MAGNETIC RESONANCE IN CHEMISTRY, VOL. 32, 705–710 (1994)

Preparation and NMR Determination of Structures of Tri-, Tetra- and Pentacyclic Isoindolone Derivatives

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From the reactions of 3-*endo*-benzoyl-6-*exo*-phenylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (2) and α,ω-diamines or *o*-aminophenol/thiophenol, different tri-, tetra- and pentacyclic phenyl-substituted norbornane-condensed heterocycles were prepared. With ethylenediamine, 2 furnished two isomeric imidazolo[2,1-*a*]isoindolones. In the formation of one of them, an *endo* → *exo* isomerizaton was observed. The stereostructures (configurations and conformations) of the compounds were elucidated by ^{1}H and ^{13}C NMR spectroscopy, with the aid of routine spectra and also DR, DNOE, DEPT, COLOC and 2D-HSC measurements.

KEY WORDS NMR ^{1}H NMR ^{13}C NMR Norbornane-fused *O,N*-heterocycles Reaction mechanism Stereostructure DR DNOE 2D-HSC DEPT COLOC

INTRODUCTION

Earlier work relating to the development of a new family of potentially anorexic compounds led to condensed saturated or partially saturated isoindolone derivatives.[1–3] To achieve a favourable pharmacological effect, methylene-bridged benzoxazine derivatives saturated in the carbocycle were also prepared.[2]

This paper presents the preparation of methylene-bridged saturated isoindolone derivatives which are phenyl-substituted on the norbornane moiety. The synthetic route involves the possibility of the formation of stereoisomers, and the occurrence of isomerization during the ring-closure reaction also cannot be excluded. Elucidation of the structure of the fairly complex tetra- and pentacyclic system lends particular interest to the topic and poses an exciting challenge from an NMR spectroscopic aspect.

SYNTHESIS

The $AlCl_3$-catalysed Friedel–Crafts reaction of bicyclo[2.2.1]hept-5-ene-2,3-di-*endo*-dicarboxylic anhydride (**1**) with benzene gives 3-*endo*-benzoyl-6-*exo*-phenybicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (**2**) in 71% yield. The similar reaction of the analogous 4-cyclohexene-*cis*-dicarboxylic anhydride and dimethyl ester[4] gives the compound which contains the 5-phenyl group *trans*-equatorial to the carboxylic group. We presume that first the benzene acylation and subsequently the addition takes place in this reaction because, for the cyclohexene analogue, the addition and subsequent acylation lead to an isomeric mixture of aroycarboxylic acids which contain the phenyl group in position 4 or 5.[3,5] Thus, Friedel–Crafts acylation of benzene with 4-phenycyclohexane-*cis*-1,2-dicarboxylic anhydride furnishes 2-benzoyl-4-phenylcyclohexane-carboxylic acid as the main product (yield (67%),[4] while the 5-phenyl regioisomer is obtained in only 11% yield. However, in the $AlCl_3$-catalysed one-step reaction of 4-cyclohexene-*cis*-1,2-dicarboxylic anhydride, we experienced a reversed regioselectivity. In this reaction, 2-benzoyl-5-phenyl-1-cyclohexanecarboxylic acid was obtained in 72% yield,[3] which lends support to the postulated reaction mechanism. This reaction is an example of a *C*-aryl substitution on the bicycloalkene ring, and provides a versatile synthon suitable for the preparation of a great variety of phenyl-disubstituted condensed-skeleton saturated heterocycles.

On boiling in toluene with *p*-toluenesulphonic acid as catalyst, the reaction of **2** and hydrazine (Scheme 1) yields the methylene-bridged 1,6-diphenyl-hexahydrophthalazine-4(3*H*)-one **3**. Benzophthalazinones analogous to **3**, containing an aromatic ring instead of the phenyl-substituted norbornane skeleton, are already known.[5,6] However, though aromatic fused-skeleton heterocycles were prepared many decades ago, their saturated carbocycle-fused analogues have not yet been described. Of course, the stereochemistry of the saturated polycyclic systems is rather involved, a feature providing spectroscopic interest.

If the bifunctional reagents contain carbon(s) between the two reactive groups, condensed tetra- or pentacyclic hetero derivatives are formed from **2**. Thus, ethylenediamine and 1,3-diaminopropane yield methylene-bridged decahydroimidazo- (**4a** and **b**) and dodecahydropyrimido[2,1-*a*]isoindolones (**5**), respectively. The imidazo[2,1-*a*]isoindolone analogous to **4**,

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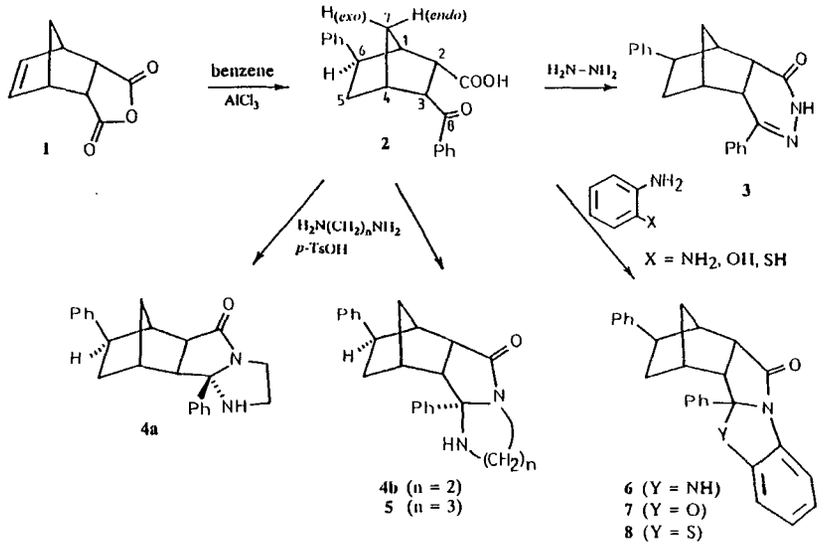
CCC 0749–1581/94/120705–06

Received 18 January 1994
Accepted (revised) 12 July 1994



Scheme 1

containing a benzene ring instead of a norbornane moiety, is already known.[7]

From the reaction of **2** and ethylenediamine, two compounds (**4a** and **b**) were isolated. Compound **4a** contains an 8-*exo*-phenyl-di-*exo*- and **4b** and 8-*endo*-phenyl-di-*endo* structural moiety. In the products **4b** and **5–8**, the di-*endo* configuration of the starting norbornane synthon remained unchanged and the 6-phenyl group on the norbornane skeleton was in the *exo*-position without exception. In the formation of **4a**, the observed isomerization in the ring closure, i.e. the change of the starting di-*endo* configuration to di-*exo*, is noteworthy. The di-*endo* compounds, e.g. di-*endo*-3-aminobicyclo[2.2.1]hexane- and -5-hexene-2-carboxylic acids, and their derivatives always retained their configuration in the target heterocyclic compounds.[8,9] In the literature, we have found only a single example of isomerization, when **1** was transformed in the di-*exo*-norbornenedicarboxylic anhydride on prolonged heating.[10] In our experience, however, the *cis* configuration of similar saturated starting compounds often changes in ring-closure reactions, and the more stable *trans* isomers are formed.[2]

The reaction of **2** with *o*-phenylenediamine led to the isoindolo[2,1-*a*]benzimidazole **6**, that with *o*-aminophenol to the corresponding benzoxazolo derivative **7** and that with *o*-aminothiophenol to the isoindolo[1,2-*b*]benzothiazole **8**.

STRUCTURE

The spectral data on the new compounds are listed in Tables 1 and 2. For easy comparison of analogous spectroscopic data, the numbering of compound **2** is applied for all derivatives in the text and tables (see Scheme 1). The IUPAC numbering can be found in the Experimental section.

For **3**, the di-*endo*- annelation of the hetero ring and the norbornane skeleton are proved unambiguously by the coupling contants J(H-1,H-2) = 4.7 Hz and J(H-3, H-4) = 3.0 Hz.[11] The differential nuclear Overhauser effect[12a,13] (DNOE) result proves the nearness of the hydrogen having the double doublet at 3.69 ppm to the phenyl substituent on the sp^2 carbon and consequently the assignment of this signal to H-3. From this and the results of the double resonance (DR) and two-dimensional heteronuclear shift correlation (2D-HSC)[14] measurements, the assignment of all the other ^1H and ^{13}C NMR signals is also unambiguous. In comparison with C-4, the large downfield shift of the C-1 line (by 5.9 ppm) indicates the position of the 6-phenyl group on the saturated carbon (the downfield shift of the C-1 line is caused by the α-effect of the tertiary C-6[12b]). The *exo* position of the phenyl group follows from the shifts of H-5,5′ and H-6 and the corresponding ^{13}C chemical shifts. For the norbornane, the ^1H NMR shift of H-*exo* is 1.46 ppm and that of H-*endo* is 1.18 ppm.[15] In the event of an *endo*-6-phenyl group (which is sterically unfavourable *ab ovo*), the H-5(*endo*) shift would decrease because of the anisotropic shielding.[12c] In contrast, we found that δH-5(*endo*) ≈ δH-5(*endo, exo*) ≈ 1.5 ppm. Hence, the shielding of the *endo*-hydrogens decreases, which can be explained by the downfield shift caused by the anisotropy of the C=O or C=N groups.[12d,16]

A comparison of the carbon shifts with those for analogous compounds[11] containing other heterorings di-*endo*-annelated to the norbornane likewise supports the *exo* position of the 6-phenyl group (see below). Hence, the stereostructure 1*R**, 2*S**, 3*R**, 4*S**, 6*R* follows.

In **4a**, the heteroring and norbornane moiety are di-*exo*-annelated, as can be concluded from the upfield shifts and doublet splits of the H-2,3 signals[11,16] and from the opposite shifts (by *ca.* 5 ppm) of the C-5 (downfield) and C-7 lines (upfield) relative to those for **3**.[16]

From the 2D-HSC and DNOE measurements, the assignments of the H-2,3 signals are unambiguous. Starting from the two unequivocally identified H-7 doublets (the 7-methylene group has an *AB* spectrum) and the DNOE spectra obtained by saturation of these doublets, the H-1 and H-4 signals can be assigned with certainty (and the 2D-HSC measurements indicate the corresponding carbon signals). As the H-2 and H-3 multiplets are absent from the above-mentioned DNOE spectra, this is again proof of the di-*exo* annelation. The DNOE spectra contain the signals *of the ortho*-hydrogens of one or the other phenyl group [on satura-

Table 1. Characteristic IR frequencies (in KBr discs, cm^{-1}) and ^1H NMR chemical shifts ($\delta_{TMS} = 0$ ppm) for compounds 3, 4a and b and 5–8 in $CDCl_3$ solution at 250 MHz[a]

Compound	νNH band	νC=O band	H-1 d(1H)[b]	H-2 dd(1H)[c]	H-3 dd(1H)[d]	H-4 ~s(1H)	H-6 dd(1H)[e]	CH_2(5) td[f]	CH_2(5) ddd[g]	CH_2(7)[h] d(1H)[f]	CH_2(7)[h] d(1H)[g]	ArH 1–5 signals 10H/14H)[i]
3	3210	1666	~2.8[j]	3.07	3.69	2.66	~2.8[j]	1.4–1.6[j]		1.4–1.6[j]		~7.15,[k] 7.25,[k,l] ~7.4,[m] 7.77[m,n]
4a	3280	1680	~2.85[j]	2.50	~2.85[j]	~2.85[j]	~1.65[j]	1.25	~1.65[j]	~1.65[j]	1.37	7.1–7.35, 7.45,[k,p] 7.62[m,n]
4b	3292	1695	2.82	~3.25[j]	~3.1[j]	2.25	~3.1[j]	1.30	1.78	1.68	1.42	~7.15,[k,n,o] 7.2–7.5
5	3268	1661	~2.80[j]	3.18	~2.55[j]	2.02	3.03	1.20	1.85	~1.6[j]	~1.3[j]	7.0–7.6[p]
6	3268	1684	~2.85[j]	3.28	2.95	~2.85[j]	3.13	1.84	2.52	1.78	1.32	6.65,[q] 6.85,[q] 6.95,[q] 7.1–7.45, 7.65[q]
7	—	1705	2.84	3.46	~3.0[j]	~2.95[j]	~3.1[j]	1.86	2.22	1.78	1.36	6.9–7.1,[r] 7.1–7.4, 7.5–7.6[r]
8	—	1729	2.91	~3.6[j]	~3.6[j]	~2.46	3.18	1.35	~1.6[j]	1.72	~1.5[j]	7.1–7.4, 7.69[m,n]

[a] Solvent DMSO-d_6 for **3**. Assignments were proved by DNOE and 2D-HSC, for **3** also by DR measurements. Further signals in ^1H NMR spectra: CONCH_2, 2 × m (2 × 1H): 3.00 and 3.90 (**4a**), ~3.25[j] and 4.05 (**4b**), for **5**: 3.38 dt (*J*: 13.0, 13.0 and 3.7 Hz) and 4.40 dd (*J*: 13.4 and 5.2 Hz); NHCH_2, 2 × m (2 × 1H): 2.60 and 3.15 (**4a**), 2.62 and ~3.1[j] (**4b**), 2.55[j] and 2.85[j] (**5**), CCH_2C (**5**), 2 × m (2 × 1H): ~1.35[j] and 1.55[j]; NH, s (1H): 11.04 sharp (**3**), ~1.8 broad (**4a**), 1.88 sharp (**4b**), ~1.75 broad (**5**), 4.45 broad (**6**).

[b] *J*(H-1,H-6): 6.0 (**4b**, **7**), 5.6 Hz (**8**).

[c] *J*(H-2,H-3) and *J*(H-1,H-2): 13.4 and 4.7 (**3**), 11.1 and 6.0 (**5**), 9.5 and 6.0 (**6**, **7**), 7.9 and <1 Hz (doublet for **4a**).

[d] *J*(H-2,H-3) and *J*(H-3,H-4): 13.4 and 3.0 (**3**), 9.4 and 4.5 Hz (**6**).

[e] *J*(H-5,H-6) and *J*(H-1,H-6): 9.0 and 5.5 (**5**), 9.0 and 4.7 (**6**) 8.4 and 5.6 Hz (**8**).

[f] *exo* (1H).

[g] *endo* (1H).

[h] *A* or *B* part of an *AB*-type spectrum, *J*(H-7,H-7'): 11.1 (**4a**), 10.2 Hz (**4b**, **6**–**8**).

[i] Separated signals for the 6-Ph and 8-Ph groups and the condensed aromatic ring, total intensity is 10H for **3**, **4a** and **b** and **5**, 14H for **6**–**8**.

[j] Overlapping multiplets.

[k] 6-Ph group.

[l] *meta* Hydrogens, dt (2H).

[m] 8-Ph group.

[n] *ortho* Hydrogens, dd (2H), dd (1H) for **4a**, **8**.

[o] *para* Hydrogen, dt (1H).

[p] Partly broadened signal (due to hindered rotation of the 8-Ph group).

[q] Signals of the condensed ring hydrogen in positions 3' (dd), 5' (dt), 4' (dt) and 6' (dd) with increasing chemical shifts.

[r] Intensity: 3H.

Table 2. ^{13}C NMR chemical shifts (δ_{TMS} = 0 ppm) of compounds 3, 4a and b and 5–8 in $CDCl_3$ solution at 62.89 MHz[a]

Compound	CH_2 (5)	CH_2 (7)	CH-1	CH-2	CH-3	CH-4	CH-6	C=O	C_q[b]	NCH_2[c]	XCH_2[d]	Lines of the 8-phenyl groups C-1′	C-2′,6′	C-3′,5′	C-4′
3	33.6	37.5	50.6	43.2	41.4	44.7	43.4	168.4	150.0	—	—	138.2	130.2	128.6	131.0
4a	36.9	31.4	46.3	49.8	54.7	45.3	40.0	181.3	90.9	44.0	44.2	139.0	125.9 126.3	127.5	128.8
4b	30.7	39.0	46.1	48.7	51.6	40.5	42.2	183.3	87.7	45.8	43.4	140.4	126.4[f]	128.0[f]	125.6
5	30.1	38.9	45.8	48.8	53.1	40.3[e]	41.4	177.5	79.0	39.2	40.4[e]	139.3	?[f]	?[f]	125.4
6	28.5	38.6	47.4	52.4	52.1	41.2	41.8	174.5	87.7	128.8	141.9	145.6	123.4	129.2	125.5[g]
7	28.8	38.9	47.1	51.9	52.9	40.8	41.5	175.2	104.6	127.6	151.9	144.2	124.1	128.7	125.8
8	29.9	38.9	46.6	48.9	52.0	41.6	42.1	180.0	86.5	133.4	139.5	143.1	125.1[f]	127.4[h]	125.9[g]

a Assignments were proved by DEPT and 2D-HSC measurements. Solvent for **3**: DMSO-d_6. Further signals: 6-phenyl group, C-1′: 147.2 (**3**, **6**), 145.4 ± 0.2 (**4a**, **b**, **5**, **7**, **8**), C-2′,6′: 127.9 (**3**), 127.2 ± 0.2 (**4–8**), C-3′,5′: 130.4 (**3**), 128.2 ± 0.2 (**4–8**), C-4′ [coalesced with the C-3′,5′ (**6**) or C-2′,6′ line (**7**)]: 127.6 ± 0.3 (**3–5**, **7**, **8**), 128.1 (**6**). Condensed benzene ring: C-2′: 120.8 (**6**, **8**), 121.9 (**7**), C-3′: 114.8 (**6**), 115.7 (**7**), 125.5[h] (**8**), C-4′: 125.7[g] (**6**), 126.0 (**7**), 123.2 (**8**), C-5′: 111.3 (**6**), 110.1 (**7**), 125.5[g] (**8**).

[b] sp^3 Carbon in the five-membered hetero ring (**4–8**), C=N for **3**.

[c] (CON)—CH_2 (**4**, **5**) or N—C-1′(Ar) group (**6–8**).

[d] CH_2 (**4a**, **b**, **5**) or X—C-6′(Ar) group, X: NH (**4a**, **b**, **5**, **6**), O (**7**), S(**8**).

[e] Two overlapping lines.

[f] *Broadened lines due to hindered rotation of the phenyl group*; in the case of **5** the chemical shift is not identifiable.

[g] Interchangeable assignments.

[h] Reversed assignments with C-2′,6′ line of the 6-phenyl group at 127.2 ppm may also be possible.

tion of the H-7(*exo*) and H-7(*endo*) doublets the enhancement of the H^{ortho}(6-Ph) or H^{ortho}(8-Ph) signals was observed], hence the *exo* position of the latter, i.e. the *trans* position of the 6- and 8-phenyl groups to H-2, 3, follows.

The structure with the configuration 1*R**, 2*R**, 3*S**, 4*S**, 6*R**, 8*S** is especially interesting, because we have found no change in the C-2, C-3 configurations in the reactions of norbornane derivatives with di-*exo* or di-*endo* substituents suitable for cyclization in positions 2 and 3. The literature includes only one such example of di-*endo* → di-*exo* isomerism.[10] In our case, however, the mobile norbornane annelation hydrogens in the α-position to the carbonyl groups can facilitate the isomerization for **2**.

For **4b**, the multiplets of the two annelation hydrogens overlap partly (H-2) or fully (H-3) with other signals. However, the double doublet splits of the H-2 signal (12.0 and 6.0 Hz) can be identified and indicate the unchanged di-*endo* configuration. In accordance, the C-7 line is downfield shifted (by 7.6 ppm) relative to that for **4a**, while the C-5 line is shifted upfield (steric compression shift,[17] manifested as an upfield shift of lines of sterically hindered carbons).

For further proof of the di-*endo* annelation, the upfield 7-methylene doublet was irradiated. In the DNOE spectrum, besides the trivial appearance of the H-1 and H-4 signals, the multiplets of H-2 and H-3 were observed, and the double doublet split of H-2 could be identified; the latter was hidden by overlapping in the routine spectrum. The response of the H-2 and H-3 signals proved the assignment of the irradiated doublet to H-7(*endo*). On saturation of the H-7(*exo*) signal, the signals of H-2,3 were absent, of course, but the doublet of the *ortho*-hydrogens of the 6-phenyl group appeared, proving the *exo* position of the substituent.

The strong NOE between *ortho*-hydrogens of the phenyl group on the quaternary carbon and H-5(*endo*) and H-4 confirms the *endo* position of the aryl group, i.e. the *trans* position to H-2,3. The hindered rotation indicated by the separated appearance of the C-2′ and C-6′ and C-3′ and C-5′ signals, respectively, supports this. Further evidence is the strong shielding of the signal of H-4 (the anisotropic effect of the phenyl ring[12c]) and the upfield shift of the lines of C-5 and the quaternary carbon relative to those for **4a** (the latter shift is due to steric hindrance[17]).

The routine spectra of **5** and the DR, DNOE and 2D-HSC results are analogous to those for **4b**, which proves the similar steric structures. These results also support the conclusions concerning the structure of **4b**. For both **4b** and **5**, the configurations are 1*R**, 2*S**, 3*R**, 4*S**, 6*R**, 8*S**.

For the benzimidazole-condensed derivative **6**, the di-*endo* annelation of the norbornane moiety is unambiguously proved by the double doublet splits of the H-2 and H-3 signals (9.4 and 6.0 Hz), the mutual NOE between H-2,3 and the more shielded 7-methylene hydrogen [which indicates at the same time that the doublet at 1.32 ppm originates from H-7(*endo*)], and the 38.6 ppm shift of the C-7 line. As a strong NOE was found between the doublet at 2.95 ppm and the *ortho*-hydrogens of the phenyl group on the quaternary carbon, the assignment of the former to H-3† and the *exo*-position of the latter are obvious.

If the phenyl substituent on the norbornane is in the 6-*exo* position, the relative configuration 1*R**, 2*S**, 3*R**, 4*S**, 6*R**, 8*R** follows from the above. Indirect proof of the 6-*exo* position of the CH-phenyl group is in the high (0.9 ppm) downfield shift of the H-5(*endo*) signal in comparison with that in **4a**, in which the 8-phenyl group is also in the *exo* position. This is a consequence of the anisotropic effect of the lone electron pair on the very close-lying (*ca.* 1.9Å) amiine-nitrogen.[12e] The 5- or 6-*endo* position of the phenyl group also cannot come into consideration for steric reasons.

† The assignment of the H-3 (2.95 ppm) and H-2 (3.28 ppm) signals was also proved by COLOC measurements[18,19] [^3J(C,H) couplings with carbonyl carbon at 174.5 ppm].

On the basis of the ^1H and ^{13}C NMR data and the analogous NOE, the benzoxazole derivatives **7** and **6** have identical structures (this means a different configuration of C-8 in **7**: 1*R**, 2*S**, 3*R**, 4*S**, 6*R**, 8*S**). For **7**, the H-1 and H-4 signals appear separately and the relationship δH-2 > δH-3 is undoubtedly due to the deshielding effect of the carbonyl vicinal to H-2[12d] and the shielding effect of the *exo*-8-phenyl group close to H-3.‡ Consequently, the assignments of the H-2 and H-3 signals are unambiguous. The mutual NOE between the signals at 3.46 ppm (H-2) and 2.84 ppm proves that the latter doublet belongs to the H-1 signal. The 2D-HSC measurements show that the downfield (47.1 ppm) of the C-1 and C-4 signals corresponds to C-1 (from the ^1H–^{13}C correlations 2.84 to 47.1 and *ca.* 3.0 to 40.8 ppm). The downfield shift can be rationalized by the β-effect of the substituent in position 6, and consequently the phenyl group on the norbornane moiety must be in position 6.[12f]

The benzthiazole **8** contains an *endo*-phenyl group on the quaternary C-8. Hence, the configuration of the latter is the reverse of the analogues **6** and **7**, i.e. 1*R**, 2*S**, 3*R**, 4*S**, 6*R**, 8*R**. This structure was confirmed by x-ray measurements,[20] and is indicated by the following changes in the spectra: (a) In the ^1H NMR spectrum of **8**, the H-3 signal is shifted downfield significantly (by *ca.* 0.6 ppm) relative to **6** and **7** [this also holds for H-2 and H-7(*endo*) to a lesser extent] because of the opposite influence of the C—S bond instead of the shielding effect of the 8-phenyl ring. (b) The rotation of the sterically unfavourable *endo*-phenyl group is hindered. Hence, its C-2′,6′ lines are broadened. (c) The anisotropic effect of the close-lying 8-phenyl group results in the shielding of H-5(*endo*) being increased to a great extent (by 0.95 and 0.6 ppm) relative to that in the analogues **6** and **7**. (d) A weak NOE was found between H-6(*endo*) and the *ortho*-hydrogens of the 8-phenyl ring, which is proof of the *endo* position of the latter. (e) For **8**, the downfield shift of the carbonyl carbon (by more than 5 ppm) relative to those for **6** and **7** indicates the different steric structure. The reasons for this steric structure is probably that the sulphur, with a larger atomic radius than that of the NH group or oxygen, would come close to H-5(*endo*) and to avoid the considerable steric hindrance, the molecule forms the structure involving the reverse position of the 8-phenyl ring on the quaternary carbon compared with that in **6** and **7**.

EXPERIMENTAL

IR spectra were run in KBr discs on a vacuum optic 113v FT spectrometer equipped with an Aspect 2000 computer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solution in 5 mm tubes at room temperature on a Bruker WM-250 FT spectrometer controlled by an Aspect 2000 computer at 250.13 (^1H) and 62.89 (^{13}C) MHz, respectively, using the deuterium signals of the solvent as the lock and TMS as internal standard. The most important measurement parameters were as follows: spectral width 5 and 15 kHz, pulse width 1 and 7 μs (*ca.* 35° flip angle), acquisition time 1.64 and 1.02 s, number of scans 4–16 and 0.5–1.5 K, computer memory 16K and 32K. Complete proton noise decoupling (*ca.* 3 W) for the ^{13}C spectra and Lorentzian exponential multiplication for signal-to-noise enhancement were used (linewidth 0.7 and 1.0 kHz).

Conventional cw irradiation of *ca.* 0.15 W was used in the DR experiments.

DEPT[21] spectra were run in a standard way,[22] using the $\theta = 135°$ pulse to separate the CH/CH_3 and CH_2 lines phased up and down, respectively. Typical acquisition data were number of scans 128–12K, relaxation delay for protons 3 s and 90° pulse widths 10.8 and 22.8 μs for ^{13}C and ^1H, respectively. The estimated value for J(C,H) resulted in a 3.7 ms delay for polarization.

The standard Bruker microprogram DNOEMULT.AU to generate NOE was used with a selective pre-irradiation time of 5 s and a decoupling power (cw mode) of *ca.* 30–40 mW; number of scans 64–256, dummy scans 4–8, pulse widths 5.0 μs (90°) and 16K data points for *ca.* 2 kHz spectral width. A line broadening of 1.0 Hz was applied to diminish signals in the difference spectra.

The 2D-HSC spectra were obtained by using the standard Bruker pulse program XHCOORD.AU. The number of data points was 4K in the ^{13}C domain, and 64–256 increments were used to give better than 5 Hz per 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 calculation of the delay.

Physical and analytical data on compounds **3**, **4a**, and **b** and **5–8** are listed in Table 3.

Preparation of *endo*-3- benzoyl-*exo*-6-phenylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (2)

To a solution of di-*endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride (20.52 g, 0.125 mol) in dry benzene (80 ml), anhydrous $AlCl_3$ (17.07 g, 0.128 mol) was added in small portions, with cooling and stirring. The mixture was refluxed for 4 h, then cooled to −10 °C and HCl (20%, 80 ml) was added dropwise with stirring. After extraction with benzene (3 × 30 ml), the organic layer was washed with water (3 × 50 ml) and dried (Na_2SO_4), and the solvent was evaporated off. To the residue, diethyl ether (30 ml) was added and the mixture was allowed to stand for crystallization. Colourless crystals from EtOAc, mp. 191–193 °C, yield 28.4 g (71%). Analysis: found, C 78.64, H 6.38: required for $C_{21}H_{20}O_3$ (320.39), C 78.73, H 6.29%.

The methyl ester of **2** was prepared with diazomethane.

Preparation of 5,8-methano-1,6-diphenyl-4a,5,6,7,8,8a-hexahydrodrophthaliazine-4(3*H*)-one (3)

A mixture of 3-*endo*-benzoyl-6-*exo*-phenylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (**2**) (8.00 g, 0.025 mol), hydrazine monohydrate (98%, 2.0 g, 0.04 mol) and *p*-toluenesulphonic acid (one crystal) in dry toluene (40 ml) was refluxed for 7 h. After evaporation of the solvent, the residue was eluted with benzene from an Al_2O_3 column (Brockmann II neutr.). The residue of the eluate was crystallized.

Preparation of 6,9-methano-7,9b-diphenyl-1,2,3,5a,6,7,8,9,9a,9b-decahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones (4a and b) and 7,10-methano-8,10b-diphenyl-1,2,3,4,6,6a,7,8,9,10,10a,10b-dodecahydropyrimido[2,1-*a*]isoindol-6-one (5)

Compound **2** (6.4 g, 0.2 mol) and ethylenediamine monohydrate (3.12 g, 0.04 mol) or 1,3-diaminopropane (2.97 g 0.04 mol) were used for **3**. The product was transferred to a silica gel column (Kieselgel 60. 0.063–0.2 mm) and eluted with EtOAc. After evaporation of the solvent, the residue was crystallized several times from EtOH to yield **4a**. The isomer **4b** was prepared from the mother liquor of **4a** by crystallization from EtOAc.

‡ For **6**, this was also proved by COLOC measurements.

Table 3. Physical and analytical data on compounds 3, 4a and b and 5–8

Compound	M.p. (°C)	Yield (%)	Formula	Mol. weight	Analysis: required/found (%) C	H	N
3	261–263[a]	33	$C_{21}H_{20}N_2O$	316.40	79.72/79.64	6.37/6.33	8.85/8.68
4a	259–261[b]	28	$C_{23}H_{24}N_2O$	344.46	80.20/80.05	7.02/7.10	8.13/7.99
4b	184–187[a]	30	$3_{23}H_{24}N_2O$	344.46	80.20/80.11	7.02/7.20	8.13/8.02
5	200–202[b]	38	$C_{24}H_{26}N_2O$	358.49	80.41/80.20	7.31/7.50	7.81/7.77
6	268–269[c]	43	$C_{27}H_{24}N_2O$	392.51	82.62/82.43	6.16/6.29	7.14/7.03
7	192–194[a]	37	$C_{27}H_{23}NO_2$	393.49	82.42/82.49	5.89/6.03	3.56/3.59
8	209–211[a]	45	$C_{27}H_{23}NOS$	409.55	79.18/79.02	5.66/5.85	3.42/3.28

[a] From EtOAc.
[b] From EtOH.
[c] From dioxane–EtOH.

For the purification of **5**, the product was chromatographed on an Al_2O_3 column (Al_2O_3 basic, 50–200 μm) with EtOAc as eluent.

Preparation of 6,9-methano- 5a,8-diphenyl-5a,5b,6,7,8,9,9a,10-octahydroisoindolo[2,1-*a*]benzimidazol- 10-one (6), 1,4-methano-2,4b-diphenyl- 1,2,3,4,4a,4b,11,11a-octahydroisoindolo[1,2-*b*]benzoxazol-11-one (7) and -isoindolo[1,2-*b*]benzthiazol-11-one (8)

Compound **2** (8.0 g, 0.025 mol) and *o*-phenylenediamine (2.70 g, 0.025 mol) or *o*-aminophenol (2.73 g, 0.025 mol) or *o*-aminothiophenol (3.13 g, 0.025 mol) were reacted as above for **3**. For purification of the products, column chromatography was used (**6**, Al_2O_3 basic Woelm, eluents EtOAc then EtOH, the latter eluate being used; 7, Al_2O_3 neutr., Woelm, EtOAc; **8**, Kieselgel, Merck, EtOAc).

Acknowledgements

Thanks are due to Mrs A. Sólyom, Mr A. Fürjes and Mr V. Bege for skilled technical assistance and to Miss M. Mörtl and Mrs. E. Csiszár-Makra for typing the manuscript. Grants OTKA 2693 and ETT T-121 are acknowledged.

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