SYNTHESIS OF 1,2,3,4,4a,5,9,10,16,16a-DECAHYDRO-2-METHYL[1]BENZAZEPINO [3,2,1-jk]PYRIDO[3,4-b][1]BENZAZEPINE: A CONFORMATIONALLY RIGID IMIPRAMINE ANALOG

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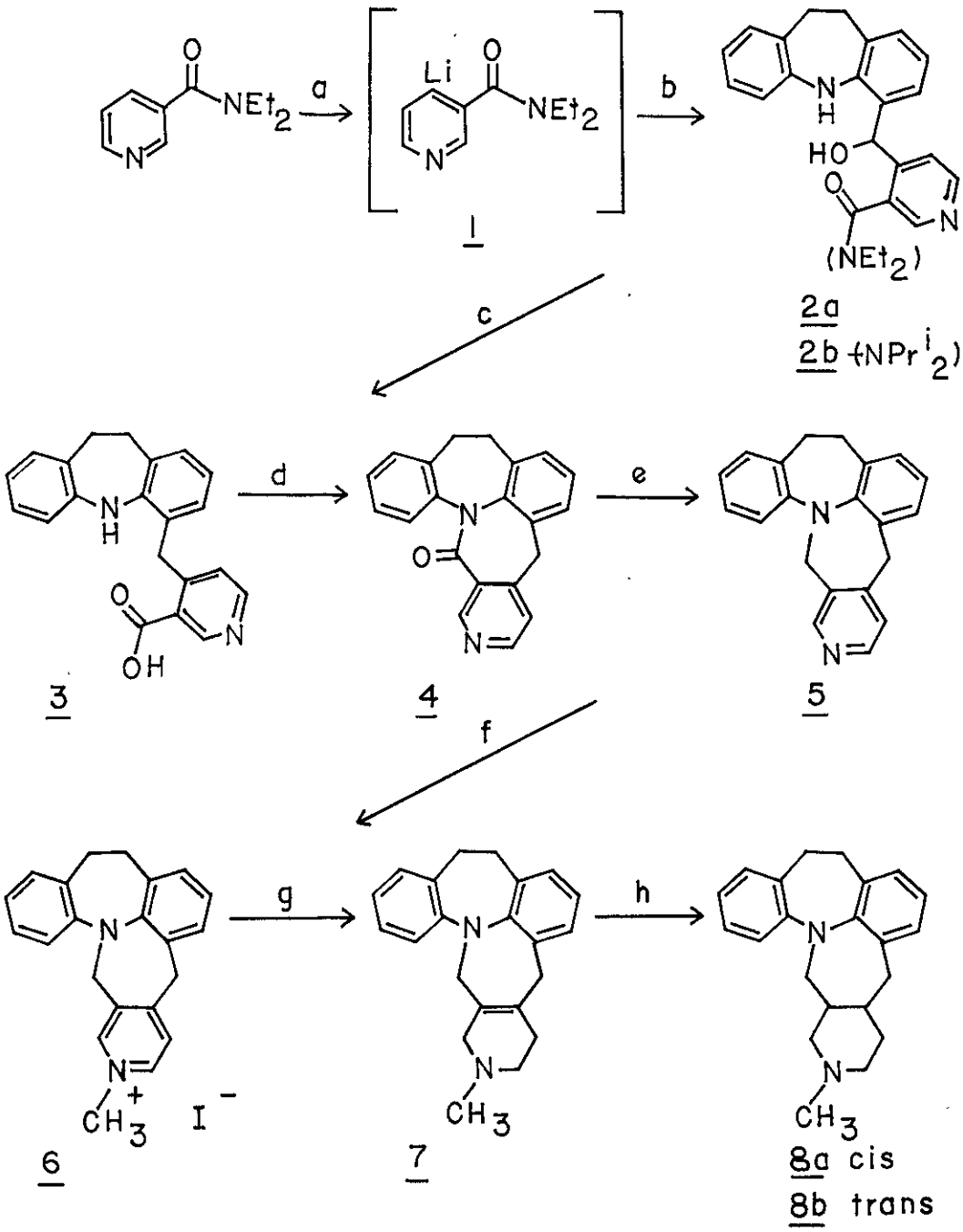
Abstract - Ortho lithiations and acylations of 10,11-dihydro-5H-dibenz[b,f]azepine and N,N-diethylnicotinamide respectively led to the convenient synthesis of the key intermediate 4-[(10,11-dihydro-5H-dibenz[b,f]azepin-4-yl)hydroxymethyl]-N,N-diethylnicotinamide 2a. Catalytic reduction of 2a, and subsequent cyclization of the resulting carboxylic acid 3, provided the pentacyclic lactam 4 required for further elaboration of the rigid imipramine analog. Difficulties in amide hydrolysis are discussed. Further reductions and N-methylation provided both cis and trans ring fusion isomers 8a and 8b identified by ^{1}H and ^{13}C nmr.

In order to mimic the extended side chain conformation of the tricyclic antidepressant imipramine in a rigid system we have undertaken the synthesis of 8. Studies of the X-ray crystal structure of imipramine indicate two side chain conformations,[1,2] one of which is fully extended and similar to Dreiding models of 8b; which appears to be quite rigid based on its proton nmr. The cis ring fusion isomer 8a is both less well conformationally defined and unlike any known imipramine conformation. It will be subjected to the same pharmacological analysis as the trans isomer.

Synthesis of the pentacyclic structure begins with the known ortho dimetalation of 10,11-dihydro-5H-dibenz[b,f]azepine, followed by acylation with DMF.[3] The resulting 10,11-dihydro-5H-dibenz[b,f]azepine-4-carboxaldehyde was used in the next reaction as an acylating agent. N,N-Diethylnicotinamide, while providing a lower yield than the diisopropylamide on acylation, can be conveniently and specifically lithiated in the 4 position of the pyridine ring at -78°C with a hindered base such as lithio-2,2,6,6-tetramethylpiperidide.[4] Acylation of this reagent within 15 min with the aldehyde, provided 2 in good yield.

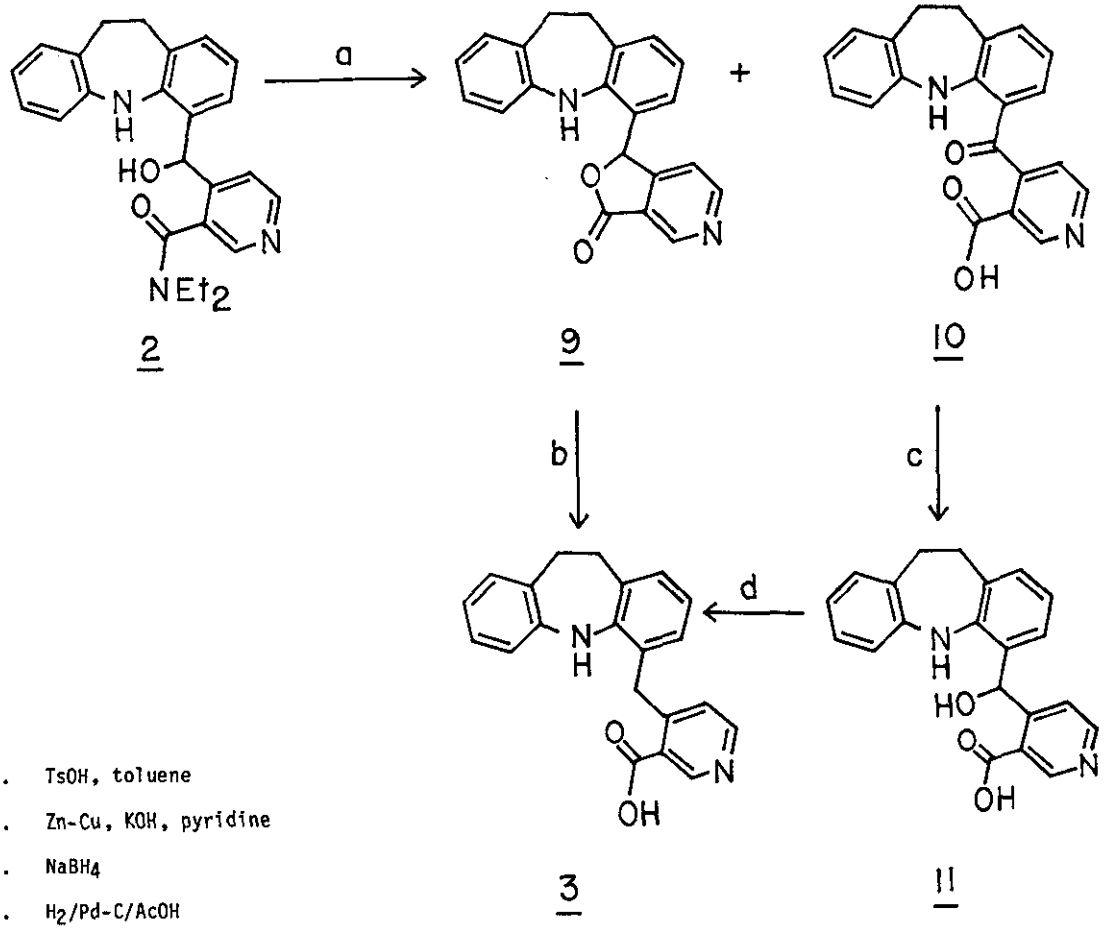
Several attempts at hydrolyzing the N,N-diisopropylamide compound 2b as well as 2a in strongly acidic and basic conditions, both before and after hydrogenolizing the hydroxyl substituent, resulted in recovery of starting material and unidentified side products. The carboxylic acid 3



a. LiTMP b. 10,11-dihydro-5H-dibenz[b,f]azepine-4-carboxaldehyde c. H_2/Pd-C/AcOH

d. $POCl_3$ e. BH_3·THF f. MeI g. $NaBH_4$ h. TFA, Et_3SiH

was obtained in a two step procedure involving lactonization to give 9,[5] which was then reduced with zinc copper couple in KOH and pyridine.[6] This reaction sequence was successful only in the N,N-diethylamide case, and was difficult to reproduce due to the instability of the lactone 9. Interestingly the lactone once isolated was easily air oxidized to the keto-acid 10,[7] which was also a major side product of the lactonization step.[8]

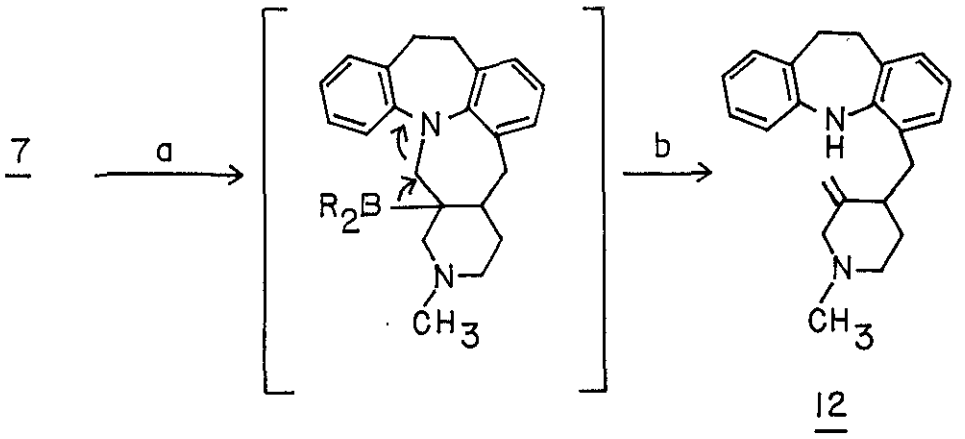


a. TsOH, toluene
b. Zn-Cu, KOH, pyridine
C. $NaBH_4$
d. H_2/Pd-C/AcOH

Despite the many problems associated with the hindered amide hydrolysis, and lactone hydrogenolysis, it was found that the carboxylic acid 3 could be obtained directly from 2 in good yield by hydrogenolysis at 1 atmosphere pressure and 85°C in glacial acetic acid.[9] No doubt lactonization followed by hydrogenolysis is the mechanism,[10] and strict exclusion of oxidizing conditions allows formation of the desired product. Conversion of the ketoacid 10 to an alcohol 11[11] with $NaBH_4$ provided another substrate that could undergo this reduction to give 3. Lactamization in neat $POCl_3$ at room temperature[12] provided the novel heterocyclic intermediate 9,10-dihydro[1]benzazepino[3,2,1-jk]pyrido[3,4-c][1]benzazepin-16(5H)-one 4.

Commercial 0.9M borane in THF was successful in reducing the lactam carbonyl[13,14] giving 5, which was then quaternized and reduced without rigorous isolation of the intermediate pyridinium methiodide 6. This two step sequence was low yielding (40%), possibly due to the incomplete quaternization in EtOH, or only partial reduction of the pyridine ring. Quaternization in THF appears to be more successful[8] and is recommended due to insolubility of the salt once formed, and thus prevention of solvolysis and establishment of an equilibrium. No dihydropyridine products were isolated; and ^{13}C nmr established the regiochemistry of the remaining double bond in the tetrahydropyridine 7.

Reduction of this tetrasubstituted ring fusion double bond proved intractable to Pd catalyzed hydrogenation, while PtO_2 appeared to reduce at least one aromatic ring as well as giving mixtures of over-reduced products.[8] Borane in THF cleaved the N(15)-C(16) bond giving a Hoffman type elimination product 12,[15] as well as other unidentified side products. Neat triethysilane and trifluoroacetic acid at reflux[16] provided a 5:1 mixture of cis:trans ring fusion isomers 8a and 8b. Ring fusion geometry was assigned based on work with similar compounds, where upfield shifts were detected in ^{13}C nmr for the ring fusion carbons in the cis fused cases due to δ-shielding effects.[17,18,19] Further evidence comes from the proton nmr where the more rigid trans compound exhibits much more fine structure for aliphatic protons, and downfield shift of the N-methyl singlet. Compounds 7 and 8b have N-methyl singlets at 2.48ppm and 2.34ppm respectively, while 8a has an N-methyl singlet at 2.12ppm. This might be explained by the ability of the N-methyl substituent to be anisotropically shielded in the cis case by being positioned over one of the aromatic rings which is not possible in either of the other two more rigid compounds.



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a. BH_3·THF b. HCl, MeOH

EXPERIMENTAL

Infrared spectra were recorded on a Beckman IR-33 spectrophotometer. NMR spectra were recorded on a Varian EM-360 (60MHz) spectrometer and a Bruker WM-250 (250MHz) spectrometer using tetramethylsilane or DSS as an internal standard. Mass spectra were recorded on a Varian MAT 311A double focusing mass spectrometer. Melting points were taken on an Electrothermal apparatus and are uncorrected.

4-[(10,11-Dihydro-5H-dibenz[b,f]azepin-4-yl)hydroxymethyl]-N,N-diethylnicotinamide 2a: Lithium tetramethylpiperidide was prepared by dropwise addition of nBuLi (2.4M) in hexane (40.6ml, 97.4mmol to 16.4ml, 97.4 mmol) of 2,2,6,6,-tetramethylpiperidine in 100ml of anhydrous ether at 0°C under nitrogen. After warming to room temperature over 1 h, this cloudy solution was added via a transfer needle over 5 minutes to a solution of N,N-diethylnicotinamide (16.4ml) in 500ml of anhydrous ether at -78°C under nitrogen. The resulting orange suspension was stirred for 15 more min at -78°C. 10,11-Dihydro-5H-dibenz[b,f]azepine-4-carboxaldehyde (10.87g, 48.7mmol) dissolved in 100ml of anhydrous ether was added rapidly via a transfer needle under nitrogen giving a dark red suspension which was stirred for 20 min at -78°C. The temperature was then raised slowly to 25°C and stirring continued overnight. The suspension was quenched with ice cold water (100ml), the ether layer decanted and aqueous layer filtered to yield 6.8g of product 2a. The aqueous layer was extracted with THF and combined with the ether layer which was then washed with saturated NaCl, dried over $MgSO_4$ and evaporated. Trituration of the combined residues with cold diethyl ether (100ml) afforded 4.5g (11.3g, 58% overall) of 2a as a white solid, mp 193-195°C; ir, 3380, 3060, 2980, 1630, 1590 cm^{-1}; ^1H nmr (60MHz), 8.9d J=5 Hz, 8.4m, 8.0s, 7.6bs, 7.3-6.4m, 6.3bs, 3.7-2.3m, 3.0s, 1.3-0.6m. Anal. calcd for $C_{25}H_{27}N_3O_2$: C 74.79; H 6.78; N 10.47. Found: C 75.01; H 6.77; N 10.33.

4-[(10,11-Dihydro-5H-dibenz[b,f]azepin-4-yl)hydroxymethyl]-N,N-diisopropylnicotinamide 2b: Preparation is similar to 2a above except for the use of N,N-diisopropylnicotinamide (4.1g, 20mmol) in the ortho lithiation step and 2.23g (10mmol) of 10,11-dihydro-5H-dibenz[b,f]azepine-4-carboxyoldehyde as well as equimolar quantities of all other reagents. Work up yielded 3.4g (80%) of 2b as a white solid, mp 195-198°C. Ms m/z 429. Anal. calcd for $C_{25}H_{29}N_3O_2$: C 75.49; H 7.27; N 9.78. Found: C 75.65; H 7.45; N 9.49.

4-[(10,11-Dihydro-5H-dibenz[b,f]azepin-4-yl)methyl]nicotinic acid 3: To a solution of 2a (10.3g, 25.6mmol) in 300ml of glacial acetic acid under nitrogen was added 2.5g of 5% Pd-on-carbon with stirring. Hydrogen gas was admitted via a balloon, and the suspension was heated at 85°C on an oil bath for 24 h. After cooling to room temperature, the acetic acid was filtered and the filtrate extracted with more acetic acid. The residue resulting from evaporation of the combined

acetic acid was taken up in 200ml of ether and extracted with 0.5M NaOH. The combined aqueous phases were acidified to pH 2-3 with 1M HCl and extracted exhaustively with EtOAc, which was washed with water and saturated NaCl, and dried over $MgSO_4$. Evaporation of the solvent gave 7.07g (84%) of 3 as a tan solid, mp 200-203°C; ir, 3360, 3260-2220, 1720, 1710, 1690, 1670, 1580, 1490, 1460 cm^{-1}; ^1H nmr (60MHz), 9.1s, 8.6d J=5 Hz, 7.2-6.5m 4.6bs, 3.0bs; Ms m/z 330. Anal. calcd for $C_{21}H_{18}N_2O_2$: C 76.34; H 5.49; N 8.48. Found: C 75.64; H 5.45; N 8.20, carbon was consistently low in reanalysis.

9,10-Dihydro[1]benzazepino[3,2,1-jk]pyrido[3,4-c][1]benzazepin-16(5H)-one 4: The carboxylic acid 3 (7.07g, 21.4mmol) was dissolved slowly, to give a dark yellow solution, in $POCl_3$ (85ml) and left to stand at room temperature for 48 hours. Excess $POCl_3$ was evaporated and the residue taken up in ice cold water (250ml), and then basified to pH 8-9 with 30% NH_4OH. The suspension was extracted with chloroform, and the combined organics washed with water and dried over $MgSO_4$. Evaporation of the chloroform gave 5.2g (78%) of 4 as a greenish solid, mp 225-227°C; ir, 3060, 3020, 2920, 1640, 1590 cm^{-1}; ^1H nmr (60MHz), 9.6d (J=5 Hz), 9.1s, 7.0m, 4.6d (J=13 Hz) C5eq, 3.6d (J=13 Hz) C5ax, 3.6-2.6m. High-resolution mass calcd for $C_{21}H_{16}N_2O$: 312.1262. Found: 312.1261.

5,9,10,16-Tetrahydro[1]benzazepino[3,2,1-jk]pyrido[3,4-c][1]benzazepine 5: Commercial 0.9M borane in THF 185ml (Aldrich) was added slowly via syringe at room temperature to 4 (5.2g 16.7mmol) under nitrogen with stirring. The resulting white suspension was refluxed for 17 hours to give a yellow solution. After cooling to room temperature and evaporating the solvents; the residue was dissolved in methanol (210ml), and concentrated HCl (40ml) was added. This yellow solution was refluxed with stirring for 12 h. On cooling to room temperature the solvents were removed in vacuo, the solid residue taken up in water (250ml), and then basified to pH 12 with 2N NaOH. Following exhaustive extraction with chloroform due to emulsions, the organic layer was washed once with water and dried over $MgSO_4$. The solution of crude product was rotary evaporated, and the solids eluted through a bed of silica gel 60 with ethyl acetate to give 3.44g (69%) of 5 as light yellow crystals from ethyl acetate, mp 217-219°C; ir, 3050, 3020, 1590, 1560 cm^{-1}; ^1H nmr (250MHz), 8.40d J=5 Hz, 8.33s, 7.17-6.95m, 67.85t J=7 Hz, 4.90bs, 3.55m, 3.62m, 3.06bs. High-resolution mass calcd for $C_{21}H_{18}N_2$: 298.146998. Found: 298.1452.

1,2,3,4,5,9,10,16-Octahydro-2-methyl[1]benzazepino[3,2,1-jk]pyrido[3,4-c][1]benzazepine 7: The novel heterocycle 5 (3.44g, 11.5mmol) was dissolved in 200ml of ethanol with heating, cooled to room temperature, and 10 equivalents of iodomethane were added. This red solution was refluxed with stirring for 36 h during which time two more 5 equivalent portions of iodomethane were added. At 36 h no further changes on TLC were noted though some starting material remained. The solvents were removed leaving a reddish-orange residue of crude 6. This substance was dissolved in 300ml of methanol, cooled to 0°C, and $NaBH_4$ (874mg, 23mmol) was added slowly with stirring to the red

suspension. On complete addition the resulting yellow suspension was stirred for 2 h at room temperature, then filtered and the solvents evaporated. Remaining solids were then taken up in ether, filtered, and again rotary evaporated to dryness. This crude product was chromatographed (silica, ethyl acetate/methanol) to yield 1.43g (40%) of 7 as an amorphous yellow solid, mp 145-148°C; ir, 2900, 2770, 1585, 1560, 1485, 1470 cm^{-1}; ^1H nmr (250MHz), 7.11-6.93m, 6.80t J=7 Hz, 4.00bs, 3.80-2.60m, 2.90bs, 2.48s, 2.40m; ^{13}C nmr (250MHz), 44.48 NCH_3 (no aliphatic methines by DEPT); High-resolution mass calcd for $C_{22}H_{24}N_2$: 316.193948. Found: 316.1942.

Cis and Trans 1,2,3,4,4a,5,9,10,16,16a-Decahydro-2-methyl[1]benzazepino[3,2,1-jk]pyrido[3,4-c][1]benzazepine 8a and 8b: To 7 (100mg, 0.31mmol) dissolved in TFA (1ml, 13mmol) was added triethylsilane (1.3ml, 8 mmol) at room temperature. The vigorously stirred solution was heated at 60°C for 24 h, and then cooled to room temperature. The resulting two phase reaction mixture was poured into saturated $NaHCO_3$ (50ml, pH8-9), extracted with chloroform, and the combined organic layers dried over $MgSO_4$. On evaporation of the solvent, preparative TLC (silica, chloroform/methanol) gave 57.5mg (57%) of 8a and 11.5mg (11%) of 8b both as amorphous yellow solids. 8a: ir, 2920, 2840, 2780, 1590, 1560, 1480, 1460 cm^{-1}; ^1H nmr (250MHz) 7.17d J=8.1 Hz, 7.08t J=7.5 Hz, 6.94m, 6.74t J=7.1 Hz, 3.72d J=11.1 Hz, 3.24m, 2.71m, 2.21dd J=3.3 Hz J=11.8 Hz, 2.12s, 1.90m, 1.27m; ^{13}C nmr (250MHz), 46.77 NCH_3, 40.12 C4a or C16a, 33.68 C4a or C16a; High-resolution mass calcd for $C_{22}H_{26}N_2$: 318.2096. Found: 318.2100. 8b: ir, 2920, 2850, 2790, 1590, 1560, 1490, 1460 cm^{-1}; ^1H nmr (250MHz), 7.20d J=7.5 Hz, 7.08t J=8.6 Hz, 6.99m, 6.76t J=7.3 Hz, 3.75dd J=2.8 Hz J=14.8 Hz, 3.36dt J=2.2 Hz J=13 Hz, 3.15dd J=2.5 Hz J=14 Hz, 2.85m, 2.46d J=13.3 Hz, 2.34s, 2.30m, 1.97dt J=2.8 Hz J=11.8 Hz, 1.79dd J=3 Hz, J=10 Hz, 1.65dt J=3.9 Hz J=12.5 Hz, 1.50t J=11.1 Hz, 1.25bs, 1.15ddd J=3.4 Hz J=11.3 Hz J=11.3 Hz; ^{13}C nmr (250MHz), 46.18 NCH_3, 44.83 C4a or C16a, 40.98 C4a or C16a; High-resolution mass calcd for $C_{22}H_{26}N_2$: 318.2096. Found: 318.2106.

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