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Synthesis of symmetrical 1,5-disubstituted granatanines

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ABSTRACT

A general entry into symmetrical 1,5-disubstituted granatanines that involves an alkylative ring-closure on a 2,6-bis enolate piperidine intermediate is described.

The piperidine alkaloid, lobelane[1] (**1**, *N*-methyl-*cis*-2,6-diphenethyl piperidine), has a unique ability to inhibit selectively the vesicular monoamine transporter-2 (VMAT2),[2] which positions it as a lead molecule for the development of therapeutics for the treatment of psychostimulant abuse.[3,4] One of the structure–activity strategies for the optimization of this lead analog was to explore the granatanine scaffold (**3**) as a conformationally rigid replacement for the central piperidine core, leading to the target molecule **2**, which incorporates a propylene bridge between the 2- and 6-positions of the piperidine ring in **1** (Fig. 1).

A literature search for a suitable synthetic methodology to **2** failed to identify a synthetic entry into granatanines bearing functionalizable substitutions on the 1- and 5-positions. For the structural requirements of our target molecules, we reasoned that the most expedient entry would incorporate an alkylative ring-closure on a 2,6-dicarbonyl-substituted piperidine precursor (see retrosynthetic analysis, Scheme 1), since the pendant carbonyls would then be amenable to further functionalization.

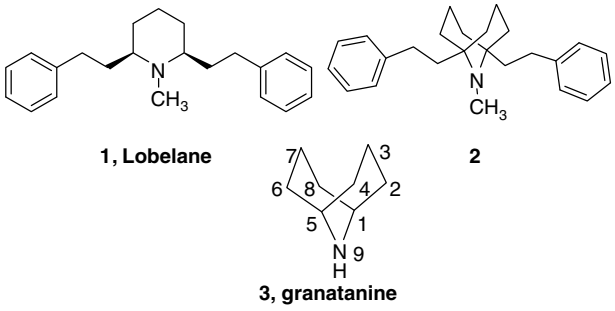
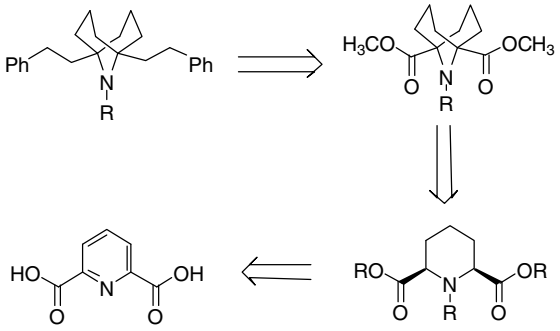


Figure 1. Structures of the lead, **1** (lobelane), the target granatanine analog **2**, and the granatanine molecule (**3**).



Scheme 1. Retrosynthetic analysis.

Scheme 2 shows the preparation of the precursor **7**, according to the method of Chênevert and Dickman,[5] albeit with a number of optimizations. Pyridine-2,6-dicarboxylic acid (**4**) was refluxed in methanolic sulfuric acid in order to obviate the need for a water-scavenger such as 2,2-dimethoxypropane, which was used in the original preparation. It was also found that if the quantity of solvent is limited to 5 mL/mmol, then the sulfate salt **5** crystallizes out completely from the reaction mixture upon cooling to 0 °C. This salt can then be used directly for the subsequent hydrogenation step, followed by basic workup, to yield **6**.[6,7] Classical Cbz-protection (Cbz-Cl/tertiary amine base) of **6** to give **7** affords a product that requires chromatographic purification. However, if Cbz-Cl is premixed with *N*-hydroxysuccinimide (effectively generating Cbz-OSu), the product is obtained in an analytically pure form after an aqueous workup.[8–10]

Having the precursor **7** in hand, an exploration of the reactivity of its dianion was conducted.[6] Treatment of **7** with 2.2 equiv of LDA at −78 °C for 1 h initially yielded a pale yellow solution that was then treated with an equivalent of 1,3-dibromopropane followed by warming to room temperature. Aside from trace degradation products, **7** as isolated unchanged in this experiment, which led us to suspect that incomplete deprotonation by LDA had occurred,

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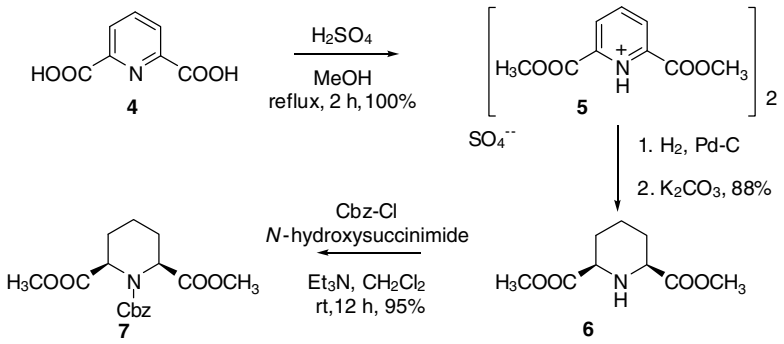
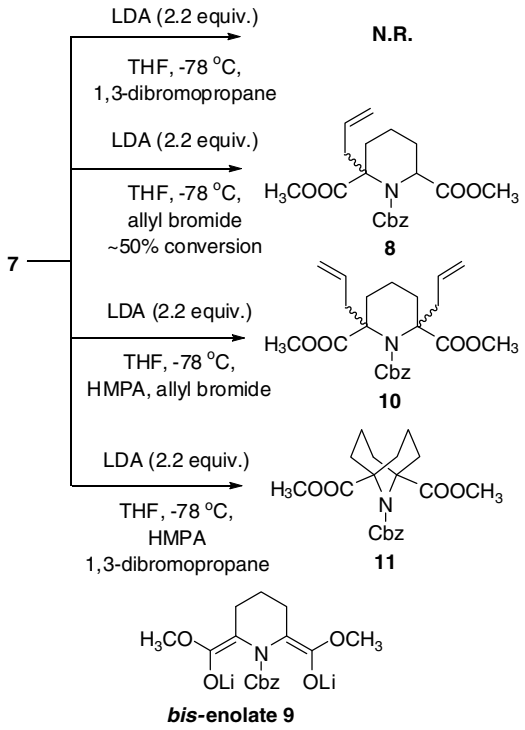


Scheme 2. Synthesis of the key intermediate **7**.

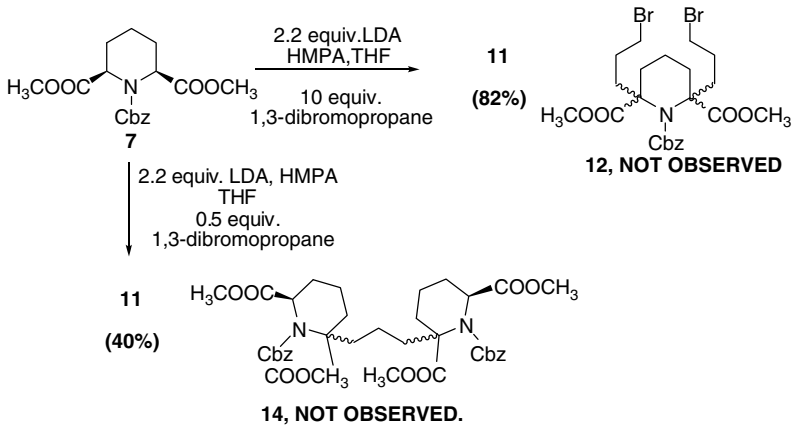


Scheme 3. Model alkylations on **7** and the synthesis of **11**.

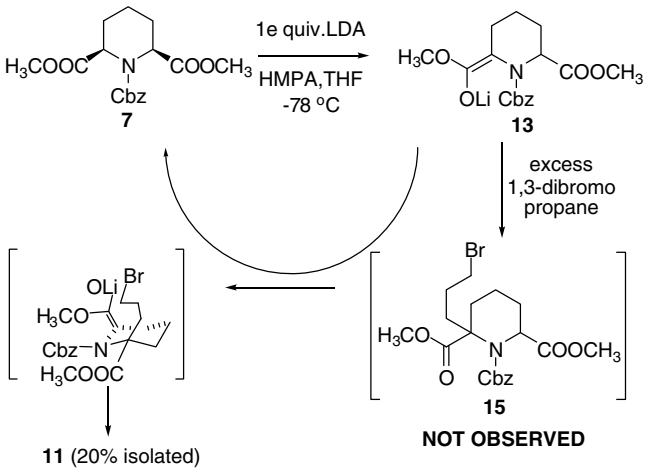
since some degree of scrambling of the relative stereochemistry should be expected upon quenching of the bis-enolate. Consequently, **7** was treated with 2.2 equiv of LDA at temperatures ranging from −78 °C to −20 °C; the use of temperatures above this range resulted in extensive degradation, as revealed by TLC analysis. Quenching of the above solution at −20 °C with 1,3-dibromopropane yielded unchanged **7**; however, treatment with the highly reactive allyl bromide yielded mixtures consisting of **7** and its mono-allyl derivatives **8**, as indicated by GC–MS analysis. Clearly, the conditions used were not only insufficient for the generation of the dienolate, **9**, but were also insufficient for alkylation with unactivated electrophiles such as 1,3-dibromopropane (Scheme 3).

Increasing the reactivity of the enolate species was explored by the addition of HMPA (Scheme 4). Treatment of **7** with 2.2 equiv of LDA at −78 °C in the presence of 0.5 mL/mmol of HMPA followed by quenching with excess allyl bromide led to extensive allylation and complete absence of **7** in the product mixture, as indicated by GC–MS analysis. Gratifyingly, the replacement of allyl bromide with 1.1 equiv of 1,3-dibromopropane caused consumption of **7** within a few seconds and yielded the required granatanine **11** in 85% yield after chromatography.[11] The effect of HMPA on such ring-closures had previously been studied by Bilyard et al. in the preparation of similar azabicycloalkanes.[7]

Interestingly, the utilization of a higher or lower number of equivalents of 1,3-dibromopropane led to no change in the types of species in the product mixture. The addition of excess (10 equiv) of 1,3-dibromopropane to the LDA/HMPA-treated solution of **7** led to no change in the yield of **11**. The dialkylated species **12** could not be detected in this experiment, which suggests that the 6-*exo*-tet ring-closure is highly favored over dialkylation of the dienolate **9** (Scheme 5). Similarly, employment of 0.5 equiv of 1,3-dibromopropane led to a corresponding reduction in the yield of **11**, with no trace of the dimer **14**.



Scheme 4. Experiments on the enolates of **7**.



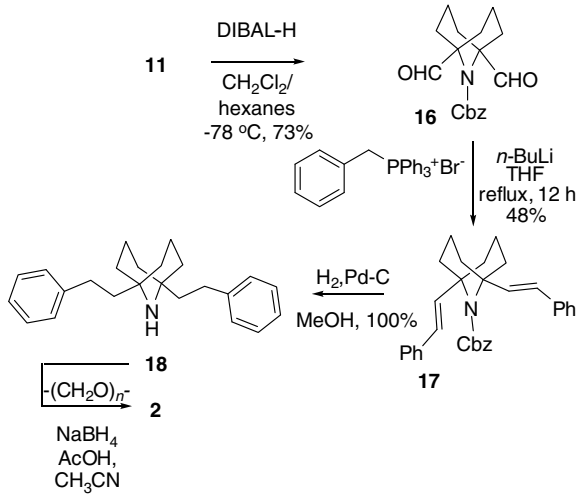
Scheme 5. Proposed deprotonation of **15** by **13**.

In another experiment, only 1 equiv of LDA in the presence of HMPA and excess 1,3-dibromopropane was employed. Surprisingly, this experiment led to a modest yield of **11**, instead of the monoalkylated species **15**, indicating that equilibration of the enolate species occurs and the monoenolate **13** can function as a base for the deprotonation of **15** in lieu of LDA (Scheme 5).

Finally, it was noted that the formation and quenching of **13** were not accompanied by scrambling of the relative stereochemistry, which suggests that reprotonation of **13** occurs trans to the carboxymethyl function at the 6-position with complete selectivity.

Having accomplished the synthesis of **11**, the controlled reduction of the methyl esters to aldehydes, so as to form precursor **16** for Wittig olefination and introduction of the phenyl side chains, was attempted (Scheme 6). The optimal conditions appeared to be 5.0 equiv of DIBAL-H at −78 °C in a 1:1 hexane–CH_2Cl_2 solvent, followed by a classical methanol quench at that temperature. Under these conditions, almost complete consumption of **11** occurred after 2.5 h with negligible formation of alcoholic species. It was noted that the omission of hexanes leads to unacceptable ratios of aldehyde and alcohol (typically 5:1, as indicated by GC–MS analysis).[12]

Wittig olefination with benzyl triphenylphosphorane (formed in situ from benzyl triphenylphosphonium bromide and *n*-BuLi) proceeded in modest yields (48%) in refluxing THF, to give exclusively the trans olefin, **17** as is typically expected from such semi-stabilized ylids.[13] A change in the ylid counterion to potassium (through the use of *t*-BuOK) and a change in solvent to DMSO did not improve the yield. Concomitant hydrogenation of the olefin side chains and Cbz-removal afforded **18** which was subjected to N-methylation with paraformaldehyde and sodium borohydride/acetic acid (sodium triacetoxyborohydride) to afford **2**.[14,15]



Scheme 6. Synthesis of the target lobeline analog **2**.

This study presents the first example of the cyclization of a piperidine analog to a granatanine analog bearing substitutions at the 1- and 5-positions. It also highlights a number of peculiarities in the formation and reactivity of certain dienolates of piperidine derivatives.

Acknowledgment

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Supplementary data

Supplementary data (spectral data for **2**, **16**–**18**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.066.

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8. *2,6-Dicarboxymethyl pyridinium sulfate* (**5**). To 2,6-pyridine dicarboxylic acid (16.7 g, 100 mmol) in methanol (500 mL) was added concd H_2SO_4 (20 mL) with vigorous stirring. The resulting hot solution was heated at reflux for 4 h, after which time stirring was stopped, and the solution was allowed to cool to ambient temperature followed by cooling in an ice-bath for 1 h. The large colorless needles deposited during this time were collected by filtration and washed with diethyl ether/CH_3OH (1:1, 2 × 50 mL) to afford 5 (24 g, 100%); mp = 91 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ ppm 11.30 (s, br, 1H), 9.42 (t, 1H, J = 5.1 Hz), 8.50 (d, 2H, J = 5.1 Hz), 3.82 (s, 6H). ^{13}C NMR (75 MHz, acetone-d_6) δ ppm 161.1, 146.7,138.0, 135.2, 53.1.
9. *cis-(2,6-Di-carboxymethyl piperidine* (**6**). To a suspension of **5** (12.00 g, 50 mmol) in water (100 mL) was added 10% palladium-on-charcoal (1.00 g). The mixture was shaken under 50 psi of hydrogen for 24 h, and filtered through Celite. The Celite plug was washed with water (3 × 10 mL) and the combined filtrates were treated with 20 g NaCl and 10 g K_2CO_3. Extraction of this mixture with dichloromethane (4 × 50 mL), drying of the organic layers (K_2CO_3), and evaporation of solvent under reduced pressure yielded a white solid that was recrystallized from hexanes to afford **6** as white crystals (8.6 g, 88%); mp = 90–94 °C, ^{1}H and ^{13}C NMR were consistent with the literature spectral data.[5]
10. *cis-(N-Benzyloxycarbonyl)-2,6-di-carboxymethyl piperidine* (**7**). To Cbz-Cl (3.40 g, 20 mmol) in CH_2Cl_2 (20 mL) was added *N*-hydroxysuccinimide (2.30 g, 20 mmol) and the resulting solution was cooled to 0 °C before being treated with Et_3N (3 mL, excess). The mixture was stirred at ambient temperature for 30 min and **6** (4.02 g, 20 mmol) was added in one portion. After stirring overnight, the reaction mixture was evaporated to dryness and partitioned between 100 mL of diethyl ether and 100 mL of water. The ether layer was washed with 5% aqueous K_2CO_3 (3 × 100 mL), 10% aq $NaHSO_4$ (2 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), and the solvent evaporated to afford **7** as a clear oil (7.3 g, 95%). ^{1}H and ^{13}C NMR were consistent with the literature spectral data.[5]
11. *N-Benzyloxycarbonyl-1,5-di-carboxymethyl granatanine* (**11**). A solution of **7** (3.35 g, 10 mmol) in THF (20 mL) was cooled to −78 °C and treated dropwise with a 1.0 M solution of LDA in THF/hexanes (11 mL, 1.1 equiv) (prepared from 12 mmol of diisopropylamine and 10 mmol of *n*-BuLi). The resulting solution was stirred for 15 min at −78 °C and treated successively with 1,3-dibromopropane (4 mL, excess, passed through a short plug of basic alumina until colorless) and HMPA (5 mL) before being warmed to 0 °C over 1 h. The resulting straw-colored solution was poured over saturated aqueous NH_4Cl and extracted with EtOAc (3 × 50 mL). The organic layers were combined and washed with 10% aq $NaHSO_4$ (2 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), and the solvent evaporated under reduced pressure to give a pale yellow oil

that was dissolved in hexanes and applied to a column of silica gel (30 g). The column was eluted with hexanes (50 mL) and then with hexanes/EtOAc (6:1, 300 mL). Fractions (20 mL) were collected, and the product was eluted in the final 50 mL of the column eluent. Evaporation of the relevant fractions afforded **11** (3.18 g, 85%) as a clear viscous oil that crystallized slowly upon standing for several days; mp = 69 °C; R_f = 0.4 (hexanes/EtOAc, 5:1) ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.12–7.39 (m, 5H, Ar), 5.12 (s, 2H), 3.72 (s, 6H), 1.82–1.70 (m, 4H), 1.68–1.23 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) 174.1, 155.8, 139.5, 127.4, 126.3, 126.0, 66.0, 58.3, 52.1, 36.6, 14.1. Anal. ($C_{20}H_{25}NO_6$) C, H, N.

12. *N-Benzyloxycarbonyl-1,5-di-formyl granatanine* (**16**). A solution of **11** (1.87 g, 5 mmol) in CH_2Cl_2/hexanes (1:1, 50 mL) was cooled to −78 °C. A 1 M solution of DIBAL-H in CH_2Cl_2 (25 mL) was diluted with anhydrous CH_2Cl_2 (25 mL) and cooled to −78 °C. The cold DIBAL-H solution was cannulated dropwise into the solution of **11** at such a rate that the addition of the entire amount of DIBAL-H was completed over 15 min. The resulting solution was stirred at −78 °C for 1.5 h, at which time GC–MS analysis indicated over 98% consumption of **11**. A solution of methanol (5 mL) in CH_2Cl_2 was cooled to −78 °C and cannulated slowly into the reaction. The resulting yellow solution was warmed to room temperature and poured over a mixture of 10% aqueous $NaHSO_4$ and ice. The entire mixture was evaporated under reduced pressure to about half its volume and partitioned between EtOAc (50 mL) and water. The organic layer was washed with brine (1 × 50 mL), dried ($MgSO_4$), and the solvent evaporated under reduced pressure to afford an oil that was dissolved in benzene and applied to a silica gel column (15 g). The column was washed with hexanes (50 mL) and then eluted with hexanes/EtOAc (4:1, 200 mL). The fractions containing the product, R_f = 0.4 (hexanes/EtOAc, 3:1; 2,4-DNP stain visualization), were evaporated to afford **16** (1.15 g, 73%) as a clear oil that resisted attempts at crystallization. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.60 (s, 2H), 7.48–7.20 (m, 5H), 5.08 (s, 2H), 2.08–1.62 (m, 4H), 1.54–0.98 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) 201.3, 156.1, 139.8, 128.0, 127.3, 127.0, 67.3, 56.2, 35.4, 14.8. Anal. ($C_{18}H_{21}NO_4$) C, H, N.

13. *N-Benzyloxycarbonyl-1,5-distyryl granatanine* (**17**). To a suspension of benzyl triphenyl phosphonium bromide (1.73 g, 4 mmol, 2 equiv) in THF (20 mL) at 0 °C was added *n*-BuLi (2.5 M in hexanes, 1.6 mL) and the resulting red solution was stirred at ambient temperature until almost clear. A solution of **16** (315 mg, 1 mmol) in THF (1 mL) was then added, and the resulting mixture was refluxed under argon until complete disappearance of starting material occurred (usually 12–18 h). The resulting red solution was cooled to ambient temperature and poured over a mixture of 1 N HCl and ice. The resulting colorless suspension was extracted with diethyl ether (4 × 20 mL), the etherial portions were combined and washed with brine (1 × 50 mL), dried ($MgSO_4$), and the solvent evaporated under reduced pressure to afford a yellow oil that was passed through a 10-g plug of silica gel with the aid of hexanes/EtOAc (100 mL). The entire eluent was evaporated, to afford a colorless oil that solidified upon trituration with ice-cold hexanes. This solid was recrystallized from hot hexanes to give **17** (222 mg, 48%); mp = 105–107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.40–7.22 (m, 15H), 6.92 (d, J = 15.4 Hz, 2H), 5.83 (d, J = 15.4 Hz, 2H), 5.07 (s, 2H), 1.97–1.63 (m, 4H), 1.50–0.92 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 155.0, 137.9, 134.2, 129.5, 128.6, 127.7, 126.7, 126.1, 124.1, 122.0, 115.1, 65.9, 58.0, 36.1, 13.8 Anal. ($C_{32}H_{33}NO_2$) C, H, N.

14. *1,5-Di-(2-phenylethyl)granatanine* (**18**). To a solution of **17** (100 mg, 0.22 mmol) in MeOH (10 mL) was added Pd–C (10 wt %, 10 mg) and the mixture was shaken under 55 psi of hydrogen gas for 48 h. The mixture was then filtered through Celite, the Celite washed with copious amounts of MeOH, and the combined eluents were evaporated under reduced pressure. The resulting clear oil was azeotroped twice with CH_2Cl_2 to remove traces of MeOH, to afford **18** (72 mg, 100%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.43–7.18 (m, 10H), 2.23–2.12 (br s, 1H), 2.46 (t, J = 8.2 Hz, 4H), 2.01–1.72 (m, 4H), 1.63–0.94 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 138.2, 126.3, 122.1, 120.5, 57.3, 39.0, 36.1, 30.6, 14.5. Anal. ($C_{24}H_{31}N$) C, H, N.

15. *N-Methyl-1,5-di-(2-phenylethyl)granatanine* (**2**). A mixture of **18** (25 mg, 0.08 mmol) and paraformaldehyde (20 mg, excess) in CH_3CN (2 mL) was treated with acetic acid (0.5 mL) and then $NaBH_4$ (10 mg, excess). After stirring for 24 h, TLC (diethyl ether, neat) indicated complete conversion of **18** (R_f = 0.3) to **2** (R_f = 0.5). The mixture was partitioned between EtOAc (10 mL) and saturated $NaHCO_3$ (10 mL). The $NaHCO_3$ layer was washed thoroughly with EtOAc (5 × 10 mL), and the combined organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to yield **3** (23 mg, 91%) as a clear viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.48–7.10 (m, 10H), 2.48 (t, J = 7.2 Hz, 4H), 2.20 (s, 3H), 1.99–1.68 (m, 4H), 1.58–0.90 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) 138.6, 126.0, 121.8, 121.0, 58.2, 39.5, 36.4, 32.0, 28.4, 14.0. Anal. ($C_{25}H_{33}N$) C, H, N.