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SYNTHESIS OF SOME NOVEL 2,14-DIMETHYL/2,3,13,14-TERAMETHYL-8-ARYL-5,6,7,9,10,11-HEXAHYDROBENZO[6,1] CYCLOHEPTA[b,e]PYRIDINE DERIVATIVES FROM SUSTITUTED BENZOSUBERONES

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Abstract:
2,14-dimethyl/2,3,13,14-tetramethyl-8-aryl-5,6,7,9,10,11-hexahydrobenzo[6,1]cyclohept [b,e]pyridine derivatives (**4a-g & 8a-g**) obtained by the condensation of 3-methyl benzocyclohepten-5-one **1** with appropriate aromatic aldehydes and ammonium acetate. The structure of **4a-g & 8a-g** were confirmed from their spectral analysis.

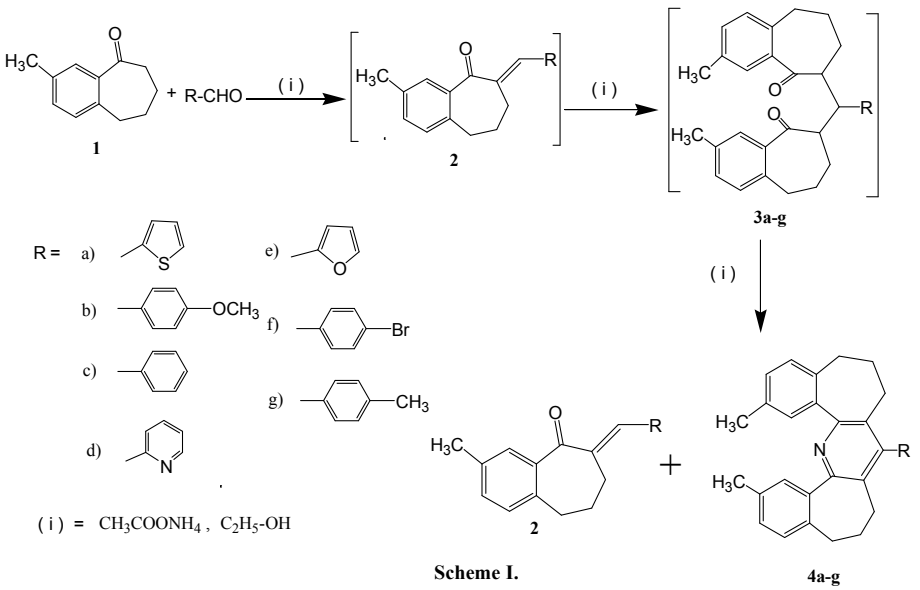
Keywords: benzosuberones, acridines, dihydronicotinamide adeninedinulcleotide (NADH).

Introduction:

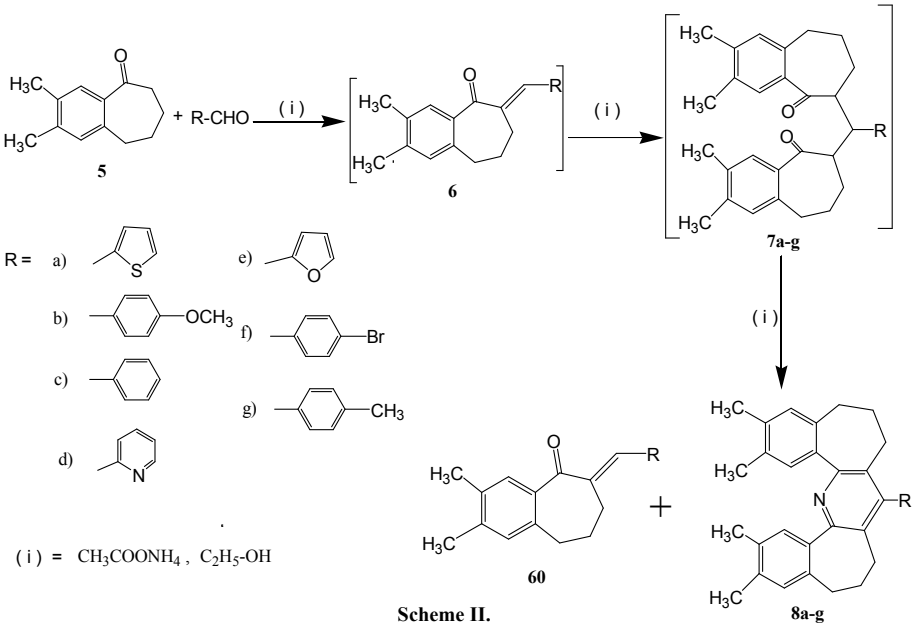
In the last two decades we have been working on synthesis of heterocyclic compounds[i-vi] using readily available precursors derived from benzosuberones and benzazepines[i] Continuing with our efforts in this area we herein report the hitherto unreported novel pyridine analogues. Similar type of compounds possesses biological applications, especially as antibacterial agents for wound therapy[vii]. The biological activity of the acridines is mainly due to its ability to interact with DNA[viii]. Acridine-1,8-dione dyes have gained importance in recent years due to similar in structure to the 1,4-dihydropyridines and the biologically important dihydronicotinamide adeninedinulcleotide (NADH) and its analogues, which are important coenzymes in biological systems[ix]. Hence, it was thought worthwhile to prepare the title compounds with the hope that these new ring systems may prove to be biologically active. Therefore the synthesis of 2,14-dimethyl/2,3,13,14-tetramethyl-8-aryl-5,6,7,9,10,11-hexahydrobenzo[6,1]cyclohept[b,e]pyridine derivatives was taken-up in this chapter and the results presented below. These compounds **4a-g** & **8a-g** were prepared by adopting the procedure reported by Perumal *et al*[x]*.,* starting from substituted benzocyclohepten-5-ones (**1** & **5**)

Results and discussion:

A homogeneous mixture of 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (0.001 mole), substituted aromatic aldehyde (0.0005 mole) and ammonium acetate (0.01 mole) in ethanol (5 mL) on refluxing for 3 hrs. gave a yellow colour crude product. TLC examination (silica gel G, petroleum ether-ethyl acetate 10%) of the crude solid revealed the presence of two spots, therefore it was purified by using column chromatography (adsorbent: silica gel G) ethyl acetate-petroleum ether (1:9) an eluents. On evaporation of the solvent yielded a light yellow solid, as a minor, which was identified as arylidiene derivatives (**2** & **6**) based on the spectroscopic methods. Further elucidation of the column with ethyl acetate-petroleum ether (2:8) yielded another yellow colour compound as a major product. It melted at 285-288^{0}C and analyzed for $C_{29}H_{27}NS$. IR Spectrum of the compound **4a** showed absorption due to C = C stretching at 1610 cm^{-1}, C =N stretching at 1678 cm^{-1} and aliphatic CH stretching at 2350 cm^{-1} and also aromatic CH stretching at 2920 cm^{-1}. The ^{1}H NMR spectra (200 MHz $CDCl_3$) of the product **4a** contained two multiplet at δ 2.10 integrating for 4H, another multiplet at δ 2.32 integrating for 4H. These two multiplets were assigned to methylene groups present at C_6, C_7, C_9 & C_{10} positions. The benzyl methylene protons at C_5 & C_{11} position appeared at δ 2.61. Another signal which appeared in the aliphatic region at δ 2.41 integrating for 6H were assigned to aromatic methyl protons at C_2 & C_{14}, These findings revealed represents of cyclohepta[b,e]pyridine moiety. Thus we assume that the formation of **4a-g** and **8a-g** proceeds by a Michael type addition of **1** and **5** to the activated double bond of the arylidine intermediates **2** and **6** (formed in situ by a Knoevenagal condensation between the ketones **1** and **5** and benzaldehyde) expected to give diketone intermediates[10] **3** and **7**. This unstable intermediate compounds subsequently react with ammonium acetate by oxidative dimerisation to give **4a-g** (**scheme-I**) and **8a-g** (**scheme-II**). We have not isolated the diketones **3** and **7** as reported earlier[10], but in all probability this may be one of the possible pathway to the final compounds. We have taken ^{13}C NMR spectra of compound **4a** as a test case. It showed the following signals at δ 27.3 (2C, 2-CH_3 & 14-CH_3), 29.7 (2C, 7-CH_2 & 9-CH_2), 30.8 (2C, 6-CH_2 & 10-CH_2), 33.8 (2C, 5-CH_2 & 11-CH_2), Ar-C: (125.7, 127.0, 129.5,130.2, 132.7, 134.5, 136.5, 138.0, 156.8). The mass spectrum of product **4a** showed the molecular ion peak [M^+] at m/z 421 which further confirms the structure. Similarly, all the structures of the newly synthesized compounds **4** and **8** were elucidated and confirmed by spectral and elemental analysis.



Scheme I.



Scheme II.

Experimental section:

Melting points were determined using Gallankamp apparatus and are uncorrected. IR spectra were recorded on a FT-IR 1605 Perkin-Elmer; ^{1}H NMR in $CDCl_3$ on a Varian FT-80A spectrometer with TMS as an internal standard; and mass spectra on a VG-micro mass 7070H mass spectrometer. TLC was run on Silica gel G coated plates and iodine vapor as visualizing agent.

Synthesis of 2,14-dimethyl-8-thiophene-5,6,7,9,10,11-hexahydrobenzo[6,1] cyclohepta[b,e]pyridine: General procedure (4a): A mixture of compound **1** (0.001 mole), thiophene-2-carbaldehyde (0.0005 mol) and ammonium acetate (0.01 mol) in ethanol (5 mL) was refluxed for 3 h. After completion of the reaction, as monitored by TLC, the excess solvent was distilled off and residue was poured into ice water. The yellow precipitate

obtained was filtered, washed with water and dried to gave a crude residue which was purified by column chromatography over silica gel with ethyl acetate-petroleum ether (3:7) as eluent to afford **4a** in 71% yield: m.p. 285-288^{0}C; IR (KBr): 1610 (C=C), 1678 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.05-2.20 (4H, m, 7-CH_2 & 9-CH_2), 2.30-2.35 (4H, m, 6-CH_2 & 10-CH_2), 2.41 (6H, s, 2-CH_3 & 14-CH_3), 2.55-2.65 (4H, m, 5-CH_2 & 11-CH_2), 6.95-7.65 (9H, m, Ar-CH); MS: m/z 421 ($M^{+\cdot}$); Anal. Found: C, 82.63; H, 6.40; N, 3.30. $C_{29}H_{27}NS$ requires C, 82.66; H, 6.41; N, 3.32%.

Compound 4b: yield: 78%; m.p. 283-285^{0}C; IR (KBr):1610 (C=C), 1676 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.00-2.10 (4H, m, 7-CH_2 & 9-CH_2), 2.20-2.30 (4H, m, 6-CH_2 & 10-CH_2), 2.45 (6H, s, 2-CH_3 & 14-CH_3), 2.60-2.70 (4H, m, 5-CH_2 & 11-CH_2), 3.90 (3H, s, OCH_3), 6.95-7.70 (10H, m, Ar-CH); MS: m/z 445 ($M^{+\cdot}$); Anal. Found: C, 86.25; H, 6.90; N, 3.12. $C_{32}H_{31}NO$ requires C, 86.29; H, 6.96; N, 3.14%.

Compound 4c: yield: 40%; m.p. 274-278^{0}C; IR (KBr): 1612 (C=C), 1670 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.00-2.18 (4H, m, 7-CH_2 & 9-CH_2), 2.18-2.30 (4H, m, 6-CH_2 & 10-CH_2), 2.42 (6H, s, 2-CH_3 & 14-CH_3), 2.55-2.65 (4H, m, 5-CH_2 & 11-CH_2), 7.10-7.70 (11H, m, Ar-CH); MS: m/z 415 ($M^{+\cdot}$); Anal. Found: C, 89.62; H, 6.96; N, 3.34. $C_{31}H_{29}N$ requires C, 89.63; H, 6.98; N, 3.37%.

Compound 4d: yield: 74%; m.p. >300^{0}C; IR (KBr): 1615 (C=C), 1678 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.10-2.20 (4H, m, 7-CH_2 & 9-CH_2), 2.35-2.45 (4H, m, 6-CH_2 & 10-CH_2), 2.38 (6H, s, 2-CH_3 & 14-CH_3), 2.58-2.68 (4H, m, 5-CH_2 & 11-CH_2), 7.10-7.85 (9H, m, Ar-CH), 7.70-7.80 (1H, d, N=CH); Anal. Found: C, 86.50; H, 6.71; N, 6.70. $C_{30}H_{28}N_2$ requires C, 86.53; H, 6.73; N, 6.73%.

Compound 4e: yield: 42%; m.p. 289-291^{0}C; IR (KBr): 1611 (C=C), 1670 (C=N) cm^{-1};^{1}H NMR ($CDCl_3$): δ 2.15-2.25 (4H, m, 7-CH_2 & 9-CH_2), 2.35-2.40 (4H, m, 6-CH_2 & 10-CH_2), 2.42 (6H, s, 2-CH_3 & 14-CH_3), 2.55-2.65 (4H, m, 5-CH_2 & 11-CH_2), 6.50-7.70 (9H, m, Ar-CH); Anal. Found: C, 85.90; H, 6.63; N, 3.43. $C_{29}H_{27}NO$ requires C, 85.92; H, 6.66; N, 3.45%.

Compound 4f: yield: 40%; m.p. 282-285^{0}C; IR (KBr): 1614 (C=C), 1675 (C=N) cm^{-1};^{1}H NMR ($CDCl_3$): δ 1.90-2.10 (4H, m, 7-CH_2 & 9-CH_2), 2.10-2.25 (4H, m, 6-CH_2 & 10-CH_2), 2.38 (6H, s, 2-CH_3 & 14-CH_3), 2.50-2.65 (4H, m, 5-CH_2 & 11-CH_2), 7.00-7.75 (10H, m, Ar-CH); Anal. Found: C, 75.12; H, 5.62; N, 2.80. $C_{31}H_{28}NBr$ requires C, 75.15; H, 5.65; N, 2.82%.

Compound 4g: yield: 45%; m.p. 260-265^{0}C; IR (KBr): 1613 (C=C), 1672 (C=N) cm^{-1};^{1}H NMR ($CDCl_3$): δ 1.95-2.15 (4H, m, 7-CH_2 & 9-CH_2), 2.15-2.35 (4H, m, 6-CH_2 & 10-CH_2), 2.38 (6H, s, 2-CH_3 & 14-CH_3), 2.40-2.50 (4H, m, 5-CH_2 & 11-CH_2), 7.30-7.78 (10H, m, Ar-CH); Anal. Found: C, 89.50; H, 7.20; N, 3.22. $C_{32}H_{31}N$ requires C, 89.51; H, 7.22; N, 3.26%.

Compound 8a: yield: 79%; m.p. 279-282^{0}C; IR (KBr): 1611 (C=C), 1678 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.00-2.10 (4H, m, 7-CH_2 & 9-CH_2), 2.20-2.30 (4H, m, 6-CH_2 & 10-CH_2), 2.45 (12H, s, 2,3-CH_3 & 14,15-CH_3), 2.60-2.70 (4H, m, 5-CH_2 & 11-CH_2), 6.95-7.70 (10H, m, Ar-CH); MS: m/z 449 ($M^{+\cdot}$); Anal. Found: C, 82.82; H, 6.88; N, 3.10. $C_{31}H_{31}NS$ requires C, 82.85; H, 6.90; N, 3.11%.

Compound 8b: yield: 72%; m.p. 287-290^{0}C; IR (KBr): 1615 (C=C), 1672 (C=N) cm^{-1};^{1}H NMR ($CDCl_3$): δ 2.05-2.20 (4H, m, 7-CH_2 & 9-CH_2), 2.30-2.35 (4H, m, 6-CH_2 & 10-CH_2), 2.44(12H, s, 2,3-CH_3 & 14,15-CH_3), 2.55-2.65 (4H, m, 5-CH_2 & 11-CH_2), 3.50 (3H, s, OCH_3), 6.95-7.65 (9H, m, Ar-CH); Anal. Found: C, 86.21; H, 7.37; N, 2.93. $C_{34}H_{35}NO$ requires C, 86.25; H, 7.39, N; 2.95%.

Compound 8c: yield: 40%; m.p. 295-298^{0}C; IR (KBr): 1613 (C=C), 1675 (C=N) cm^{-1};^{1}H NMR ($CDCl_3$): δ 2.00-2.18 (4H, m, 7-CH_2 & 9-CH_2), 2.18-2.30 (4H, m, 6-CH_2 & 10-CH_2), 2.35(12H, s, 2,3-CH_3 & 14,15-CH_3), 2.55-2.65 (4H, m, 5-CH_2 & 11-CH_2), 6.95-7.65 (9H, m,

Ar-CH); Anal. Found: C, 89.36; H, 7.42; N, 3.14. $C_{33}H_{33}N$ requires C, 89.39; H, 7.44; N, 3.16%.

Compound 8d: yield: 70%; m.p. 295-300^{0}C; IR (KBr): 1610 (C=C), 1674 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.10-2.20 (4H, m, 7-CH_2 & 9-CH_2), 2.25-2.35 (4H, m, 6-CH_2 & 10-CH_2), 2.35 (12H, s, 2-CH_3 & 14-CH_3), 2.58-2.68 (4H, m, 5-CH_2 & 11-CH_2),
7.10-7.85 (9H, m, Ar-CH), 7.70-7.80 (1H, d, N=CH); Anal. Found: C, 86.45; H, 7.18; N, 6.28. $C_{32}H_{32}N_2$ requires C, 86.48; H, 7.20; N, 6.30%.

Compound 8e: yield: 50%; m.p. 268-273^{0}C; IR (KBr): 1610 (C=C), 1672 (C=N) cm^{-1};^{1}H NMR ($CDCl_3$): δ 2.15-2.25 (4H, m, 7-CH_2 & 9-CH_2), 2.25-2.30 (4H, m, 6-CH_2 & 10-CH_2), 2.30 (12H, s, 2,3-CH_3 & 14,15-CH_3), 2.55-2.65 (4H, m, 5-CH_2 & 11-CH_2), 6.40-7.60 (7H, m, Ar-CH); Anal. Found: C, 85.90; H, 7.12; N, 3.20. $C_{31}H_{31}NO$ requires C, 85.91; H, 7.15; N, 3.23%.

Compound 8f: yield: 40%; m.p. 274-278^{0}C; IR (KBr): 1615 (C=C), 1676 (C=N) cm^{-1};^{1}H NMR ($CDCl_3$): δ 1.95-2.10 (4H, m, 7-CH_2 & 9-CH_2), 2.25 (12H, s, 2,3-CH_3 & 14,15-CH_3), 2.25-2.15 (4H, m, 6-CH_2 & 10-CH_2), 2 50-2.65 (4H, m, 5-CH_2 & 11-CH_2), 6.95-7.65 (7H, m, Ar-CH); Anal. Found: C, 75.68; H, 6.10; N, 2.64. $C_{33}H_{32}NBr$ requires C, 75.71; H, 6.11; N, 2.67%.

Compound 8g: yield: 40%; m.p. 283-286^{0}C; IR (KBr): 1611 (C=C), 1676 (C=N) cm^{-1};^{1}H NMR ($CDCl_3$): δ 1.95-2.15 (4H, m, 7-CH_2 & 9-CH_2), 2.15-2.35 (4H, m, 6-CH_2 & 10-CH_2), 2.38 (12H, s, 2,3-CH_3 & 14,15-CH_3), 2.40-2.50 (4H, m, 5-CH_2 & 11-CH_2), 7.30-7.780 (10H, m, Ar-CH); Anal. Found: C, 89.24; H, 7.63; N, 3.02. $C_{34}H_{35}N$ requires C, 89.27; H, 7.65; N, 3.06%.

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