SYNTHESIS AND STRUCTURAL STUDY OF NOVEL 1,2-DIAZEPINONES AND AZABICYCLOOCTANE DERIVATIVES

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Abstract: Condensation of 3-toluoyl-1,2,2-trimethylcyclopentane-1-carboxylic acid **2** with hydrazine, diamines or 3-aminopropanol afforded the novel bicyclic 1,2-diazepinone **3** or various condensed azabicyclooctane derivatives **4-6**, respectively. Further transformations of the 1,2-diazepinone **3** to its perhydro **7** and *N*-methyl **8** derivatives are also described. Compound **3** when treated with Zn/HCl resulted in the azabicyclo[3.2.1] octanone derivative **9** by a stereoselective ring contraction. Lactone formation from **3** on treatment with acetic anhydride has also been attempted.

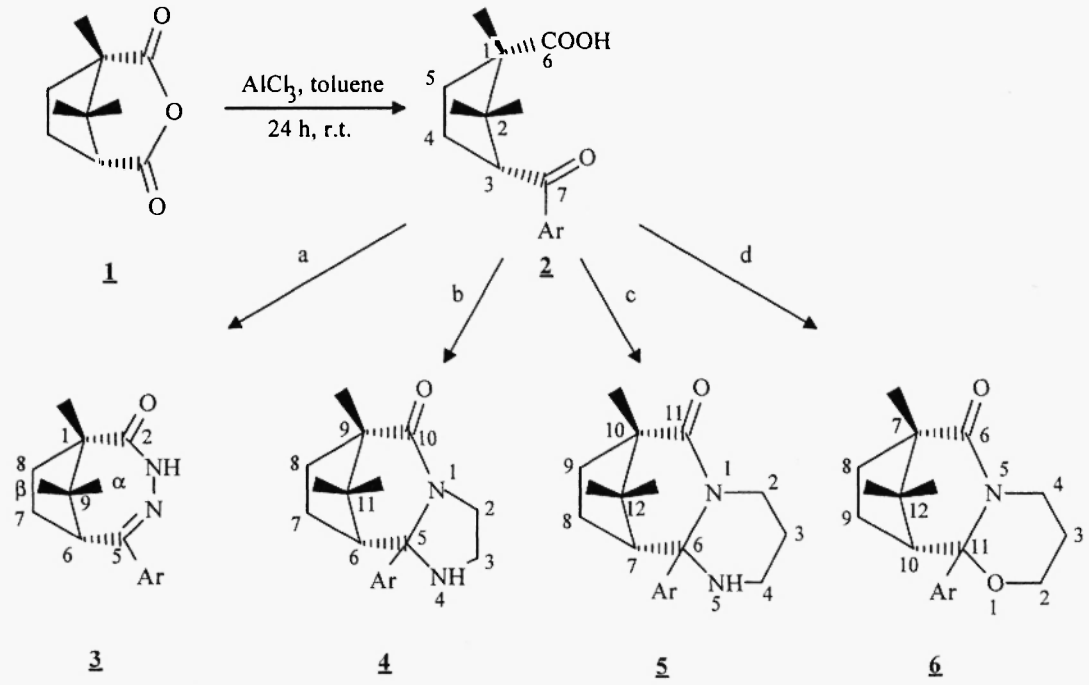
Introduction

δ-Oxocarboxylic acids are useful and versatile synthons for synthesis of several alkaloids and heterocycles possessing a range of pharmacological properties (1-11). These results prompted us to investigate the reaction of 3-aroyl-1,2,2-trimethylcyclopentane-1-carboxylic acids with bidentate nucleophiles since such cyclocondensation reactions of δ-oxocarboxylic acids having a cyclopentane skeleton have not been reported. The starting oxocarboxylic acids can be prepared easily from camphoric anhydride by Friedel-Crafts reaction which was studied recently in detail including a qualitative structure-reactivity relationship on substituted benzene derivatives (12-15).

Results and Discussion

In this paper we wish to report on the cyclocondensation reactions of 3-*p*-toluoyl-1,2,2-trimethyl-cyclopentane-1-carboxylic acid **2** with hydrazine, 1,2-ethylendiamine, 1,3-propylendiamine and 3-amino-propanol leading to representatives of new ring systems. Some further transformations of the products and our efforts to prepare a new lactone by intramolecular cyclisation of **2** are also reported.

We tried in vain to cyclize **2** with hydrazine under reflux in toluene for several hours according to the widely used method for the cyclocondensation of δ-ketoacids with hydrazine. Therefore we modified the reaction conditions and refluxing (~180 °C) 1,2-dichlorobenzene was found to be the best solvent. Thus we obtained the bicyclic 5,6-dihydro-4*H*-1,2-diazepin-7(1*H*)-one derivative **3**, a novel type of the diazepinones after 3 hours reflux in moderate (37 %) yield (Scheme 1).



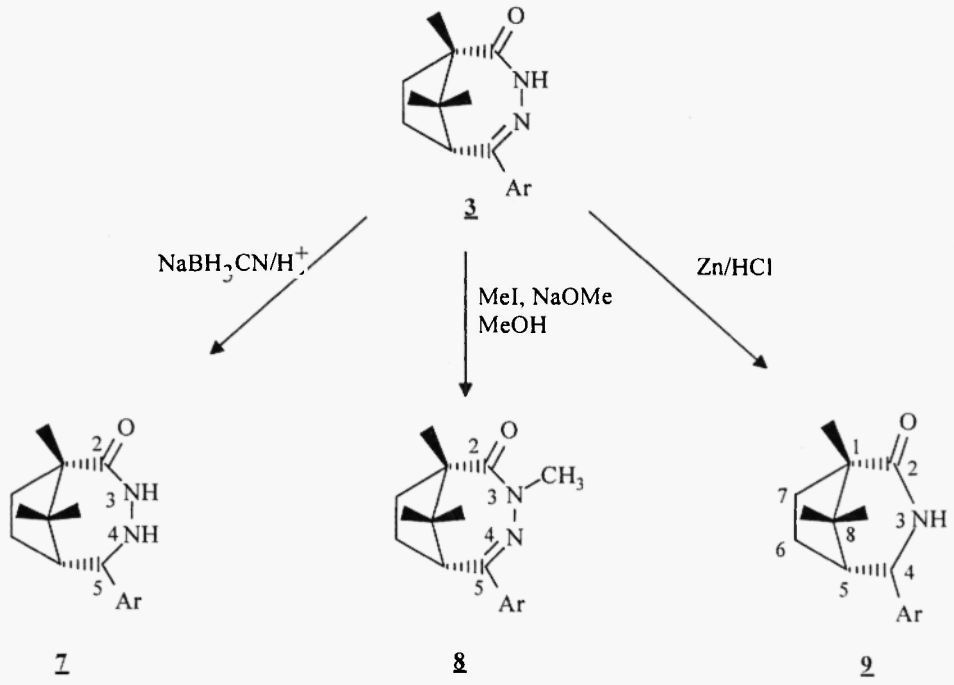
a: N_2H_4,; b: H_2N-$(CH_2)_2$-NH_2; c: H_2N-$(CH_2)_3$-NH_2; d: H_2N-$(CH_2)_3$-OH

Ar = *p*-tolyl

Scheme 1

Similarly, the cyclocondensation of **2** with α,ω-diaminoalkanes required vigorous conditions. Heating of ethylenediamine and **2** at 150-160 °C for 4 hours resulted in the new imidazolidine condensed azabicyclooctane **4**, while the 1,3-diaminopropane required an even higher temperature (~200 °C) to yield the new condensed pyrimidino derivative **5**. The reduced reactivity of **2** compared to the open chain analogues is more probably due to its cyclopentane skeleton, since the desired conformation for the cyclocondensation is energetically unfavourable. Interestingly, 3-amino-1-propanol still reacted readily in refluxing xylene in the presence of catalytic amount of the *p*-toluenesulphonic acid giving the fused oxazolidine **6**.

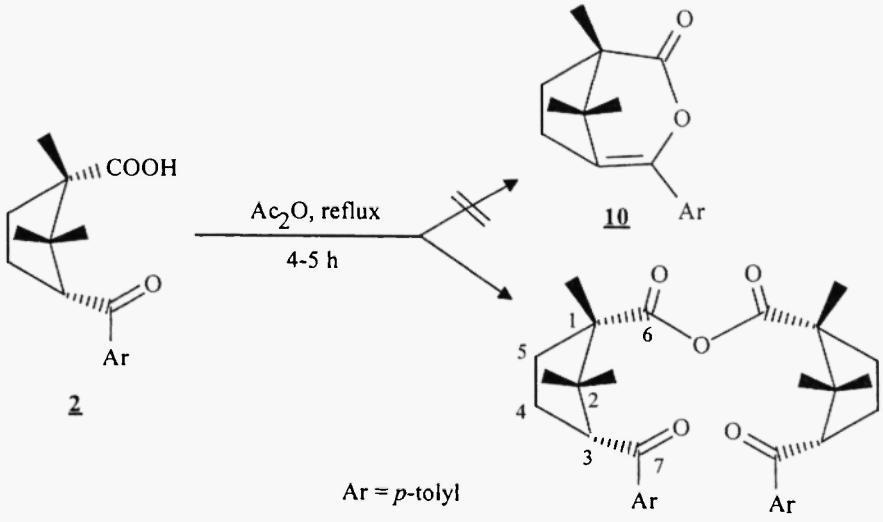
Some transformations of **3** were also attempted. When treated with $NaBH_3CN$ and hydrochloric acid in methanol at room temperature, its perhydro derivative **7** was formed (Scheme 2) by stereoselective reduction of the C=N double bond. For the synthesis of the *N*-methyl substituted diazepinone **8**, MeI was added to the compound **3** in MeOH in the presence of NaOMe and the mixture was refluxed for 6 hours. We have to mention here, that all our efforts to cyclocondense of **2** with monosubstituted (phenyl-, methyl-) hydrazines were unsuccessful. Only the corresponding hydrazone derivatives could be isolated. Treatment of **3** with Zn/HCl in aqueous solution resulted in the azabicyclooctane derivative **9** by ring contraction. This reaction proved also to be stereoselective like the reduction of **3** with $NaBH_3CN$.



Ar = *p*-tolyl

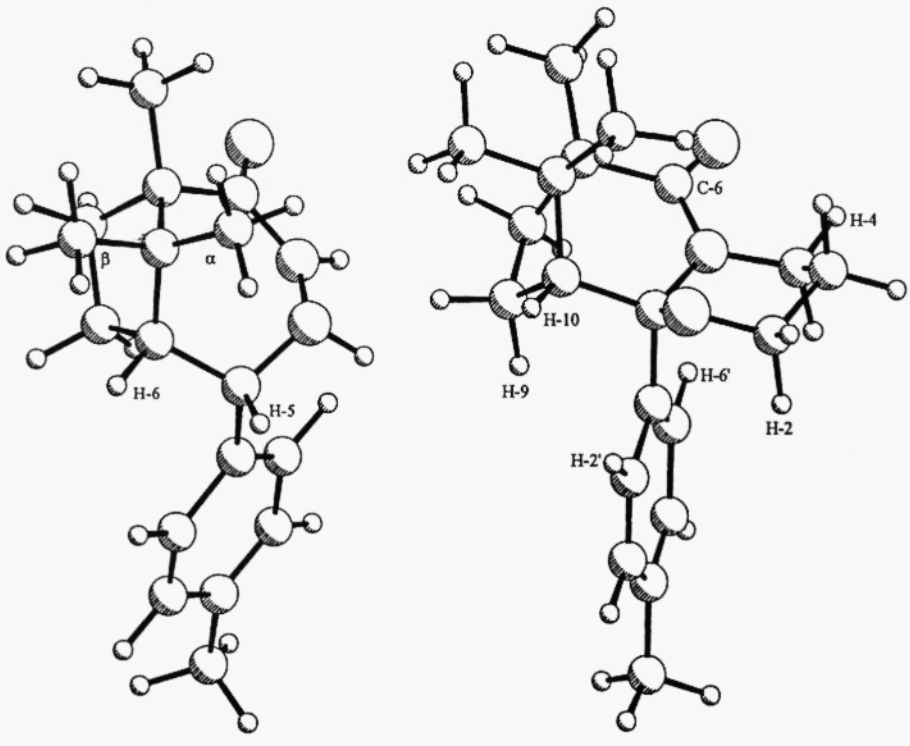
Scheme 2

It is known from the literature that γ-oxocarboxylic acids can be converted to unsaturated lactone derivatives *via* enolisation and dehydration by Ac_2O or AcCl (16,17). The fact that **2** is less prone to cyclocondense than its open chain analogues, induced us to investigate its propensity for lactone formation. When **2** was refluxed in Ac_2O for 5 hours it was converted almost quantitatively to an anhydride **11** instead of the expected lactone **10** (Scheme 3). The failure can also be attributed to the unfavourability of that cyclopentane conformation which is necessary for lactone ring formation.



Scheme 3

The structure of the compounds prepared were confirmed by ^{1}H and ^{13}C NMR, IR and mass spectroscopy, as well as by their elemental analysis data. The ^{1}H and ^{13}C NMR chemical shifts are given in Tables 1 and 2. To establish the stereochemistry homonuclear NOE difference experiments proved to be a very useful tool. For example, in the case of compound **3** and **8**, the proton signals of the methyl groups on C-9 could be distinguished by saturating the H-6 proton, which resulted in larger NOE on the β-methyl signal. In the case of compounds **7** and **9** the assignments of these methyl signals were achieved by saturating the H-5 (**7**) or H-4 (**9**) protons. During these experiments only one of the methyl signals (α-methyl) showed NOE besides the aromatic protons and H-6 (**7**) or H-5 (**9**), confirming the configuration of C-6 or C-5 in these compounds as it is shown in Figure 1 (a) for **7**. For compounds **4**, **5** and **6** the signals of H-2' and H-6', as well as the signals of H-3' and H-5' aromatic protons could be observed at different chemical shifts which is due to a hindered rotation of the phenyl ring caused by the quasi-diaxial position one of the H-7 and H-3 (**4**), H-8 and H-4 (**5**) and H-9 and H-2 (**6**) methylene protons as can be seen in Figure 1 (b) for compound **6**. Since the aliphatic region of the proton spectra of these compounds was quite crowded, the configuration of C-5 (**4**), C-6 (**5**) and C-11 (**6**) carbons were confirmed by saturating the H-2' aromatic proton, when significant NOEs were observed on H-6 (**4**), H-7 (**5**) and H-10 (**6**) signals reflecting their close proximity. It is noteworthy that one of the H-2 (**4** and **5**) or H-4 (**6**) methylene protons appeared at a relatively high chemical shift, possibly due to the anisotropy caused by the closely located carbonyl group.



(a) (b)

Figure 1 Stereoviews for compounds **7** (a) and **6** (b)

Table 1 ^{1}H NMR chemical shift of compounds investigated ($CDCl_3$, δ(ppm))

^{1}H	2	3	4	5	6	7	8	9	11
2	-	-	3.99, 2.95-3.15	4.72, 2.80-3.00	3.67, 3.80	-	-	-	-
3	3.90	-	2.95-3.15, 2.47	1.45-1.80, 1.20-1.40	1.20-1.30, 1.45-2.05	-	-	-	3.94
4	1.80, 2.38	-	-	2.68, 2.80-3.00	4.68, 2.95	-	-	4.80	1.82, 2.42
5	1.60, 2.60	-	-	-	-	4.40	-	1.95	1.62, 2.60
6	-	3.23	2.32	-	-	2.22	3.18	1.50-1.80	-
7	-	2.00-2.30	1.50-2.00, 0.90	1.85	-	1.60, 1.80-2.10	1.75-2.05, 2.10-2.40	1.50-1.60, 1.90-2.00	-
8	-	2.40-2.50, 1.90-2.10	1.50-2.00	1.45-1.80, 0.80-1.00	1.45-2.05	1.80-2.10, 2.20-2.40	1.75-2.05, 2.10-2.40	-	-
9	-	-	-	1.45-1.80	1.45-2.05, 0.95-1.10	-	-	-	-
10	-	-	-	-	1.95	-	-	-	-
2'	7.20	7.50	7.38	7.49	7.31	7.10-7.20	7.55	7.10-7.20	7.25
3'	7.80	7.18	7.20	7.22	7.24	7.10-7.20	7.18	7.10-7.20	7.78
5'	7.80	7.18	7.13	7.13	7.18	7.10-7.20	7.18	7.10-7.20	7.78
6'	7.20	7.50	7.06	6.97	7.01	7.10-7.20	7.55	7.10-7.20	7.25
-$CH_3(\alpha)$	1.09	1.07	1.07	1.38	1.32	1.19	1.00	1.21	1.10
-$CH_3(\beta)$	1.36	1.14	1.01	0.95	0.93	1.05	1.12	1.01	1.38
-CH_3	0.81	1.26	1.14	1.16	1.16	1.17	1.28	1.14	0.86
4'-CH_3	2.40	2.36	2.34	2.35	2.37	2.31	2.30	2.35	2.40
NH	-	8.45	2.60	2.45	-	4.00	-	5.40	-
N-CH_3	-	-	-	-	-	-	3.50	-	-
-COOH	11.50	-	-	-	-	-	-	-	-

Table 2 ^{13}C NMR chemical shift of compounds investigated ($CDCl_3$, δ(ppm))

^{13}C	2	3	4	5	6	7	8	9	11
1	57.16	56.10	-	-	-	53.45	55.90	51.45	58.12
2	47.25	176.29	43.77	41.22	62.34	181.68	174.85	179.72	47.48
3	53.00	-	41.51	26.24	24.65	-	-	-	52.91
4	23.42	-	-	37.96	37.13	-	-	57.92	23.19
5	32.54	156.27	85.94	-	-	59.55	153.68	51.11	32.65
6	182.10	53.84	51.35	79.82	177.63	57.62	54.63	20.37	171.62
7	201.70	28.72	25.55	56.74	51.80	23.31	30.56	36.79	201.50
8	-	40.29	33.03	24.81	34.06	35.36	39.12	44.02	-
9	-	40.44	50.85	33.84	23.77	45.16	40.06	-	-
10	-	-	177.39	51.58	56.37	-	-		-
11	-	-	45.08	176.27	94.02	-	-	-	-
12	-			43.67	44.02				-
1'	136.54	137.05	137.09	137.04	137.25	136.44	137.60	137.17	136.59
2'	129.24	126.41	126.18	127.55	126.96	126.63	126.50	126.16	129.32
3'	128.13	129.24	129.92	130.16	130.24	128.96	129.07	129.38	128.62
4'	143.63	139.16	140.75	139.11	137.66	138.43	138.83	138.12	143.87
5'	128.13	129.24	128.06	128.25	128.65	128.96	129.07	129.38	128.62
6'	129.24	126.41	125.39	127.87	128.35	126.63	126.50	126.16	129.32
$-CH_3(\alpha)$	21.63	20.27	21.30	22.17	21.66	20.24	20.54	19.38	21.07
$-CH_3(\beta)$	23.80	25.91	25.14	25.22	24.88	27.14	25.82	23.22	23.80
$-CH_3$	21.52	17.53	15.02	15.12	14.88	19.76	19.24	13.31	21.35
4'-CH_3	21.63	20.99	20.82	20.82	20.90	20.77	20.99	20.89	21.35
N-CH_3	-	-	-	-	-	-	43.32	-	-

Experimental

Melting points were determined using an Electrothermal block and are uncorrected. Infrared spectra were recorded in KBr discs with Perkin-Elmer 177 instrument. ^1H (200 MHz) and ^{13}C (50 MHz) NMR spectra were measured in $CDCl_3$ solutions on a Varian Gemini-200 instrument using a 5 mm dual probe head at a probe temperature of 25 °C. Chemical shift (δ) are in ppm from internal TMS (δ = 0) or referenced to $CDCl_3$

(δ = 77.0) for carbon measurements. The ^{1}H and ^{13}C assignments (presented in Tables 1 and 2) are based on COSY-45 and HETCOR experiments, as well as on the results of selective-INEPT experiments using DANTE-type excitation of suitable protons. NOE difference spectra were measured by running standard NOEDIF sequence. 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 VG TRIO-2 spectrometer in EI mode at 70 eV.

Preparation of 3-p-toluoyl-1,2,2-trimethylcyclopentane-1-carboxylic acid **2**

16.06 g (0.128 mol) of powdered anhydrous $AlCl_3$ was added slowly to a stirred solution of 11.66 g (0.064 mol) of *d,l*-camphoric anhydride in dry toluene (42 ml). Stirring was continued for 4 hours whereupon the mixture was kept at room temperature overnight. The mixture was decomposed with ice and hydrochloric acid and extracted with dichloromethane (3 x 50 ml). The extract was washed with water, dried (Na_2SO_4) and evaporated. The residue was crystallized from ethanol to obtain 11.23 g (64%) of **2**, mp 154-155 °C. Anal. Calcd for $C_{17}H_{22}O_3$: C: 74.42; H: 8.08; Found: C: 74.69; H: 8.27. IR (cm^{-1})(KBr): 3420, 2970, 1690, 1650, 1273; MS: m/z 274 (M^+,6), 257 (10), 224 (100).

Preparation of 5-p-tolyl-1,9,9-trimethyl-3,4-diazabicyclo[4.2.1]non-4-en-2-one **3**

A mixture of 2.74 g (0.01 mol) of keto acid **2** and 0.51 g (0.01 mol) of hydrazine monohydrate (98 %) was refluxed in 1,2-dichlorobenzene (20 ml) for 3 hours and then cooled to room temperature and the precipitate was filtered off. Yield of **3** 1.00 g (37%), mp 157-159°C. Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.93; H, 8.47; N, 10.49. IR (cm^{-1})(KBr): 3246, 2973, 1653, 1618, 1335; MS: m/z 270 (M^+,100), 241 (20), 213 (22), 199 (15).

Preparation of 5-p-tolyl-9,11,11-trimethyl-1,4-diazatricyclo[$2^{1,5}.2^{6,9}.1^{6,9}.1^{5,10}$]undecan-10-one **4**

A mixture of 2.74 g (0.01 mol) of keto acid **2** and 0.90 g (0.015 mol) of ethylenediamine was heated at about 150-160°C for 5 hours. After cooling to room temperature the mixture was dissolved in 10 ml of chloroform and was purified by column chromatography (activated basic aluminium oxide packing, chloroform eluent). The eluate was evaporated and the residue was crystallized from hexane. After recrystallization (from ethanol) the precipitate was filtered off to give **4**, 1.34 g (45%), mp 133-135°C. Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 75.70; H, 9.05; N, 9.69. IR (cm^{-1})(KBr): 3362, 2983, 1643, 1398. MS: m/z 298 (M^+,69), 297 (100), 268 (28), 207 (70).

Preparation of 6-p-tolyl-10,12,12-trimethyl-1,5-diazatricyclo[$3^{1,6}.2^{7,10}.1^{7,10}.1^{6,11}$] dodecan-11-one **5**

Similarly to the above procedure a mixture of 2.74 g (0.01 mol) of keto acid **2** and 1.11 g (0.015 mol) of 1,3-

diaminopropane was heated at about 200°C for 30 minutes. The product was separated by column chromatography on silica gel (Kieselgel 60, 0.063-0.2 mm) with chloroform as eluent. After evaporation of the eluate the residue was crystallized twice from ethanol to obtain 1.89 g (60%) of **5**, mp 180-181°C. Anal. Calcd for $C_{20}H_{28}N_2O$: C, 76.93; H, 9.04; N, 8.97. Found: C, 76.63; H, 9.12; N, 9.78. IR (cm^{-1})(KBr): 3378, 2940, 1626, 1399. MS: m/z 312 (M^+, 2), 382 (5), 343 (7), 221 (100).

Preparation of 11-p-tolyl-7,12,12-trimethyl-1-oxa-5-azatricyclo[$3^{5,11}.2^{7,10}.1^{7,10}.1^{6,11}$]dodecan-6-one **6**

A solution of 2.74 g (0.01 mol) of the keto acid **2**, 3-amino-1-propanol (1.13 g ;0.015 mol) and 0.10 g of *p*-toluenesulphonic acid in dry xylene (30ml) was refluxed for 4 hours in a Dean-Stark apparatus. After evaporation the residue was dissolved in toluene (10 ml) and purified by column chromatography (silica gel packing, toluene eluent). The collected eluates were evaporated and the residue was crystallized from ether-hexane. Yield of **6** 1.25 g (40%), mp 139-140°C. Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.63; H,8.68; N, 4.47. Found: C, 76.44; H, 8.72; N, 4.73. IR (cm^{-1})(KBr): 2942, 1654, 1388. MS: m/z 313 (M^+,4), 282 (18), 268 (43), 222 (100).

Preparation of 5-p-tolyl-1,9,9-trimethyl-3,4-diazabicyclo[4.2.1]nonan-2-one **7**

To a solution of 1.16 g (0.0043 mol) of **3** in 20 ml of methanol 0.675 g (0.0086 mol) of $NaBH_3CN$ was added at 0°C. Then 0.8 ml of 32 % HCl was added dropwise at the same temperature. The ice bath was then removed and the solution was stirred at room temperature for 3 hours. 1 N NaOH was added dropwise till all the solid dissolved (pH ~ 7.5). The mixture was evaporated and the residue was chromatographed (silica gel packing, CH_2Cl_2 - MeOH (20:1) eluent), then the product was crystallized from ethanol to yield 0.99 g (85%) of **7**, mp 220-222°C. Anal. Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 75.21; H, 8.94; N, 10.40. IR (cm^{-1})(KBr): 3271, 3232, 2942, 1642, 797. MS: m/z 272 (M^+,8), 228 (4), 203 (100), 154 (7).

Preparation of 5-p-tolyl-1,3,9,9-tetramethyl-3,4-diazabicyclo[4.2.1]non-4-en-2-one **8**

To a mixture of 2.70 g (0.01 mol) of **3** and 10 ml of methanol 5.67 g (0.04 mol) of MeI was added at room temperature, then the mixture was added portionswise to a solution of 0.54 g (0.01 mol) of NaOMe in 10 ml of methanol. The mixture was refluxed for 6 hours, then evaporated and chromatographed on a silica gel column with toluene as eluent. The evaporation residue of the eluate was crystallized from ether - *n*-hexane. Yield of **8** 0.99 g (35%), mp 57-59°C. Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 76.29; H, 8.73; N, 9.82. IR (cm^{-1})(KBr): 2962, 1647, 1323, 1046. MS: m/z 284 (M^+,100), 255 (25), 213 (42), 199 (12).

Preparation of 4-p-tolyl-1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-2-one **9**

A mixture of 2.74 g (0.01 mol) of **3** and 2.00 g (0.30 mol) of zinc powder and 20 ml of 20 % aqueous

hydrochloric acid solution was refluxed for 5 hours. After cooling the reaction mixture was extracted with CH_2Cl_2 (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 1.23 g (48%) of **9**, mp 206-207°C. Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.00; N, 5.44. Found: C, 79.52; H, 9.21; N, 5.60. IR (cm^{-1})(KBr): 3211, 2968, 1649, 787. MS: m/z 257 (M^+,62), 242 (18), 229 (12), 188 (43), 69 (100).

Preparation of 3-p-toluoyl-1,2,2-trimethylcyclopentanecarboxylic anhydride **11**

A mixture of 2.74 g (0.01 mol) of **2** and 30 ml of acetic anhydride was refluxed for 5 hours. After evaporation the residue was crystallized from ether to give 2.10 g (82%) of **11**, mp 138-140°C. Anal. Calcd for $C_{34}H_{42}O_5$: C, 76.98; H, 7.92. Found: C, 76.86; H, 7.90. IR (cm^{-1})(KBr): 2970, 1795, 1735, 1668, 1233, 1020. MS (TS): m/z 548 (M^++18, 4), 275 (17), 257 (100). MS (EI): m/z 313 (7), 282 (20), 268 (33), 222 (100).

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