

SYNTHESIS OF 7,12-DIHYDRO-12-PHENYL-5*H*-6,12-METHANODIBENZ[*c,f*]AZOCINES VIA *N,N*-DIBENZYLPHENACYLAMINES

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Abstract - *N,N*-Dibenzylphenacylamines (**1**) were prepared in high yields by a one-pot reaction and cyclized at room temperature to give 7,12-dihydro-12-phenyl-5*H*-6,12-methanodibenz[*c,f*]azocines in high yields. 95% H₂SO₄ or 70% HClO₄ was used as cyclization catalysts. The double-cyclization proceeds smoothly in the cases where electron-donating groups are present in both benzene ring. *N*-2,3-dimethoxybenzyl-*N*-benzylphenacylamine (**1f**) gave the corresponding *N*-benzyl-1,2-dihydro-4-phenylisoquinoline on treatment with 95% H₂SO₄ while *N*-3,4-dimethoxybenzyl-*N*-benzylphenacylamine (**1a**) at the same reaction conditions and reaction time cyclized to the corresponding dibenzazocine. However **1a** gave the corresponding dihydroisoquinoline which disproportionates to give *N*-benzyl-1,2,3,4-tetrahydro-4-phenylisoquinoline and *N*-benzyl-4-phenylisoquinolinium when treated with 70% perchloric acid at room temperature.

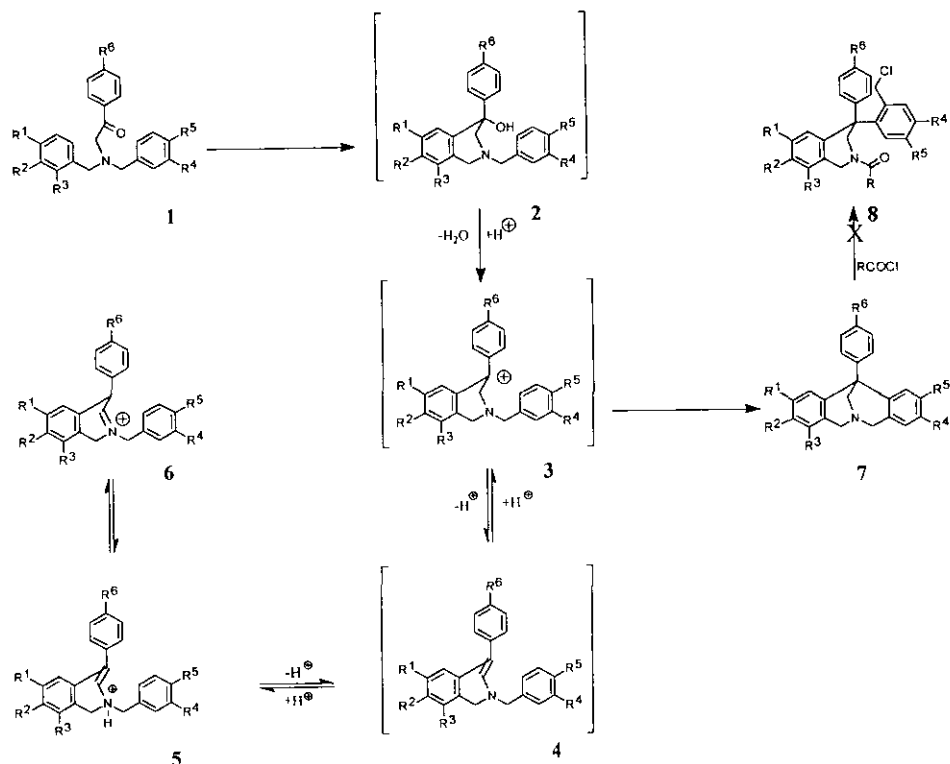
It was reported that the reaction of *N,N*-dibenzylaminoacetaldehyde diethyl acetals with 70% perchloric acid gave the corresponding dibenz[*c,f*]azocines some of which possess remarkable antihistaminic activity.¹ In the same work the cyclization is achieved even when electron-withdrawing groups such as chlorine and fluorine are present in the benzene rings. Dibenz[*c,f*]azocine structures were used in the synthesis of isopavine alkaloids such as amurensinine and reframine.² The same authors reported the synthesis of 12-substituted dibenz[*c,f*]azocines starting from 1-dibenzylamino-2-propanones where 70% perchloric acid at 70-80°C or F₃CSO₃H at room temperature was used as cyclization catalysts.³

N-Benzyl-1,2,3,4-tetrahydro-4-phenylisoquinolin-4-ol derivatives have been converted to 12-phenyl-5*H*-6,12-methanodibenz[*c,f*]azocines by an intramolecular Friedel-Crafts reaction.⁴

Recently we have reported the synthesis of 1,2,3,4-tetrahydro-4-arylisoquinolin-4-ols starting from the corresponding *N*-benzyl-*N*-alkylphenacylamines.⁵ We have also reported the reaction of these phenacylamines with acid chlorides where some of the products of selective benzyl cleavage were used for the synthesis of *N*-acyl-1,2,3,4-tetrahydro-4-phenylisoquinolines.⁶ The 4-phenylisoquinolin-4-ols were found to have a nomifensine-like effect on dopamine uptake in striatal synaptosomes. In order to study the structure-activity relationships of 4-arylisoquinolin-4-ols we attempted to prepare different *N*-benzyl-

1,2,3,4-tetrahydro-4-arylisquinolin-4-ols. For this purpose we used our method for the synthesis of *N*-benzyl-*N*-alkylphenacylamines for the preparation of compounds (**1a-l**).⁵ But our efforts to convert them into *N*-benzyl-1,2,3,4-tetrahydro-4-arylisquinolin-4-ol derivatives using 95% sulfuric acid failed. When we have treated compounds (**1a-e**) with sulfuric acid at room temperature the products isolated were dibenz[*c,f*]azocines but not the expected isoquinolin-4-ols. Therefore we have prepared compounds (**1a-l**) and investigated the limits of the double-cyclization using 95% H₂SO₄ or 70% HClO₄ at room temperature. Compounds (**1a-e**) were converted smoothly to **7** when treated with sulfuric acid at room temperature. Compound (**1f**) gave the corresponding *N*-benzyl-1,2-dihydro-4-phenylisoquinoline when treated with sulfuric acid while (**1h,k**) were recovered unchanged at the same reaction conditions. Compound (**1a**) gave **7a** after treatment with sulfuric acid at room temperature while the same compound gave nearly an equimolecular mixture of *N*-benzyl-1,2,3,4-tetrahydro-4-phenylisoquinoline perchlorate and fully aromatic *N*-benzyl-4-phenylisoquinolinium perchlorate when treated with 70% perchloric acid at room temperature. It is known that some 1,2-dihydroisoquinolines may undergo disproportionation in the presence of acids.⁶ *N*-Methyl-1,2-dihydro-4-phenylisoquinolines behave similarly in the presence of sulfuric acid.⁷ We assume that in strongly acidic conditions carbonium ion (**3**) may undergo cyclization to give **7** or eliminate proton to give **4** which probably is in equilibrium with **3**. But the protonation of **4** may occur at the nitrogen leading to **5** which tautomerize to iminium (**6**). Probably a hydride transfer from **4** to **6** lead to the formation of corresponding tetrahydroisoquinoline and aromatic isoquinolinium salt. Thus cyclization reaction is favored in 95% sulfuric acid while in 70% perchloric acid disproportionation is the main reaction in the cases where one of the benzyl groups is unsubstituted. But it remains unclear why the amino ketone (**1f**) which is different from **1a** only in the positions of methoxy groups at the benzylic phenyl behaves differently from **1a** in 95% H₂SO₄.

Compound (**1b**) was converted to **7b** using both 95% sulfuric and 75% perchloric acids. In the cases of **1g,i,j,l** complex mixtures were obtained when treated with sulfuric acid. Compounds (**7**) can be obtained starting from isolated **1** as well as by a one-pot procedure as it is demonstrated for **1b**. Furthermore we decided to convert compounds (**7**) into *N*-acyl-1,2,3,4-tetrahydro-4,4-diphenylisoquinoline derivatives (**8**) by the reaction which we have reported for *N*-benzyl-*N*-alkyl(arylalkyl)phenacylamines.⁸ We have treated compound (**7b**) with equimolar amount of 3,4-dimethoxyphenylacetyl chloride in refluxing dichloroethane for 3 h but no conversion was observed. The same compound was recovered unchanged after refluxing in acetyl chloride for 24 h. Probably compounds (**7**) can not form the corresponding acylammonium chlorides due to sterical reasons.



Scheme

- a) $R^1=R^2=MeO$, $R^3=R^4=R^5=R^6=H$
 b) $R^1=R^2=MeO$, $R^3=H$, $R^4=R^5=MeO$, $R^6=H$
 c) $R^1=R^2=MeO$, $R^3=H$, $R^4=R^5=R^6=MeO$
 d) $R^1=H$, $R^2=R^3=R^4=R^5=MeO$, $R^6=H$
 e) $R^1=H$, $R^2=MeO$, $R^3=H$, $R^4=R^5=MeO$, $R^6=H$
 f) $R^1=H$, $R^2=R^3=MeO$, $R^4=R^5=R^6=H$
 g) $R^1+R^2=OCH_2O$, $R^3=R^4=R^5=R^6=H$
 h) $R^1=R^2=R^3=R^4=R^5=R^6=H$
 i) $R^1=R^2=MeO$, $R^3=R^4=R^5=R^6=MeO$
 j) $R^1=R^2=MeO$, $R^3=R^4=R^5=H$, $R^6=MeO$
 k) $R^1=H$, $R^2=R^3=R^4=R^5=R^6=MeO$
 l) $R^1+R^2=OCH_2O$, $R^3=H$, $R^4=R^5=MeO$, $R^6=H$

EXPERIMENTAL

Melting points were taken on a Electrothermal digital melting point apparatus and are uncorrected. IR spectra were taken on a Mattson 1000 spectrophotometer. 1H NMR spectra were obtained on a Bruker 200 MHz instrument. MS spectra were obtained on a Hewlett-Packard GC-MS. Starting dibenzylamino

ketones (**1**) were prepared by method similar to those which we have already reported for the preparation of *N*-benzyl-*N*-alkylaminoacetophenones.⁷

***N,N*-Dibenzylphenacylamines (1a-l). General Procedure** -To a solution of aromatic aldehyde (25 mmol) in benzene (70 mL) benzylamine (25 mmol) was added dropwise. The mixture was refluxed for 5 h under condenser equipped with Dean-Stark trap. The solvent was evaporated and the residue dissolved in methanol (60 mL). KBH_4 (0.675 g, 12.5 mmol) was added in portions and the mixture stirred for 1.5 h. K_2CO_3 (0.875 g, 6.25 mmol) and phenacyl bromide (4.98 g, 25 mmol) were added and the stirring continued for 2 h more. The solvent was evaporated on a rotary-evaporator. The residue was extracted with warm ether (4 x 30 mL). The combined extracts were filtered. The solution of maleic acid (2.9 g, 25 mmol) in ethanol (15 mL) was dropped slowly to the ethereal solution of the amino ketone. The white precipitate formed was separated by filtration and dissolved in ethanol (25 mL). Ether (50 mL) was added and the mixture left to crystallise at rt. White needle shaped crystals were filtered and dried under vacuum. **1a** yield 82%; Recrystallized from ethanol-ether (1:2), mp 126-127 °C; IR $\nu_{\text{C=O}}$ 1680 cm^{-1} ; MS m/z 375 (M^+); Anal. Calcd for $\text{C}_{26}\text{H}_{27}\text{NO}_5$: C,72.03; H,6.28; N,3.23. Found: C,72.20; H,6.40; N,3.30. **1b** yield 92%; Recrystallized from ethanol-ether (1:2), mp 133-135 °C; IR $\nu_{\text{C=O}}$ 1680 cm^{-1} ; MS m/z 435 (M^+); Anal. Calcd for $\text{C}_{28}\text{H}_{31}\text{NO}_7$: C,68.13; H,6.33; N,2.84. Found: C,68.00; H,6.42; N,2.75. **1c** yield 93%; Recrystallized from ethanol-ether (1:2), mp 105-106 °C; IR $\nu_{\text{C=O}}$ 1680 cm^{-1} ; MS m/z 465 (M^+); Anal. Calcd for $\text{C}_{29}\text{H}_{33}\text{NO}_8$: C,66.52; H,6.35; N,2.68. Found: C,66.45; H,6.50; N,2.90. **1d** yield 89%; oil; IR $\nu_{\text{C=O}}$ 1680 cm^{-1} ; MS m/z 435 (M^+); Anal. Calcd for $\text{C}_{26}\text{H}_{29}\text{NO}_5$: C,71.70; H,6.71; N,3.22. Found: C,71.80; H,6.65; N,3.30. **1e** yield 91%; oil; IR $\nu_{\text{C=O}}$ 1680 cm^{-1} ; MS m/z 405 (M^+); Anal. Calcd for $\text{C}_{25}\text{H}_{27}\text{NO}_4$: C,74.05; H,6.71; N,3.45. Found: C,74.20; H,6.60; N,3.40. **1f** yield 85%; oil; IR $\nu_{\text{C=O}}$ 1680 cm^{-1} ; MS m/z 375 (M^+); Anal. Calcd for $\text{C}_{24}\text{H}_{25}\text{NO}_3$: C,76.77; H,6.71; N,3.73. Found: C,76.50; H,6.75; N,3.60. **1g** yield 88%; Recrystallized from ethanol-ether (1:2), mp 125-126.5 °C; IR $\nu_{\text{C=O}}$ 1680 cm^{-1} ; MS m/z 359 (M^+); Anal. Calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_5$: C,71.92; H,5.55; N,3.35. Found: C,72.05; H,5.65; N,3.38. **1h** yield 90%; Recrystallized from ethanol-ether (1:2), mp 131-133 °C; IR $\nu_{\text{C=O}}$ 1680 cm^{-1} ; MS m/z 315 (M^+); Anal. Calcd for $\text{C}_{24}\text{H}_{23}\text{NO}_3$: C,77.18; H,6.21; N,3.75. Found: C,77.20; H,6.25; N,3.70. **1i** yield 95%; Recrystallized from ether, mp of the free base 87-87.5 °C; IR $\nu_{\text{C=O}}$ 1680 cm^{-1} ; MS m/z 345 (M^+); Anal. Calcd for $\text{C}_{23}\text{H}_{23}\text{NO}_2$: C,79.96; H,6.71; N,4.05. Found: C,79.90; H,6.75; N,3.98. **1j** yield 90%; oil; IR $\nu_{\text{C=O}}$ 1680 cm^{-1} ; MS m/z 405 (M^+); Anal. Calcd for $\text{C}_{25}\text{H}_{27}\text{NO}_4$: C,74.05; H,6.71; N,3.45. Found: C,74.10; H,6.65; N,3.39. **1k** yield 93%; oil; IR $\nu_{\text{C=O}}$ 1680 cm^{-1} ; MS m/z 465 (M^+); Anal. Calcd for $\text{C}_{27}\text{H}_{31}\text{NO}_6$: C,69.65; H,6.71; N,3.00. Found: C,69.70; H,6.60; N,3.10. **1l** yield 87%; oil; IR $\nu_{\text{C=O}}$ 1680 cm^{-1} ; MS m/z 419 (M^+); Anal. Calcd for $\text{C}_{25}\text{H}_{25}\text{NO}_3$: C,71.57; H,6.00; N,3.34. Found: C,71.60; H,6.10;

N,3,25. Compounds (**1d,e,f,j-l**) were purified by column chromatography using ether-petroleum ether (1:3) as eluent and silica gel as an adsorbent. They did not give crystallisable materials.

2,3-Dimethoxy-7,12-dihydro-12-phenyl-5H-6,12-methanodibenz[*c,f*]azocine (7a). Method A - To a solution of compound (**1a**) maleate (0.433 g, 1 mmol) in CH_2Cl_2 (10 mL) 2 mL of 95% H_2SO_4 was added dropwise and the mixture stirred at rt for 16h. The mixture was poured into crushed ice (30 g) and basified with 20% NaOH. The mixture was extracted with CH_2Cl_2 (4 x 15 mL). The combined extracts were dried over Na_2SO_4 and filtered. The solvent was removed and the residue subjected to preparative TLC. Compound (**3a**) was obtained as a colourless oil. Yield 0.21g, 59%. The compound was converted into the hydrochloride salt passing HCl through its ethereal solution: mp 211-213 °C (lit.,⁴ mp 212-214 °C)

Treatment of compound (1a) with 70% HClO_4 - Compound (**1a**) maleate (0.867 g, 2 mmol) was dissolved in 5 mL of 70% HClO_4 and the mixture stirred at room temperature for 16 h. The mixture was poured into ice-water (20 mL) at stirring. The formed white amorphous solid was filtered and washed with water (2 x 5 mL) and dried under vacuum. Recrystallization from ethanol (10 mL) gave a product with mp 200-201 °C. Yield 0.550 g, 60%. The ^1H NMR spectrum showed that it is a mixture of *N*-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydro-4-phenylisoquinoline perchlorate and *N*-benzyl-6,7-dimethoxy-4-phenylisoquinolinium perchlorate. 0.350 g of the mixture was dissolved in 20 mL of ethanol at reflux and left to crystallize at rt for three days. There were two type of crystals formed: white and light-blue. The crystals were easily separated mechanically. The white crystals (95 mg) melts at 236-238 °C. This compound was proven to be *N*-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydro-4-phenylisoquinoline perchlorate comparing it with a sample obtained from the cyclization of the corresponding *N*-3,4-dimethoxybenzyl-*N*-benzyl-2-amino-1-phenylethanol in the presence of concentrated sulfuric acid. The free base forms of both compounds have the same R_f values in all developing systems attempted. Their MS and IR spectra have also been superimposable. MS m/z 359 (M^+ , 55.55), 268(11.11), 240(100), 209(91.11), 194(10), 165(15), 91(44.44). The second light blue coloured product (92 mg) melts at 180.2 °C. IR spectrum of the compound shows a complex band at 1600-1640 cm^{-1} which is characteristic for isoquinolinium salts. ^1H NMR spectrum ($\text{DMSO-}d_6$) of the mixture showed two singlets at 9.74 and 8.83 ppm. The downfield resonance corresponds to the C-1H, while those at 8.83 to the C-3H in the fully aromatic isoquinolinium perchlorate. Benzylic methylene appeared at δ 5.91 ppm as a singlet. Two singlets corresponding to methoxy groups' protons appeared at 3.94 and 4.03 ppm.

2,3,9,10-Tetramethoxy-7,12-dihydro-12-phenyl-5H-6,12-methanodibenz[*c,f*]azocine (7b). Method A - To a solution of amino ketone (**1b**).1/2 maleate (0.493 g, 1 mmol) in CH_2Cl_2 (10 mL) 2 mL of 95% H_2SO_4 was added dropwise and the mixture stirred at rt for 16 h. The mixture was poured into crushed ice (30 g) and basified with 20% NaOH. The mixture was extracted with CH_2Cl_2 (4 x 10 mL). The

combined extracts were dried over Na_2SO_4 and filtered. The solvent was evaporated and the residue dissolved in ether (10 mL) and petroleum ether (40-60°C, 20 mL) mixture and left to crystallise at rt. The white crystals formed were collected by filtration. The crude product was recrystallized from ethanol. Yield 0.375 g, 90%, mp 150-151.5°C; ^1H NMR (CDCl_3) δ 3.27(2H, s), 3.70(6H, s), 3.81(6H, s), 3.89 and 4.66(4H, AB system, $J_{\text{AB}}=17.45$), 6.51(2H,s), 6.74(2H,s), 7.25-7.47(5H, m); MS m/z 417 (M^+); Anal. Calcd for $\text{C}_{26}\text{H}_{27}\text{NO}_4$: C,74.80; H,6.52; N,3.35. Found: C,74.75; H,6.48; N,3.30.

Compound (7c); Oil, Yield 75%. ^1H NMR ($\text{DMSO}-d_6$) δ 3.06(2H, s), 3.57(6H, s), 3.68(6H, s), 3.77(3H, s), 3.85(2H, d, $J=16.03$), 4.56(2H, d, $J=19.26$), 6.61-7.40(8H, m); MS m/z 447 (M^+); Anal. Calcd for $\text{C}_{27}\text{H}_{29}\text{NO}_5$: C,72.46; H,6.53; N,3.13. Found: C,72.30; H,6.50; N,3.20.

Compound (7d); Yield 60%.The compound was recrystallised from methanol-petroleum ether, mp 83-84.5°C; ^1H NMR (CDCl_3) δ 3.23(2H, s), 3.70(3H, s), 3.80(3H, s), 3.81(6H, s), 3.85(1H, d, $J=18.40$), 4.08(1H, d, $J=18.47$), 4.59(1H, d, $J=18.43$), 4.64(1H, d, $J=17.39$), 6.49(1H, s), 6.68(1H, d, $J=8.65$), 6.73(1H, s), 6.98(1H, d, $J=8.52$), 7.26-7.46(5H, m); MS m/z 417 (M^+); Anal. Calcd for $\text{C}_{26}\text{H}_{27}\text{NO}_4$ C,74.80; H,6.52; N,3.35. Found: C,74.73; H,6.45; N,3.38.

Compound(7e);Oil, Yield 62%. ^1H NMR (CDCl_3) δ 3.31(2H, s), 3.70 and 3.81(9H, two s), 3.93 and 4.72(4H, AB system, $J_{\text{AB}}=17.31$), 6.51(1H, s), 6.56-6.67(2H, m), 6.72(1H, s), 7.25-7.50(6H, m); MS m/z 387 (M^+); Anal. Calcd for $\text{C}_{25}\text{H}_{25}\text{NO}_3$: C,77.49; H,6.50; N,3.61. Found: C,77.60; H,6.39; N,3.55.

2,3,9,10-Tetramethoxy-7,12-dihydro-12-phenyl-5H-6,12-methanodibenz[*c,f*]azocine (7b). Method B- Amino ketone (**1b**) maleate (0.493 g, 1 mmol) was dissolved in 3 mL of 70% HClO_4 and stirred at room temperature for 16 h. The mixture was poured into ice-water (10 mL) at stirring. The formed white amorphous solid was collected by filtration and dissolved in ethanol (2 mL). Water was added and basified with 10% NH_4OH . The mixture was extracted with chloroform (2 x 15 mL). The combined extracts were dried over Na_2SO_4 and filtered. The solvent was evaporated on a rotary-evaporator. The residue was dissolved in ether (10 mL) and petroleum ether (40-60°C, 20 mL) was added and the solution left to crystallise at rt. The white crystals formed were collected by filtration (0.415 g, 99%). The compound has the same mp as the compound obtained by method A. Their IR spectra have also been superimposable. **One-pot Procedure** - To a solution of 3,4-dimethoxybenzaldehyde (0.831 g, 5 mmol) in benzene (30 mL) veratrylamine (0.835 g, 5 mmol) was added dropwise. The mixture was refluxed for 5 h under condenser equipped with Dean-Stark trap. The solvent was evaporated and the residue dissolved in methanol (20 mL). KBH_4 (0.135 g, 2.5 mmol) was added in portions and the mixture stirred for 2 h. K_2CO_3 (0.175 g, 1.25 mmol) and phenacyl bromide (0.996 g, 5 mmol) were added and the stirring continued for 2 h. The solvent was evaporated on a rotary-evaporator. The residue was extracted with warm ether (4 x 15 mL). The organic solvent was evaporated and the residue dissolved in

dichloromethane (30 mL). 95% H₂SO₄ (10 mL) was added dropwise and the mixture stirred at rt for 2 h. The mixture was poured into crushed ice (60 g) and basified with 20% NaOH. The mixture was extracted with CH₂Cl₂ (4 x 20 mL). The combined extracts were dried over Na₂SO₄ and filtered. The solvent was evaporated and the residue dissolved in ether (30 mL) and petroleum ether (40-60°C, 60 mL) mixture and left to crystallise at rt. The product (**7b**) isolated was identical to those obtained by methods A and B. Yield 1.49 g, 72%.

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