselectively from the less hindered *anti* face.

A byproduct was isolated by crystallization from the mother liquor of **22**. Since the analytical data proved the presence of two phenyl groups, we propose structure *rac*-**26**. The configuration is supported by singlets in the ^{1}H-NMR spectrum at $\delta = 6.12$ and 6.85, which we assign to the hydroxy protons involved in intramolecular hydrogen bonds. In an attempt to crystallize *rac*-**26** from hot methanol, a new compound was quantitatively obtained, the structure of which (*rac*-**30**) was established by X-ray diffraction analysis (Figure 3, Table 8[3]). The dehydration of *rac*-**26** to *rac*-**30** could take place via an *N*-acylimonium intermediate formed by loss of the hydroxy group at C-3 and attacked by the hydroxy group at C-8.

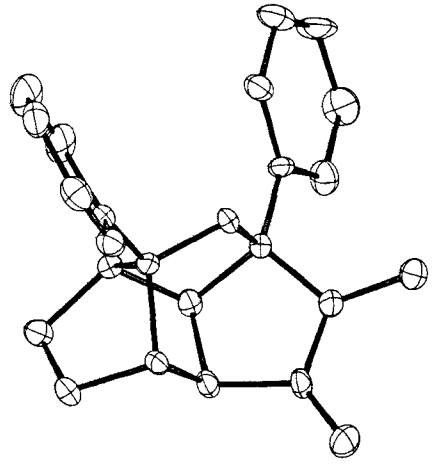


Figure 3. Perspective drawing (ORTEP) of compound *rac*-**30**

Initial attempts aimed at reductive amination of ketone **4c** with ammonium acetate and $NaBH_3CN$ in anhydrous methanol[8] led to the amine **19b** in only 19% yield. In addition, a 3:1 mixture of alcohol **15b** and cyanohydrine **17b** was obtained. Similarly, hydrate **3b** gave **19a** in only 2% yield.

In view of the low yields, we applied a three-step procedure involving formation of a benzylimine, followed by its reduction under aprotic conditions and hydrogenolysis of the benzylamine formed. Thus, reaction of hydrate **3b** with benzylamine in toluene under acid catalysis afforded benzylimine *rac*-**20a**, that was reduced with $NaBH(OAc)_3$ in 1,2-dichloroethane[9] to amine **23a** in 63% overall yield from **3b**. Similarly, from ketones **4c** and **4d**, the corresponding amines **23b** and **23c** were prepared via the benzylimines *rac*-**20b** and *rac*-**20c**, respectively.

Imines *rac*-**20** are chiral compounds due to the imine double bond[10]. This is evident from the ^{13}C-NMR spectra (Table 5) in which the number of resonances coincides with the number of carbon atoms.

Catalytic hydrogenation of **23a**, **23b**, and **23c** gave the primary amines **19a**, **19b**, and **19c**, respectively in high yields. Interestingly, compound **23b** was debenzylated selectively at the benzylamino group.

The reaction of ketone **4d** with aniline under acid catalysis produced the expected imine, the reduction of which with $NaBH(OAc)_3$ led to aniline derivative **21** in 62% overall yield.

In all these reductive aminations, only one of two stereoisomeric amines was obtained. A comparison of the ^{13}C-NMR data of **21** and **23** (Table 4) shows only very small differences in chemical shifts of the carbon atoms of the tricyclic skeletons. Therefore, the configuration of C-8 in these compounds should be the same. Since compounds **19** have been prepared from **23** without affecting the stereogenic centre, the configuration of C-8 of the former must be the same as that of **23**.

The configuration of **19a** has been established by X-ray diffraction analysis, showing indeed the *syn* arrangement of the amino group (Figure 4)[3].

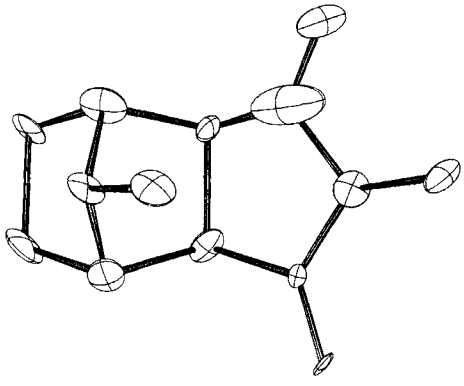


Figure 4. Perspective drawing (ORTEP) of amine **19a**

Moreover, when compound **23b** was reduced with $LiAlH_4$ a non-symmetric product was isolated in 35% yield. The structure of this compound was established by X-ray diffraction analysis as *rac*-**27** (Figure 5, Table 8[3]).

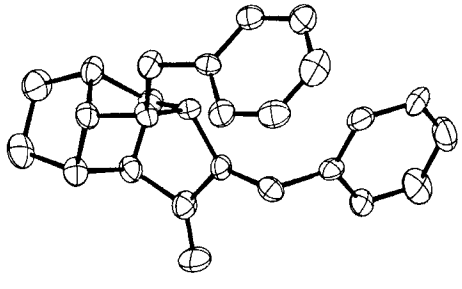


Figure 5. Perspective drawing (ORTEP) of compound *rac*-**27**

The formation of this compound clearly established the configuration of **23b** as having the benzylamino substituent at C-8 on the side of the pyrrolidine ring. As to the mechanism, the pathway from **23b** to *rac*-**27** could be an intramolecular nucleophilic addition of the amino group at C-8 to an *N*-acylimonium intermediate, formed by partial reduction of the imide function and subsequent hydroxide elimination, analogous to the conversion of diol *rac*-**26** into the cyclic ether *rac*-**30**.

Reduction of **23b** with $LiAlH_4$ in THF under vigorous conditions gave a crude product, the spectral data of which by comparison with those of *rac*-**27** (see Tables 2, 3 and 5) were in accord with aminal *rac*-**28**. Further reduction of this crude product under conditions of reductive amination ($NaBH_3CN$ at pH = 5) gave diamine **24** in 69% overall yield. The ^1H-NMR spectrum of this compound shows a broad NH absorption at $\delta = 5.3$, indicating an intramolecular hydrogen bond which confirms the *syn* configuration at C-8.

Similarly, reduction of amine **21** with an excess of $LiAlH_4$ in DME under vigorous conditions gave a 5:1 mixture of diamine **25** and another compound, the structure of which could be *rac*-**29**, as deduced from spectral data by comparison with those of *rac*-**28**. Since this mixture could not be separated, it was treated with $NaBH_3CN$ in anhydrous methanol at pH = 5 and yielded pure **25** in 40% overall yield.

The fact that the tetracyclic intermediate *rac*-**29** resulted in lower yield than *rac*-**28** reflects the lower nucleophilicity of the aniline nitrogen atom of **21** as compared with the benzylamine functionality of **23b**.

In conclusion, for the first time several norbornan-7-one derivatives have been shown to exist preferentially in the hydrated form. Ketones **4a,b** (or hydrates **3a–c**) react with most nucleophiles exclusively at the less hindered *anti* face of the ketone functionality to give products having the *syn* configuration of C-8. Only in the case of methanol mixtures of stereoisomers (**13**, **14**) resulted probably by equilibration of the initially generated hemiacetal **14**. Work is in progress to test several of the prepared perhydro-4,7-methanoisoindole derivatives for an anticipated analgesic activity.

We thank the *Serveis Científico-Tècnics* of the University of Barcelona and particularly Dr. *M. Feliz* and Dr. *A. Linares* for recording the NMR spectra, Ms. *P. Domenech* from the *Centro de Investigación y Desarrollo* (Barcelona, Spain) for carrying out the elemental analyses.

Experimental

Melting points: open capillary tubes, Gallenkamp model MFB 595010M. – IR: FT-IR Perkin Elmer, model 1600. – NMR: Varian Gemini 200 and Varian VXR 500. ^1H- and ^{13}C-NMR signals have been assigned on the basis of $^1H/^1H$ and $^1H/^{13}C$ COSY experiments. – Thin-layer chromatography: silica gel 60 F254 (Alugran R sil G/UV254). – Column chromatography: silica gel 60 (Merck, 230–440 mesh). – Ozonizations: ozon/oxygen stream generated with a Fischer OZON 500 apparatus. – Microanalyses: Microanalysis Service of the Centro de Investigación y Desarrollo, C.I.D., Barcelona, Spain. – Spectral and analytical data are collected in Tables: ^1H-NMR, Tab. 1–3; ^{13}C-NMR, Tab. 4, 5; elemental analysis (Tab. 6); yields, melting points, boiling points, and IR (Tab. 7).

(3aR,4R,7S,7aS)-Hexahydro-8-isopropylidene-4,7-methano-1H-isoindole-1,3(2H)-dione (**2a**): A suspension of anhydride **1** (6.69 g, 32.6 mmol) in conc. ammonia (100 ml) was heated under reflux for 3 h. During this period, portions of conc. ammonia (4 × 30 ml)

Table 1. ^{1}H-NMR chemical shifts (δ values) of the C_s-symmetric perhydro-4,7-methanoisoindole derivatives and reference compounds **1** and **9**[a,b,c]

	1-H				5-H			R[(N-(C-α)-(C-β)-(Ph)] and C-8-Ph or C-8-NH-(C-α')-Ph						
Comp.	endo	exo	3a-H	4-H	endo	exo	8-H	α-H	β-H	ar-H	$C(CH_3)_2$	OCH_3	N-H	O-H
1			2.97	3.20	1.40--1.80						1.66			
2a			2.69	3.06	1.20--1.80						1.60		8.70	
2b			2.67	3.08	1.45	1.70		2.87			1.58			
2c			2.67	3.01	1.40	1.65		4.54		7.20-7.40	1.25			
2d[d]			2.67	3.09	1.46	1.72		3.60	2.06	7.20-7.32	1.58			
3a[e]			2.58	2.03	1.14	1.79							10.60[f]	5.96/6.01
3b[e]			2.66	2.05	1.20	1.81		2.68						5.93/5.98
3c[e]			2.75	2.09	1.21	1.82		4.41		7.22-7.26				6.00/6.02
4a			3.00	2.41	1.70	2.02							8.65	
4b			2.98	2.40	1.73	2.06		2.93						
4c			2.92	2.37	1.67	2.00		4.55		7.22-7.26				
4d[d]			2.93	2.41	1.72	2.06		3.67	2.77	7.15-7.30				
5a.HCl[e]	3.65	2.35	2.60	1.99	1.60--1.85								9.70	
6a	2.85	2.10	1.85	2.25	1.10	1.35					1.49		2.30	
6a.HCl[e]	3.40	2.20	2.20	2.54	1.25	1.50					1.66		9.10/9.20	
6b[d]	3.05	1.45	2.19	2.38	1.23	1.55		2.22			1.65			
9			3.37*	3.19*	1.40--1.80						1.68			
10			3.11	3.11	1.30	1.60		2.98			1.68			
11[e]			3.17	2.00	0.90	1.70		2.80						6.12/6.16
12			3.33	2.53	1.45	1.85		3.08						
13a/14a			2.67*	2.46	1.25	1.90						3.10#	5.60	5.60[g]
			2.69*									3.23#		
13b/14b			2.60*	2.37#	1.23	1.90		2.77				2.99+		4.20
			2.63*	2.47#				2.80				3.18+		
15a			2.77	2.64	1.30	1.80	4.05	2.84						2.98[g]
15b[d]			2.73	2.59	1.24	1.67	3.95	4.50		7.15-7.35				1.62[g]
15c			2.76	2.67	1.30	1.75	4.06	2.82	3.62	7.10-7.40				1.75[g]
16a	2.80	2.99[h]	2.20	1.86	1.10	1.60	3.69						---	---
16b	2.25	2.90[h]	2.25	1.85	1.00	1.55	3.69	2.32						8.90[g]
16c	2.25	2.92[i]	2.25	1.86	1.05	1.60	3.70[j]	3.63		7.20-7.40				8.80[j]
16d[d]	2.22	3.05[h]	2.28	1.88	1.05	1.57	3.68[k]	2.71*	2.81*	7.16-7.31				8.52[k]
17a[e]			2.97	2.68	1.45	1.85		2.68						7.29
17b[e]			3.03	2.74	1.50	1.85		4.42		7.25-7.27				7.28
18	2.30	3.10[l]	2.50	2.30	1.00	1.40		2.30		7.20-7.50				10.10[g]
19a			2.72	2.58	1.30	1.80	3.24	2.84					1.17[f]	
19b			2.68	2.52	1.25	1.70	3.16[m]	4.50		7.10-7.40			1.10	
19b.HCl[n]			3.01	2.77	1.25	1.65	3.14	4.53		7.10 7.30			4.85	
19c			2.66	2.57	1.30	1.70	3.21	3.60	2.85	7.10-7.40			1.30	
21			2.77	2.96	1.40	1.90	3.28	3.60	2.70	7.00-7.30			3.48	
										6.54-7.30				
22			2.88	3.08	1.30	1.60		2.82		7.20-7.50				2.32
23a			2.70	2.70	1.30	1.70	2.91	2.70					1.15	
								3.52		7.10-7.40				
23b			2.69	2.69	1.25	1.70	2.83	4.41		7.20-7.40			1.10	
								3.27[o]		7.00-7.40				
23c			2.62	2.69	1.30	1.70	2.80	3.50	2.80	7.00-7.40			1.20	
								3.50		7.00-7.40				
24[d]	2.29	2.87[p]	2.22	2.02	1.03	1.53	2.68	3.76*		6.94-7.38			5.30	
								3.47*		6.94-7.38				
25	2.20	2.95	2.20	2.00	1.05	1.55	3.34	2.50--2.85		6.90-7.30			---	
										6.40-7.30				

[a] If not stated otherwise these spectra were recorded at 200 MHz in $CDCl_3$. – [b] Concerning equivalent hydrogen atoms, only those with the lower number are indicated. Signals originating from a compound or from mixtures of **13a/14a** and **13b/14b** marked with *, #, or + can be interchanged. – [c] If not indicated otherwise, the signals of 1-H, 4-H, and 5-H are multiplets, while those of 3a-H and 8-H are singlets, the other signals show the expected multiplicity, i.e. multiplets for α-H and β-H in 2-phenylethyl derivatives and for ar-H, singlets for α-H in methyl and benzyl derivatives, isopropylidene methyls and OH, and broad singlets for NH protons. – [d] This spectrum was recorded at 500 MHz. – [e] This spectrum was taken in [D_6]DMSO. – [f] Singlet. – [g] Broad singlet. – [h] Doublet, J = 10.0 Hz. – [i] Doublet, J=9.4 Hz. – [j] Doublet, J=6.0 Hz. – [k] Doublet, J=7.0 Hz. – [l] Doublet, J = 10.2 Hz. – [m] Triplet, J=3.5 Hz. – [n] This spectrum was taken in D_2O. – [o] Doublet, J=4.4 Hz. – [p] Doublet, J=10.5 Hz.

were added every 20 min from the beginning. The solution was cooled and acidified with conc. HCl, whereby a white crystalline solid precipitated which was filtered, washed with water (20 ml), and dried in vacuo to give pure **2a** (3.48 g). The acidic filtrates were extracted with CH_2Cl_2 (3 × 25 ml), the combined extracts were dried with Na_2SO_4 and concentrated in vacuo to give more **2a** (3.13 g, total yield 6.61 g).

(3aR,4R,7S,7aS)-Hexahydro-8-isopropylidene-2-methyl-4,7-methano-1H-isoindole-1,3(2H)-dione (**2b**): A suspension of anhy-

Table 2. ^{1}H-NMR chemical shifts (δ values) of the non-symmetric perhydro-4,7-methanoisoindole derivatives and related compounds *rac*-**27**, *rac*-**28** and *rac*-**30**[a,b,c]

	1-H		3-H		5-H and 6-H							R[(N-(C-α)-(C-β)-(Ph)] and C-1(3)-Ph C-8-Ph or C-8-N-(C-α')-Ph			
Comp.	**endo**	**exo**	**endo**	**exo**	**3a-H**	**4-H**	**endo**	**exo**	**7-H**	**7a-H**	**8-H**	**α-H**	**β-H**	**ar-H**	**C(CH3)2**
5b[d]	3.62	3.33	3.61	3.17	2.54	1.79	1.50–1.54	1.82–1.88	1.79	2.44			1.92		1.46
6c	3.55	2.73	3.45	2.73	2.10	2.28	1.00–1.20	1.30–1.40	2.28	2.05			1.77		1.46
6d	3.71	2.94	3.71	2.86	2.26	2.48*	1.25–1.35	1.50–1.60	2.51*	2.26		8.03			1.67
rac-7a[e]			3.47	2.78	2.40	2.53	1.20–1.45	1.45–1.84	2.95	2.40					1.67
rac-7b			3.48	2.76	2.39	2.53	1.20–1.50	1.50–1.80	2.96	2.46		2.75			1.68
rac-8			3.65	3.11	2.63	1.92	1.60–1.80	1.95–2.05	2.31	2.77		2.79			
rac-20a					2.81	3.29	1.50–1.80	1.80–2.20	2.71	2.88		2.68			
												4.34/4.50		7.10–7.40	
rac-20b					2.84*	3.23	1.60–1.80	1.90–2.10	2.78	2.88*		4.42/4.46		7.10–7.40	
												4.00/4.26		7.10–7.40	
rac-20c					2.80*	3.31	1.50–1.80	1.90–2.10	2.76	2.89*		3.51	2.62	7.00–7.40	
												4.39/4.46		7.00–7.40	
rac-26[f,g]					2.90	2.90	0.90–1.40		2.90	2.56		2.35		7.20–7.50	
														7.20–7.50	
rac-27			4.18		2.05	2.39	1.30–1.80		2.50	2.80	3.15	3.41/4.84		6.80–7.50	
												3.54/3.68		7.10–7.50	
rac-28	4.00		3.20	2.40	2.15	1.80	1.10–1.80		2.35	2.55	2.80	3.60*		7.10–7.50	
												3.70*		7.10–7.50	
rac-30[d]					2.48	2.72	1.35–1.66		2.66	2.92		2.50		7.10–7.25	
														7.10–7.25	

[a] If not stated otherwise these spectra were taken at 200 MHz in $CDCl_3$. – [b] IUPAC systematic numbering for each compound was used. In the case of the *N*-acyl derivatives **5b**, **6c**, and **6d**, in which the non-symmetric nature originates from the restricted rotation around the amide bond, the lower number was assigned to the carbon atom *syn* to the carbonyl oxygen atom. For the imines *rac*-**20a**, *rac*-**20b**, and *rac*-**20c**, the numbering gives the lower values to the bridgehead carbon atoms *syn* to the imine benzyl group. Signals originating from the same compound marked with * can be interchanged. – [c] For the observed coupling constants see Table 3. – [d] This spectrum was taken at 500 MHz. – [e] δ_{nH}=6.50 (s). – [f] This spectrum was recorded in [D_6]DMSO. – [g] δ_{OH} = 6.12 (s) and 6.85 (s).

Table 3. ^{1}H-NMR coupling constants (Hz) of the non-symmetric perhydro-4,7-methanoisoindole derivatives and related compounds *rac*-**27**, *rac*-**28**, and *rac*-**30**[a,b]

	1-H*endo*	1-H*exo*	3-H*endo*		3-H*exo*	3a-H	4-H	6-H*exo*	7-H	8-N-CH*R*	2-CH*R*
Comp.	**1-Hexo**	**7a-H**	**7a-H**	**3-Hexo**	**3a-H**	**3a-H**	**7a-H**	**5-Hexo**	**7-H**	**7a-H**	**8-N-CHs**	**2-CHs**
5b[c]	13.0	9.0	4.0	11.5	9.0	4.5	9.0	---	---			
6c	12.6	8.8	5.0	10.7	8.8	5.2	8.8	---	---			
6d	12.2	---	4.2	11.0	---	4.4	---	---	---			
rac-7a				9.5	---	---	9.5	---	2.4			
rac-7b				9.5	9.5	3.5	8.4	3.4	3.4			
rac-8				10.5	9.0	3.6	9.0	3.6	4.0			
rac-20a							7.9	3.5	3.6		13.5	
rac-20b							7.8	3.7	4.0		13.9	14.0
rac-20c							7.7	3.6	3.6		14.0	
rac-26[d]							9.6	---	---			
rac-27		4.0					5.0	---	---		13.5	15.0
rac-28		4.0		10.0	8.0	1.5					---	---
rac-30[c]							5.0	---	5.0	2.5		

[a] If not stated otherwise these spectra were taken at 200 MHz in $CDCl_3$. – [b] For the numbering of the different compounds see caption[b] of Table 2. – [c] This spectrum was taken at 500 MHz. – [d] This spectrum was recorded in [D_6]DMSO.

dride **1** (10.1 g, 49 mmol) in 40% aqueous methylamine (20 ml) was heated under reflux for 1.5 h. Then, more 40% aqueous methylamine (20 ml) was added, and heating was continued for further 1.5 h. The solution was cooled and acidified with conc. HCl; the white precipitate formed was filtered, washed with water (30 ml), and dried in vacuo to give pure **2b** (10.1 g). The acidic filtrates were extracted with CH_2Cl_2 (3 × 30 ml), the combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo to give more **2b** (0.53 g, total yield 10.63 g).

(3aR,4R,7S,7aS)-2-Benzylhexahydro-8-isopropylidene-4,7methano-1H-isoindole-1,3(2H)-dione (**2c**): A mixture of anhydride **1** (14.7 g, 71.3 mmol), benzylamine (15.6 ml, 143 mmol), and toluene (100 ml) was heated under reflux for 6 h. The solution was cooled

Table 4. ^{13}C-NMR chemical shifts (δ values) of the C_s-symmetric perhydro-4,7-methanoisoindole derivatives and reference compounds **1** and **9**[a,b]

						R[N-(C-α)-(C-β)-(Ph)] and C-8-Ph or C-8-NR-(C-α')-(Ph)									
Comp.	C-1	C-3a	C-4	C-5	C-8	C-α	C-β	C-*i*	C-*o*	C-*m*	C-*p*	C(CH$_3$)$_2$	C(CH$_3$)$_2$	CN	OCH$_3$
1	180.0	48.5	40.3	26.7	133.6							123.2	20.4		
2a	180.0	49.2	39.4	27.0	134.5							121.6	20.3		
2b	178.8	47.7	39.5	26.9	134.4	24.0						121.3	20.1		
2c	178.6	47.8	39.5	27.2	134.1	41.9		136.1	128.4*	129.1*	127.6	121.7	19.9		
2d	178.7	47.7	39.8	27.1	134.9	39.4	33.5	137.9	128.6*	128.8*	126.6	121.4	20.4		
3a[c]	181.8	49.1	45.6	26.5	105.2										
3b[c]	180.1	47.4	45.6	26.3	104.8	24.5									
3c[c]	179.9	47.6	45.7	26.5	105.0	41.7		137.1	128.1*	128.8*	127.6				
4a	176.8	45.4	41.5	22.0	210.2										
4b	177.0	44.5	41.3	22.5	210.7	25.3									
4c	177.4	43.7	41.7	21.5	212.2	41.7		136.1	127.7*	128.9*	127.9				
4d	176.2	43.8	41.5	22.0	210.2	40.0	33.4	137.6	128.6*	128.8*	126.8				
5a.HCl[c]	48.7	40.6*	39.7*	21.3	214.0										
6a	52.7	48.1	40.0	27.1	140.5							116.9	20.5		
6a.HCl[c]	49.2	44.8	39.1	26.7	138.1							120.5	21.0		
6b	61.1	47.0	39.1	27.1	140.2	41.5						117.8	20.7		
9	172.3	48.6	38.8	24.3	139.8							119.2	20.5		
10	178.5	47.4	38.0	23.8	141.0	24.1						117.4	20.3		
11[c]	179.2	46.9*	44.5*	23.0	108.3	24.3									
12	176.4	40.2*	40.5*	18.7	208.0	24.7									
13a/14a	181.3*	48.6#	43.3+	26.0	108.8										50.5∇
	182.0*	48.8#	43.6+		109.0										50.7∇
13b/14b	179.9*	47.1#	43.2+	26.0×	108.6	24.4∇									50.5‡
	180.2*	47.3#	43.4+	26.1×		24.6∇									50.9‡
15a	180.8	47.6	44.1	24.9	78.7	24.7									
15b	180.1	47.6	44.1	25.0	78.8	42.2		135.8	128.4*	129.0*	127.6				
15c	180.3	47.5	44.2	24.9	78.9	39.8	32.4	138.4	128.5*	128.8*	126.5				
16a	50.5	46.1*	45.9*	26.0	78.7										
16b	60.3	47.0	45.4	25.8	78.8	39.9									
16c	58.2	46.4	45.6	26.0	79.1	58.9		137.6	128.5	128.5	127.3				
16d	58.7	46.4	45.8	26.0	79.2	56.2	34.8	139.7	128.5	128.5	126.2				
17a[c]	179.0	46.9	48.0	24.9	77.8	24.7								120.0	
17b[c]	178.7	47.0	48.0	25.0	77.9	41.9		136.6	128.3*	128.7*	127.7			120.0	
18	59.8	48.3	46.9	27.0	86.0	39.4		144.9	126.9*	128.3*	126.5				
19a	180.6	47.7	44.6	27.0	59.8	25.1									
19b	180.2	47.6	44.4	26.8	59.7	42.3		135.8	128.2*	129.1*	127.4				
19b.HCl[d]	181.4	49.7	43.2	28.0	59.4	44.4		136.7	130.4*	131.2*	130.6				
19c	180.4	47.7	44.4	26.9	60.0	40.1	32.2	138.9	128.6*	128.9*	126.4				
21	178.9	48.0	43.3	26.5	63.1	39.9	33.2	138.1	128.4*	129.0*	126.4				
								147.0	114.2	128.7*	119.2				
22	180.6	48.5	45.7	25.7	87.4	24.7		140.3	126.8*	128.9*	128.3				
23a	179.9	47.8	42.4	26.6	66.1	24.8									
						52.7		139.2	128.1*	128.3*	126.9				
23b	179.5	47.8	42.2	26.5	65.1	42.1		136.2*	128.2#	129.1#	127.0+				
						51.7		139.7*	128.2#	128.4#	127.5+				
23c	179.8	47.7	42.2	26.6	65.5	39.7	32.7	138.7*	128.3#	128.8#	126.4+				
						52.3		139.5*	128.4#	128.8#	127.1+				
24	58.6	47.5	42.7	28.1	68.1	60.3		138.6	128.2*	128.6*	126.6#				
						53.7		141.2	128.2*	128.8*	126.8#				
25	58.8	47.4	43.3	28.0	61.5	57.8	35.6	140.1	128.5*	129.0*	126.2				
								149.7	113.3	128.5*	116.2				

[a] If not stated otherwise these spectra were taken at 50.3 MHz in $CDCl_3$. – [b] For equivalent carbon atoms, only those with the lower number are indicated. Signals originating from the same compound or from mixtures of **13a/14a** and **13b/14b** marked with *, #, +, ×, ∇, or ∓ can be interchanged. – [c] This spectrum was taken in [D_6]DMSO. – [d] This spectrum was recorded in D_2O.

and extracted with aqueous 2 N HCl (2 × 100 ml) and water (100 ml). The organic phase was dried with Na_2SO_4 and concentrated in vacuo to give pure **2c** (19.5 g).

(3aR,4R,7S,7aS)-Hexahydro-8-isopropylidene-2-(2-phenylethyl)-4,7-methano-1H-isoindole-1,3(2H)-dione (**2d**): From anhydride **1** (38.4 g, 186 mmol) and (2-phenylethyl)amine (35 ml, 274 mmol) imide **2d** (57.2 g) was obtained according to the procedure described for **2c**.

(3aR,4R,7S,7aS)-Hexahydro-8,8-dihydroxy-4,7-methano-1H-isoindole-1,3(2H)-dione (**3a**): Through a solution of imide **2a** (2.0 g, 9.7 mmol) in ethyl acetate (150 ml) cooled to −78°C an oxygen/ozone stream was bubbled until the solution became blue. The mixture was allowed to warm slowly to room temp., then 5% Pd on charcoal (100 mg) was added, and the mixture was hydrogenated at atmospheric pressure until no more hydrogen absorption took place. The precipitate formed and the catalyst were separated from the solution by filtration through Celite, and the solid material was continuously extracted in a Soxhlet for 24 h with ethyl acetate. The filtrate combined with the organic extracts were concentrated to 20 ml and cooled to 0°C. The precipitate was collected by filtration and dried in vacuo to give pure hydrate **3a** (1.8 g).

Table 5. ^{13}C-NMR chemical shifts (δ values) of the non-symmetric perhydro-4,7-methanoisoindole derivatives and related compounds *rac*-**27**, *rac*-**28**, and *rac*-**30**[a,b]

										R [N-C-α-(C-β)-(Ph)] and C-1(3)-Ph C-8-Ph or C-8-N-(C-a')-Ph							
Comp.	C-1	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	C-8	C-α(C-α')	C-β	C-*i*	C-*o*	C-*m*	C-*p*	C(CH$_3$)$_2$	C(CH)$_3$
5b	49.4	51.6	42.7*	43.6#	21.7+	22.0+	43.8#	40.8*	214.6	169.0	22.1						
6c	49.9	52.2	46.1*	40.8	26.6	26.6	40.8	44.6*	138.0	168.0	21.9					118.5	20.4
6d	47.0	51.0	45.1#	40.5*	26.8	26.8	40.7*	44.8#	138.2	159.7						118.8	20.6
rac-7a	179.7	46.9	39.2	42.4	26.7*	27.6*	40.6	49.4	137.3							119.3	20.5
																	20.9
rac-7b	176.0	54.3	37.1	42.1	26.5*	27.2*	39.3	50.1	137.1	28.7						118.9	20.2
																	20.7
rac-8	172.9	53.1	32.9	43.8	21.4*	21.3*	40.8	45.4	213.4	28.6							
rac-20a	176.9*	177.2*	45.5#	34.8	24.4+	24.7+	43.1	46.0#	174.1	24.4							
										58.7		138.9	127.7	128.5	126.9		
rac-20b	176.8*	177.0*	45.3#	34.6	24.1+	24.4+	42.8	45.6#	174.4	41.9		135.4	127.8X	128.4X	127.6X		
										57.8		139.0	128.1X	128.6X	126.8X		
rac-20c	176.9*	177.2*	45.3#	34.7	24.4	24.4	43.0	45.8#	174.5	39.6	33.1	137.7+	128.5X	128.7X	126.6		
										58.6		139.0+	127.8X	128.5X	127.0		
rac-26[c]	176.2	92.1	55.0	43.1	25.8*	25.6*	45.0	50.6	86.1	24.7		141.7#	127.7+	128.7+	125.6+		
												145.8#	127.8+	128.8+	125.6+		
rac-27	79.7	178.0	45.2	42.4	28.7	19.9	41.7	50.5	71.9	44.4		137.0*	128.0#	128.5#	127.2+		
										58.1		139.3*	128.3#	129.5#	127.4+		
rac-28	87.2	57.1*	49.7	41.0	28.2	21.4	39.9	52.4	68.9	55.7*		140.0#	128.0+	128.3+	126.5X		
										59.7		141.0#	128.3+	128.5+	126.6X		
rac-30	100.9	179.5	47.2	45.5	28.0	19.0	44.7	57.2	95.7	27.0		136.2*	128.4#	128.7#	126.6#		
												137.3*	128.5#	128.7#	127.7#		

[a] If not stated otherwise these spectra were taken at 50.3 MHz in $CDCl_3$. – [b] For the numbering of the different compounds see caption[b] of Table 2. Signals stemming from a compound marked with *, #, +, or × can be interchanged. – [c] This spectrum was taken in [D_6]DMSO.

(3aR,4R,7S,7aS)-Hexahydro-8,8-dihydroxy-2-methyl-4,7-methano-1H-isoindole-1,3(2H)-dione (**3b**)

a) *By Ozonization of* **2b**: After ozonization of imide **2b** (1.79 g, 8.2 mmol) and hydrogenation of the ozonide as described for **2a**, the resulting mixture was filtered, the filtrate was concentrated in vacuo, and the residue was crystallized from ethyl acetate to give 1.70 g of pure **3b** in two crops.

b) *By Methylation of* **3a**: A mixture of hydrate **3a** (0.88 g, 4.5 mmol) and anhydrous K_2CO_3 (3.1 g, 22.3 mmol) in anhydrous acetonitrile (30 ml) was heated at 80°C under argon for 10 min. Dimethyl sulfate (0.64 ml, 6.7 mmol) was added, and the reaction mixture was maintained at 80°C for 2 d. The mixture was filtered, and the solid residue was washed several times with ethyl acetate. The filtrate combined with the washings was concentrated in vacuo, and the solid residue was crystallized from ether to give pure **3b** (0.42 g in three crops).

(3aR,4R,7S,7aS)-2-Benzylhexahydro-8,8-dihydroxy-4,7-methano-1H-isoindole-1,3(2H)-dione (**3c**): From **3a** (1.90 g, 9.64 mmol) and benzyl chloride (1.8 ml, 14.5 mmol) hydrate **3c** (1.41 g in two crops) was obtained in a similar procedure as described for **3b** and purified by crystallization from ether without heating.

(3aR,4R,7S,7aS)-Hexahydro-4,7-methano-1H-isoindole-1,3,8(2H)-trione (**4a**): A mixture of hydrate **3a** (197 mg, 1.0 mmol) and P_2O_5 (100 mg, 0.7 mmol) in $CHCl_3$ (10 ml) was heated under reflux for 1 h. Additional amounts of P_2O_5 (4 × 100 mg) were added every 10 min from the beginning. The resultant suspension was filtered, and the residue was washed with anhydrous $CHCl_3$ (3 × 2 ml). The filtrate combined with the washings was concentrated in vacuo (0.5 Torr) to give **4a** (174 mg) as an oil contaminated with and easily hydrating back to **3a**.

(3aR,4R,7S,7aS)-Hexahydro-2-methyl-4,7-methano-1H-isoindole-1,3,8(2H)-trione (**4b**): As described for **4a** trione **4b** (190 mg) was obtained from **3b** (210 mg, 1.0 mmol) as an oil that easily underwent hydration back to **3b**.

(3aR,4R,7S,7aS)-2-Benzylhexahydro-4,7-methano-1H-isoindole-1,3,8(2H)-trione (**4c**)

a) *By Ozonization of* **2c** *Followed by Dehydration:* After ozonization of imide **2c** (7.38 g, 25.0 mmol) and hydrogenation of the ozonide as described for **2a**, a solution of a mixture of ketone **4c** and hydrate **3c** in the ratio 2:1 (^{1}H and ^{13}C NMR) resulted. This solution was concentrated to a final volume of 125 ml, decolorized with charcoal, and further concentrated in vacuo. The solution of the residue (6.60 g) in chloroform (50 ml) was treated with P_2O_5 (5.0 g, 35 mmol) at room temp. for 2 h. After workup as described for **4a**, pure **4c** (5.96 g) was obtained.

b) *By Benzylation of* **3a**: From hydrate **3a** (0.53 g, 2.7 mmol) and benzyl chloride (0.5 ml, 4.1 mmol) hydrate **3c** was prepared and converted into **4c** by crystallization from an ether solution that had been heated at reflux (0.53 g in three crops).

c) *By Dehydration of* **3c**: From **3c** (220 mg, 0.7 mmol) **4c** (190 mg) was obtained as described for **4a**.

(3aR,4R,7S,7aS)-Hexahydro-2-(2-phenylethyl)-4,7-methano-1H-isoindole-1,3,8(2H)-trione (**4d**) was prepared as described for **4c** (procedure a) from imide **2d** (18.9 g, 61.3 mmol). The crude product was sublimed to give ketone **4d** (15.5 g).

(3aR,4R,7S,7aS)-Octahydro-8-isopropylidene-4,7-methano-1H-isoindole Hydrochloride (**6a** · HCl): To a cold (ice bath) and stirred suspension of $LiAlH_4$ (15.1 g, 398 mmol) in anhydrous THF (200 ml) a solution of imide **2a** (13.5 g, 65.8 mmol) in the same solvent (50 ml) was added dropwise under argon. Stirring was continued at room temp. for 48 h. After cooling aqueous 10 N NaOH was carefully added to destroy excess $LiAlH_4$. The organic phase was decanted, and the residue was extracted with ether (3 × 50 ml). The combined organic phases were dried with Na_2SO_4 and concentrated in vacuo. The ether (50 ml) solution of the residue was treated with excess 2 N HCl in ether until no more precipitation was observed. The solid was collected by filtration and crystallized from ethanol/ether to give **6a** · HCl containing 2/3 H_2O (12.6 g).

Table 6. Molecular formula, molecular mass, and elemental analysis of the perhydro-4,7-methanoisoindole derivatives and related compounds

Comp.	Molecular formula	Molecular mass	Elemental analysis[a]	C	H	N
2a	$C_{12}H_{15}NO_2$	205.3	Calc.	70.22	7.37	6.82
			Found	70.29	7.40	6.80
2b	$C_{13}H_{17}NO_2$	219.3	Calc.	71.21	7.81	6.39
			Found	71.25	7.86	6.30
2c	$C_{19}H_{21}NO_2$	295.4	Calc.	77.26	7.17	4.74
			Found	77.26	7.19	4.73
2d	$C_{20}H_{23}NO_2$	309.4	Calc.	77.64	7.49	4.53
			Found	77.68	7.50	4.60
3a	$C_9H_{11}NO_4$	197.2	Calc.	54.82	5.62	7.10
			Found	54.80	5.66	6.99
3b	$C_{10}H_{13}NO_4$	211.2	Calc.	56.87	6.20	6.63
			Found	56.66	6.23	6.52
3c	$C_{16}H_{17}NO_4$	287.3	Calc.	66.89	5.96	4.88
			Found	66.88	5.99	4.77
4c	$C_{16}H_{15}NO_3$	269.3	Calc.	71.36	5.61	5.20
			Found	71.17	5.64	5.11
4d	$C_{17}H_{17}NO_3$	283.3	Calc.	72.07	6.05	4.94
			Found	72.22	6.08	4.92
5b	$C_{11}H_{15}NO_2$	193.2	Calc.	68.37	7.82	7.25
			Found	68.34	7.85	7.24
6a.HCl	$C_{12}H_{20}ClN$ $2/3H_2O$	225.8	Calc.	63.85	9.53	6.20
			Found	63.91	9.45	6.08
6b	$C_{13}H_{21}N$	191.3	Calc.	81.61	11.06	7.32
			Found	81.69	11.08	7.30
6c	$C_{14}H_{21}NO$	219.3	Calc.	76.67	9.65	6.39
			Found	76.69	9.74	6.35
6d	$C_{13}H_{19}NO$	205.3	Calc.	76.06	9.33	6.82
			Found	76.00	9.36	6.61
rac-7a	$C_{12}H_{17}NO$	191.3	Calc.	75.35	8.96	7.32
			Found	75.33	8.91	7.27
rac-7b	$C_{13}H_{19}NO$	205.3	Calc.	76.06	9.33	6.82
			Found	76.12	9.52	6.70
10	$C_{13}H_{17}NO_2$	219.3	Calc.	71.21	7.81	6.39
			Found	71.20	8.04	6.28
11	$C_{10}H_{13}NO_4$ $1/4H_2O$	215.7	Calc.	55.68	6.31	6.49
			Found	55.89	6.23	6.45
15a	$C_{10}H_{13}NO_3$	195.2	Calc.	61.53	6.71	7.18
			Found	61.70	6.76	7.16
15b	$C_{16}H_{17}NO_3$	271.3	Calc.	70.83	6.32	5.16
			Found	70.71	6.38	5.21
15c	$C_{17}H_{19}NO_3$	285.3	Calc.	71.56	6.71	4.91
			Found	71.66	6.81	4.90
16d	$C_{17}H_{23}NO$	257.4	Calc.	79.33	9.01	5.44
			Found	79.23	9.06	5.40
17a	$C_{11}H_{12}N_2O_3$	220.2	Calc.	59.99	5.49	12.72
			Found	59.95	5.44	12.70
17b	$C_{17}H_{16}N_2O_3$	296.3	Calc.	68.91	5.44	9.45
			Found	69.04	5.39	9.40
18	$C_{16}H_{21}NO$	243.3	Calc.	78.97	8.70	5.76
			Found	78.94	8.73	5.59
19a	$C_{10}H_{14}N_2O_2$	194.2	Calc.	61.84	7.27	14.22
			Found	61.69	7.22	14.40
19b.HCl	$C_{16}H_{19}ClN_2O_2$ $2/3H_2O$	318.8	Calc.	60.28	6.43	8.79
			Found	60.30	6.06	8.76
19c	$C_{17}H_{20}N_2O_2$	284.4	Calc.	71.81	7.09	9.85
			Found	71.86	7.09	9.73
rac-20c	$C_{24}H_{24}N_2O_2$	372.5	Calc.	77.39	6.50	7.52
			Found	76.99	6.54	7.36
21	$C_{23}H_{24}N_2O_2$	360.5	Calc.	76.64	6.71	7.77
			Found	76.62	6.76	7.77
22	$C_{16}H_{17}NO_3$	271.3	Calc.	70.83	6.32	5.16
			Found	70.90	6.40	5.30
23a	$C_{17}H_{20}N_2O_2$	284.4	Calc.	71.81	7.09	9.85
			Found	72.02	7.05	9.86
23b	$C_{23}H_{24}N_2O_2$	360.5	Calc.	76.64	6.71	7.77
			Found	76.64	6.75	7.72
23c	$C_{24}H_{26}N_2O_2$	374.5	Calc.	76.96	7.00	7.48
			Found	76.89	7.04	7.48
24.2HCl	$C_{23}H_{30}Cl_2N_2$ $3/4H_2O$	418.9	Calc.	65.94	7.58	6.69
			Found	65.98	7.76	6.67
25	$C_{23}H_{28}N_2$	332.5	Calc.	83.09	8.49	8.43
			Found	83.40	8.21	8.33
rac-26	$C_{22}H_{23}NO_3$	349.4	Calc.	75.62	6.63	4.01
			Found	75.29	6.68	4.01
rac-27	$C_{23}H_{24}N_2O$	344.5	Calc.	80.20	7.02	8.13
			Found	80.09	7.17	8.05
rac-30	$C_{22}H_{21}NO_2$	331.4	Calc.	79.73	6.39	4.23
			Found	79.69	6.36	4.19

[a] For **6a** · HCl: calcd. Cl 15.70; found Cl 15.87. For **19b** · HCl: calcd. Cl 11.12; found Cl 11.36. For **24** · 2 HCl: Cl not determined.

(3aR,4R,7S,7aS)-Octahydro-8-isopropylidene-2-methyl-4,7-methano-1H-isoindole (**6b**) was prepared from **2b** (16.5 g, 75.2 mmol) as described for **6a** without workup with HCl. Sublimation afforded pure **6b** (11.7 g).

(3aR,4R,7S,7aS)-2-Acetyloctahydro-8-isopropylidene-4,7-methano-1H-isoindole (**6c**): To a stirred solution of amine **6a**, prepared by reaction of **6a** · HCl · 2/3 H_2O (0.56 g, 2.5 mmol) with K_2CO_3 (1.0 g, 7.2 mmol) in chloroform (10 ml), a solution of acetyl chloride (2 ml, 28 mmol) in chloroform (10 ml) was added dropwise, and stirring was continued at room temp. for 5 h. After filtration, the solution was washed with 2 N HCl (3 × 20 ml) dried with Na_2SO_4 and concentrated in vacuo. Sublimation of the residue gave pure **6c** (420 mg).

(3aR,4R,7S,7aS)-2-Formyloctahydro-8-isopropylidene-4,7-methano-1H-isoindole (**6d**): A solution of amine **6a** (1.02 g, 5.7 mmol), formamide (17.5 ml), and formic acid (8.7 ml) was heated under reflux for 1 h. Water (50 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 × 30 ml). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. The residue was crystallized from hexane to give pure **6d** (747 mg).

(3aR,4R,7S,7aS)-Octahydro-4,7-methano-1H-isoindol-8-one Hydrochloride (**5a** · HCl) was prepared according to the procedure for **3a**, except for the use of methanol instead of ethyl acetate as solvent. Thus, from **6a** · HCl · 2/3 H_2O (0.68 g, 3.0 mmol) a solid product was obtained. Purification by heating in acetone (15 ml) at reflux, in which it is not soluble, gave essentially pure **5a** · HCl (260 mg).

(3aR,4R,7S,7aS)-2-Acetyloctahydro-4,7-methano-1H-isoindol-8-one (**5b**): Crude **5a** · HCl, obtained from **6a** · HCl · 2/3 H_2O (1.00 g, 4.43 mmol), was treated with K_2CO_3 (2.0 g, 14.4 mmol) and acetyl chloride (1.0 ml, 28 mmol) in chloroform (10 ml) at room temp. for 5 h. After separation from insoluble material by filtration, the solution was washed with aqueous 1.5 N HCl (3 × 30 ml), dried with Na_2SO_4, and concentrated in vacuo to give **5b** (290 mg) as a white solid after sublimation.

(3aRS,4RS,7SR,7aSR)-Octahydro-8-isopropylidene-4,7-methano-1H-isoindol-1-one (*rac*-**7a**): To a solution of amine **6a** (1.04 g, 5.8 mmol) in anhydrous CH_2Cl_2 (30 ml) dry benzyltriethylammonium permanganate (3.00 g, 9.6 mmol) was added. The mixture was stirred at room temp. for 48 h and, thereafter, treated with a 10% aqueous solution of sodium disulfite until excess permanganate had been reduced. The organic phase was separated, and the aqueous one was extracted with CH_2Cl_2 (3 × 30 ml). The combined organic phases were washed with aqueous 2 N HCl (3 × 20 ml), dried with Na_2SO_4, and concentrated in vacuo. The residue was sublimed to give *rac*-**7a** (141 mg) as a white solid.

(3aRS,4RS,7SR,7aSR)-Octahydro-8-isopropylidene-2-methyl-4,7-methano-1H-isoindol-1-one (*rac*-**7b**) was prepared according to the procedure for *rac*-**7a** from amine **6b** (2.21 g, 11.5 mmol) and benzyltriethylammonium permanganate (5.35 g, 17.2 mmol). The product consisted of *rac*-**7b** and **6d** (relative areas by GLC *rac*-**7b**:**6d** = 95:5) and was heated at reflux in methanol/water (1:1, 40 ml) and 40% aqueous KOH (5 ml) for 20 min. The organic solvent was evaporated in vacuo. The remaining aqueous mixture was acidified with 2 N HCl and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo to give pure *rac*-**7b** as a white solid (1.23 g).

(3aRS,4RS,7SR,7aSR)-Octahydro-2-methyl-4,7-methano-1H-isoindole-1,8-dione (*rac*-**8**) was prepared according to the procedure for **3b** by ozonization of *rac*-**7b** (720 mg, 3.5 mmol). *rac*-**8** (561 mg)

Table 7. Yields, melting points, boiling points, and IR data of the perhydro-4,7-methanoisoindole derivatives and related compounds

Comp.	Yield [%]	Mp [°C]	Bp[a] [°C]/[Torr]	IR [cm^{-1}] (KBr) OH and/or NH	C=O and C=N
2a	99	205–206[b]		3250	1771, 1708
2b	98	99–100	110/0.1		1766, 1690
2c	93	144–145[c]			1760, 1689
2d	99	155–156[d]			1760, 1690
3a	94	143–144[b]		3450, 3400, 3225	1775, 1700
3b	97[e] 49[f]	130–131[b]		3420	1762, 1686
3c	54[f]	126–127[g]		3350, 3200	1766, 1680
4a[h]	97			3395	1780, 1731
4b[h]	97				1786, 1707
4c[h]	89[e] 73[f] 90[i]	136–137[g]			1785, 1708
4d	90	156–159	180/0.15		1781, 1714
5b	34	132–133	100/0.5		1764, 1631
6a.HCl	85	128–129[j]		3600–2500	
6b	81	54–55	60/0.5		
6c	76	134–135	110/0.5		1637
6d	64	120–121	90/0.5		1654
rac-7a	12	196–197	115/3	3215, 3100	1682
rac-7b	52	84–85	80/0.5		1672
rac-8[h]	86	---	140/1.5		1766, 1678
10	95	141–142	110/0.1		1766, 1694
11	85	110–112[g]		3381	1758, 1694
12[h]	98	---			1775, 1699
13a/14a[h]				3400, 3300	1770, 1720
13b/14b[h]				3620, 3565	1765, 1695
15a	83[k] 88[l]	162–163[d]		3420	1762, 1686
15b	82[k] 77[l]	144–145[d]		3429	1782, 1683
15c	88[k] 92[l]	169–170[d]		3499	1773, 1678
16a	20[m]		100/0.3	3297, 3200–2500	
16b[h]	62[m]		100/2	3200–2600	
16c	55[m] 58[n]		100/0.6	3200–2600	
16d	51[m] 43[n]	74–75[o]	170/2	3200–2600	
17a[p]	74	230–231[d]		3338	1769, 1684
17b[p]	93	209–212[d]		3361	1773, 1682
18	66	115–116[c]		3250–2200	
19a	2[q] 95[s]	226–228[r]		3422, 3361, 3309	1754, 1679
19b.HCl	19[q] 73[s]	195–196[j]		3586, 3447, 3288 2788, 2600, 2537 2473	1774, 1694
19c	100[s]	218–220[d]		3367	1770, 1688
rac-20c	58	84–85[d]			1773, 1699
21	62	157–158[d]		3350	1764, 1687
22	53	198–199[d]		3356	1770, 1687
23a	63	92–93[d]		3436, 3312	1768, 1687
23b	40	99–100[d]		3295	1768, 1689
23c	45	113–114[d]		3328	1764, 1690
24.2HCl	69	110–130[t]		3600–2200	
25[h]	40	81–82[g]		3166	
rac-26	4	239–240[u]		3286	1673
rac-27	35	152–153[d]			1693
rac-30	100	209–210[v]			1711

[a] Or sublimation conditions in the case of solid compounds. – [b] Crystallized from ethyl acetate. – [c] Crystallized from hexane. – [d] Crystallized from ethyl acetate/hexane. – [e] By ozonization of the corresponding isopropylidene derivative. – [f] By alkylation of **6**. – [g] Crystallized from ether. – [h] IR, solution in $CHCl_3$. – [i] By dehydration of **3c**. – [j] Crystallized from ethanol/ether. – [k] By $NaBH_4$ reduction. – [l] By $Al(iPrO)_3$ reduction. – [m] By $LiAlH_4$ reduction of the corresponding hydrate or ketone. – [n] By $LiAlH_4$ reduction of the corresponding alcohol. – [o] The distilled oily product solidified on standing. – [p] CN st at 2236 cm^{-1}. – [q] By reductive amination of **4c**. – [r] Crystallized from ethanol/ethyl acetate. – [s] By hydrogenation of **23a**, **23b**, or **23c**. – [t] Crystallized from 2-propanol/ether. – [u] Crystallized from methanol. – [v] Crystallized from methanol/ether.

was obtained by distillation as an unstable oil that rapidly took a yellow color.

(3aR,4S,7R,7aS)-Hexahydro-8-isopropylidene-2-methyl-4,7-methano-1H-isoindole-1,3(2H)-dione (**10**)

a) *From Anhydride* **9**: From **9**[5] (7.8 g, 38 mmol) imide **10** (7.9 g) was obtained as described for **2b**.

b) *From a Mixture of Anhydrides* **1** *and* **9**: From a 3:2 mixture (relative area by GLC) of **1** and **9** (15.0 g, 72.7 mmol) a mixture of imides **2b** and **10** (13.4 g, 84% yield) was obtained as described for **2b**. Controlled sublimation at 90°C/0.2 Torr and then at 110°C/0.2 Torr gave a 3:7 mixture of **2b** and **10** (8.9 g, relative areas by GLC) and pure **10** (3.5 g, 55% yield from **9**).

(3aR,4S,7R,7aS)-Hexahydro-8,8-dihydroxy-2-methyl-4,7-methano-1H-isoindole-1,3(2H)-dione (**11**): According to the procedure for **3b** from **10** (7.88 g, 36 mmol) a white solid (7.20 g) as a mixture of **11** and **12** in the ratio of 2:1 was obtained. Crystallization from ether afforded pure **11** (6.42 g in three crops).

(3aR,4S,7R,7aS)-Hexahydro-2-methyl-4,7-methano-1H-isoindole-1,3,8(2H)-trione (**12**) was prepared according to the procedure for **4a** from **11** (190 mg, 0.9 mmol). Ketone **12** (170 mg) was obtained as an oil that was rapidly reverted to **11**.

(3aR,4R,7S,7aS,8r)- (**13a**) *and (3aR,4R,7S,7aS,8s)-Hexahydro-8-hydroxy-8-methoxy-4,7-methano-1H-isoindole-1,3(2H)-dione* (**14a**): Hydrate **3a** (140 mg, 0.7 mmol) was heated in methanol (40 ml) at reflux for 1 h. Evaporation of the solvent in vacuo gave an oily mixture of hemiacetals **13a** and **14a** (ratio close to 1:1) in quantitative yield. A similar mixture was obtained from **3a** by stirring in methanol at room temp. for 3 d or by silica gel column chromatography using methanol as eluent.

(3aR,4R,7S,7aS,8r)- (**13b**) *and (3aR,4R,7S,7aS,8s)-Hexahydro-8-hydroxy-8-methoxy-2-methyl-4,7-methano-1H-isoindole-1,3(2H)-dione* (**14b**): From hydrate **3b** (75 mg, 0.35 mmol) after heating in methanol (40 ml) at reflux for 1 h an oily mixture of **13b** and **14b** (ratio close to 1:1) was obtained quantitatively.

(3aR,4R,7S,7aS,8r)-Hexahydro-8-hydroxy-2-methyl-4,7-methano-1H-isoindole-1,3(2H)-dione (**15a**)

a) *By Reduction of Hydrate* **3b** *with* $NaBH_4$: A mixture of **3b** (300 mg, 1.42 mmol) and $NaBH_4$ (50 mg, 1.32 mmol) in methanol (25 ml) was heated under reflux for 2 d. Additional portions of $NaBH_4$ (5 × 50 mg) were added after 0.5, 1, 1.5, 2, and 24 h from the beginning. Water (30 ml) was added to destroy excess $NaBH_4$, the organic solvent was evaporated in vacuo, and the residue was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo to give alcohol **15a** (230 mg).

b) *By Reduction of* **3b** *with Aluminium Triisopropoxide:* A mixture of hydrate **3b** (1.06 g, 5.0 mmol) and $Al(iPrO)_3$ (3.13 g, 15 mmol) in 2-propanol (50 ml) was heated at reflux for 3 h under argon. The solvent was removed by distillation at atmospheric pressure and finally at 30 Torr. The residue was acidified with aqueous 3 N HCl (50 ml), and the mixture was extracted with CH_2Cl_2 (4 × 30 ml). The combined organic extracts were washed with aqueous 3 N HCl (50 ml) and brine (50 ml), dried with Na_2SO_4 and concentrated in vacuo to give pure (TLC) **15a** (0.93 g).

(3aR,4R,7S,7aS,8r)-2-Benzylhexahydro-8-hydroxy-4,7-methano-1H-isoindole-1,3(2H)-dione (**15b**) was prepared by reduction of ketone **4c** as described for **15a**.

a) *By Reduction with* $NaBH_4$: Ketone **4c** (240 mg, 0.89 mmol) and $NaBH_4$ (8 × 17 mg, 3.60 mmol, portions added at the beginning of the reaction and after 0.5, 1, 1.5, 24, 24.5, 25, and 26 h) gave **15b** (200 mg).

b) *By Reduction with Aluminium Triisopropoxide:* From **4c** (1.35 g, 5.0 mmol) and $Al(iPrO)_3$ (2.08 g, 10 mmol) alcohol **15b** (1.05 g) was obtained.

(3aR,4R,7S,7aS,8r)-Hexahydro-8-hydroxy-2-(2-phenylethyl)-4,7-methano-1H-isoindole-1,3(2H)-dione (**15c**) was prepared by reduction of ketone **4d** as described for **15a**.

a) *By Reduction with* $NaBH_4$: Ketone **4d** (1.21 g, 4.27 mmol) and $NaBH_4$ (0.15 g, 4.0 mmol, added at the beginning of the reaction plus 2 × 0.30 g added after 6 and 24 h) gave **15c** (1.13 g).

b) *By Reduction with Aluminium Triisopropoxide:* From **4d** (1.42 g, 5.0 mmol) and $Al(iPrO)_3$ (2.08 g, 10 mmol) **15c** (1.26 g) was obtained.

(3aR,4S,7R,7aS,8r)-Octahydro-8-hydroxy-4,7-methano-1H-isoindole (**16a**): To a cold (ice bath) suspension of $LiAlH_4$ (1.33 g, 35 mmol) in anhydrous THF (250 ml) solid hydrate **3a** (1.97 g, 10.0 mmol) was added slowly under argon. The mixture was stirred at 45–50°C for 3 d. Then, to the cold mixture water was carefully added to destroy excess $LiAlH_4$. After the extraction of the mixture with ether (5 × 30 ml) the combined organic phases were extracted with aqueous 2 N HCl (3 × 10 ml). The aqueous extracts were made alkaline with aqueous 10 N NaOH and extracted with ether (3 × 30 ml). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. From the residue amino alcohol **16a** (310 mg) was obtained by distillation as a colorless oil that rapidly became yellow with total decomposition within 24 h.

(3aR,4S,7R,7aS,8r)-Octahydro-8-hydroxy-2-methyl-4,7-methano-1H-isoindole (**16b**): According to the above procedure for **16a**, from hydrate **3b** (10.55 g, 50 mmol) and $LiAlH_4$ (5.70 g, 150 mmol) in anhydrous THF (200 ml) **16b** (5.19 g) was obtained after distillation as a colorless oil that rapidly became yellow.

(3aR,4S,7R,7aS,8r)-2-Benzyloctahydro-8-hydroxy-4,7-methano-1H-isoindole (**16c**)

a) *From Hydrate* **3c**: As described above for **16b**, from hydrate **3c** (6.00 g, 20.9 mmol) and $LiAlH_4$ (1.99 g, 52.3 mmol) **16c** (2.77 g) was obtained, after distillation, as a colorless oil that rapidly became yellow.

b) *From Alcohol* **15b**: A procedure similar to that used in the preparation of **16b** was followed. From **15b** (250 mg, 0.92 mmol) and $LiAlH_4$ (88 mg, 2.3 mmol) **16c** (130 mg) was obtained.

(3aR,4S,7R,7aS,8r)-Octahydro-8-hydroxy-2-(2-phenylethyl)-4,7-methano-1H-isoindole (**16d**)

a) *From Ketone* **4d**: A procedure similar to that used in the preparation of **16b** was followed. From **4d** (2.83 g, 10.0 mmol) and $LiAlH_4$ (0.95 g, 25.0 mmol) **16d** (1.31 g) was obtained, after distillation, as a colorless oil that solidified on standing.

b) *From Alcohol* **15c**: Under conditions as in a) from **15c** (460 mg, 1.6 mmol) and $LiAlH_4$ (153 mg, 4.0 mmol) **16d** (180 mg) was obtained.

(3aR,4R,7S,7aS,8r)-Octahydro-8-hydroxy-2-methyl-1,3-dioxo-4,7-methano-1H-isoindole-8-carbonitrile (**17a**): To a cooled (ice bath) solution of **3b** (1.05 g, 5.0 mmol) and sodium cyanide (2.45 g, 50 mmol) in water (40 ml) 40% H_2SO_4 (13 ml, 100 mmol) was added dropwise with stirring. The mixture was stirred for 3 h and extracted with ether (3 × 50 + 7 × 25 ml). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo to give slightly impure **17a** (0.80 g), that was purified by crystallization from a mixture of ethyl acetate and hexane.

(3aR,4R,7S,7aS,8r)-2-Benzyloctahydro-8-hydroxy-1,3-dioxo-4,7-methano-1H-isoindole-8-carbonitrile (**17b**): Solutions of **3c** (350 mg, 1.2 mmol) in acetonitrile (10 ml) and sodium cyanide (590 mg, 12 mmol) in water (10 ml) were mixed, cooled (ice bath), treated with stirring dropwise with 40% H_2SO_4 (3.2 ml, 24 mmol), and stirred for additional 3 h. The volatile compounds were evaporated in vacuo, the residue was diluted with water (30 ml), and the mixture was extracted with CH_2Cl_2 (5 × 20 ml). After evaporation of the combined extracts in vacuo the residue was purified by chromatography (silica gel, ethyl acetate) to give **17b** (330 mg).

(3aR,4R,7S,7aS,8r)-Hexahydro-8-hydroxy-2-methyl-8-phenyl-4,7-methano-1H-isoindole-1,3(2H)-dione (**22**), *(3RS,3aSR,4SR,7RS,7aRS,8RS)-Octahydro-3,8-dihydroxy-2-methyl-3,8-diphenyl-4,7-methano-1H-isoindol-1-one* (*rac*-**26**) *and (1RS,3aRS,4RS,7SR,7aSR,8RS)-Octahydro-2-methyl-1,8-diphenyl-1,4,7-(epoxymetheno)-3H-isoindol-3-one* (*rac*-**30**): A mixture of **3b** (10.55 g, 50 mmol) and P_2O_5 (14.2 g, 100 mmol) in anhydrous THF (70 ml) was heated at reflux for 3 h. The solution was decanted from the solid material under argon into a dry flask. The solid residue was washed with anhydrous THF (2 × 10 ml), and the washing liquids were combined with the above solution of ketone **4b**. A solution of phenylmagnesium bromide, prepared from bromobenzene (5.3 ml, 50 mmol) and magnesium (1.70 g, 70 mmol) in anhydrous THF (50 ml), was added dropwise with stirring to the solution of **4b** under argon. After stirring had been continued at 55°C overnight the cooled mixture was treated slowly with 10% aqueous ammonium chloride (100 ml), and the organic solvent was evaporated in vacuo. The remaining aqueous mixture was extracted with CH_2Cl_2 (150 + 100 + 3 × 50 ml). The combined organic extracts were washed with water (3 × 50 ml), dried with Na_2SO_4, and concentrated in vacuo. The residue was crystallized from ethyl acetate/hexane to give **22** (5.80 g, m.p. 194–195°C). After concentration of the mother liquor in vacuo the residue was treated with hot ethyl acetate (25 ml). Insoluble material was collected by filtration and recrystallized from ethyl acetate/hexane to give pure *rac*-**26** (0.66 g). The filtrate was concentrated in vacuo and the residue purified by chromatography (silica gel, ether) to give another crop of pure **22** (1.32 g, m.p. 198–199°C, total yield 7.12 g), after recrystallization from ethyl acetate/hexane. An attempt to crystallize *rac*-**26** from ethanol gave quantitatively *rac*-**30**.

(3aR,4S,7R,7aS,8r)-Octahydro-8-hydroxy-2-methyl-8-phenyl-4,7-methano-1H-isoindole (**18**): According to a procedure for the preparation of **16a**, from alcohol **22** (6.0 g, 21.1 mmol) and $LiAlH_4$ (2.1 g, 55 mmol) in anhydrous THF (150 ml) amino alcohol **18** (3.54 g) was obtained.

(3aRS,4RS,7SR,7aSR)-8-(Benzylimino)hexahydro-2-methyl-4,7-methano-1H-isoindole-1,3(2H)-dione (*rac*-**20a**) *and (3aR,4R,7S,7aS,8r)-8-(Benzylamino)hexahydro-2-methyl-4,7-methano-1H-isoindole-1,3(2H)-dione* (**23a**): A solution of hydrate **3b** (3.17 g, 15 mmol), benzylamine (1.8 ml, 16 mmol), and *p*-toluenesulfonic acid monohydrate (10 mg) in toluene (100 ml) was heated at reflux for 12 h in a Dean-Stark apparatus with azeotropic distillation of water. The cooled solution was dried with K_2CO_3 and concentrated in vacuo to give imine *rac*-**20a** (5.0 g) that was used without purification in the next step. Glacial acetic acid (4.5 ml, 78 mmol) was added dropwise under argon to a suspension of $NaBH_4$ (0.94 g, 24.7 mmol) in anhydrous 1,2-dichloroethane (100 ml), and the mixture was heated at reflux for 0.5 h. To the solution of $NaBH(OAc)_3$ thus formed a solution of crude *rac*-**20a** (4.88 g) in anhydrous 1,2-dichloroethane (20 ml) was added, and the mixture was stirred at room temp. for 3 h. The cooled mixture (ice bath) was treated with aqueous 2 N HCl (50 ml). When the gas evolution had ceased, the mixture was made alkaline with aqueous 2 N NaOH, the organic phase was separated, washed with 2 N NaOH (2 × 50 ml), dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography (silica gel, hexane/ethyl acetate) to give **23a** (2.60 g).

(3aRS,4RS,7SR,7aSR)-2-Benzyl-8-(benzylimino)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (*rac*-**20b**) *and (3aR,4R,7S,7aS,8r)-2-Benzyl-8-(benzylamino)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione* (**23b**) were prepared in a manner similar to that described above for *rac*-**20a** and **23a**. From ketone **4c** (5.75 g, 21.4 mmol) and benzylamine (2.45 ml, 22.4 mmol) crude imine *rac*-**20b** (7.69 g) was obtained as a yellow oil. Reduction of this imine (7.62 g) with $NaBH(OAc)_3$, prepared from $NaBH_4$ (1.34 g, 35.4 mmol) and glacial acetic acid (6.35 ml, 111 mmol) in anhydrous 1,2-dichloromethane (100 ml), gave pure **23b** (3.05 g) after chromatography and crystallization.

(3aRS,4RS,7SR,7aSR)-8-(Benzylimino)hexahydro-2-(2-phenylethyl)-4,7-methano-1H-isoindole-1,3(2H)-dione (*rac*-**20c**) *and (3aR,4R,7S,7aS,8r)-8-(Benzylamino)hexahydro-2-(2-phenylethyl)-4,7-methano-1H-isoindole-1,3(2H)-dione* (**23c**) were prepared as *rac*-**20b** and **23b**. From ketone **4d** (1.40 g, 4.95 mmol) and benzylamine (0.58 ml, 5.25 mmol) crude imine *rac*-**20c** (1.76 g) was obtained as a yellow oil that gave pure crystals of *rac*-**20c** (1.06 g) from ethyl acetate. Reduction of this imine (0.92 g, 2.47 mmol) with $NaBH(OAc)_3$ gave pure **23c** (0.42 g) after chromatography and crystallization. By the chromatography 140 mg of the starting ketone **4d** were recovered.

(3aR,4R,7S,7aS,8r)-8-Aminohexahydro-2-methyl-4,7-methano-1H-isoindole-1,3(2H)-dione **19a**)

a) *By Hydrogenolysis of* **23a**: A solution of **23a** (950 mg, 3.45 mmol) in methanol (30 ml) was hydrogenated at room temp. and atmospheric pressure by using $Pd(OH)_2$ on charcoal as catalyst (Pearlman's catalyst, 90 mg). After hydrogen consumption had ceased, the mixture was filtered and the filtrate concentrated in vacuo to give pure **19a** (0.55 g).

b) *By Reductive Amination of* **3b**: To a mixture of 4-Å molecular sieves (5.0 g), hydrate **3b** (0.84 g, 5.0 mmol), and ammonium acetate (3.85 g, 50 mmol) in anhydrous methanol (15 ml) a solution of 85% $NaBH_3CN$ (0.26 g, 3.5 mmol) in anhydrous methanol (5 ml) and sodium methoxide (0.54 g, 10 mmol) were added. The mixture was stirred at room temp. under argon for 5 d, filtered thereafter, and concentrated in vacuo. Having been made alkaline with aqueous 2 N NaOH, the residue was extracted with chloroform (5 × 30 ml). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo to give a white solid containing impure amine **19a** (20 mg).

(3aR,4R,7S,7aS,8r)-8-Amino-2-benzylhexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione Hydrochloride (**19b** · HCl)

a) *By Hydrogenolysis of* **23b**: In a manner similar to that described for **19a**, from **23b** (500 mg, 1.39 mmol) by hydrogenation with $Pd(OH)_2$ on charcoal crude **19b** was obtained and treated with a solution of excess HCl in 2-propanol. The solution formed was concentrated in vacuo to dryness, and the residue was recrystallized from ethanol/ether to give pure **19b** · HCl (310 mg).

b) *By Reductive Amination of* **4c**: To a mixture of ketone **4c** (1.08 g, 4.0 mmol) and ammonium acetate (3.08 g, 40 mmol) in anhydrous methanol (15 ml) a solution of 85% $NaBH_3CN$ (310 mg, 4.2 mmol) in anhydrous methanol (5 ml) was added. The mixture was stirred at room temp. under argon for 2 d and then acidified with aqueous 5 N HCl. After the methanol had been evaporated in vacuo the aqueous residue was extracted with ether (3 × 50 ml). The combined organic extracts were dried with Na_2SO_4 and concen-

Table 8. Experimental data of the X-ray crystal structure determination of **3b**, **19a**, *rac*-**27**, and *rac*-**30**[3]

Compound	**3b**	**19a**	**rac-27**	**rac-30**
Molecular formula	$C_{10}H_{13}NO_4$	$C_{10}H_{14}N_2O_2$	$C_{23}H_{24}N_2O$	$C_{22}H_{21}NO_2$
Molecular mass	211.22	194.24	344.45	331.42
Crystal system	monoclinic	orthorhombic	monoclinic	orthorhombic
Space grup	$P2_1/n$	$P2_12_12_1$	$P2_1/a$	Pcab
Cell parameters	[a]	[a]	[b]	[b]
a [Å]	7.131(2)	8.380(2)	10.518(3)	26.461(4)
b [Å]	13.263(3)	9.709(2)	21.336(6)	11.019(2)
c [Å]	10.114(3)	12.005(3)	8.182(2)	11.706(2)
β [°]	98.19(2)	-	94.28(2)	-
V [$Å^3$]	946.8(8)	976.7(7)	1831(1)	3413(2)
Z	4	4	4	8
F(000)	448.0	416.0	732.0	1408.0
d(calcd) [g cm^{-3}]	1.481	1.326	1.245	1.289
Size of crystal [mm]	0.1x0.1x0.2	0.1x0.1x0.2	0.1x0.1x0.2	0.1x0.1x0.2
Measured reflect.	3024	1626	4174	3124
Independent reflect.	2894	1626	1047	3124
Observed reflect.	2248	814	919	2031
μ(Mo Kα) [cm^{-1}][c]	1.24	1.01	0.83	0.89
R	0.053	0.056	0.069	0.043
Rw	0.065	0.056	0.070	0.043
Diff. Four. $\Delta\rho_{max}$[d]	0.3	0.6	0.4	0.3
$\Delta\rho_{min}$[e]	-0.3	0.6	-0.3	-0.3
Refined parameters	167	127	305	227
Max. shift / e.s.d.	0.06	0.2	0.06	0.1

[a] Determined by automatic centring of 25 reflections ($12 \leq \Theta \leq 22°$). – [b] Determined by automatic centring of 25 reflections ($8 \leq \Theta \leq 16°$). – [c] μ(Mo-K_α), Linear absorption coefficient. Radiation Mo-K_α ($\lambda = 0.71069$ Å). – [d] Max. and [e] min. peaks in final difference synthesis.

trated in vacuo to give an oily residue containing alcohol **15b** and cyanohydrine **17b** in the ratio of 3:1 (0.61 g, 45% yield). The aqueous phase was made alkaline with aqueous 10 N KOH and extacted with ether (3 × 50 ml). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo to give **19b** as a white solid (250 mg), which was transformed to **19b** · HCl by treatment with an excess of HCl in ether, concentration of the resulting solution in vacuo and recrystallization of the residue.

(3aR,4R,7S,7aS,8r)-8-Aminohexahydro-2-(2-phenylethyl)-4,7-methano-1H-isoindole-1,3(2H)-dione (**19c**): By hydrogenation of amine **23c** (300 mg, 0.80 mmol) as described above for **23b** pure **19c** (230 mg) was obtained.

(3aR,4R,7S,7aS,8r)-Hexahydro-8-(phenylamino)-2-(2-phenylethyl)-4,7-methano-1H-isoindole-1,3(2H)-dione (**21**) was prepared in a manner similar to that described for **23c**. From ketone **4d** (5.09 g, 18 mmol) and aniline (2.0 ml, 22 mmol) with acid catalysis and azeotropic distillation of water, the corresponding imine (6.92 g) was obtained as an oil, that was treated with $NaBH(OAc)_3$, prepared from $NaBH_4$ (1.13 g, 29 mmol) and glacial acetic acid (5.3 ml, 93 mmol) in anhydrous 1,2-dichloroethane (90 ml). The crude product was purified by sequential chromatography and recrystallization from hexane/ethyl acetate to give pure **21** (3.97 g).

(1RS,3aRS,4RS,7SR,7aSR,8RS)-2,9-Dibenzyloctahydro-1,4,7-(iminometheno)-3H-isoindol-3-one (*rac*-**27**): To a cold (ice bath) stirred solution of amine **23b** (2.64 g, 7.3 mmol) in anhydrous THF (100 ml) $LiAlH_4$ (0.70 g, 18.3 mmol) was added slowly under argon. The mixture was stirred at room temp. for 4 d and after cooling treated carefully with water to destroy excess $LiAlH_4$. Solid material was removed by filtration and washed several times with ether. Filtrate and washing ether were combined and concentrated in vacuo. Brine was added to the residue, and the mixture was extracted with ether (3 × 50 ml). The combined organic phases were extracted with aqueous 2 N HCl (5 × 30 ml). The combined aqueous extracts were made alkaline with aqueous 10 N NaOH and extracted with ether (5 × 30 ml). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. The resulting yellow oil (2.75 g) was purified by chromatography (neutral alumina, ether) to give *rac*-**27** (0.93 g).

(1RS,3aSR,4SR,7RS,7aRS,8RS)-2,9-Dibenzyloctahydro-1,4,7-(iminometheno)-1H-isoindole (*rac*-**28**) *and (3aR,4R,7S,7aS,8r)-2-Benzyl-8-(benzylamino)octahydro-4,7-methano-1H-isoindole Dihydrochloride* (**24** · 2 HCl): To a cold (ice bath) solution of amine **23b** (1.65 g, 4.6 mmol) in anhydrous DME (50 ml) $LiAlH_4$ (0.45 g, 11.5 mmol) was added slowly under argon. The mixture was heated at reflux for 4 d and worked up as described above for *rac*-**27**. A yellow oil consisting mainly of *rac*-**28** (1.37 g, 90% yield) was obtained. No significant change of the crude product was observed on extension of the reaction time to 7 d. The solution of the crude product in anhydrous methanol (50 ml) was treated with 85% $NaBH_3CN$ (340 mg, 4.6 mmol) dissolved in anhydrous methanol (10 ml) and glacial acetic acid, until pH 5 was reached, stirred at room temp. under argon for 16 h, and acidified (pH < 2) thereafter with aqueous 6 N HCl. The organic solvent was evaporated in va-

cuo. The residual aqueous solution was washed with ether (2 × 30 ml), made alkaline with aqueous 10 N NaOH, and extracted with ether (3 × 30 ml). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (silica gel, dichloromethane/methanol/triethylamine 95:2.5:2.5). Pure diamine **24** (1.05 g) thus obtained was transformed into **24** · 2 HCl by treatment with an excess of HCl in ether, concentration of the resulting solution in vacuo and recrystallization of the residue from 2-propanol/ether.

(3aR,4R,7S,7aS,8r)-Octahydro-8-(phenylamino)-2-(2-phenylethyl)-4,7-methano-1H-isoindole (**25**). *Detection of (1RS,3aSR,4SR,7RS,7aRS,8RS)-Octahydro-9-phenyl-2-(2-phenylethyl)-1,4,7-(iminometheno)-1H-isoindole* (*rac*-**29**): According to the procedure described for the conversion of **23b** into **24**, from amine **21** (1.00 g, 2.8 mmol) and $LiAlH_4$ (550 mg, 14 mmol) in anhydrous DME (100 ml) a 4:1 mixture of diamine **25** and aminal *rac*-**29** (^{13}C NMR) was obtained. This mixture was reduced with 85% $NaBH_3CN$ (140 mg, 1.9 mmol) at pH 5 as described above. The product was purified by chromatography (silica gel, dichloromethane/methanol 95:5) to give **25** (250 mg). The analytical sample was obtained by decolorization with charcoal in ether.

X-Ray Crystal Structure Determinations of **3b**, **19a**, *rac*-**27**, *and rac*-**30** (Table 8): A prismatic crystal was mounted on an Enraf-Nonius CAD4 diffractometer (compounds **3b** and **19a**) or Philips PW-1100 (*rac*-**27** and *rac*-**30**). The cell parameters were determined by automatic centring of 25 reflections and refined by the least-squares method. Intensities were collected with graphite-monochromatized Mo-K_α radiation by using the $\omega/2\theta$ scan technique. Reflections were measured in the range $2 \leq \theta \leq 30$ and were assumed as observed by applying the condition $I \geq 2.5\sigma(I)$. Three reflections were measured every two hours as orientation and intensity control, a significant intensity decay was not observed. Lorentz polarization, but no absorption corrections were made. The structure was solved by Patterson synthesis by using the SHELX computer program[11] and refined by the full-matrix least-squares method with the SHELX-76 computer program[12]. The function minimized was $\Sigma w[|F_o| - |F_c|]^2$, where $w = (\sigma^2|F_o| + k|F_c|^2)^{-1}$ with $k = 0.012$, 0.000, 0.017, and 0.004 for **3b**, **19a**, *rac*-**27**, and *rac*-**30**, respectively. f, f', and f'' were taken from International Tables of X-ray Crystallography[13]. The positions of the hydrogen atoms were computed and refined with an overall isotropic temperature factor by using a riding model and anisotropically the remaining atoms (for *rac*-**30**) or from a difference synthesis (for **3b** and *rac*-**27**).

---

[1] D. C. Ress, J. C. Hunter in *Comprehensive Medicinal Chemistry* (Eds.: C. Hansch, P. G. Sammes, J. B. Taylor, J. C. Emmett), Pergamon Press, Oxford, **1990**, vol 3, p. 827–828.

[2] P. Camps, D. Mauleón, C. Minguillón, X. Parcerisa, F. Pérez, *Chem. Ber.* **1990**, *123*, 1715–1718.

[3] Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, on quoting the depository number CSD-58610, the names of the authors, and the journal citation. – Gloman Editions: **1979**, *91*, 78. – **1979**, *91*, 852. – **1979**, *91*, 852. – **1981**, *93*, 124–125.

[4] [4a] H.-J. Schmidt, H. J. Schäfer, *Angew. Chem.* **1979**, *91*, 78; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 69–70. – [4b] H. Jäger, J. Lütolf, M. W. Meyer, *Angew. Chem.* **1979**, *91*, 852; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 786–787. – [4c] H.-J. Schmidt, H. J. Schäfer, *Angew. Chem.* **1979**, *91*, 852; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 787. – [4d] H.-J. Schmidt, H. J. Schäfer, *Angew. Chem.* **1981**, *93*, 124; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 109–109.

[5] L. R. Corwin, D. M. McDaniel, R. J. Bushby, J. A. Berson, *J. Am. Chem. Soc.* **1980**, *102*, 276–287.

[6] For non-hydrated 7-norbornanone derivatives see also: [6a] P. Wilder, Jr., A. Winston, *J. Am. Chem. Soc.* **1956**, *78*, 868–871. – [6b] P. G. Gassman, P. G. Pape, *J. Org. Chem.* **1964**, *29*, 160–163. – [6c] P. E. Eaton, R. A. Hudson, *J. Am. Chem. Soc.* **1965**, *87*, 2769–2771. – [6d] E. W. Garbisch, Jr., R. F. Sprecher, *J. Am. Chem. Soc.* **1969**, *91*, 6785–6795. – [6e] D. E. Eckroth, *J. Org. Chem.* **1976**, *41*, 394–395. – [6f] J. R. Neff, J. E. Nordlander, *J. Org. Chem.* **1976**, *41*, 2590–2596. – [6g] S. A. Khattab, M. A. Khalifa, S. A. Mahgoug, *J. Prakt. Chem.* **1977**, *319*, 432–438; *Chem. Abstr.* **1977**, *87*, 151940d. – [6h] K. Matsumoto, Y. Kono, T. Uchida, *J. Org. Chem.* **1977**, *42*, 1103–1105. – [6i] B. Fuchs, G. Scharf, *J. Org. Chem.* **1979**, *44*, 604–609. – [6j] R. Y. S. Tan, R. A. Russell, R. N. Warrener, *Tetrahedron Lett.* **1979**, *20*, 5031–5034. – [6k] M. Mori, A. Hayamizu, K. Kanematsu, *J. Chem. Soc., Perkin Trans 1*, **1981**, 1259–1272. – [6l] P. Camps, J. Castañé, M. T. Santos, *Chem. Lett.* **1984**, 1367–1370. – [6m] P. Camps, J. Castañé, M. Feliz, M. Figueredo, *Tetrahedron. Lett.* **1984**, *40*, 5235–5242. – [6n] A. Nickon, S. S. Jones, B. J. Parkhill, *Heterocycles* **1989**, *28*, 187–194. – [6o] A. Tenaglia, E. Terranova, B. Waegell, *Tetrahedron Lett.* **1989**, *30*, 5275–5276. – [6p] K. Okada, S. Tomita, M. Oda, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 459–468. – [6q] M. Peeran, J. W. Wilt, M. D. Tufano, R. Subramanian, D. S. Crumrine, *J. Org. Chem.* **1990**, *55*, 4225–4226. – [6r] G. Mehta, F. A. Khan, *J. Am. Chem. Soc.* **1990**, *112*, 6140–6142. – [6s] D. Mackay, D. Papadopoulos, N. J. Taylor, *J. Chem. Soc., Chem. Commun.* **1992**, 325–327.

[7] For hydrated simple ketones, see: [7a] J. Bonjoch, J. Quirante, I. Serret, J. Bosch, *Tetrahedron Lett.* **1989**, *30*, 1861–1862. – [7b] G. W. Caldwell, A. D. Gauthier, F. J. Villani, C. A. Maryanoff, G. Leo, *Tetrahedron Lett.* **1991**, *32*, 3763–3766. – For a hydrated γ-lactame, see: [7c] S. Dugar, J. R. Crouse, P. R. Das, *J. Org. Chem.* **1992**, *57*, 5766–5768. – About the hydration of organic molecules, see: [7d] G. R. Desiraju, *J. Chem. Soc., Chem. Commun.* **1991**, 426–428.

[8] R. F. Borch, M. D. Bernstein, H. Dupont Durst, *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.

[9] A. F. Abdel-Magid, C. A. Maryanoff, K. G. Carson, *Tetrahedron Lett.* **1990**, *31*, 5595–5598.

[10] [10a] K. Mislow, *Introduction to Sterochemistry*, W. A. Benjamin, Inc., Menlo Park, **1965**, p. 85. – [10b] R. A. Aitken, S. N. Kilényi, *Asymmetric Synthesis*, Blachie Academic & Professional, Glasgow, **1992**, p. 14.

[11] G. M. Sheldrick, *Acta Cryst. allogr., Sect. A*, **1992**, *46*, 467–473.

[12] G. M. Sheldrick, *SHELX-76, Computer Program for Crystal Structure Determination*, University of Cambridge, **1976**.

[13] *International Tables of X-ray Crystallography*, Kynock Press, Birmingham, **1974**, vol. IV, p. 99–100 and 149.

[89/94]