

SYNTHESIS AND STRUCTURAL STUDY OF NEW SATURATED ISOINDOL-1-ONE DERIVATIVES

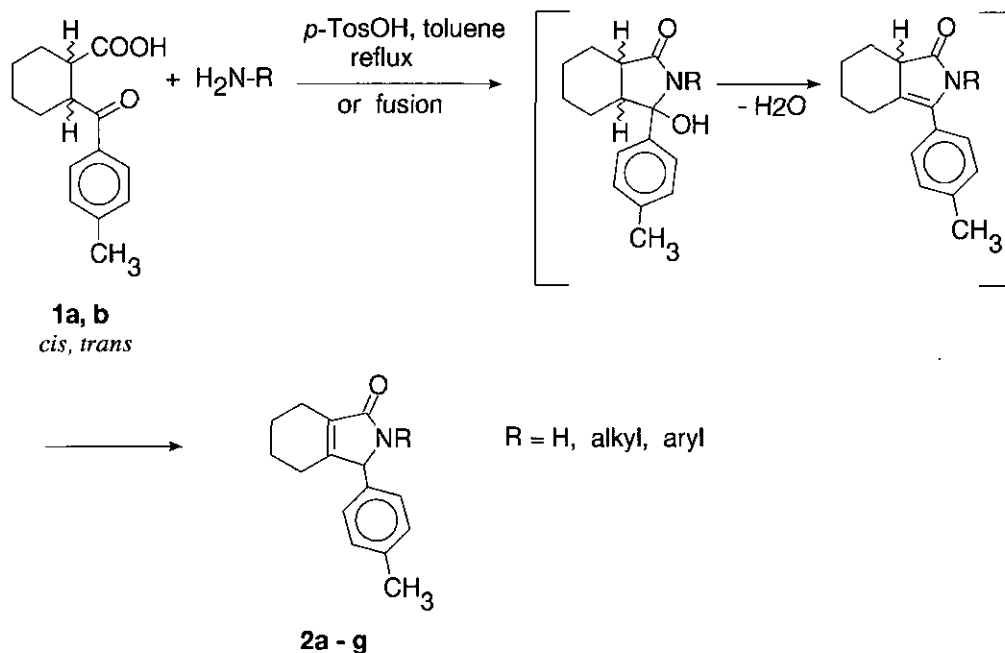
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Abstract- Condensation of 2-*p*-toluoylcyclohexanecarboxylic acid (**1a,b**) with primary amines gave the corresponding hexahydroisoindol-1-ones (**2a-g**) in good yield. The octahydro derivatives (**4a-g**) were prepared from *cis*- and *trans*-hexahydro-1(2*H*)-phthalazinone (**3a,b**) by reduction with zinc-hydrochloric acid *via* ring contraction. Stereoselective synthesis of *cis*-*N*-phenyloctahydroisoindol-1-one (**4h**) was performed starting from **2b** by reduction with magnesium-methanol at room temperature. Configurational assignments of *cis* and *trans* isomers were based on ¹H- and ¹³C-nmr spectroscopic studies.

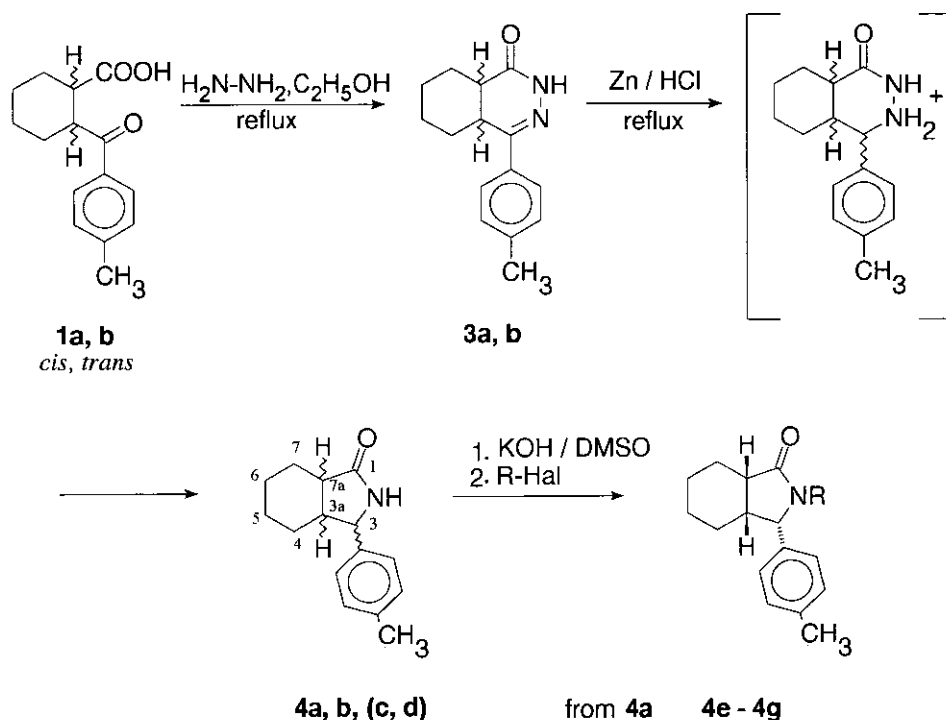
The 3-arylisoindol-1-one derivatives have been associated with important pharmacological properties, such as antiarrhythmic, antitussive, and antiinflammatory activities among others.¹⁻⁴ Synthesis of these compounds was carried out mostly from corresponding 1,4-dicarbonyl compounds by reductive cyclisation with primary amines.²⁻⁶ Yamamoto *et al.* prepared *N*-phenyl substituted isoindolines from aromatic isocyanates.⁷ In the course of our work we investigated the reactions of the cyclohexane condensed keto acids with primary amines, with the aim to synthesize pharmacologically active derivatives. The conditions of these reactions were strongly determined by the basicity of applied amines. Alkyl- or cycloalkylamines (e.g. cyclohexylamine) reacted readily under relatively mild conditions (reflux in benzene or toluene for several hours) with keto acid (**1a,b**) but condensation with aromatic amines took place only by fusion at 150-180°C (Scheme 1).



Scheme 1

Reaction of aromatic and aliphatic keto acids with amines give various keto amides, and their ring-chain tautomerism is well known from literature.⁸ However in our case carbon-carbon double bond comes into being at the annelation, and the molecule was stabilized by the ring formation.

Synthesis of *N*-unsubstituted hexahydro derivative (**2a**) was performed by heating of keto acid (**1a,b**) with formamide or urea at 180-200°C. In fact ammonia rises *in situ* at this temperature and it reacts with keto acid. The ring contraction of phthalazinone derivatives by zinc-hydrochloric acid reduction to isoindolines is well known.^{4,9,10} In this way we prepared *cis*- and *trans*- octahydroisoindoles (**4a,b**) in moderate yield (Scheme 2). We found the reaction highly stereoselective (>90% by hplc), furthermore the *cis* and *trans* junctions were unchanged in the course of ring contraction.



Scheme 2

This reaction theoretically could result two *cis*- and two *trans*-isomers depending on the configurations of C-3 as shown in Scheme 3. In order to prove the structure of stereoisomers prepared we used different nmr techniques. The configurational assignments of compounds investigated are based on their homo- and heteronuclear correlation spectra as well as their APT and NOE difference spectra (Figures 1,2). Saturating the H-3 proton (4.8 ppm) in the *cis* isomer we could observe nearly the same strong NOEs on two aliphatic protons besides the homoaromatic protons and NH proton. On the basis of 2D heteronuclear correlation (HETCOR) spectrum these aliphatic protons belong to the carbons at 41.00 and 43.23ppm. Because these carbons proved to be methine carbons (APT spectrum), these protons must be H-3a and H-7a. 2D Homonuclear correlation (COSY) spectrum showed a strong cross peak between H-3 and a proton which gave NOE at ~2.5ppm reflecting their scalar coupling so it can be assigned as H-3a. In this way we managed to assign those protons which are nearly the same distance from H-3, confirming *cis* junction of H-3 and H-3a. From these results the *cis* isomer can be given as **4a**.

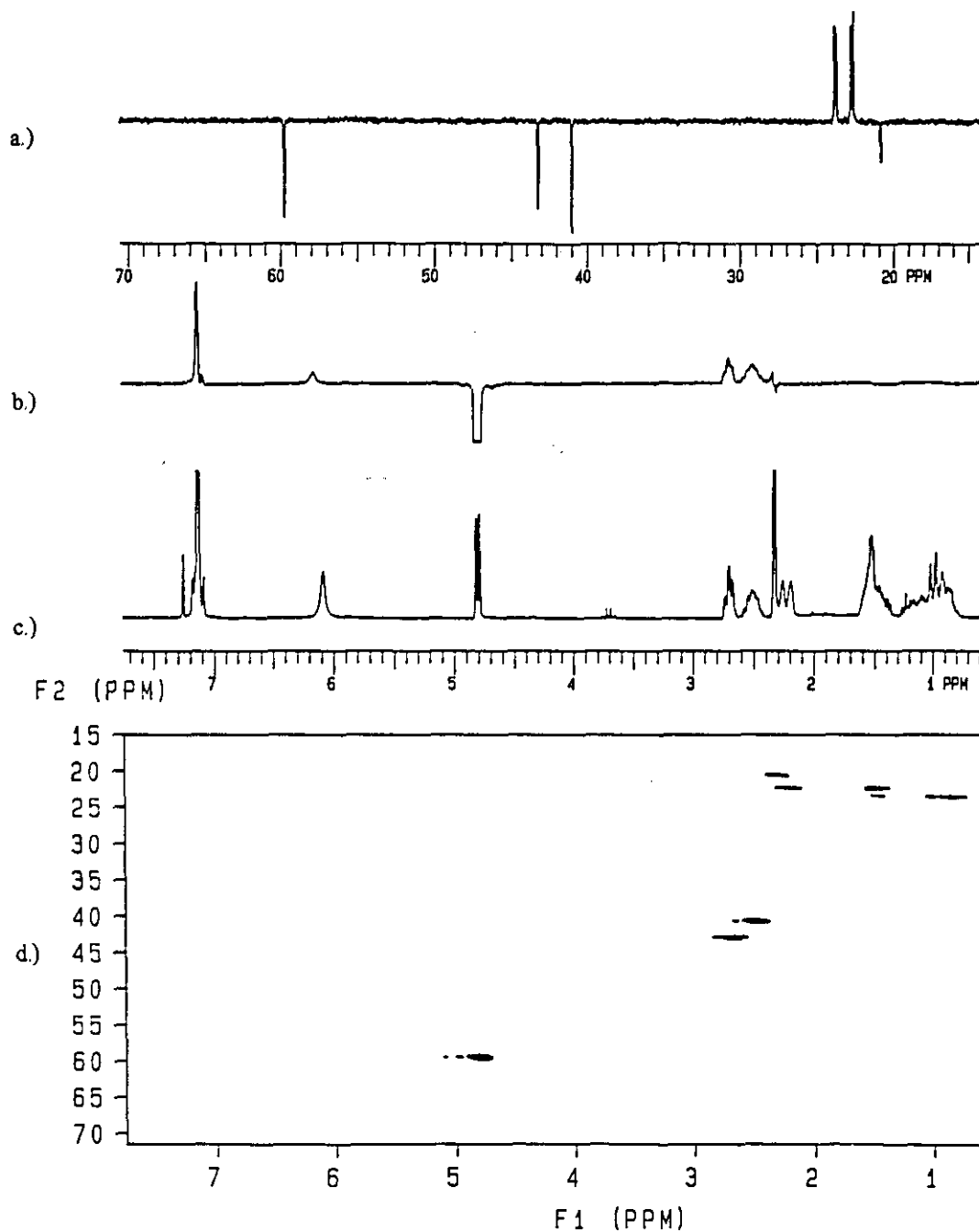


Figure 1 a.) Partial APT, b.) NOE difference, c.) proton and d.) 2D heteronuclear correlation (HETCOR) spectra of compound (**4a**)

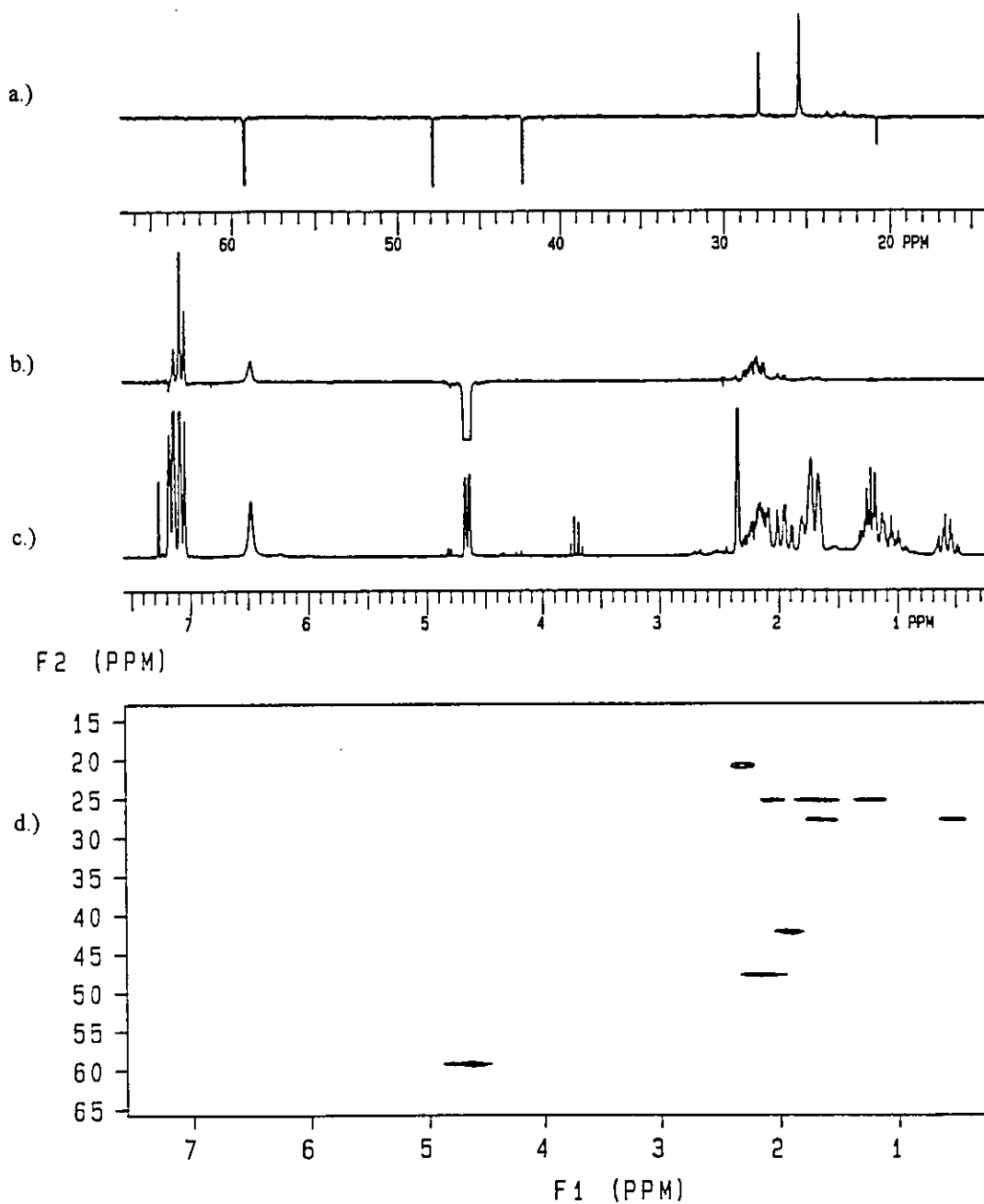
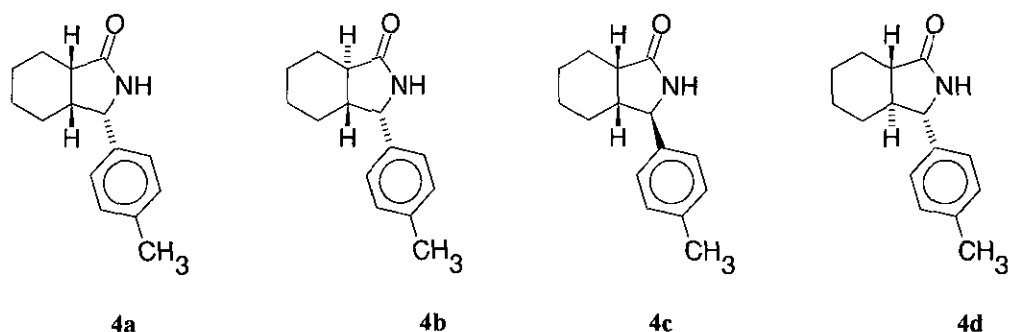


Figure 2 a.) Partial APT, b.) NOE difference, c.) proton and d.) 2D heteronuclear correlation (HETCOR) spectra of compound (4b)



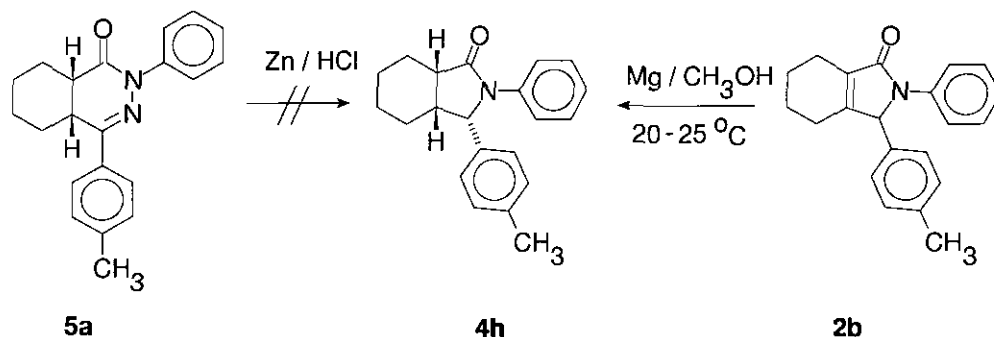
Scheme 3

In case of *trans* isomer, saturating also H-3 proton (~ 4.65 ppm), the NOE difference spectrum also showed NOEs on homoaromatic protons and NH proton, but in aliphatic region the intensities of observed signals were very different. Besides a weak signal at about 1.95 ppm a strong NOE could be observed between 2.10 and 2.30 ppm. The proton spectrum showed that two protons gave signal in this region. On the basis of HETCOR and APT spectra, one of them proved to be methine proton and the other might be assigned to one of the methylene protons, probably on C-7. From the COSY spectrum this methine proton could be assigned as H-3a because it gave strong cross peak with H-3. Consequently, the proton gave a weak signal in NOEDIF spectrum at ~ 1.95 ppm must be H-7a because it belongs to the other methine carbon at 42.34 ppm. Based on these results, the structure of *trans* isomer investigated could be written as **4b**. Chemical shifts of H-3 protons and their coupling constants with H-3a for compounds prepared are given in Table 1.

Table 1. Selected ^1H -nmr data of 2-substituted 3-(*p*-tolyl)-1-oxo-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindoles (**4a-4h**).

Compound	R	H-3 (δ , ppm)	$^3J_{\text{H-3, H-3a}}$ (Hz)
4a (<i>cis</i>)	H	4.83	5.3
4b (<i>trans</i>)	H	4.65	7.0
4e	Ph-CH ₂ -	4.35	5.5
4f	Ph-(CH ₂) ₂ -	4.35	5.5
4g	<i>N</i> -morpholinylethyl-	4.73	5.5
4h	Ph	5.30	5.5

We prepared several *cis*-*N*-substituted derivatives by alkylation using strong basic condition (potassium hydroxide-dimethyl sulfoxide) at various temperatures from **4a** according to Isele and Lüttringhaus.¹¹ Thus, benzyl chloride gave a 69% yield of **4e** in 30 minutes at 20–25°C, however phenethyl bromide was less reactive. In this case the alkylation was slower and resulted in the formation of **4f** only 24% yield in 5 hours, even at 60°C.



Scheme 4

Because of diminished reactivity of aryl halides, the synthesis of *N*-phenyl substituted isoindol-1-one (**4h**) was impossible in this way. Similarly the reduction of compound (**5a**) was unsuccessful by zinc-hydrochloric acid, therefore we applied selective reduction of α,β -olefinic amides by magnesium-methanol at 20–25°C.^{12,13} The reaction is extremely simple to carry out, there is a short induction period, before a moderate exothermic reaction occurs, if necessary the reaction can be controlled by external cooling. This method proved highly stereoselective and gave all *cis* isomer in a fairly good yield. The structure of **4h** was elucidated by similar nmr investigations as it was described for **4a**. In other cases (**2c-g**) the reduction was not successful.

In conclusion, we elaborated novel synthetic routes for the preparation of saturated isoindol-1-one derivatives. These methods are more simple, convenient and useful comparing the existing ones. Stereochemistry of these new compounds synthesized was unambiguously proved by combined nmr methods.

EXPERIMENTAL

Melting points were determined using an Electrothermal block and are uncorrected. Infrared spectra were recorded for KBr discs with a Perkin-Elmer 177 instrument. ^1H and ^{13}C nmr spectra were measured in CDCl_3 solutions on a Varian Gemini-200 instrument operating at 200.13 and 50.3 MHz, respectively, at a probe temperature of 20°C . A 5 mm dual probe head was used. Chemical shifts (δ) are in ppm from internal tetramethylsilane ($\delta=0$) or referenced to CDCl_3 ($\delta=77.0$) for carbon measurements. Magnitude-mode ^1H - ^1H correlation (COSY) spectra were recorded with 2K datapoints and 256 t_1 increments in 1500-1800 Hz spectral windows. Heteronuclear ^1H - ^{13}C correlation (HETCOR) spectra were measured by running standard Varian HETCOR sequence using decoupling in f_1 dimension. Typically $1\text{K} \times 64 t_1$ datapoints were acquired with 7 kHz carbon spectral window. Carbon multiplicities could be determined with the aid of standard Varian APT (Attached Proton Test) sequence using a 7 msec delay period which gives quaternary or secondary carbons up and primary or tertiary carbons down. NOE difference spectra were measured using standard NOEDIF experiment. A presaturation time of 6 sec was applied. Ascending thin layer chromatography was performed on precoated plates of silicagel 60F 254(Merck) and spots were visualized by using UV lamp or iodine vapor. Mass spectra were scanned on a VG TRIO-2 spectrometer in EI mode at 70eV.

Preparation of cis- and trans-2-p-toluoylcyclohexanecarboxylic acids (1a and 1b).

The starting compound (**1a**) was prepared by the procedure reported by Fieser and Novello.¹⁴ Yield of **1a** 92%, mp $127\text{--}129^\circ\text{C}$. Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_3$: C, 73.14; H, 7.36. Found: C, 73.32; H, 7.40. ^1H -Nmr (CDCl_3): δ 1.20-1.50 (m, 3H), 1.65-2.37 (m, 5H), 2.40 (s, 3H, methyl protons), 2.62-2.70 (m, 1H), 3.82-3.92 (m, 1H), 7.22 (d, $J=8.0$ Hz, 2H), 7.78 (d, $J=7.4$ Hz, 2H), 10.77 (br, s, 1H); ir (cm^{-1})(KBr): 2970, 1705, 1690; ms: m/z 246 (M^+ , 3), 231 (3), 137 (9), 119 (100).

The *trans* keto acid (**1b**) was obtained as colourless needles from epimerization of **1a** with 2M sodium hydroxide solution according to the method of Jucker and Süess.¹⁵ Yield of **1b** 87%, mp $171\text{--}172^\circ\text{C}$. Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_3$: C, 73.14; H, 7.36. Found: C, 73.25; H, 7.42. ^1H -Nmr (CDCl_3): δ 1.07-1.55 (m, 4H), 1.72-2.26 (m, 4H), 2.40 (s, 3H, methyl protons), 2.80-2.97 (m, 1H), 3.40-3.57 (m, 1H), 7.20 (d, $J=7.4$ Hz, 2H), 7.82 (d, $J=8.0$ Hz, 2H), 11.15 (br, s, 1H); ir (cm^{-1})(KBr): 2962, 1710, 1680; ms: m/z 246 (M^+ , 3), 231 (3), 137 (7), 119 (100).

3-(p-Tolyl)-1-oxo-2,3,4,5,6,7-hexahydro-1H-isoindole (2a).

Mixture of 2.46 g (0.01 mol) of *cis*- or *trans*-2-*p*-toluoylcyclohexanecarboxylic acid (**1a,b**) and 10 ml of formamide was heated at 180-200°C for 4-5 h. 20 ml water was added to the cooled reaction mixture, the precipitate was filtered and washed with 10% sodium hydroxide solution (3X10 ml), and water, to obtain 0.93 g (41%) of **2a**, mp 172-174°C. Anal. Calcd for C₁₃H₁₇NO: C, 79.25; H, 7.54; N, 6.16. Found: C, 79.38; H, 7.60; N, 6.25. ¹H-Nmr (CDCl₃): δ 1.50-2.28 (m, 8H, aliphatic protons), 2.30 (s, 3H), 4.85 (s, 1H, a benzylic proton), 6.85 (s, 1H, NH), 7.00-7.15 (m, 4H, aromatic protons); ir (cm⁻¹)(KBr): 3206, 2944, 1684; ms: m/z 227 (M⁺, 100), 198 (50), 185 (65).

Preparation of 2-alkyl-3-(p-tolyl)-1-oxo-2,3,4,5,6,7-hexahydro-1H-isoindoles (2c-2g). General procedure.

A solution of 2.46 g (0.01 mol) of keto acid (**1a,b**) in dry benzene or toluene (30 ml) was treated with the corresponding amine (0.015 mol) and 0.10 g of *p*-toluenesulfonic acid, then refluxed 5-8 h in a Dean-Stark apparatus placed in a 120°C bath. The reaction mixture was evaporated and the residue was purified by crystallisation or by column chromatography (silica gel packing, chloroform eluent).

Table 2. Physical and analytical data of 2-substituted 3-(*p*-tolyl)-1-oxo-2,3,4,5,6,7-hexahydro-1H-isoindoles (**2c-2g**).

Compound	R	mp(°C)	Yield(%)	Formula	Elemental analysis (%)		
					Calcd (Found)		
					C	H	N
2c	Ph-CH ₂ -	103-105 ^a	66	C ₂₂ H ₂₃ NO	83.24(83.60)	7.30(7.22)	4.41(4.50)
2d	Ph-(CH ₂) ₂ -	151-153 ^b	85	C ₂₃ H ₂₅ NO	83.34(83.59)	7.60(7.53)	4.22(4.27)
2e	Cyclohexyl-	108-110 ^a	70	C ₂₁ H ₂₇ NO	81.50(81.73)	8.79(8.85)	4.52(4.49)
2f	(C ₂ H ₅) ₂ N(CH ₂) ₂ -	oil ^c	80	C ₂₁ H ₃₀ N ₂ O	77.25(77.62)	9.26(9.40)	8.58(8.63)
2g	<i>N</i> -morpholinylethyl-	73-75 ^d	77	C ₂₁ H ₂₈ N ₂ O ₂	74.08(74.29)	8.29(8.38)	8.23(8.18)

^a From hexane; ^b From ethanol; ^c As hydrochloride salt, mp 147-149°C; ^d From ether-pentane

2-Phenyl-3-(p-tolyl)-1-oxo-2,3,4,5,6,7-hexahydro-1H-isoindole (2b).

Mixture of 2.46 g (0.01 mol) of keto acid (**1a,b**) and 1.12 g (0.012 mol) of aniline was heated at about 150-160°C for 3 h. After cooling to room temperature was added 10 ml of ethanol, and kept in refrigerator overnight. The precipitate was collected, washed with cold ethanol and crystallized from ethanol to give **2b**, 1.82 g (60%), mp 155-157°C. Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.58; H, 7.02; N, 4.70. 1H -Nmr ($CDCl_3$): δ 1.50-1.95 (m, 5H), 2.10-2.40 (m, 6H), 5.35 (s, 1H, a benzylic proton), 6.93-7.12 (m, 5H), 7.22 (t, $J=7.1$ Hz, 2H), 7.52 (d, $J=7.9$ Hz, 2H); ir (cm^{-1})(KBr): 2917, 1666; ms: m/z 303 (M^+ , 20), 228 (50), 119 (100).

cis- and trans- 4a,5,6,7,8,8a-Hexahydro-4-(p-tolyl)-phthalazin-1(2H)-one (3a,b). General procedure.

The mixture of 4.92 g (0.02 mol) of keto acid (**1a** or **1b**) and 1.02 g (0.02 mol) of hydrazine monohydrate (98%) was refluxed in ethanol (25 ml) for 2 h, cooled to room temperature and the precipitate was filtered off and washed with water. Yield of **3a** 3.78 g (78%), mp 169-170°C. Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.48; N, 11.56. Found: C, 74.72; H, 7.57; N, 11.64. 1H -Nmr ($CDCl_3$): δ 1.20-1.90 (m, 7H), 2.37 (s, 3H, methyl protons), 2.50-2.60 (d, 1H), 2.75 (s, 1H), 3.05-3.20 (m, 1H), 7.20 (m, 2H), 7.65 (d, $J=9.7$ Hz, 2H), 8.75 (s, 1H, NH); ir (cm^{-1})(KBr): 3210, 2937, 2926, 1666; ms: m/z 242 (M^+ , 88), 187 (100).

Yield of **3b** 3.39 g (70%), mp 191-193°C. Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.48; N, 11.56. Found: C, 74.50; H, 7.36; N, 11.70. 1H -Nmr ($CDCl_3$): δ 1.00-1.40 (m, 4H), 1.70-1.90 (m, 2H), 2.00-2.20 (m, 2H), 2.35 (s, 3H, methyl protons), 2.40-2.70 (m, 2H), 7.20 (s, 4H), 8.75 (s, 1H, NH); ir (cm^{-1})(KBr): 3250, 2950, 2875, 1680; ms: m/z 242 (M^+ , 92), 187 (100).

cis- and trans-3-(p-Tolyl)-1-oxo-2,3,3a,4,5,6,7,7a-octahydro-1H-isoindole (4a,b). General procedure.

2.46 g (0.01 mol) of **3a** or **3b** was added to mixture of 5.0 g (0.76 mol) zinc powder and 30 ml of 1:1 hydrochloric acid, and the reaction mixture was refluxed for 5 h. After cooling to room temperature the reaction mixture was extracted with dichloromethane (3X25 ml). The extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure and the residue was crystallized from ethanol to obtain 1.03 g (45%) of **4a**, mp 195-197°C. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.75; H, 8.50; N, 6.16. 1H -Nmr ($CDCl_3$): δ 0.80-1.25 (m, 4H), 1.37-1.65 (m, 3H), 2.18-2.77 (m, 3H), 2.33 (s, 3H, methyl protons), 4.83 (d, $J=5.3$ Hz, 1H, a benzylic proton), 5.83 (s, 1H, NH), 7.08-7.21 (m, 4H, aromatic protons); ir (cm^{-1})(KBr): 3208, 2939, 2856, 1693; ms: m/z 229 (M^+ , 62), 214 (28), 186 (10), 120 (100).

Yield of **4b** 0.92 g (40%), mp 198-199°C. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.81; H, 8.46; N, 6.06. 1H -Nmr ($CDCl_3$): δ 0.46-0.68 (m, 1H), 0.90-1.35 (m, 3H), 1.62-2.31 (m, 6H), 2.35 (s, 3H, methyl protons), 4.65 (d, $J=7.0$ Hz, 1H, a benzylic proton), 6.07 (s, 1H, NH), 7.02-7.20 (m, 4H, aromatic protons); ir (cm^{-1})(KBr): 3225, 2940, 2870, 1705; ms: m/z 229 (M^+ , 73), 214 (20), 186 (10), 120 (100).

cis-2-Alkyl-3-(p-tolyl)-1-oxo-2,3,3a,4,5,6,7,7a-octahydro-1H-isoindole (4e-4g). General procedure.

0.45 g (0.008 mol) of powdered potassium hydroxide was added to 4 ml of dimethyl sulfoxide. After stirring for 5 min, 0.46 g (0.002 mol) of **3a** was added, followed immediately by the alkyl halide (0.004 mol). Stirring was continued at 20-25°C for 1 h (**4e**) or at 60°C for 5-10 h (**4f,g**). The mixture was poured into water (40 ml), and extracted with dichloromethane (3X20 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by crystallisation or by column chromatography (silica gel packing, chloroform eluent).

Table 3. Physical and analytical data of *cis-2*-substituted 3-(*p*-tolyl)-1-oxo-2,3,3a,4,5,6,7,7a-octahydro-1H-isoindoles (**4e-4g**).

Compound	R	mp(°C)	Yield(%)	Formula	Elemental analysis (%)		
					Calcd (Found)		
					C	H	N
4e	Ph-CH ₂ -	113-115 ^a	69	$C_{22}H_{25}NO$	82.72(82.98)	7.89(7.81)	4.38(4.50)
4f	Ph-(CH ₂) ₂ -	oil	24	$C_{23}H_{27}NO$	82.84(83.15)	8.16(8.22)	4.20(4.31)
4g	<i>N</i> -morpholinylethyl-	oil	28	$C_{21}H_{23}NO$	73.64(73.97)	6.77(6.85)	4.09(4.15)

^a From ethanol

cis-2-Phenyl-3-(p-tolyl)-1-oxo-2,3,3a,4,5,6,7,7a-octahydro-1H-isoindole (4h).

The compound (**2b**) (1.51 g, 0.005 mol) was reduced using 0.24 g (0.01 mol) of magnesium turnings covered by methanol (25 ml) at 20-25°C. After an induction period an exothermic reaction ensued, which was controlled by immersing the reaction flask in an ice-bath. The resultant slurry was then stirred at 20-25°C for 8-10 h. 20 ml of 3M hydrochloric acid was added dropwise and the resultant solution was extracted with dichloromethane (3X20 ml). The combined extracts were washed with water, dried (Na_2SO_4), and the solvent was removed.

The residue was crystallized from ethanol to afford 0.61 g (40%) of **4h**, mp 162-164°C. Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.58. Found: C, 82.73; H, 7.65; N, 4.52. 1H -Nmr ($CDCl_3$): δ 0.80-1.70 (m, 7H, aliphatic protons), 2.25 (s, 3H), 2.28-2.40 (m, 1H), 2.50-2.65 (m, 1H), 2.75-2.85 (m, 1H), 5.30 (d, $J=5.5$ Hz, 1H, a benzylic proton), 6.90-7.10 (m, 5H), 7.18-7.35 (m, 4H); ir (cm^{-1})(KBr): 2960, 2940, 2870, 1712; ms: m/z 305 (M^+ , 75), 194 (75), 77 (100).

Table 4. 1H -Nmr and mass spectral data of compounds (**2c-2g** and **4e-4g**).

Compound	1H -nmr ^a δ (ppm), J (Hz)	ms: m/z (%)
2c	1.50-2.32 (m, 8H, aliphatic protons), 2.36 (s, 3H, methyl protons), 3.57 (d, $J=14.5$, 1H), 4.53 (s, 1H, a benzylic proton), 5.18 (d, $J=14.5$, 1H), 6.90 (d, $J=8.3$, 2H), 7.09-7.27 (m, 7H, aromatic protons).	317 (M^+ , 47), 91(100).
2d	1.50-2.23(m, 8H, aliphatic protons), 2.32 (s, 3H, methyl protons), 2.64-3.00(m, 3H), 3.90-4.05 (m, 1H), 4.46(s, 1H, a benzylic proton), 6.83 (d, $J=8.2$, 2H), 7.07-7.30 (m, 7H, aromatic protons).	331 (M^+ , 5), 240 (100).
2e	0.80-2.40 (m, 18H, aliphatic protons), 2.35 (s, 3H, methyl protons), 3.72-3.90 (m, 1H), 4.75 (s, 1H, a benzylic proton), 7.00 (d, $J=8.3$, 2H), 7.13 (d, $J=7.4$, 2H).	309 (M^+ , 100), 266 (90), 227 (80).
2f	0.95 (t, $J=7.6$, 5H), 1.52-2.33 (m, 10H), 2.34 (s, 3H, methyl protons), 2.35-2.65 (m, 5H), 2.75-2.90 (m, 1H), 3.70-3.83 (m, 1H), 4.94 (s, 1H, a benzylic proton), 6.97 (d, $J=8.5$, 2H), 7.15 (d, $J=8.5$, 2H).	326 (M^+ , 30), 252 (35),
2g	1.50-2.40 (m, 10H), 2.35 (s, 3H, methyl protons), 2.40-2.55 (m, 1H), 2.80-2.93 (m, 1H), 3.65 (t, $J=4.8$, 4H), 3.78-3.93 (m, 1H), 4.98 (s, 1H, a benzylic proton), 6.95 (d, $J=8.0$, 2H), 7.15 (d, $J=8.0$, 2H).	340 (M^+ , 8), 228 (5), 112 (40), 100 (100).
4e	0.84-1.65 (m, 7H), 2.18-2.35 (m, 2H), 2.37 (s, 3H, methyl protons), 2.45-2.58 (m, 1H), 3.80 (d, $J=14.2$, 1H), 4.35 (d, $J=5.5$, 1H), 5.20 (d, $J=14.2$, 1H), 6.92-7.26 (m, 9H, aromatic protons).	319 (M^+ , 21), 228 (36), 91 (100).

4f	0.79-1.62 (m, 8H, aliphatic protons), 2.12-2.32 (m, 1H), 2.34 (s, 3H, methyl protons), 2.40-2.49 (m, 1H), 2.60-3.12 (m, 3H), 4.00-4.16 (m, 1H), 4.35 (d, J=5.5, 1H, a benzylic proton), 6.85-7.30 (m, 9H, aromatic protons).	333 (M ⁺ , 4), 242 (46), 91 (100).
4g	0.80-1.60 (m, 7H), 2.15-2.95 (m, 10H), 2.35 (s, 3H, methyl protons), 3.60 (t, J=4.3, 3H), 3.68-3.76(m, 1H), 3.92-4.09 (m, 1H), 4.73 (d, J=5.5, 1H), 4.73 (d, J=5.5, 1H), 7.06 (d, J=8.1, 2H), 7.17 (d, J=7.7, 2H).	342 (M ⁺ , 3), 228 (4), 100(100).

a) Spectra were recorded in deuteriochloroform

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