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REACTIONS OF α,ω-BIS(BROMOMAGNESIO)ALKANES WITH HETEROCYCLIC ANHYDRIDES. A NOVEL SYNTHESIS OF FIVE AND SIX-MEMBERED 1-(o-AMINOPHENYL)CYCLOALKANOLS AND 1-(2'-AMINO-3'-PYRIDINYL)CYCLOALKANOLS

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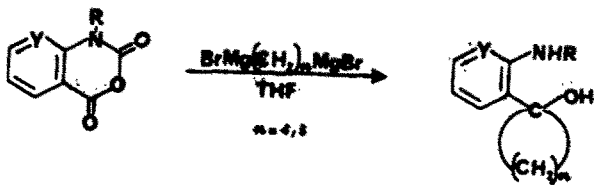
Abstract. Isatoic anhydrides and azaisatoic anhydrides are converted by reaction with 1,4-bis(bromomagnesio)butane and 1,5-bis(bromomagnesio) pentane into the corresponding 1-(o-aminophenyl)cycloalkanols and 1-(2'-amino-3'-pyridinyl)cycloalcanols.

We have recently developed a useful one-step synthesis of 1-(ω-hydroxylalkyl) cycloalkanols[1] and spirolactones[2] using the reaction of α,ω-diprimary di-Grignard reagents with lactones and dicarboxylic acid anhydrides. To demonstrate the versatility of this cyclisation reaction, we have extended now the reactions of 1,4-bis(bromomagnesio)butane and 1,5-bis(bromomagnesio)pentane to more complex heteroaromatic bicyclic anhydrides such as isatoic and azaisatoic anhydrides (1-9).

The great advantage of isatoic anhydrides (2H-3,1-benzoxazine-2,4 (1H)-diones), and their aza homologues, is that, after the nucleophilic attack of the carbonyl in position 4, the intermediate compound leads to the formation of aminoalcohols by loss of carbon dioxide.[3] In previous studies[4] it was reported that, generally, isatoic anhydrides showed this remarkable regioselectivity toward nucleophilic attack. It was reported recently, that 2-aminobenzylalcohols[5] can readily be obtained by reduction of N-substituted isatoic anhydrides. Surprisingly, the formation of 1-(o-aminophenyl)carbinols by the reaction of Grignard reagents with azaisatoic anhydrides has not been attempted. For instance, 1-(o-aminophenyl)cycloalkanols have not been reported, although the starting anhydrides (1-4) are easily obtained by alkylation of isatoic anhydride.[6] Our cyclisation provides a useful path for their synthesis (Scheme 1).

Furthermore, the azaisatoic anhydrides are readily available. The unsubstituted azaisatoic anhydride 5 has been prepared, in good yields, by the reaction of 2-carbamylnicotinic acid with lead tetra-acetate.[7] The unknown alkylated aza derivatives (6-9) have been readily synthesized in high yields according the same method as the N-alkylated isatoic anhydrides.

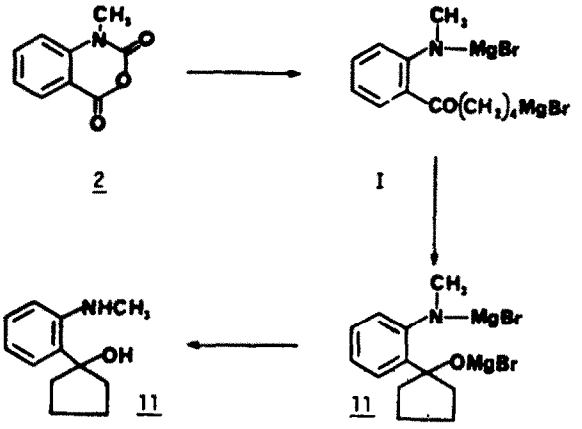
We undertook the reactions of bis(bromomagnesio)alkanes with isatoic anhydrides, hoping to obtain the corresponding 1-(o-aminophenyl)cycloalkanols, and 1-(2'-amino-3'-pyridyl)-cycloalkanols difficult to prepare by other methods.[8]



1 : y=CH; R=H
2 : y=CH; R=CH_3
3 : y=CH; R=CH_2CH_3
4 : y=CH; R=$CH_2C_6H_5$

5 : y=N; R=H
6 : y=N; R=CH_3
7 : y=N; R=CH_2CH_3
8 : y=N; R=$(CH_2)_2CH_3$
9 : y=N; R=$CH_2C_6H_5$

Scheme 1



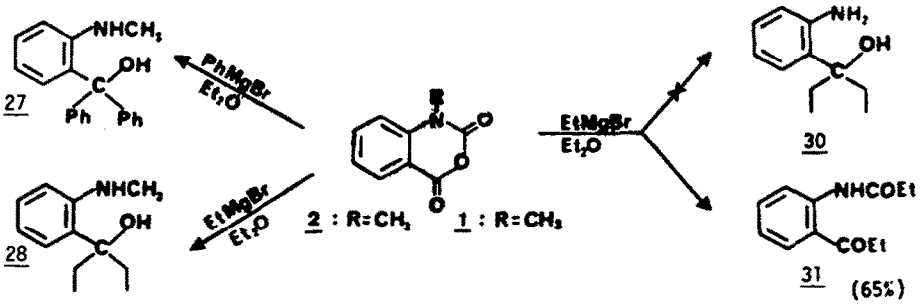
Scheme 2

Also the choice of alkyl- and phenylmagnesium bromides allows comparison with the results from the reaction of indolylmagnesium bromide with 5-chloro-N-methylisatoic anhydride.[9]

Both the 1,4-bis(bromomagnesio)butane and 1,5-bis(bromomagnesio)pentane were prepared in high yield, using an excess of magnesium turnings in tetrahydrofuran. The solutions were kept for a few hours at 0°C before use. To remove any trace of magnesium we used the syringe-septum cap technique. The reactions occurred, as described previously,[2] with an equimolar mixture of di-Grignard reagent and dicarboxylic anhydride[1] at room temperature. We found that the reactions of 1,4-bis(bromomagnesio)butane with isatoic and azaisatoic anhydrides give the corresponding 1-(o-aminophenyl)cyclopentanols and 1-(2'-amino-3'-pyridinyl)cyclopentanols in higher yield than the reactions of 1,5-bis(bromomagnesio)pentane with the same anhydrides to give cyclohexanols (table I). These differences occur in the formation of all five-membered rings. However, the yields are good even with the anhydrides 1, 4, 5 and 9. In these cases a large amount of di-Grignard reagent was used for the preparation of the corresponding 1-(o-aminophenyl)cycloalkanols (10, 13, 14, 22) as well as for the preparation of 1-(2'amino-3'-pyridinyl)cycloalkanols (14, 18, 23, 27). These results, together with others, indicate that the scope of this cyclisation process is rather limited.

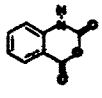
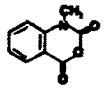
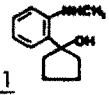
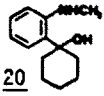
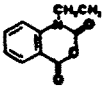
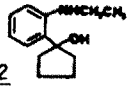
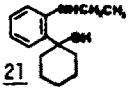
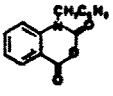
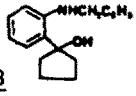
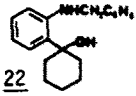
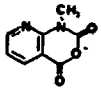
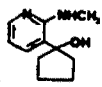
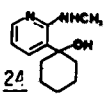
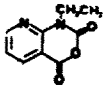
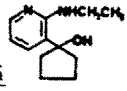
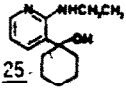
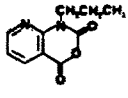
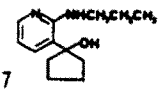
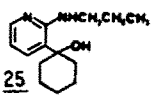
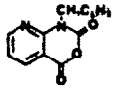
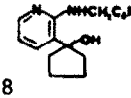
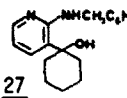
In scheme 2, we report a typical example of the reaction of 1,4-bis(bromomagnesio)butane with isatoic anhydride 2. Initially, the attack of the di-Grignard reagent takes place at C-4 yielding the corresponding intermediate I, which, in turn, is rapidly transformed into alcoholate II by the intramolecular attack of the Grignard reagent and the loss of CO_2. With these two Grignard reagents we found no polymeric compound corresponding to an intermolecular addition.

Consequently, we explored the reactions of ethylmagnesium and phenylmagnesium bromides with N-methylisatoic anhydride (2) in order to compare the reactivity of intramolecular and intermolecular addition reactions at the intermediate I.



Scheme 3

Table 1: Reaction of α,ω-Bis(bromomagnesio)alkanes with Isatoic and Azaisatoic Anhydrides

		$BrMg(CH_2)_4MgBr$		$BrMg(CH_2)_5MgBr$	
	Anhydride	Product	Yield %	Product	Yield %
1		10 	53	19 	38
2		11 	70	20 	32
3		12 	70	21 	44
4		13 	86	22 	38
5		14 	38	23 	42
6		15 	88	24 	81
7		16 	98	25 	80
8		17 	88	25 	89
9		18 	82	27 	32

These two organomagnesium compounds have been prepared in a diethylether solution and the anhydride 2 was dissolved in tetrahydrofuran. After hydrolysis, we observed that these reactions give similar products to those obtained in the reactions of 1,4-bis(bromomagnesio)butane furnishing the corresponding aminophenylalcohols 28 and 29 in good yields (Scheme 3). In contrast the reaction of ethylmagnesium bromide with isatoic anhydride 1 leads to the formation of compound 31. IR and NMR spectroscopic data revealed only traces of the expected 1-(o-aminophenyl)pentanol-3 (30).

The results observed from this di-Grignard annelation process suggest that this procedure may have additional utility within the scope of synthetic applications.

Experimental section

Melting points were determined in capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Analytical thin-layer chromatography was performed on Woelm Silica Gel 60F 254 plates (0.25 mm). Column chromatography was carried on Woelm silica 32-63 for flash chromatography. Infrared spectra were obtained on a Beckman IR-4250 spectrophotometer. ^1H NMR spectra were determined on a Bruker HX-90 and a Varian XL-200 spectrometer in $CDCl_3$ or DMSO-d_6 solution and are reported in δ units downfield from Me_4Si. ^{13}C NMR spectra were determined on a Bruker WP-80 (20.1 MHz) apparatus in $CDCl_3$ or DMSO-d_6 solution (0.75 mol/L) by using Me_4Si as an internal standard. Mass spectra were obtained in a Varian M-66 spectrometer, and microanalyses were performed by Centre d'analyse, Villeurbanne, France.

Starting materials. Magnesium turnings, 1,4-dibromobutane, 1,5-dibromopentane, isatoic anhydride

(1) and N-methylisatoic anhydride (2) were commercially available. Tetrahydrofuran was distilled from lithium aluminium hydride into oven dried flasks and kept over sodium wire.

N-Ethyl isatoic anhydride (3).
This anhydride was prepared according to Hartmann[8] from isatoic anhydride and ethyl bromide and recrystallized as white powder from acetonitrile; mp 124°C; 61% yield; ^{1}H NMR δ 1.40 (t, 3H) 4.14 (q, 2H), 7.21-7.34 (2H, m), 7.76-7.83 (m, 1H); 8.14-8.17 (m, 1H); IR (Nujol) 1710,1760 cm^{-1}.

N-Benzylisatoic anhydride (4).
This anhydride was prepared according to Hartmann[8] from isatoic anhydride and benzyl chloride and recrystallized as light brown powder from benzene-ligroin; mp 138-9 °C; 70% yield; ^{1}H NMR δ 4.3-4.7 (s, 2H), 6.4-7.6 (m, 9H); ^{13}C NMR δ 156.11, 141.37, 137.08, 134.23, 130.64, 128.49, 128.12, 127.97, 126.44, 124.04, 114.64, 111.65; MS, m/e 253 (M^+, 31%), 91.1 (86%) 119 (100%); IR (Nujol) 1700,1765 cm^{-1}.

Preparation of the 2H-pyrido[2,3-d][1,3]oxazine-2,4-1H-dione (15).
This anhydride was prepared according to Beckwith[7] from lead tetraacetate and 2-carbamylnicotinic acid[19] in dimethylformamide. Crystallization of the residue gave the expected pyridooxazine; mp. 217-219°C; 75% yield; ^{1}H NMR δ 7.24-7.42 (s, 1H and dd, 1H), 8.28-8.36 (dd, 2H), 8.60-8.74 (dd, 1H); IR (Nujol) 3150, 3080, 1850, 1770 cm^{-1} MS, m/e 164 (m^+, 35%), 120 (M^+-CO_2, 100%); Anal. Calcd. for $C_7H_4N_2O_3$: C, 51.2; H, 2.5; N, 17.1. Found: C, 51.3; H, 2.7, N, 17.05.

Alkylation of the 2H-pyrido[2,3-d] [1,3] oxazine-2,4-1H-dione: General method.
Sodium hydride (0.11 mole) was added with stirring to 0.10 mole of anhydride 5 prepared in dimethylformamide (~200 mL). The reaction mixture was stirred 1h at room temperature. The corresponding alkyl halides was added dropwise to the solution and stirred 3h more. The solution was evaporated (2/3) and after hydrolysis with ice water mixture, the residue was purified by crystallization.

N-Methyl 2H-pyrido[2,3-d][1,3]oxazine-2,4-1H-dione (6).
mp: 160-2°C; 80% yield; ^{1}H NMR δ 3.70 (s, 3H), 7.24-7.31 (dd, 1H), 8.40-8.45 (dd, 1H), 8.72-8.74 (dd, 1H); ^{13}C NMR δ 155.31, 146.37, 138.58, 137.00, 119.60, 110,52, 107.78, 28.91; IR (Nujol) 1715, 1765 cm^{-1} MS, m/e 178 (M^+, 29%), 134 (M^+-CO_2, 45%), 79 (100%). Anal. Calcd. for $C_9H_6N_2O_3$: C, 53.91; H, 3.41; N, 15.70; Found: C, 54.07; H, 3.40; N, 15.65.

N-Ethyl 2H-pyrido[2,3-d][1,3]oxazine-2,4 1H-dione (7).
mp: 148-9°C 91% yield; ^{1}H NMR δ 1.07-1.25 (t, 3H), 4.11-4.22 (q, 2H), 7.33-7.44 (dd, 1H), 8.34-8.40 (dd, 1H), 8.74-8.78 (dd, 1H); ^{13}C NMR δ 158.64, 149.55, 139.47, 138.95, 120.11, 111.78, 109.97, 34.68, 15.02; IR (Nujol) 1715,1760-cm^{-1} MS, m/e 142 (M^+, 14%), 133 (M^+-CO_2, 38%), 119 (100%). Anal. Calcd. for $C_9H_8N_2O_3$: C, 56.31; H, 4.20; N, 14.62; Found: C, 56.15; H, 4.28; N, 14.71.

N-Propyl-2H-pyrido[2,3-d][1,3]oxazine-2,4 1H-dione (8).
mp: 135-6°C 85% yield; ^{1}H NMR δ 1.01-1.06 (t, 3H), 1.74-1.86 (m, 2H), 4.21-4.29 (t, 2H), 7.27-7.33 (dd, 1H), 8.40-8.45 (1H, dd), 8.53-8.73 (1H, dd); IR (Nujol) 1720, 1770 cm^{-1} MS, m/e 206 (M^+, 22%), 162 (M^+, 22%), 162 (M^+-CO_2, 60%), 133 (100%). Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.65 N, 13.59; Found: C, 57.89; H, 4.54; N, 13.62.

N-Benzyl-2H-pyrido[2,3-d][1.3]oxazine-2,4 1H-dione (9).
mp: 158-9°C; 79% yield; ^{1}H NMR δ 5.49-5.51 (s, 2H), 7.2-8.9 (m, 8H); ^{13}C NMR δ 158.83, 134.49, 135,58, 128.93d, 128.49, 128.04, 127.99, 119.89, 112.55, 46.37; MS, m/e (M^+, 14%), 210 (M^+-CO_2, 2%), 181 (100%). Anal. Calcd. for $C_{15}H_{10}N_2O_3$: C, 66.14, H, 3.92; N, 11.09; Found: 66.22; H, 3.89; N, 11.09.

Preparation of 1-(o-Aminophenyl) cyclanols (10-13, 19-22).
The anhydride 2 (15.3 mmol) in anhydrous THF (~ 50 mL) was added dropwise with stirring under nitrogen to 15.3 mmol of the organodimagnesium compound prepared in the same solvent (50 mL). The reaction mixture was stirred for 1h under an atmosphere of nitrogen. After hydrolysis with saturated ammonium chloride, the organic layer was separated, the aqueous layer was extracted with ether, and the combined organic layers were dried over anhydrous magnesium sulfate. The solution was concentrated in vacuo and the residue was separated by column chromatography using petroleum ether (40-60°) ethyl acetate (9:1-4:1) as eluent.

1-(o-Aminophenyl) cyclopentanol (10).
mp: 86-8°C; recrystallized from hexane-ethyl acetate; 53% yield; ^{1}H NMR δ 0.2-2.2 (m, 9H), 6.3-7.4 (m, 4H), 12.1 (s, 2H); ^{13}C NMR δ 146.49, 129.80, 128.40, 125.60, 117.60, 117.40, 84.10, 38.52, 23.13; IR (Nujol), 3100-3400 cm^{-1}. Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.51; H, 8.47; N, 7.91. Found: C, 74.34; H, 8.60; N, 7.99.

1-(o-Methylaminophenyl) cyclopentanol (11).
70% yield; ^{1}H NMR δ 1.5-2.3 (m, 9H), 2.9 (s, 3H), 3.5 (a, 1H), 6.4-7.5 (m, 4H); ^{13}C NMR δ 149.12; 129.29, 128.78, 125.78, 115.90, 111.07, 84.44, 38.56, 30.59, 23.12; IR (Nujol) 3140-3520 cm^{-1}; MS, m/e 191 (M^+, 22%) 173 (M^+-H_2O, 10%), 130 (100%). Anal. Calcd. for $C_{12}H_{15}NO$: C, 75.39; H, 8.37; N, 7.32. Found: C, 75.19; H, 8.44; N, 7.10.

1-(o-Ethylaminophenyl) cyclopentanol (12).
Red oil; 70% yield; ^{1}H NMR δ 1.3 (t, 3H) 1.5-2.5 (m, 9H), 3.2 (q, 2H), 3.8 (s, 1H), 6.4-7.4 (m, 4H); ^{13}C NMR δ 148.17, 129.37, 128.71, 125.19, 115.40, 111.73, 84.37, 38.63, 38.41, 23.19, 14.85; MS, m/e 205 (M^+, 12%), 187 (M^+-H_2O, 23%), 144 (100%). Anal. Calcd. for $C_{13}H_{19}NO$: C, 76,10; H, 9.26; N, 6.83. Found: C, 76.07; H, 9.30; N, 6.85.

1-(o-Benzylaminophenyl) cyclopentanol (13).
mp: 75°C; 56% yield; ^{1}H NMR δ 1.3-2.1 (m, 8H), 2.2-2.6 (s, 1H), 3.45 (s, 2H), 5.5-5.7 (s, 1H), 6.25-6.54 (m, 2H), 6.7-7.3 (m, 7H); ^{13}C NMR δ 148.09, 140.34, 128.99. 128.41, 127.75, 127.38, 125.49, 116.49, 112.17, 84.88, 48.44, 38.99, 23.49; IR (Nujol) 3120-3600 cm^{-1}. Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.89; H, 7.86; N, 5.24. Found: C, 81.07; H, 7.68; N, 5.36.

1-(o-Aminophenyl) cyclohexanol (19).
mp: 91°C; 42% yield; ^{1}H NMR δ 0.7-2.4 (m, 1H), 5.5 (s, 2H), 6.5-7.7 (m, 4H). Anal. Calcd. for $C_{12}H_{17}NO$: C, 75,39; H, 8.90; N, 7.32. Found: C, 75.48; H, 8.99; N, 7.20.

1-(o-Methylaminophenyl) cyclohexanol (20).
mp: 92-93°C; 47% yield; ^{1}H-NMR δ 0.8-2.3 (m, 9H), 2.8 (s, 3H), 9.7 (s, 1H), 6.3-7.4 (m, 4H); ^{13}C NMR δ 148.76, 131.05, 128.49, 125.27, 116.05, 111.22, 74.85, 36.22, 30.44, 25.98, 22.09; IR ($CHCl_3$) 3520, 3400 cm^{-1}; MS, m/e 205 (M^+, 39%), 187 (M^+-H_2O, 20%), 130 (100%). Anal. Calcd. for $C_{13}N_{19}NO$: C, 76,90; H, 9.45; N, 6.81. Found: C, 77.07; H, 9.55; N, 6.82.

1-(o-Ethylaminophenyl) cyclohexanol (21).
mp: 54-5°C; 59% yield; ^{1}H NMR δ 1.2 (t, 3H), 1.4-2.4 (m, 9H), 3.1 (q, 2H), 3.9 (s, 1H), 6.3-7.4 (m, 4H), ^{13}C NMR δ 147.80, 131.24, 128.41, 125.41, 116.05, 111.88, 74.85, 38.41, 36.29, 25.98, 22.09, 146.96; IR ($CHCl_3$) 3390, 3580 cm^{-1}; MS, m/e. 219 (M^+, 33%), 201 (M^+-H_2O, 5%), 172 (100%). Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.61; H, 9.57; N, 6.38. Found: C, 76.49; H, 9.67; N, 6.21.

1-(o-Benzylaminophenyl) cyclohexanol (22).
mp: 119-121°C (hexane); 38% yield; ^{1}H NMR δ 1.1-2.3 (m, 12H), 3.0-3.7 (s, 2H), 4.0-4.3 (s, 1H) 6.5-7.5 (m, 8H); ^{13}C NMR δ 147.51, 140.27, 131.12, 128.71, 127.39, 127.02, 125.49, 116.41. 112.17, 75.59, 48.15, 36.37, 25.47, 22.09; IR (Nujol) 3400, 3580 cm^{-1}; MS, m/e 281 (M^+, 14%), 263 (M^+-H_2O, 1%), 91 (100%). Anal. Calcd. for $C_{19}H_{23}NO$: C, 81.05; H, 6.75; N, 4.97. Found: C, 81.28; H, 6.61; N, 4.95.

o-(Propylamido)butyrophenone (31).
mp: 38-40°C (hexane) 65% yield; ^{1}H NMR δ 1.20 (t, 3H) 1.26 (t, 3H); 2.46 (q, 2H), 3.06 (m, 2H), 7.06 (m, 1H), 7.53 (m, 1H), 7.93 (m, 1H), 8.82 (m, 1H); ^{13}C NMR δ 205.46, 173.41, 141.36, 134.95, 130.68, 122.34, 121.75, 121.17, 35.22, 31.90, 4.66, 8.48; IR (KBr) 3200, 1690, 1660 cm^{-1}; MS. m/e 205 (m^+, 20%), 120 (100%), 176 (m^+-C_2H_5, 73%). Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.31; N, 6.82. Found: C, 70.27; H, 7.28; N, 6.92.

Preparation of 1-(2'-Amino-3'-pyridinyl) cyclanols (14-18, 23-27).
The anhydride 5-8 (15.3 mmol) in anhydrous THF (50 mL) was added with stirring under nitrogen to 15.3 mmol of the organomagnesium compound prepared in the same solvent (~ 50 mL). The reaction mixture was stirred for 1 h under an atmosphere of nitrogen. After hydrolysis with saturated ammonium chloride, the organic layer was separated, the aqueous layer was extracted with ether and the combined organic layers were dried over anhydrous magnesium sulfate. The solution was concentrated in vacuo and the residue was separated by column chromatography, using petroleum ether (40-60°) ethyl acetate (9:1-4:1) as eluent.

1-(2'-amino-3'-pyridinyl) cyclopentanol (14).
mp: 96-7°C; 50% yield; ^{1}H NMR δ 1.68-2.20 (m, 9H), 5.30-5.36 (s, 2H), 6.50-6.60 (dd, 1H), 7.27-7.38 (dd, 1H), 7.88-7.91 (dd, 1H); ^{13}C NMR δ 152.83, 146.02, 132.89, 112.88, 124.30, 82.30, 38.02, 22.94. Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.41; H, 7.86; N, 15.73. Found: C, 67.58; H, 7.79; N, 15.60.

1-(2'-Methylamino-3'-pyridinyl) cyclopentanol (15).
65% yield; ^{1}H NMR δ 1.66-2.08 (m, 8H), 2.02-2.08 (s, 1H), 2.94 (s, 3H), 6.38-6.41 (s, 1H), 6.42-6.45 (dd, 1H), 7.21-7.26 (dd, 1H, 7.95-7.98 (dd, 1H); ^{13}C NMR δ 158.41, 146.71, 131,93, 124.02, 111.15, 83.19, 39.48, 28.39, 23.12; MS, m/e 191 (m^+, 90%), 173 (m^+-H_2O, 48%), 146 (100%). Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 69.10; H, 8.37; N, 14.66. Found: C, 69.26; H, 8.43; N, 14.78.

1-(2'-Ethylamino-3'-pyridinyl) cyclopentanol (16).
White powder; mp 105-8°C; 80% yield; ^{1}H NMR δ 1.20-2.32 (t, 3H), 1.55-2.11 (m, 8H), 2.30-2.80 (s, 1H), 3.37-3.48 (q, 2H) 6.40-6.50 (dd, 1H), 7.24-7.29 (dd 1H), 7.85-7.94 (dd, 1H); MS, m/e 206 (m^+, 44%), 183 (m^+-H_2O, 18%), 173 (100%). Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.90; H, 8.74; N, 13.59. Found: C, 69.81; H, 8.81, N, 13.65.

1-(2'-Propylamino-3'-pyridinyl) cyclopentanol (17).
mp: 135-6°C; 80% yield; ^{1}H NMR δ 0.8-1.3 (t, 3H), 1.4-2.9 (m, 12H), 3.1-3.7 (t, 2H), 5.8-6.2 (s, 1H), 6.2-6.7 (dd, 1H), 7.1-7.5 (dd, 1H), 7.8-8.3 (dd, 1H), ^{13}C NMR δ 157.40, 146.78, 131.43, 125.13, 112.49, 83.19, 50.66, 43.13, 38.34, 23.12, 11.78; MS, m/e 220 (m^+, 18%), 202 (m^+-H_2O, 2%), 173 (100%). Anal. Calcd. for $C_{13}H_{20}N_2O$: C, 70.90; H, 9.09; N, 12.71; Found: C, 70.71; H, 8.90; N, 12.58.

1-(2'-Benzylamino-3'-pyridinyl) cyclopentanol (18).

mp: 150°C, 52% yield; ^{1}H NMR δ 1.5-2.4 (m, 10H), 4.6 (s, 2H), 6.3-6.8 (dd, 1H), 7.1-7.7 (m, 7H), 7.8-8.3 (dd, 1H); ^{13}C NMR δ 157.54, 146.93, 140.63, 132.22, 128.63, 127.83, 126.95, 123.95, 111.73, 83.34, 46.66, 38.79, 23.19; IR (Nujol) 3100-3600 cm^{-1}; MS, m/e 268 (m$^+$, 15%), 250 (m$^+$-H_2O, 12%), 91 (100%). Anal. Calcd. for $C_{17}H_{20}N_2O$, C, 76.11, H, 7.46, N, 10.45. Found: C, 75.98; H, 7.40; N, 10.45.

1-(2'-Amino-3'-pyridinyl) cyclohexanol (23).
mp: 134°C; 42% yield; ^{1}H NMR δ 1.20-2.20 (m, 10H), 3.30-3.40 (s, 1H), 5.54-5.64 (s, 2H), 6.49-6.57 (dd, 1H), 7.27-7.35 (dd, 1H), 7.77-7.80 (dd, 1H); ^{13}C NMR δ 157.27, 145.72, 133.30, 113.02, 126.20, 72.79, 35.58, 25.64, 21.69; IR (CCl_4) 3350, 3460 cm^{-1}; MS, m/e 192 (m$^+$, 15%), 174 (m$^+$-H_2O, 18%). Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68.75; H, 8.33, N, 14.58. Found: C, 68.89; H, 8.24; N, 14.70.

1-(2'-Methylamino-3'-pyridinyl) cyclohexanol (24).
61% yield; ^{1}H NMR δ 1.16-1.84 (m, 10H), 2.03-2.10 (s, 1H), 2.94-2.96 (s, 3H), 5.71-5.77 (s, 1H), 6.42-6.48 (dd, 1H), 7.09-7.13 (dd, 1H), 7.98-8.01 (dd, 1H); ^{13}C NMR δ 157.31, 145.60, 131.93, 124.02, 110.67, 75.35, 38.41, 28.39, 25.15, 23.12; MS, m/e 206 (m$^+$, 60%), 188 (m$^+$-H_2O, 13%), 137 (100%). Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.90; H, 8.74; N, 13.59. Found: C, 70.05; H, 8.81; N, 13.71.

1-(2'-Ethylamino-3'-pyridine)-1-cyclohexanol (25).
mp: 34°C; 60% yield; ^{1}H NMR δ 0.34-1.71 (m, 10H), 1.30-1.52 (t, 3H), 2.89-2.96 (s, 1H), 3.41-3.68 (q, 2H), 6.47-6.50 (dd, 1H), 7.11-7.15 (dd, 1H), 7.47-7.49 (dd, 1H); ^{13}C NMR δ 156.52, 146.17, 134.22, 114.58, 111.13, 73.71, 38.66, 35.88, 25.36, 21.67, 14.81; IR (CCl_4) 3400: 3590 cm^{-1}; MS, m/e 220 (m$^+$, 60%) 202 (m$^+$-H_2O, 13%), 123 (100%). Anal. Calcd. for $C_{13}H_{20}N_2O$: C, 70.91; H, 9.09; N, 12.73. Found: C, 71.06; H, 9.14; N, 12.65.

1-(2'-Propylamino-3'-pyridinyl)cyclohexanol (26).
mp: 30°C; 59% yield; ^{1}H NMR δ 0.96-1.03 (m, 3H), 1.56-1.80 (m, 12H), 1.26-1.28 (s, 1H), 2.12-2.16 (s, 1H), 3.35-3.42 (t, 2H), 6.44-6.50 (dd, 1H), 7.26-7.30 (dd, 1H), 8.00-8.03 (dd, 1H); ^{13}C NMR δ 157.39, 146.63, 132.29, 125.49, 111.14, 73.76, 43.32, 35.93, 25.83, 22.98, 21.95, 11.86; IR (CCl_4) 3400, 3580 cm^{-1}; MS, m/e 234 (M$^+$, 17%), 216 (m$^+$-H_2O, 3%), 187 (100%). Anal. Calcd. for $C_{14}H_{22}N_2O$: C, 71.99; H, 9.40; N, 4.97.

1-(2'-Benzylamino-3'-pyridinyl) cyclohexanol (27).
mp: 77.8°C; 32% yield; ^{1}H NMR δ 114-216 (m, 12H), 4.6-4.8 (s, 2H), 6.3-8.3 (m, 9H); ^{13}C NMR δ 157.02, 146.63, 142.86, 132.51, 128.56, 127.76, 126.88, 125.71, 111.88, 73.83, 35.99, 25.76, 21.88, 20.71; IR (CCl_4), 3380, 3520 cm^{-1}; MS, m/e 282 (m$^+$, 24%), 264 (m$^+$-H_2O, 25%), 91(100%). Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 76.60; H, 7.80, N, 9.93. Found: C, 76.78; H, 7.68, N, 7.08.

Preparation of 1-(o-Aminophenyl) carbinols (28-29). General method.
The anhydride 2 (15.3 mmol) in anhydrous THF (100 mL) was added dropwise with stirring under nitrogen to 30.6 mmol of the organomagnesium compound prepared in the same solvent (50 mL). The reaction mixture was stirred for 1 h under an atmosphere of nitrogen. After hydrolysis with saturated ammonium chloride, the organic layer was separated, the aqueous layer was extracted with ether and the combined organic layers were dried over anhydrous magnesium sulfate. The solution was concentrated in vacuo, and the residue was separated by column chromatography using petroleum ether (40-60°) ethyl acetate (9:1-4:1) as eluent.

1-(o-Methylaminophenyl)-3-pentanol (28).
65% yield; ^{1}H NMR δ 0.8 (t, 3H), 1.8 (q, 2H), 2.1 (s, 1H), 4.0 (s, 1H), 2.7 (s, 3H), 6.3-7.4 (m, 4H); ^{13}C NMR δ 149.27, 128.34, 127.46, 127.17, 115.90, 111.66, 80.19, 31.32, 30.73; IR ($CHCl_3$) 3100-3400 cm^{-1}; MS, m/e 193 (m$^+$, 40%), 164 (m$^+$-C_2H_5, 87%), 146 (100%). Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.61; H, 9.33; N, 7.25. Found: C, 74.33; H, 9.77; N, 7.29.

1-(o-Methylaminophenyl) diphenyl carbinol (27).
66% yield; ^{1}H NMR δ 2.61 (s, 3H), 4.3-4.7 (s, 2H), 6.47-6.80 (m, 4H), 7.22-7.29 (m, 8H); ^{13}C NMR δ 146.41, 145.63, 132.28, 129.72, 129.35, 128.79, 128.39, 128.32, 128.24, 128.19, 127.42, 127.64, 124.46, 127.22, 122.08, 117.52, 115.22, 112.89, 82.60, 39.78. Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.04; H, 6.57; N, 4.84. Found: C, 83.19; H, 6.59; N, 4.78.

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