PREPARATION AND STERIC STRUCTURE OF TRICYCLIC AND TETRACYCLIC SATURATED OR PARTIALLY SATURATED 1,3-HETEROCYCLES CONTAINING A SATURATED ISOINDOLONE MOIETY[1]

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Dedicated to Professor A. R. Katritzky on the occasion of his 65th birthday.

Abstract – From *cis*-2-(*p*-methylbenzoyl)-1-cyclohexanecarboxylic acid (**1**) and *diendo*-3-(*p*-methylbenzoyl)bicyclo[2.2.1]heptane-2-carboxylic acid (**2**) with α,ω-alkylenediamines, the perhydroimidazo[2,1-*a*]isoindolone (**3**), the corresponding perhydropyrimido and perhydrodiazepino derivatives (**4**) and (**5**) and their methylene-bridged tetracyclic analogues (**6-8**) were obtained. Compound (**1**) and ethanolamine yielded the perhydro-1,3-oxazolo[2,3-*a*]isoindolone derivative (**9**), while **1** with 3-amino-1-propanol or 2-aminoethanethiol gave the homologous saturated 1,3-oxazino derivative (**10**) and thiazoloisoindolone derivative (**11**), respectively. On boiling in xylene, **9** was transformed to the hydroxyethylisoindolone (**12**). From **1** and *o*-phenylenediamine, the *trans*-isoindolo[2,1-*a*]benzimidazole derivative (**13**) was formed, while **1** and *o*-aminothiophenol gave the partly saturated *cis*-benzthiazole analogue (**14**).

We recently reported the preparation and conformational analysis of numerous cycloalkane-condensed 1,2-oxazinone and pyridazinone derivatives. These bicyclic and tricyclic compounds were prepared from the stereoisomeric 2-aroylcyclohexanecarboxylic acids[2-4] and *diendo*-3-(*p*-methylbenzoyl)bicyclo[2.2.1]heptane-2-carboxylic acid. Besides the chemical and stereochemical interest of these fused-skeleton saturated heterocycles, they are of importance from pharmacological points of view, too. Compounds with structural elements similar to those in **3-5** and **9-11** possess an anorexic effect and are applied in therapy.[5, 6]

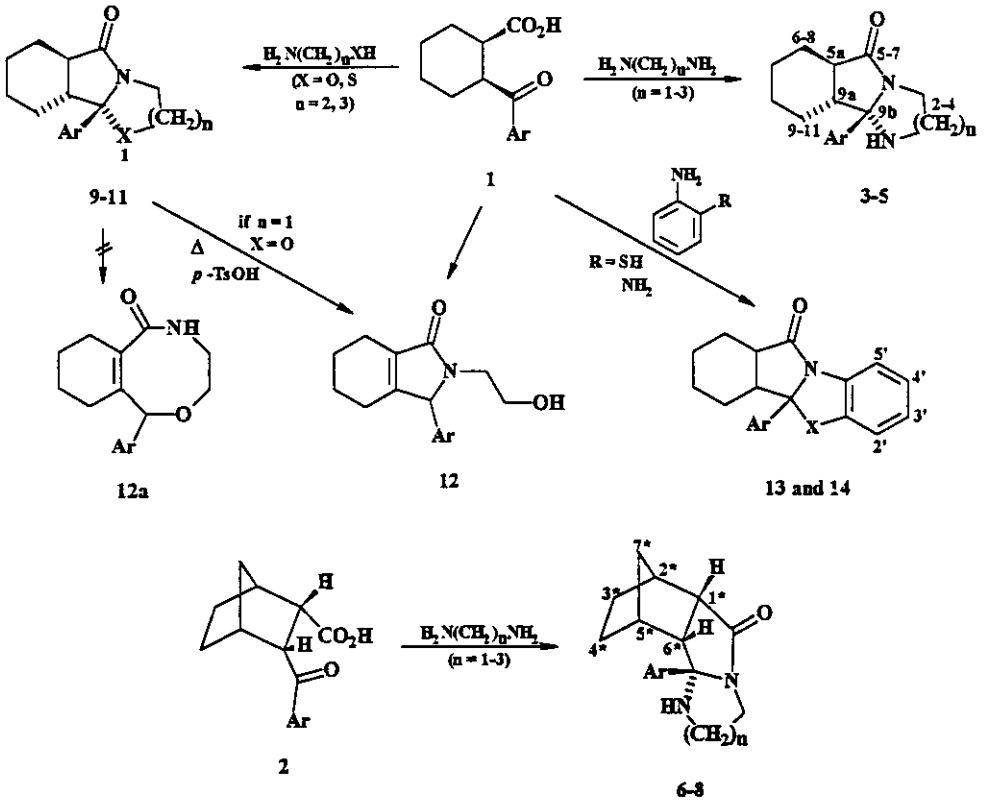
To date, merely compounds containing an aromatic ring A have been described. Obviously, in such a case the stereochemistry of the resulting tetracyclic compounds is much simpler, as no *cis* or *trans* A/B ring anellation occurs and the steric position of the 9b-phenyl substituent relative to this ring anellation need not be considered.

The present work, which is a continuation of our systematic synthetic and stereochemical investigations on fused-skeleton saturated or partially saturated 1,3-heterocycles,[7-9] reports the ring-closure reactions of *cis*-2-(*p*-methylbenzoyl)-1-cyclohexanecarboxylic acid[2] (**1**) and its *diendo* norbornane analogue (**2**) with bifunctional reagents, *e.g.* α,ω-alkylenediamines and alkanolamines. The products of the former processes are tricyclic and tetracyclic, stereochemically highly complex new ring systems. Elucidation of the

stereostructure of these complex molecules was possible by application of ^{1}H- and ^{13}C-nmr investigations, including special measurements such as DNOE, 2D-HSC, DEPT and INEPT.

RESULTS

In dry toluene, a mixture of 1 or *diendo*-3-(*p*-methylbenzoyl)bicyclo[2.2.1]heptane-2-carboxylic acid (2) and the α,ω-alkylenediamine (ethylenediamine, 1,3-diaminopropane or 1,4-diaminobutane) was refluxed in the presence of *p*-toluenesulphonic acid as catalyst. After evaporation and purification by chromatography, the products furnished saturated isoindolones fused with a nitrogen-containing ring (3-5) in good yields (Scheme). From the starting norbornane compound (2), the corresponding tetracyclic compounds, the methylene-bridged perhydroisoindolones (6-8), were formed with the above reagents.



Ar = *p*-tolyl; n = 1 (3, 6, 9, 11), n = 2 (1, 4, 7, 10), n = 3 (5, 8)
X = NH (13), X = O (9, 10), X = S (11, 14); 13: *trans*, 14: *cis*

Scheme

Compounds analogous to 3, but containing an aromatic ring A instead of cyclohexane or norbornane, were earlier prepared from 2-aroylbenzoic acid and ethylenediamine.[10-15] The presence of the aromatic ring A means that these compounds have no stereoisomers. However, for the compounds described in this paper, several (up to 4) stereoisomers are possible. In compounds (3-5), because of the saturated ring A, the hetero rings can be condensed in two different steric positions. Hence, starting from the *cis* compound (1), the products (3-5) can contain the aryl substituent at the B/C ring anellation *cis* or *trans*

to the A/B anellation hydrogens. A further fact which emphasizes the importance of determination of the stereostructure is that the *cis* or *trans* fusion of the cyclohexane and hetero ring depends on the reaction conditions, so the configurations of the starting compounds and the products often differ.[16] For the intramolecular transacylation of cyclohexane-condensed azetidinones, *cis* ⟶ *trans* isomerizations have been observed,[8a] while a reverse *trans* ⟶ *cis* isomerization occurred in the thermal cyclization of the *cis*-ethoxycarbonylcyclohexylureas to cyclohexane-condensed dihydrouracils.[17]

With ethanolamine, **1** yielded the oxazoloisoindolone (**9**), while the tetrahydro-1,3-oxazino homologue (**10**) was formed with 3-amino-1-propanol. The aromatic analogue of **9** was prepared earlier.[18] With 2-aminoethanethiol, the thio analogue (**11**) was prepared.

From the reaction of **1** and ethanolamine in toluene, with *p*-TsOH as catalyst, **12** was isolated besides **9**. In the next step of this reaction, transformation of **9** to the more stable **12** takes place by ring opening and rearrangement of the two anellation hydrogens. The prolonged refluxing of **9** in xylene resulted in **12** quantitatively.

With *o*-phenylenediamine, **1** gave the isoindolobenzimidazole (**13**), while **1** and *o*-aminothiophenol furnished the thio derivative (**14**). In these reactions, the *trans*-condensed cyclohexane derivatives (**3-5**, **9-11** and **13**) were formed, and only the reaction with *o*-aminothiophenol yielded the *cis* product (**14**). The formation of the *trans* (**13**) and *cis* (**14**) compounds from the same starting compound (**1**) with *cis* configuration can be explained by the different sizes of the NH and S groups. Further, the more alkaline *o*-phenylenediamine promotes enolization and the formation of a *trans* compound.

For cyclohexane-fused six-membered heterocycles, the *trans* structure is more favourable than the *cis*, but for cyclopentane-condensed six-membered systems containing two heteroatoms, the *cis* anellation is much more stable and the *trans*-condensed bicycle can be prepared only in exceptional cases.[8a, 19] In the present case, the prepared tricyclic compounds (**3-5**) and (**9-11**) contain two condensed five- or one five- and one six- or seven-membered heterocycles fused to the cyclohexane ring. The results show that the relations in these strained systems are similar to those in the cyclohexane-fused six-membered heterocycles, *i.e.* the *trans* fusion of rings A and B is more favourable.

DETERMINATION OF STEREOSTRUCTURES

The ir and ^{1}H- and ^{13}C-nmr data on **3-14** are listed in Tables 1 and 2.

The imidazolidine derivative (**3**) contains a *trans*-anellated cyclohexane ring, in which the anellation hydrogen vicinal to the carbonyl group (H-5a) and the *p*-tolyl substituent are *cis* relative to the pyrrolidone ring. The triplet split by ~13 Hz of the H-5a signal corresponds to two *diaxial* interactions, which proves the *trans-diaxial* position of H-5a and H-9a. In this structure, H-9*ax* is strongly shielded (0.65 ppm) by the aryl ring. In accordance, DNOE measurements prove the close arrangement of H-5a, H-9*ax* and the *p*-tolyl group.

The ^{1}H-nmr spectra of the homologues (**4**) and (**5**) are very similar. Rotation of the aryl group in **4** is hindered, as demonstrated by the broadening of its ^{1}H-nmr signal and the 4.3 ppm upfield shift (relative to that for **3**) of the C-5a line (field effect[20]) in the ^{13}C-nmr spectrum. All this indicates a more strained skeleton due to the rigid chair conformation of the perhydropyrimidine ring relative to that of the more flexible imidazolidine moiety in **3**. The practically unchanged chemical shifts of the other cyclohexane carbons prove the *trans* anellation of the cyclohexane and pyrrolidone rings. A *trans*⟶*cis* difference in the structure would cause significantly stronger shielding on the cyclohexane carbons.

For the norbornane-condensed analogues (**6-8**), the *diendo* anellation to the pyrrolidone ring follows from the chemical shift of the bridging methylene carbon line and the double doublet splitting of the signal of the anellated hydrogens.[21, 22]

The *cis* (*exo*) position of the tolyl group and the anellated hydrogens relative to the pyrrolidone ring is only probable. NOE measurements gave no direct proof of the *exo* configuration of the *p*-tolyl group, but

the NOE for H-5* and its lack on H-4* (*endo*)# when the *ortho*-aryl hydrogens were saturated support this structure, as does the fact that H-6* is more shielded for **7**, *i. e.* the 1,3-*diaxial* hydrogens in the rigid chair form of the six-membered hetero ring hinder rotation of the aryl group (signal broadening!), and consequently that rotamer of the latter is preferred in which the aryl ring shields the vicinal H-6*. For homologues (**6**) and (**8**), the flexibility of the hetero ring containing two nitrogens permits free rotation of the aryl group.

The rotation of an *endo*-aryl group would be hindered in every homologue, including **6** and **8**, and a shielding effect would appear at H-4* (*endo*).

Table 1. Characteristic ir data and ^{1}H-nmr chemical shifts of compounds (**3-14**)[a]

	νC=O	νNH	CH_3	CCH_2C + CH groups[b]	XCH_2[c]		$CONCH_2$		ArH (tolyl)[d]		NH
			s(3H)	3-6 partly overlapping signals (9-14H)	2*xm*(2x1H)		2*xm*(2x1H)		2x~*d*(2x2H)		br(1H)
3	1686	3287	2.36	0.65[e] 0.90-1.4[f] ~1.7[g] ~1.85[g] ~2.05[g,h] 2.25[i]	3.05	3.20	2.90	3.75	7.18	7.31	2.05[h]
4	1678	3295	2.36	0.42[e] 1.05[j] ~1.25[g] 1.5-1.9[h,k] 2.20[l]	2.62	~2.9[m]	~2.9[m]	4.25	~7.2[n]		~1.7[h]
5	1680	3332	2.35	0.45[e] 1.00[j] 1.1-1.4[f] 1.4-2.0[h,o] 2.15[l]	2.78	3.05	2.54	4.12	7.10	7.18	~1.7[h]
6	1674	3256	2.34	0.98[p,q] 1.3-1.6[r] 2.10[s] 2.60[t] 3.05[h,u,v]	2.58	3.05[h]	3.25	4.00	7.13	7.26	1.90
7	1680	3277	2.36	0.90[p,q] 1.2-1.7[w] 1.90[s] 2.50[l,v] 2.65[h,t] 3.05[l,u]	~2.65[h]	2.78	3.35	4.35	7.2[n]		2.00
8	1667	3365	2.34[h]	1.3-1.5[f,q,x] 1.6-1.8[w] ~2.30[h,v] 2.50[s] 2.65[m,t,u]	2.65[m]	2.95	3.15	3.90	7.16[y]		~2.2
9	1726	–	2.36	1.0-1.5[y] 1.7-1.9[y] 2.1-2.3[g]	~3.90		2.98	3.68	7.18	7.35	–
10	1713	–	2.38	1.05[p] 1.1-1.3[f] 1.3-1.5[g] ~1.6[p] 1.7-1.9[f] ~2.25[g]	~3.80		3.00	4.10	7.22	7.30	–
11	1718	–	2.35	1.0-1.5[y] 1.75-2.0[y] ~2.25[g]	~2.95[h]	3.08	~2.95[h]	4.35	7.16	7.37	–
12	1660	3322[z]	2.34[h]	~1.6[y] ~1.9[g] ~2.3[h,r] 4.92	3.65[m]		~3.02	3.65[m]	6.95	7.15	4.24[z]
13	1693	3321	2.34[h]	0.87[e] 1.05[j] 1.2-1.4[g] 1.78[g] ~2.1[f] ~2.45[h,y]	–		–		7.18	7.25	~4.5
14	1720 1700	–	2.29[h]	1.1-1.4[f] ~1.55[g] ~1.75[l] ~2.1[p] ~2.25[h,y] 2.7-2.9[g]	–		–		7.10[m]	7.20	–

[a]For the numbering of the condensed benzene ring and the norbornane moiety, denoted by ' and *, respectively, see the Scheme. ir: KBr discs, cm^{-1}; nmr: chemical shifts ppm, (δ_{TMS}= 0 ppm), coupling constants, Hz; solvent: $CDCl_3$, measuring frequency: 250 MHz. Assignments were proved by DNOE (**3, 4, 6-11, 13, 14**), by 2D-HSC measurements (**3, 4, 6, 7, 10, 11, 13**) and for **12** by INEPT. Signals for the condensed benzene ring: H-2': 6.62 *d*, H-4': 6.85 *t*, H-3': 6.92 *t*, H-5': 7.55 d (**13**) and H-2',3': ~7.0[h], H-4': 7.10[m] *t*, H-5': 7.88 *d* (**14**); [b]Total intensity: 10H (**3, 6, 9, 11, 13, 14**), 12H (**4, 7, 10**), 14H (**5, 8**) or 9H (**12**); [c]X: NH (**3-8**), O (**9, 10, 12**) or S (**11**); [d]Parts *A* and *B* of an *AA' BB'* multiplet, $J(A,B)$ = 8.1 ± 0.1; singlet signal ($\delta A \approx \delta B$) for **8**; [e/i/j/l/p]Multiplicity: *dqa* (1H)/*dt*(1H)/*tt*(1H)/*dd*(1H)/*m*(1H); [f/g/k/o/r/w/y]Intensity: 3H/2H/8H/9H/5H/7H/4H/; [h/m]Overlapping signals; [n]Broadened signal due to hindered rotation; [q]H-4*; [s]H-5*, ~*t* (with coalesced lines); [t]H-2*, ~*t* (with coalesced lines); [u]H-1*; [v]H-6*; [x]H-7,7'*; [z]OH group: νOH band in the ir, triplet in ^{1}H-nmr, $J(CH_2, OH)$: 5.0.

Compound (**9**) decomposed during the carbon measurement, and thus the structure elucidation can be based only on the ^{1}H-nmr data. As the signals of the anellated hydrogens at ~2.2 ppm mutually overlap, the *cis* or *trans* anellation of the cyclohexane ring can not be proved. However, the H-9*ax* and H-9a signals are downfield-shifted (by ~0.35 ppm) relative to those in **3**, and hence the structure must be different for the two compounds. The ^{1}H-nmr signals of the cyclohexane hydrogens in the thio analogue **11** show a close analogy to those in **9**, which renders the analogous stereostructure probable. As for **3** and **11**, the ^{13}C-nmr shifts of the cyclohexane carbons do not differ essentially (except for that of C-9a, due to the β-effect[23] of the different heteroatoms), and thus the *trans* anellation of the carbocylic ring and the *S** configuration of the thio-substituted quaternary carbon (and hence the *trans* position of the aryl group relative to H-5a) for **11** and **9** are probable.

The ^{1}H-nmr spectrum of **10** also differs considerably from that of the analogue (**4**): the extremely upfield-shifted multiplet of one of the carbocyclic methylene hydrogens (probably H-10*ax*), at 0.42 ppm for **4**, does not appear in the spectrum of **10** and the H-10a signal is downfield-shifted as compared with **4**. The shifts of the cyclohexane carbons hardly differ, and thus the *trans* anellation of the cyclohexane-pyrrolidone rings is obvious. Hence, for **9-11**, the analogous stereostructure can be deduced, in which the position of the aryl group is different from that in the nitrogen analogues (**3-5**): the anellated hydrogens

#For easy comparison of analogous spectral data, the numbering to be seen in the Scheme was used.

are in the *trans* position. In agreement, the spectral data show no hindrance to the rotation of the aryl substituent.

Table 2. ^{13}C-Nmr chemical shifts for compounds (3-8) and (10-14)[a]

Compd	CCH_2C	CH[b]	C=O	C_q[c]	CH_3	C-1[d]	C-2,6[d]	C-3,5[d]	C-4[d]	CH_2[e]	CH_2[f]
3	25.1 25.4 25.8 27.9	48.4[g] 56.8	176.7	89.1	20.9	136.1	126.1	129.0	137.6	47.7	41.9
4	25.5 25.6 25.8 26.3 26.4	44.1[g] 55.7	173.5	79.6	21.0	133.3	127.5[h]	129.3	137.5	36.3	40.2
5	25.5 25.8 26.7 28.0[i] 33.6[j]	44.6[g] 50.3	174.8	84.3	20.9	136.2	126.3	129.2	137.7	39.6[k]	41.6[k]
6	22.8[l] 25.7 41.8[m]	49.2 50.6	183.8	87.4	21.0	136.8	126.2	128.4	137.4	43.3	45.8
7	22.4[l] 25.0 26.3 41.7[m]	48.0[g] 53.7	178.1	78.7	20.9	136.2[k]	~128[h]		136.6[k]	40.2[n]	39.1[n]
8	24.3 25.0 25.9 31.0[j] 41.2[m]	46.6[g] 55.0	175.4	83.1	21.0	142.7	126.4	129.6	137.1	42.1	40.8
10	23.2 25.2 25.7 25.8 26.0	45.9[g] 53.8	179.2	93.5	21.1	136.0[k]	126.5	129.6	137.6[k]	62.2	37.6
11	25.3 25.7 26.0 26.7	46.9[g] 51.2	181.2	86.6	21.0	140.9	125.7	129.1	137.4	33.9	44.7
12	20.2 21.0 21.9 22.8	130.2[k] 155.1	172.6	67.9	22.1	132.2[k]	127.1	129.5	137.8	61.0	43.0
13	25.0 25.2 25.5 27.6	47.3[g] 58.9	175.9	89.0	21.1	142.1	125.1	129.4	138.2	–	–
14	22.3 22.5 24.0 29.4	43.5[g] 48.1	173.3	86.4	20.9	142.2	124.0	129.2	137.6	–	–

[a]Chemical shifts in ppm (δ_{TMS} = 0 ppm) in $CDCl_3$ solution, at 63 MHz. Measuring frequency 63 MHz, 20 MHz for 3 and 12. Assignments were proved by DEPT (except for 12 and 14) and for 3, 4, 6, 7, 10, 11 and 13 also by 2D-HSC measurements. *Further signals*: CH (norbornane): 39.6 and 39.9 (6), 39.3 and 39.7 (7), 39.0 and 39.6 (8); condensed benzene ring (13 and 14) C-1': 129.3 and 134.3, C-2': 136.4 and 130.5, C-3': 111.1 and 116.0, C-4': 125.0 and 125.3,[j] C-5': 115.2 and 125.2,[j] C-6': 120.7 and 122.5; [b]Anellated carbons of the condensed alicyclic and pyrrolidinone rings, quaternary C(sp^2) atoms for 12; [c]Quaternary anellated carbon of the two hetero rings, CH for 12; [d]Tolyl group; [e] Vicinal to the NH/O/S; [f] Vicinal to the amide-N; [g]Vicinal to the carbonyl group; [h]Broadened signal due to hindered rotation; [i]Two coalesced lines; [j] Hetero ring; [k/n]Interchangeable assignments; [l]Pos. 4*; [m]Pos. 7* (for numbering denoted by * or ', see the Scheme).

Structure (**12**) is in accordance with the spectral data: the νOH band appears at 3322 cm^{-1} in the ir spectrum and the amide-I frequency decreases from 1726 (**9**) to 1660 cm^{-1} in consequence of the *N*-substitution and association. In the ^{1}H-nmr spectrum, the OH signal (triplet at 4.24 ppm; exchangeable by D_2O) also appears and the multiplets of the two anellated CH groups are substituted by one downfield-shifted signal of only 1H intensity. The lines of the highly polarized C=C bond, which appear in the region characteristic of unsaturated carbons at 132.2 and 155.1 ppm, unequivocally prove the conjugated enone bond system[24a] by their high shift difference.

All these spectral data would also accord in principle with an oxazocine ring structure of lactam type (**12a**). To exclude this, INEPT measurements were made. On irradiation of the triplet of the acidic (OH) proton, only the two side-chain methylene carbons gave signals. In the presence of **12a**, saturation of the corresponding NH hydrogen should also have produced a response of the carbonyl carbon (at a two-bond distance) and that of the olefinic carbon vicinal to the carbonyl (separated by three bonds). On saturation of the NCH_2 signal, the methine carbon also responded, which would not be expected in structure (**12a**) as the ^4J(C,H) interaction is «7 Hz.

For **3** and **13**, the similar shifts of the lines of the cyclohexane carbons strongly suggest the *trans* anellation of the carbocyclic ring in the latter. The H-9a signal in **13** is a double triplet involving two large (> 10 Hz) splittings, which proves *trans* anellation. On saturation of the aromatic hydrogens of the *p*-tolyl group, a weak response from H-5a can be seen in the DNOE spectrum, which suggests their *cis* position relative to the pyrrolidone ring; hence, **3** and **13** have analogous structures.

On the basis of the nmr data, which differ significantly from those for **13**, the sulphur analogue **14** has another structure. The signals of the anellated hydrogens are appreciably downfield-shifted, while the overall shift for the six cyclohexyl carbons is 20 ppm less than for **13**, which is proof of the *cis* anellation.[24b] The strong NOE between the aromatic hydrogens of the *p*-tolyl group and the two anellated hydrogens proves their *cis* position.

The characteristic different widths and splits of the ^{1}H-nmr signals of the anellated hydrogens suggest a conformationally homogeneous compound. If the chair form of the cyclohexane ring is assumed, two relatively stable conformers must be considered. In accordance with our experience,[25] the carbonyl is in the *axial* position to the carbocycle in the preferred conformation, as indicated by the following arguments: (a) molecular models demonstrate that the skeleton is more strained in the conformer containing an *equatorial* carbonyl group, (b) two methylene hydrogens (H-8*eq* and H-11*eq*) are strongly deshielded (they are coplanar with the carbonyl and C-S bonds, respectively, and the anisotropic effect[24c] of the latter causes the downfield shifts of their signals), and (c) for the other possible conformer, a NOE effect would be measured for H-11a instead of H-8*eq* on irradiation of the aromatic *p*-tolyl hydrogens, as was expected and also observed for the proposed structure.

EXPERIMENTAL

The nmr spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature on a Bruker WM-250 FT-spectrometer controlled by an Aspect 2000 computer at 250 (^{1}H) and 63 (^{13}C) MHz, with the ^{2}H-signal of the solvent as the lock and TMS as internal standard. The most important measuring parameters were as follows: spectral width 5 and 18.5 kHz, pulse width 1.0 (^{1}H) and 7.0 (^{13}C) μs (~20° and ~90° flip angle, respectively), acquisition time 1.64 and 0.40 s, number of scans 16 (^{1}H) and 256-3.5 K (^{13}C), computer memory 16 K, Lorentzian exponential multiplication for signal-to-noise enhancement (line width 0.7 or 1.0 Hz), and complete proton noise decoupling (*ca.* 0.5 W) for the ^{13}C-nmr spectrum. The standard Bruker microprogram "DNOEMULT.AU" was used to generate NOE with a selective pre-irradiation time of 5 s and a decoupling power (CW mode) of *ca.* 3-40 mW. The 2D-HSC spectra were obtained by using the standard Bruker pulse program "XHCORRD. AU". Data points: 4 K (^{13}C domain), increments: 64-256, digital resolution (^{1}H domain): better than 5 Hz/point, transients: 256, relaxation delay: 3 s. All C-H correlations were found by using J(C,H) = 135 Hz for calculation of the delay. DEPT spectra[26] were run in a standard way,[27] using only the $\theta = 135°$ pulse to separate the CH/CH_3 and CH_2 lines phased up and down, respectively. Selective INEPT experiments (INAPT) were performed according to the literature,[28] using a modified version of the Bruker microprogram "INEPTRD". The polarization transfer delays were set to 36 ms, corresponding to J(C,H) = 7 Hz, and the pulse width of the soft pulse (90°, ^{1}H decoupler) was set to 10 ms.

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

The physical and analytical data on compounds (**3-14**) are listed in Table 3.

9b-(*p*-Tolyl)-1,2,3,5a,6,7,8,9,9a,9b-decahydro-5*H*-imidazo- (3), 10b-(*p*-tolyl)-1,2,3,4,5,6a,7,8,9,10,10a,10b-dodecahydro-6*H*-pyrimido- (4) and 11b-(*p*-tolyl)-1,2,3,4,5,7a,8,9,10,11,11a,11b-dodecahydro[1,3]diazepino [2,1-*a*]isoindolone (5) (General method)

A solution of *cis*-2-(*p*-methylbenzoyl)-1-cyclohexanecarboxylic acid (**1**) (6.15 g; 25 mmol), ethylenediamine or 1,3-diaminopropane or 1,4-diaminobutane (75 mmol) and *p*-toluenesulphonic acid (one crystal) in dry toluene (50 ml) was refluxed for 5-6 h, a water separator being applied. After evaporation of the mixture, the residue was dissolved in benzene (10 ml) and chromatographed on a silica gel column (Kieselgel 60, 0.063-0.2 mm) with EtOAc. The eluate was evaporated off and the residue was crystallized. The methylene-bridged derivatives (**6-8**) were prepared from *diendo*-3-(*p*-methylbenzoyl)bicyclo[2.2.1]heptane-2-carboxylic acid (**2**) (6.2 g; 25 mmol) as above.

9b-(*p*-Tolyl)-2,3,5a,6,7,8,9,9a-octahydrooxazolo[2,3-*a*]isoindol-5(9b*H*)-one (9) and 10b-(*p*-tolyl)-2,3,4,5,6a,7,8,9,10,10a-decahydro-10b*H*-[1,3]oxazino[2,3-*a*]isoindol-6-one (10)

A mixture of **1** (6.15 g; 25 mmol), ethanolamine or 3-amino-1-propanol (1.88 g; 25 mmol) and *p*-toluenesulphonic acid (1 crystal) in dry benzene (50 ml) was refluxed for 5-6 h, a water separator being applied.

After evaporation, the residue was dissolved in benzene (10 ml) and the solution was chromatographed on a silica gel column with benzene. The residue of the eluate was crystallized from EtOH.

Table 3. Physical and analytical data on compounds **3-14**

Compound	mp °C	Yield %	Molecular formula	Found % C	H	N	Required % C	H	N
3	168-170[a]	46	$C_{17}H_{22}N_2O$	75.33	8.28	10.42	75.52	8.20	10.36
4	216-218[b]	43	$C_{18}H_{24}N_2O$	76.19	8.59	9.91	76.02	8.50	9.50
5	160-162[a]	40	$C_{19}H_{26}N_2O$	76.50	8.80	9.45	76.47	8.78	9.39
6	220-222[c]	27	$C_{18}H_{22}N_2O$	76.47	7.95	9.87	76.56	7.85	9.92
7	178-180[a]	38	$C_{19}H_{24}N_2O$	76.80	8.30	9.55	76.98	8.16	9.45
8	195-197[c]	30	$C_{20}H_{26}N_2O$	77.40	8.50	9.20	77.38	8.44	9.02
9	178-180[b]	44	$C_{17}H_{21}NO_2$	75.35	7.85	5.20	75.24	7.80	5.16
10	135-137[d]	35	$C_{18}H_{23}NO_2$	75.60	8.15	5.03	75.75	8.12	4.91
11	138-140[b]	56	$C_{17}H_{21}NOS$	71.21	7.45	4.70	71.05	7.36	4.87
12	110-112[d]	30	$C_{17}H_{21}NO_2$	75.31	7.93	5.13	75.24	7.80	5.16
13	188-190[a]	52	$C_{21}H_{22}N_2O$	79.40	6.81	8.67	79.21	6.96	8.80
14	155-157[a]	49	$C_{21}H_{21}NOS$	75.33	6.33	4.06	75.18	6.31	4.17

[a] From benzene–*n*-hexane; [b] From EtOH; [c] From EtOAc; [d] From EtOH – Et_2O

9-(*p*-Tolyl)-2,3,5a,6,7,8,9a-octahydrothiazolo[2,3-*a*]isoindolone (11)

A mixture of **1** (1.93 g; 25 mmol), 2-aminoethanethiol (1.93 g; 25 mmol) and *p*-toluenesulphonic acid (1 crystal) in dry toluene (50 ml) was refluxed for 5-6 h, a water separator being applied. After evaporation, the residue was chromatographed and crystallized as above.

1-(*p*-Tolyl)-2-hydroxyethyl-1,3,4,5,6,7-hexahydroisoindol-3-one (12)

A mixture of **1** (6.15 g; 25 mmol), 2-aminoethanol (1.53 g; 25 mmol) and *p*-toluenesulphonic acid (1 crystal) in xylene (50 ml) was refluxed for 5-6 h. The solvent was evaporated off and the residue was eluted from a silica gel column, first with benzene, and then with EtOAc. **12** was isolated from the residue of the EtOAc eluate.

11b-(*p*-Tolyl)-5a,5b,6,7,8,9,9a,11-octahydroisoindolo[2,1-*a*]benzimidazol-10-one (13) and 5a-(*p*-tolyl)-5a,5b,6,7,8,9,9a,11-octahydroisoindolo[2,3-*a*]benzthiazol-10-one (14)

A mixture of **1** (6.15 g; 25 mmol), *o*-phenylenediamine (2.70 g; 25 mmol) or *o*-aminothiophenol (3.13 g; 25 mmol) and *p*-toluenesulphonic acid (1 crystal) in dry toluene (50 ml) was refluxed for 3 h, a water separator being used. After removal of the solvent, the residue was purified by column chromatography as above; solvent: benzene.

* * *

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