The Mannich Reaction. 1-Alkyl-3,3-diphenyl-4-piperidinones, 1,6′-Dialkyl-3′,4′,5′,6′,7′,8′-hexahydro-5,5,8′,8′-tetraphenylspiro[piperidine-3,2′-[2*H*]pyrano[3,2-*c*]pyridin]-4-ones and Their Derivatives

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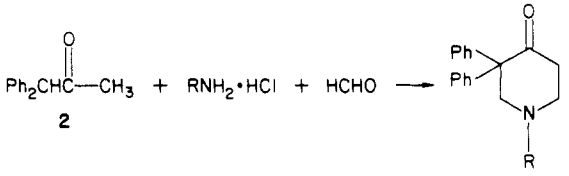
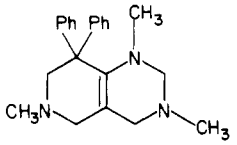
Condensation of 1,1-diphenyl-2-propanone with methyl- and ethylamine hydrochloride and a large exces of paraformaldehyde in refluxing methanol gave 1-alkyl-3,3-diphenyl-4-piperidinones (**1**) as the main isolable products. When the reaction was carried out at 120 °C, there resulted dimeric compounds 1,6′-dialkyl-3′,4′,5′,6′,7′,8′-hexahydro-5,5,8′,8′-tetraphenylspiro[piperidine-3,2′-[2*H*]pyrano[3,2-*c*]pyridin]-4-ones (**4**) as the major products. Reduction of the dimer **4a** (alkyl = methyl) gave 3′,4′,5′,6′,7′,8′-hexahydro-1,6′-dimethyl-5,5,8′,8′-tetraphenylspiro[piperidine-3,2′-[2*H*]pyrano[3,2-*c*]pyridin]-4-ol (**10**) which, on treatment with hot hydrobromic acid, was transformed into the tetracyclic ketal decahydro-2,8-dimethyl-4,4,6,6-tetraphenyl-4a,9a-epoxy-2*H*,7*H*-oxepino-[3,2,*c*:6,7,*c*′]dipyridine (**11**).

In the course of research on drugs with psychopharmacological properties, we were interested in obtaining 1-alkyl-3,3-diphenyl-4-piperidinones of type **1** as intermediates for further elaborations. Compounds of type **1** have not been heretofore reported. One synthetic route to **1** was explored by allowing 1,1-diphenyl-2-propanone (**2**) to react with a primary amine hydrochloride and excess paraformaldehyde. Thus, 1 mol of CH_3NH_2·HCl, 1 mol of **2**, and excess HCHO in boiling methanol gave **1a** in



2 → **1a**, R = CH_3; **b**, R = C_2H_5



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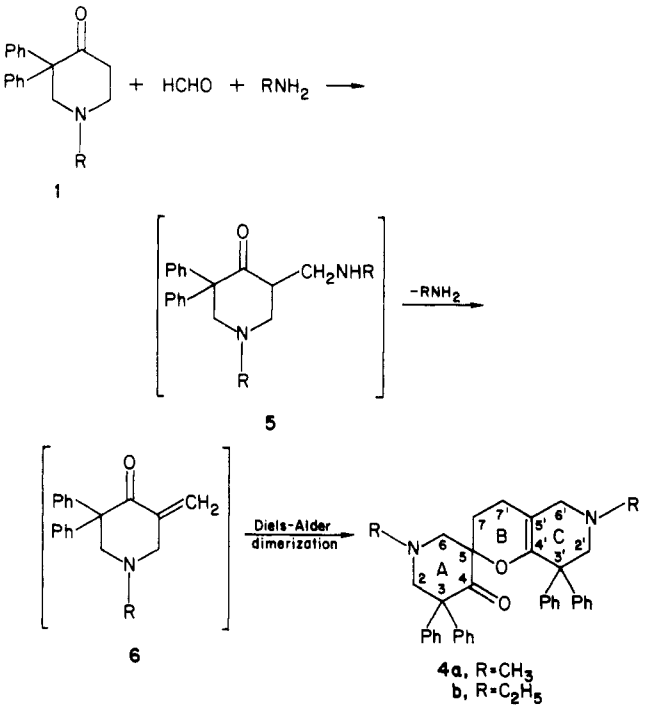
about 40% yield along with a 5% yield of the further reaction product **3** obtained previously as the only product isolated when **2**, methylamine, and aqueous formaldehyde were allowed to react under basic conditions in a ratio of 1:3:4.[1]

Compound **1a** behaved as a typical, somewhat hindered ketone (see Experimental Section).

When $C_2H_5NH_2$·HCl was used under the same conditions, **1b** was obtained in comparable yield. Attempts to synthesize higher homologues of **1** such as 1-isopropyl, 1-*tert*-butyl, or 1-benzyl by employing corresponding primary amines were unsuccessful.

When attempts were made to accelerate the preparation of **1a** and **1b** by increasing the reaction temperature to ~120 °C, the major products isolated were tricyclic compounds **4a** and **4b** in moderate yield.[2] Product **4a** was also

Scheme I



obtained in comparable yield when **1a** was allowed to react with 1 mol of CH_3NH_2·HCl and excess paraformaldehyde at ~120 °C. No reaction was observed at room temperature or at ~65 °C. The formation of **4** appears to occur by elimination of alkylamine from the Mannich bases **5** (or those formed from **5** + **1** + HCHO)[3] to give α,β-unsaturated ketones **6**,[4] which undergo a Diels–Alder-type dimerization[5–7] (Scheme I).

(1) Plati, J. T.; Wenner, W. German Patent 957 842 2.7.195, 1958; *Chem. Abstr.* **1958**, *52*, 3874.

(2) The numbering indicated is for reference to spectral data cited in this and the Experimental Sections.

(3) (a) Tramontini, M. *Synthesis* **1973**, 703. (b) Blicke, F. F. *Org. React.* **1942**, *1*, 303. (c) Mannich, C.; Hof, W. *Arch. Pharm. (Weinheim, Germany)* **1927**, *265*, 589. (d) Mannich, C.; Braun, R. *Ber.* **1920**, *53*, 1874. (e) Mannich, C.; Hoenig, P. *Arch. Pharm. (Weinheim, Germany)* **1927**, *265*, 598.

(4) A related intermediate is presumably involved in the formation of compound **3**; however, the latter is formed in significant quantity only in the presence of excess amine under basic conditions.[1]

(5) (a) Alder, K.; Offermanns, H.; Rueden, E. *Ber.* **1938**, *71*, 373. (b) Alder, K.; Offermanns, H.; Rueden, E. *Ibid.* **1941**, *74*, 905. (c) Alder, K.; Offermanns, H.; Rueden, E. *Ibid.* **1941**, *74*, 926.

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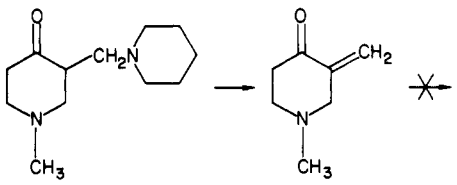
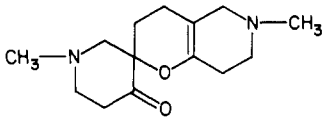
This kind of Diels–Alder dimerization was previously observed in the carbocyclic series in the dimerization of 1-methylene-2(1*H*)-naphthalenone.[8] It has also been reported with vinyl alkyl ketones,[5,7] 1,2-diphenyl-2-propan-1-one,[9] 2-methylenecyclohexanone,[3c,d,5-7,10] 2,6-dibenzalcyclohexanone,[11] octahydro-1-methylene-2(1*H*)-naphthalenone derivatives,[12] and 2-methylenecycloalkanones and a variety of their analogues with fused aromatic rings.[13a-d]

However, attempted conversion of 1-methyl-3-(1-piperidinylmethyl)-4-piperidinone (**7**) into **8** and/or **9** gave



7 **8**



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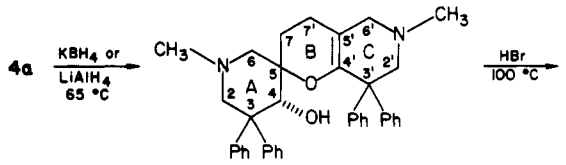
only polymers.[13a] In the present case, it is likely that the geminal phenyl substituents serve to prevent polymerization by blocking enolization of the α' position of the piperidinone.

Compound **4a** is remarkably stable. Treatment with 48% hydrobromic acid at ~100 °C left it unchanged. Attempts to form an oxime or hydrazone failed. Attempted hydrogenation, even under forcig conditions, was unsuccessful. Treatment of **4a** with KBH_4 at ~65 °C for 8 h or with $LiAlH_4$ gave the alcohol **10**, which on being heated with 48% hydrobromic acid was converted to the saturated tetracyclic ketal **11**.[2]



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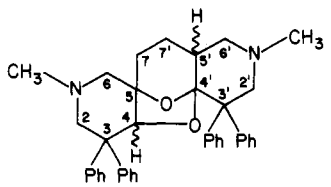


11

This sequence is analogous to reactions observed by Mannich[7] with dimeric 2-methylenecyclohexanone **12**.

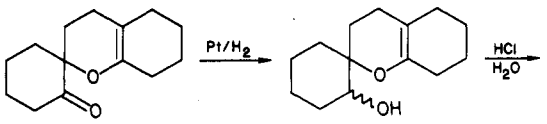
(6) Dimroth, K.; Resin, K.; Zertsch, H. *Ber.* **1940**, *73*, 1399.
(7) Mannich, C. *Ber.* **1941**, *74*, 557.
(8) Pummerer, K.; Cherbuliez, E. *Ber.* **1919**, *52*, 1392.
(9) Fiesselmann, H.; Ribka, J. *Ber.* **1956**, *89*, 40.
(10) Roth, H. J.; Dvorak, G. *Arch. Pharm. (Weinheim, Germany)* **1963**, *296*, 510.
(11) House, H. O.; Hortmann, A. G. *J. Org. Chem.* **1961**, *26*, 2190.
(12) Roman, E.; Frey, A. J.; Stadler, P. A.; Eschenmoser, A. *Helv. Chim. Acta* **1957**, *40*, 1900.
(13) (a) Roth, H. J.; Haupt, M. *Arch. Pharm. (Weinheim, Germany)* **1975**, *308*, 241. (b) Roth, H. J.; Schwenke, C.; Dvorak, G. *Ibid.* **1965**, *298*, 326. (c) Roth, H. J.; Dvorak, G.; Schwenke, C. *Ibid.* **1964**, *297*, 298. (d) Roth, H. J.; Schumann, E. *Ibid.* **1969**, *302*, 387.

Table I. ^{13}C NMR Spectra of Compounds 1a, 4a, 10, and 11

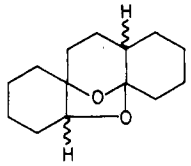
carbon	compound 1a	4a	10	11
2	66.8	66.8*	59.1*	60.0*
3	63.4	62.7	50.3	49.6
4	207.3	205.2	74.0	75.9
5	39.6	79.3	76.9	83.6
6	56.0	64.1*	68.5[b]	62.6*
7		29.7	27.9	31.0
2′		67.7*	68.5[b]	52.9**
3′		52.9	52.7	54.3
4′		*c*	*d*	109.1
5′		104.7	104.8	36.3
6′		58.1	58.7*	50.7**
7′		20.1	20.8	21.6
CH_3N	45.4	44.9	44.8	46.2
		45.6	45.4	47.0

[a] Compounds **1a** and **4a** in $CDCl_3$; **10** and **11** in $CDCl_3/Me_2SO$-d_6. Signal multiplicities in SFORD spectra are in accord with the assignments. Aromatic carbon signals are not given. Some assignments are tentative (see text); the assignments of sets of signals marked with single or double asterisks are interchangeable. [b] Superimposed signals. [c] One of five signals in the δ 140–146 region (see text). [d] One of five signals in the δ 144–148 region.

When subjected to catalytic hydrogenation, **12** gave alcohol **13**, which on treatment with hydrochloric acid gave the tetracyclic acetal **14**.



12 **13**



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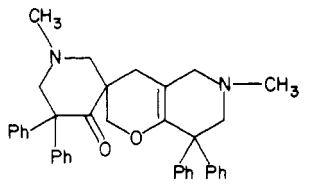
The IR and ^1H NMR spectroscopic data for compound **1a** and its derivatives and compound **1b** (see Experimental Section) are in full agreement with the structural assignments. The signals assigned to C-4, C-5, and C-6 in the ^{13}C NMR spectrum of **1a** (Table I) parallel closely the corresponding signals of 1-methyl-4-piperidinone[14] while those assigned to C-2 and C-3 show the anticipated considerable downfield shift caused by the geminal phenyl substituents.

The IR spectrum of the dimer **4a** shows a carbonyl band at 1720 cm^{-1} and a moderately strong band due to the vinyl ether linkage, C=CO,[12] at 1690 cm^{-1}. Its ^1H NMR spectrum shows the two neighboring methylene groups (C-7, C-7′) to be accidentally equivalent, giving rise to a singlet at δ 1.60; a singlet arising from both *N*-methyl groups appears at δ 2.30 and a multiplet arising from the *N*-methylene protons at δ 2.60–3.60. Four aromatic protons are unusually shielded, giving a multiplet at δ 6.75. The equivalence of the C-7 and C-7′ protons excludes the alternative structure **15**.

Proposed assignments for the signals in the ^{13}C NMR spectrum of **4a** (Table I) are in good accord with the assignments for **1a**. Thus, of the sp^3 carbon signals of **4a**, those of C-5 and C-6 show the anticipated considerable downfield shifts relative to the corresponding signals of **1a**, and that of C-3′ shows a considerable upfield shift,

(14) Hirsch, J. A.; Havinga, E. *J. Org. Chem.* **1976**, *41*, 455.



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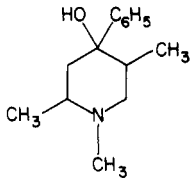

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while the signals assigned to C-2, C-3, C-2′, and C-6′ show only small differential shifts. The sp^2 C-5′ signal is readily identified at δ 104.7, showing the characteristic large upfield shift associated with the β-ethylenic carbon of a enol ether.[15] The other ethylenic carbon (C-4′) signal cannot be identified unambiguously but must be one of a set of five singlets in the SFORD spectrum at δ 140–146, the other four arising from the substituted carbons of the four phenyl rings.

The IR spectrum of alcohol **10** shows a hydroxyl band at 3570 cm^{-1} and a vinyl ether band at 1690 cm^{-1}. Its ^1H NMR spectrum displays considerably more complexity than that of **4a**. The *N*-methyl groups are no longer equivalent, their signals being separated by δ 0.15; the neighboring C-7 and C-7′ methylene protons (which are equivalent in **4a**) give rise to multiplets at δ 1.40–1.90. The hydroxyl proton signal of **10** gives rise to a doublet at δ 1.74 (J = 10.0 Hz), being coupled with the methine proton (CHO, J = 10.0 Hz) at δ 4.23. This suggests that the hydroxyl proton is intramolecularly hydrogen bonded, as in the case of 1,2,5-trimethyl-4-phenyl-4-piperidinol (**16**).[16,17] Again four aromatic protons are more shielded than the others, giving rise to an envelope at δ 6.70. The SFORD ^{13}C NMR spectrum of **10** shows a CHOH signal as a doublet at δ 74.0. The retention of the enol other grouping in **10** is established by the C-5′ singlet at δ 104.8 and a set of five singlets in the region δ 144–148.

Examination of molecular models suggests that the reduction of the carbonyl group of **4a** should have little effect on the chemical shifts of the sp^3 carbon atoms in ring C; consequently, the signals assigned to C-2′, C-3′, and C-6′ of **10** are very close to those for ring C of the ketone **4a** (Table I). The signal assigned to C-2 of **10** is shifted significantly upfield relative to that of **4a**; this could reflect a preferred axial orientation of the hydroxyl group as in the case of 2,2-diphenylcyclohexanol.[18] Other changes may result from changed orientations of the phenyl rings in **4a** and **10** or a preferred twist-boat conformation for ring A in **10** as proposed in the case of **16**.[16,17] In the latter connection it may be pointed out that twist-boat forms cannot be excluded in these cases of **1a** and ring A of **4a** because of the serious steric interaction[19] between the carbonyl oxygen and an equatorial phenyl group in the chair forms.

The IR spectrum of **11** shows the absence of the hydroxyl and enol ether functions. Its ^1H NMR spectrum displays two nonequivalent *N*-methyl signals and the other aliphatic protons give rise to a broad multiplet at δ 1.50–3.40. Two aromatic protons are unusually deshielded giving rise to doublets of doublets at δ 7.71 (J = 6.0 and 2.0 Hz). Several features of the SFORD ^{13}C NMR spectrum of **11** corroborate the structural assignment. The number of signals in the δ 140–150 region is reduced to four in accord with the absence of the vinyl ether system and a singlet at δ 109.1 and doublet at δ 36.3 are readily identifiable as arising from C-4′ and C-5′, respectively. A doublet at δ 75.9 confirms the retention of the CHO function at C-4. The only signal in the ^1H NMR spectrum of **11** that can be assigned to the proton of this function is a doublet (J = 2 Hz) at δ 5.10. Its unusual position is attributed to deshielding by one of the phenyl rings and its multiplicity to long-range coupling. The location of this proton at C-4 was confirmed by single-frequency decoupling in the ^{13}C NMR spectrum at the frequency of the proton, which led to the collapse of the doublet in the SFORD spectrum at δ 75.9 to a singlet. As in the case of **10**, the ^{13}C NMR assignments to some of the other carbons of **11** are tentative.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus which was calibrated against known standards. The ultraviolet (UV) and infrared (IR) spectra were obtained respectively with a Beckman DK-1 spectrophotometer and a Baird Model 455 double-beam spectrograph. The ^1H NMR spectra were obtained on a Varian A-60 and a Bruker WH90 spectrometer with tetramethylsilane as an internal reference. Carbon magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker WH90 with a 22.63-MHz operating frequency in deuteriochloroform and Me_2SO-d_6. The mass spectra were recorded on a Finnigan 1015 Quadrupole Mass Spectrometer.

1-Methyl-3,3-diphenyl-4-piperidinone (1a). A solution of 21.0 g (0.1 mol) of 1,1-diphenyl-2-propanone (**2**), 6.8 g (0.1 mol) of CH_3NH_2·HCl, and 6.0 g of paraformaldehyde and five drops of concentrated hydrochloric acid in 150 mL of methanol was refluxed for 24 h under nitrogen. Paraformaldehyde (4.5 g) was added and the refluxing was continued for an additional 100 h. Four portions of paraformaldehyde (1.5 g each) were added every 36 h until most of **2** was consumed (total 240 h). After the solution was evaporated, the residue was taken up with ice–water, treated with dilute H_2SO_4 to pH 1.0, and extracted twice with 75 mL of ethyl acetate. The aqueous acidic phase was made basic with aqueous NH_3 and extracted twice with 200 mL of CH_2Cl_2. The CH_2Cl_2 extracts were dried over Na_2SO_4 and evaporated. The residue was crystallized from isopropyl ether giving 11.6 g (46% crude yield) of **1a**, mp 134–137 °C. Recrystallization from acetonitrile gave 9.7 g of analytically pure **1a** as white crystals: mp 137–138 °C; IR ($CHCl_3$) 1715 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (NCH_3), 2.45 (m, 2 H, CH_2-5), 2.81 (m, 2 H, CH_2-6), 3.13 (s, 2 H, CH_2-2), 7.00–7.50 (m, 10 H, Ar); mass spectrum, m/z 265. Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.57; H, 7.12; N, 5.27.

1,2,3,4,5,6,7,8-Octahydro-1,3,6-trimethyl-8,8-diphenylpyrido[4,3-*d*]pyrimidine (3). The original basic mother liquor from the preparation of **1a** was passed over Florisil with Skelly B–diethyl ether (1:1) as an eluent. The first few fractions contained faster moving material on TLC (silica gel G; chloroform–toluene, 2:1, R_f 0.3) from which 1.9 g of additional **1a** was obtained, mp 136–137 °C. Further eluate contained a slower moving product (R_f 0.15) which on crystallization from diisopropyl ether gave 1.2 g of pure **3**: mp 107–108 °C; IR ($CHCl_3$) 1670 cm^{-1} (C=CN); ^1H NMR ($CDCl_3$) δ 2.10 (s, 3 H, CH_3N-3), 2.18 (s, 3 H, CH_3N-6), 2.38 (s, 3 H, CH_3N-1), 2.98 (s, 2 H, CH_2-7), 3.05 (s, 4 H, CH_2-4, CH_2-5), 3.45 (s, 2 H, CH_2-2), 7.15–7.50 (m, 10 H, Ar); mass spectrum, m/z 333. Anal. Calcd for $C_{22}H_{27}N_3$: C, 79.24; H, 8.16; N, 12.60. Found: C, 79.34; H, 8.26; N, 12.61.

By following the published procedure,[1] product **3** was obtained as a dihydrochloride monohydrate in 55% yield, mp 193–194 °C (lit.[1] mp of dihydrochloride 186–187 °C). Anal. Calcd for $C_{22}H_{27}N_3$·2HCl·H_2O: C, 62.29; H, 7.19; N, 9.88; Cl^-, 16.67. Found: C, 62.48; H, 7.26; N, 9.88; Cl^-, 16.71.

The regenerated free base **3**, mp 107–108 °C, is identical with that obtained as a byproduct during the preparation of **1a** above.

1-Ethyl-3,3-diphenyl-4-piperidinone (1b). The exact procedure as for the preparation of the *N*-methyl analogue **1a** was

(15) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972; pp 183–184.
(16) (a) Casy, A. F.; McErlane, K. M. J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 334. (b) Jones, A. J.; Beeman, C. P.; Casy, A. F.; McErlane, K. M. J. *Can. J. Chem.* **1973**, *51*, 1790.
(17) Vlasova, T. F.; Sheinker, Yu. N. *Zh. Struct. Khim.* **1970**, *11*, 640.
(18) Mursakulov, I. G.; Ramazanov, E. A.; Guisenov, M. M.; Zefirov, N. S.; Samoshin, V. V.; Eliel, E. L. *Tetrahedron* **1980**, *36*, 1885.
(19) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis"; Wiley Interscience: New York, 1965; p 113.

followed. Thus, boiling a solution of 31.5 g (0.15 mol) of **2**, 12.3 g (0.15 mol) of $C_2H_5NH_2$·HCl, and 12.0 g of paraformaldehyde in 200 mL of methanol gave (after 270 h) 9.4 g of **1b**, mp 109–110 °C. An analytical sample, mp 110–111 °C, was obtained by recrystallization from methanol: IR ($CHCl_3$) 1717 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.3 (t, J = 7.0 Hz, 3 H, CH_3), 2.38–3.00 (m, 6H, CH_2CH_3, CH_2-5, CH_2-6), 3.20 (s, 2 H, CH_2-2), 7.00–7.45 (m, 10 H, Ar); ^{13}C NMR ($CDCl_3$) δ 208.8, 141.4, 129.1, 128.2, 127.0, 63.8, 63.5, 54.1, 51.7, 39.9, 12.3; mass spectrum, m/z 279. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.53; H, 7.65; N, 5.00.

1-Methyl-3,3-diphenyl-4-piperidinone Oxime. This oxime was obtained from **1a** in 80% yield by the use of standard conditions: mp 207–208 °C; ^1H NMR ($CDCl_3$) δ 2.28 (s, 3 H, CH_3N), 2.58 (s, 4 H, CH_2-5 and CH_2-6), 3.13 (s, 2 H, CH_2-2), 7.20 (s, br, 10 H, Ar), 8.20 (s, br, 1 H, NOH); mass spectrum, m/z 280. Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.03; H, 7.24; N, 10.02.

1-Methyl-3,3-diphenyl-4-piperidinamine Dihydrochloride. A solution of 6.7 g of the above oxime in 60 mL of dry tetrahydrofuran was added dropwise to a suspension of 1.8 g of $LiAlH_4$ in 20 mL of the same solvent and allowed to reflux for 4 h. The excess reagent was destroyed by ethyl acetate (150 mL) and water at 10 °C. The organic phase was washed (NaCl–H_2O), dried (Na_2SO_4), and evaporated. The residue was taken up with 2-propanol and treated with anhydrous HCl to pH 1.5 to give 2.8 g of pure dihydrochloride trihydrate as white crystals, mp 237–239 °C dec; mass spectrum, m/z 266. Anal. Calcd for $C_{18}H_{22}N_2$·2HCl·3H_2O: C, 54.96; H, 7.69; N, 7.12; Cl^-, 18.03. Found: C, 55.18; H, 7.64; N, 7.08; Cl^-, 18.31.

1-Methyl-3,3-diphenyl-4-piperidinol Hydrochloride. A solution of **1a** (6.6 g) in 50 mL of methanol was treated with 2.0 g of KBH_4 at 23 °C for 2 h. After the solution was evaporated in vacuo at 30 °C, the solid residue was taken up with ice–water and extracted twice with 100 mL of EtOAc. The extracts were washed (NaCl–H_2O), dried over Na_2SO_4, and evaporated in vacuo. The noncrystallizable, nearly colorless semisolid was redissolved in 15 mL of 2-propanol and treated with anhydrous HCl to pH 2.5 giving 5.6 g (74%) of analytically pure hydrochloride: mp 228–229 °C dec; ^1H NMR (Me_2SO-d_6) δ 2.05 (m, 2 H, CH_2-5), 2.93 (d, J = 4.5 Hz, 3 H, CH_3NH^+), 3.17 (m, 2 H, CH_2-6), 3.85, 4.70 (d, d, J = 11.0 Hz, 2 H, CH_2-2), 5.14 (d, 1 H, CHO), 4.43 (d, 1 H, OH); ^1H NMR (base, Me_2SO-d_6) δ 2.45, 3.05 (d, d, J = 10.0 Hz, 2 H, CH_2-2), 4.40 (m, 1 H, CHO), 4.60 (d, J = 4.0 Hz, 1 H, OH, D_2O exchangeable); mass spectrum, m/z 267. Anal. Calcd for $C_{18}H_{21}NO$·HCl: C, 71.16; H, 7.30; N, 4.61. Found: C, 70.87; H, 7.43; N, 4.50.

α-Phenylbenzeneacetic Acid, 1-Methyl-3,3-diphenylpiperidin-4-yl Ester Hydrochloride. A solution of 7.6 g (0.033 mol) of diphenylacetyl chloride in 25 mL of CH_2Cl_2 was added dropwise to a solution of 1-methyl-3,3-diphenyl-4-piperidinol in 100 mL of CH_2Cl_2 and 15 mL of dry pyridine with stirring at 20 °C. After the reaction mixture was allowed to stand at 23 °C overnight, the hydrochloride (13.9 g) was collected, mp 260–262 °C dec. Two recrystallizations from methanol gave an analytical sample as white crystals: mp 261–262 °C dec; IR (KBr) 1745 (C=O) cm^{-1}. Anal. Calcd for $C_{32}H_{21}NO_2$·HCl: C, 77.17; H, 6.48; N, 2.81; Cl^-, 7.12. Found: C, 76.89; H, 6.53; N, 2.63; Cl^-, 7.27.

1-Methyl-5,5-diphenyl-3,4-piperidinedione 3-Oxime. To a stirred solution of 20 mL of isoamyl alcohol was added potassium (0.3 g) in small pieces at 0 °C. After the solution became clear, 0.6 g of **1a** in 25 mL of isoamyl nitrite was added and the temperature was allowed to rise to 35 °C (0.5 h). The solution was evaporated *in vacuo*, and the residue was taken up with ice–water and extracted twice with 25 mL of EtOAc. The combined extracts were dried (Na_2SO_4) and concentrated to a low volume giving 1.1 g (75%) of the 3-oxime, as white crystals: mp 172–173 °C; IR ($CHCl_3$) 1710 (C=O), 1623 (C=N) cm^{-1}; UV (CH_3OH) 244 nm (ε 10 800); ^1H NMR ($CDCl_3$) δ 2.40 (s, 3 H, CH_3N), 3.33 (s, 2 H, CH_2-2), 3.70 (s, 2 H, CH_2-6), 7.20 (s, 1 H, 10 Ar and OH); mass spectrum, m/z 294. Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.35; H, 6.20; N, 9.45.

1-Methyl-3,3-diphenyl-5-(phenylmethylene)-4-piperidinone. A solution of 5.3 g (0.02 mol) of **1a**, 2.3 g (0.022 mol) of benzaldehyde, and 1.2 g of $NaOCH_3$ in 100 mL of methanol was refluxed for 3 h and subsequently evaporated to dryness in vacuo. The residue was taken up with cold water and extracted with 100 mL of CH_2Cl_2. The CH_2Cl_2 extract was dried over Na_2SO_4 and evaporated and the residue crystallized from ethanol giving 4.9 g (69%) of the benzylidene derivative of **1a** as faint yellow crystals: mp 124–125 °C; IR ($CHCl_3$) 1600 (C=C), 1685 (C=O) cm^{-1}; UV (CH_3OH) 293 nm (ε 18 160); ^1H NMR ($CDCl_3$) δ 2.48 (s, 3 H, CH_3N), 3.35 (s, 2 H, CH_2-2), 3.82 (d, J = 2.0 Hz, 2 H, CH_2-6), 7.25–7.45 (m, 15 H, Ar), 7.65 (t, J = 2.0 Hz, 1 H, vinylic). Anal. Calcd for $C_{25}H_{23}NO$: C, 84.95; H, 6.56; N, 3.96. Found: C, 84.92; H, 6.72; N, 3.86.

5-[(3,4-Dimethoxyphenyl)methylene]-1-methyl-3,3-diphenyl-4-piperidinone. By a procedure analogous to the above the title compound was obtained in 82% yield as yellow crystals: mp 140–141 °C; IR ($CHCl_3$) 1682 (C=O), 1595 (C=C) cm^{-1}; UV (CH_3OH) 248 nm (ε 10 880), 340 (1750); ^1H NMR ($CDCl_3$) 2.51 (s, 3 H, CH_3N), 3.35 (s, 2 H, CH_2-2), 3.83 (d, J = 1.4 Hz, 2 H, CH_2-6), 3.89 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 6.88–7.01 (m, 1 H, Ar), 7.27–7.33 (m, 2 H, Ar), 7.63 (d, J = 1.4 Hz, vinylic). Anal. Calcd for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39. Found: C, 78.19; H, 6.61; N, 3.32.

3′,4′,5′,6′,7′,8′-Hexahydro-1,6′-dimethyl-5,5,8,8′-tetraphenylspiro[piperidine-3,2′-[2*H*]pyrano[3,2-*c*]pyridin]-4-one (4a). A solution of 21.0 g (0.1 mol) of **2**, 6.7 g (0.1 mol) of CH_3NH_2·HCl, 9.5 g of paraformaldehyde, and five drops of hydrochloric acid in 100 mL of 1-butanol was refluxed in a nitrogen atmosphere for 80 h after which time about 95% of **2** was consumed. The brown solution was evaporated in vacuo; the residue was taken up with ice–water and adjusted to pH 1.0 with H_2SO_4. The neutral materials were extracted with 200 mL of EtOAc and discarded. The aqueous acidic phase was made basic with K_2CO_3 at 0 °C and extracted twice with 200 mL of CH_2Cl_2. The combined extracts were washed, dried (Na_2SO_4), and evaporated. The gummy residue was triturated with CH_3CN to give 9.6 g of **4a**, mp 221–222 °C. Two recrystallizations gave 6.6 g of analytically and chromatographically (TLC: silica gel G; chloroform–toluene, 2:1; R_f 0.15) pure **4a** as white crystals: mp 228–229 °C; IR ($CHCl_3$) 1720 (C=O), 1690 (C=CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.60 (s, 4 H, CH_2-7, CH_2-7′), 2.30 [s, 6 H, $(NCH_3)_2$], 2.60–3.60 (m, 8 H, 4 *N*-methylene groups), 6.75 (m, 4 H, Ar), 7.00–7.50 (m, 16 H, Ar); mass spectrum, m/z 554. Anal. Calcd for $C_{38}H_{38}N_2O_2$: C, 82.28; H, 6.91; N, 5.05. Found: C, 82.02; H, 7.01; N, 5.06.

The original mother liquor from 9.6 g of **4a** was evaporated to dryness and the residue was crystallized from diisopropyl ether to give 1.9 g of white crystals containing ca. 97% of **1a**, mp 132–134 °C. Recrystallization from acetonitrile–isopropyl ether gave 1.5 g of pure **1a**: mp 137–138 °C.

Transformation of 1a into 4a. A solution of 1.07 g (0.004 mol) of **1a**, 0.84 g (0.004 mol) of **2**, 0.27 g (0.004 mol) of CH_3NH_2·HCl, and 0.24 g (0.008 mol) of paraformaldehyde in 15 mL of 1-butanol was refluxed for 24 h, after which time the ratio of **1a** and **4a** was about 1:1. The heating was continued for an additional 48 h while the starting **1a** was practically all consumed. The mixture was evaporated to dryness in vacuo. The residue was taken up with ice and H_2SO_4 to pH 1.0; the neutral materials were extracted with ethyl acetate and discarded. The aqueous acidic layer was made basic with aqueous NH_3 at 5 °C and the product extracted with chloroform. The dried (Na_2SO_4) chloroform extract was evaporated and the residue was crystallized from acetonitrile giving 0.7 g of the dimer **4a**: mp 223–224 °C. Recrystallization from acetonitrile gave pure **4a**, mp 227–228 °C. This product is identical in all respects with that obtained previously. Anal. Calcd for $C_{38}H_{38}N_2O_2$: C, 82.28; H, 6.91; N, 5.05. Found: C, 82.07; H, 7.04; N, 4.96.

1,6′-Diethyl-3′,4′,5′,6′,7′,8′-hexahydro-5,5,8′,8′-tetraphenylspiro[piperidine-3,2′-[2*H*]pyrano[3,2-*c*]pyridin]-4-one (4b). The same procedure as for the preparation of **4a** was followed. Thus, boiling a solution of 21.0 g (0.1 mol) of **2**, 8.2 g (0.1 mol) of $C_2H_5NH_2$·HCl, 5.0 g of paraformaldehyde, and five drops of concentrated hydrochloric acid in 150 mL of 1-butanol for 120 h gave (after recrystallization from acetonitrile) 3.9 of **4b** as transparent rhombohedrons: mp 184–185 °C; IR ($CHCl_3$) 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (t, t, 6 H, $(CH_2CH_3)_2$), 1.6 (s, 4 H, CH_2-7, CH_2-7′), 2.25–3.60 [m, 10 H, $(CH_2CH_3)_2$, CH_2-5, CH_2-6, CH_2-2], 6.60–6.90 (m, 2 H, Ar), 7.05–7.55 (m, 18 H, Ar); mass spectrum, m/z 582. Anal. Calcd for $C_{40}H_{42}N_2O_2$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.36; H, 7.31; N, 4.81.

In a separate experiment when the reaction was carried out at 120 °C until the intermediate **1b** was no longer detectable (220 h), there was extensive decomposition and only the dimer **4b** was isolated in low (8%) yield.

3′,4′,5′,6′,7′,8′-Hexahydro-1,6′-dimethyl-5,5,8′,8′-tetraphenylspiro[piperidine-3,2-[2*H*]pyrano[3,2-*c*]pyridin]-4-ol (10). Method A. A solution–suspension of 1.3 g of **4a** and 0.6 g of KBH_4 in 75 mL of methanol was heated under reflux until the carbonyl function was no longer present as shown by IR spectroscopy (8 h). After the solvent was removed, the residue was taken up with cold water and the product extracted twice with 30 mL of $CHCl_3$. The combined $CHCl_3$ extracts were washed, dried (Na_2SO_4), and evaporated. Trituration of the residue with 2-propanol gave 0.96 g (73%) of **10**, mp 222–224 °C. An analytical sample of **10** was obtained by recrystallization from acetonitrile: mp 223–224 °C; IR ($CHCl_3$) 3560 (OH), 1690 (C=CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (d, J = 10.0 Hz, 1 H, OH, D_2O exchangeable), 2.30 (s, 3 H, NCH_3), 2.45 (s, 3 H, NCH_3), 4.23 (d, J = 10.0 Hz, 1 H, CHO), 6.52–6.82 (m, 4 H, Ar), 6.92–7.40 (m, 16 H, Ar); mass spectrum, m/z 556. Anal. Calcd for $C_{38}H_{40}N_2O_2$: C, 81.98; H, 7.24; N, 5.03. Found: C, 82.81; H, 7.27; N, 5.07.

Method B. To a stirred suspension of 2.0 g of $LiAlH_4$ in 50 mL of anhydrous tetrahydrofuran was added a solution of 5.5 g of **4a** in 25 mL of the same solvent and allowed to reflux until the carbonyl function was no longer detectable by IR spectroscopy (6 h). Ethyl acetate (150 mL) was added cautiously at 0 °C followed by the addition of water (100 mL). The organic phase was washed, dried (Na_2SO_4), and evaporated in vacuo to give 5.4 g of nearly colorless cake. Crystallization from acetonitrile gave 2.8 g of **10**, mp 223–224 °C. This product is identical with that obtained by method A. Anal. Calcd for $C_{38}H_{40}N_2O_2$: C, 81.98; H, 7.24; N, 5.03. Found: C, 81.72; H, 7.36; N, 4.97.

Decahydro-2,8-dimethyl-4,4,6,6-tetraphenyl-4a,9a-epoxy-2*H*,7*H*-oxepino[3,2-*c*:6,7-*c*′]dipyridine (11). A solution of alcohol **10** (0.5 g) in 10 mL of 48% hydrobromic acid was heated on a steam bath for 1.5 h and the contents were subsequently poured onto ice water. The mixture was made basic with aqueous NH_3 and extracted twice with 25 mL of CH_2Cl_2. The CH_2Cl_2 extracts were washed, dried (Na_2SO_4), and evaporated to give 0.4 g of off-white solid. Trituration with 2-propanol gave 0.3 g of **11**, mp 248–249 °C dec. Recrystallization from acetonitrile gave analytically pure **11** as white crystals: mp 252–253 °C dec; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3 H, NCH_3), 2.28 (s, 3 H, NCH_3), 5.10 (d, J = 2 Hz, 1 H, C*H*O), 6.55–7.25 (m, 18 H, Ar), 7.71 (dd, J = 6.0 and 2.0 Hz, 2 H, Ar); mass spectrum, m/z 556. Anal. Calcd for $C_{38}H_{40}N_2O_2$: C, 81.98; H, 7.24; N, 5.03. Found: C, 81.70; H, 7.31; N, 5.06.

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Registry No. **1a**, 96129-85-0; **1a** (4-oxime), 96129-89-4; **1a** (4-amine), 96129-90-7; **1a** (4-amine)·2HCl, 96129-91-8; **1a** (4-alcohol), 96129-92-9; **1a** (4-alcohol)·HCl, 96129-93-0; **1a** (4-2,2-diphenylacetate)·HCl, 96129-94-1; **1a** (3-oxime), 96129-95-2; **1a** (benzylidene derivative), 96129-96-3; **1a** (3,4-dimethoxybenzylidene derivative), 96129-97-4; **1b**, 96129-88-3; **2**, 781-35-1; **3**, 96129-86-1; **3**·2HCl, 96129-87-2; **4a**, 96129-98-5; **4b**, 96129-99-6; **10**, 96130-00-6; **11**, 96130-01-7; paraformaldehyde, 30525-89-4; $MeNH_2$·HCl, 593-51-1; $EtNH_2$·HCl, 557-66-4; $Ph_2CHCOCl$, 1871-76-7; PhCHO, 100-52-7.

Preparation of Optically Active, Functionalized *cis*-Δ^6-1-Octalones

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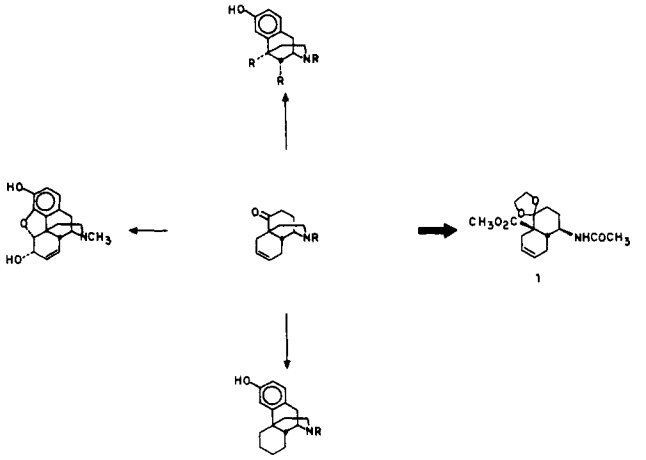
A preparation of optically pure, functionalized *cis*-Δ^6-1-octalones starting with (−)-β-pinene (92% ee) is detailed. The conversion of (−)-β-pinene to (−)-*cis*-nopinol (>97% ee) and its utilization in the preparation of (4*R*,9*R*,10*R*)-(+)-4-(acetylamino)-9-(methoxycarbonyl)-*cis*-Δ^6-1-octalone ethylene ketal (**1**), a *cis*-Δ^6-1-octalone possessing the correct absolute configuration at three appropriately functionalized chiral centers characteristic of the morphine-related analgesics, is described.

Central to the development of a divergent[2] synthesis of the morphine-related analgesics, including the morphinan- and benzomorphan-based analgesics, is the stereo- and enantiocontrolled synthesis of the aliphatic carbon framework composing the BC ring system of morphine. Control of the absolute configuration at three, contiguous stereocenters, C-9, C-13, and C-14 on the morphine skeleton, provides the necessary capabilities for a stereo- and enantioselective preparation of the morphine-based analgesics.[3,4] Herein we detail a preparation of (4*R*,9*R*,10*R*)-(+)-4-(acetylamino)-9-(methoxycarbonyl)-*cis*-Δ^6-1-octalone ethylene ketal (**1**), from (1*S*,5*S*)-(−)-β-pinene (**2**), which possesses the required absolute configuration at three functionalized chiral centers suitable for further elaboration to the morphine-related analgesics.



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Optical Purification of Pinene Derivatives. (1*S*,5*S*)-(−)-β-Pinene (**2**) and its ozonolysis product

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