the data to sin $\theta/\lambda = 0.54$ Å^{-1}, four cycles of least-squares refinement on the nonhydrogen atoms and their isotropic thermal parameters reduced R to 0.14. The anisotropic thermal parameters for these atoms were introduced as well as the hydrogen atoms in positions calculated 1 Å from the attached atom with isotropic thermal parameters. Two further cycles lowered R to 0.088. One further cycle followed by introduction of a weighting scheme corresponding to $1/\sigma(F)^2$, together with a $1\sigma(F)$ cutoff and the inclusion of the remainder of the data (to sin $\theta/\lambda = 0.60$ Å^{-1}) and ignoring 17 reflections with large F_o considered to be affected by secondary extinction, led to a suitable conclusion with $R = 0.069$, $R_w = 0.044$.

Acknowledgment. The authors gratefully acknowledge the assistance of Mr. Thomas Kreger and Mr. Greg Williams. This investigation was supported in part (W.R.P.) by the American Foundation for Pharmaceutical Education and (in part) by NIH Research Career Development Award (No. 1K04GM00211) from the Institute of General Medical Sciences (W.F.T.).

Supplementary Material Available: A listing of structure-factor amplitudes and the thermal parameters for the coordinates listed in Tables III and IV (27 pages). Ordering information is given on any current masthead page.

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Notes

Azabicyclo Chemistry. 6. An Investigation of One of the Chemical Parameters for Analgetic Activity. Synthesis of 2-Methyl-2-azabicyclo[3.3.1]non-6-ene and -non-7-ene[1]

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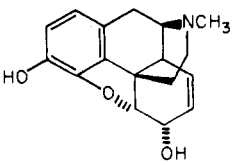
The olefins 2-methyl-2-azabicyclo[3.3.1]non-6-ene (**3**) and -non-7-ene (**6**) were prepared in order to evaluate their analgetic activity. The reduction of 2-methyl-2-azabicyclo[3.3.1]nonan-7-one (**4**) with $NaBH_4$ gave, stereospecifically, the axial alcohol **5**. Reaction of **5** with CH_3SO_2Cl–pyridine gave directly the olefins **3** and **6**, both of which upon hydrogenation gave the known 2-methyl-2-azabicyclo[3.3.1]nonane (**7**). The structural proof of **3**, **5**, and **6** was ascertained by spectral methods. Of the compounds prepared, **3**, **5**, and **6** were essentially inactive as analgetics when tested in mice by the hot-plate method, while **4** had marginal activity.

It has been recognized for some time that certain structural features of morphine (**1**) should be maintained in any modification of its structure in order to retain analgetic potency. They are (1) the phenyl nucleus, (2) the quaternary carbon attached to this nucleus, and (3) the tertiary nitrogen two carbon atoms removed from the quaternary carbon.[2] Several years ago, May and coworkers[3] described the synthesis and biological evaluation of 2-methyl-6,7-benzomorphan (**2**), the simplest member of a family of strong analgetics,[2] a class which has begun to yield compounds which are devoid of any physical dependence capacity.[4]

Inasmuch as the biologically active benzomorphan **2** represents an abbreviated morphine structure wherein the



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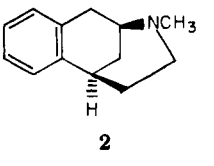

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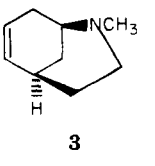

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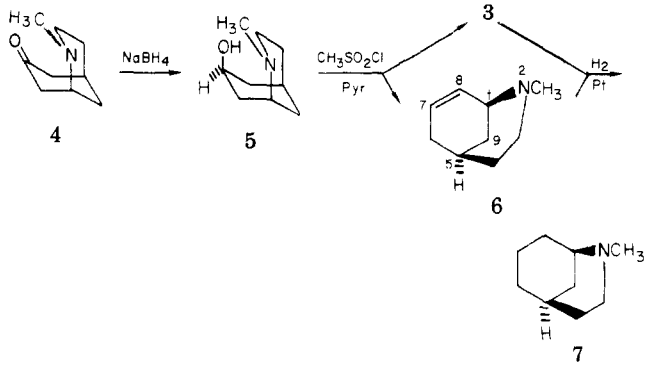
Scheme I



important quaternary carbon is also absent, we sought to test the necessity of the aromatic ring for analgetic activity. This paper thus deals with the synthesis and structural proof of 2-methyl-2-azabicyclo[3.3.1]non-6-ene (**3**) and -non-7-ene (**6**). The 6,7 double bond in **3** is postulated to provide the π-electron density that is usually imparted by the aromatic ring.

Chemistry. The synthesis of **3** and **6** involved the intermediacy of the bicyclic ketone **4**, a compound whose preparation has been previously reported by us[5a] and later by other workers.[5b] Reduction of **4** with sodium borohydride in methanol afforded the axial amino alcohol **5**, homogeneous on thin-layer and gas chromatography (Scheme I). Chemical evidence[6] suggests that metal hydride reduction of **4** in the double chair conformation should yield exclusively axial alcohol **5** because steric hindrance prevents approach of the reducing agent from the "endo" side of the carbonyl. Once formed, **5** could theoretically exist in a number of conformations.

The NMR spectrum of **5** showed a quintet for H_7 centered at δ 3.98 with spacings of 4.0 Hz. In the double chair form of **5**, H_7 is equatorial and is expected to give rise to the X part of an A_2B_2X system. Chen and LeFevre[7] have indicated that when $J_{AX} >> J_{BX}$, the X part should exhibit a nine-line spectrum, but when $J_{AX} = J_{BX}$, the X part should degenerate into a five-line spectrum with the spacing between neighboring lines equal to J_{AX} or J_{BX}. Dreiding molecular models show that with H_7 equatorial, the dihedral angles between H_{AX} and H_{BX} are almost identical, and thus the five-line spectrum is to be expected. Bishop et al.[8] have also indicated that in the tropine series a 3-equatorial proton, in an undistorted chair conformation, would require a quintet pattern.

Reaction of amino alcohol **5** with methanesulfonyl chloride in pyridine, or in dry 1,2-dimethoxyethane in the absence of pyridine, did not give the expected mesylate ester but instead underwent a facile elimination affording, after column chromatography, the desired olefin **3** and its position isomer **6** (Scheme I). The relative ease of olefin formation, with or without an external base, suggests that the requirements for elimination are already present in the starting alcohol component, namely, the basic tertiary amine. Furthermore, the ease of olefin formation suggests that the alcohol function is axial, thus leading to a trans elimination of the intermediate sulfonate ester via either an intra- or intermolecular proton abstraction by the tertiary amine. Dreiding models do not support the intramolecular route.

Mass spectral analysis of **3** and **6** indicated identical molecular ions, but by virtue of their differing base-peak ions we were able to tentatively assign the less polar (by TLC) compound as the Δ^6 olefin **3** and the more polar compound as the Δ^7 olefin **6** (see Experimental Section). These assignments have been confirmed by examination of the 250-MHz NMR spectra of both compounds, as solutions of their picrate salts[9] in dimethyl-d_6 sulfoxide. The NMR spectrum of **3** picrate showed a single multiplet centered at 1459 Hz (δ 5.84), which was assigned as the vinyl protons $H_{6,7}$. The chemical shift of these vinyl protons would be expected to be nearly the same, just as they are in cyclohexene. Furthermore, double resonance experiments, wherein the H_1 multiplet (920 Hz, δ 3.68) was irradiated, caused no decoupling at δ 5.84.

On the other hand, in isomer **6** picrate one would expect the positively charged nitrogen to influence the vinyl protons $H_{7,8}$ differentially and, thus, their respective chemical shifts to be different. Indeed, the NMR spectrum of **6** picrate showed two multiplets in the vinyl region. A similar spectrum was reported[10] for the analogous 9-methyl-9-azabicyclo[3.3.1]non-2-ene, as its picrate salt. The lower field resonance appeared at 1612 Hz (δ 6.45) as a doublet of triplets, with a doublet spacing ($J_{7,8}$) of 10 Hz and triplet spacing ($J_{7,6}$) of 4 Hz, and was assigned as H_7. The higher field H_8 was observed at 1454 Hz (δ 5.82) as a poorly resolved triplet (doublet of doublets?). These assignments were confirmed by double-resonance experiments, which also confirmed the position of H_1 at δ 3.90.

In cyclohexenone[11] and 2-butenoic acid γ-lactone,[12] the β proton also appears as a doublet of triplets, with a reported[13] doublet spacing of 10 Hz ($J_{2,3}$) and triplet spacing of 4 Hz ($J_{3,4}$) for the former compound. In cyclohexenone and other α,β-unsaturated carbonyls,[14] the β protons always appear downfield from the α protons because of deshielding of the former by mesomeric electron withdrawal.[15] The inductive effect of the positively charged nitrogen in **6** influences H_7 and H_8 in a similar manner.

The isomeric nature of **3** and **6** was further confirmed by the fact that upon catalytic hydrogenation both compounds were converted to 2-methyl-2-azabicyclo-[3.3.1]nonane (**7**, Scheme I) which was identical (as their picrate salts) with authentic **7** prepared by an unambiguous route from *m*-nitrophenylacetic acid.[16]

Biological Results. The analgetic activities of **3–6** were determined in mice by the hot-plate method[17] and compared with several benzomorphan compounds as indicated in Table I. All of the azabicyclo compounds reported in this paper either were devoid of, or had significantly less, analgetic activity when compared to the benzomorphan **2**. Similar results (little or no analgetic activity) were observed by Pirkle and Gates[18] in studies in the morphinan series wherein the aromatic ring was partially saturated.

Table I. Analgetic Evaluation of Azabicyclo Analogues[a]

Compd	ED_{50}, mg/kg
2-Methyl-2-azabicyclo[3.3.1]nonan-7-one (4)	40
2-Methyl-2-azabicyclo[3.3.1]nonan-7-ol (5)	Inactive to 100
2-Methyl-2-azabicyclo[3.3.1]non-6-ene (3)	Inactive to 50 Marginal act. at 100[b]
2-Methyl-2-azabicyclo[3.3.1]non-7-ene (6)	Inactive to 100
2-Methyl-6,7-benzomorphan (2)	11.2[c]
2'-Hydroxy-2-methyl-6,7-benzomorphan	4.5[c]
2,5-Dimethyl-6,7-benzomorphan	11.0[c]
Morphine (1)	1.2[c]

[a] All compounds were administered to white mice, sc, as HCl salts in water except morphine (sulfate) and **5** (free base in dilute HCl) and evaluated by the hot-plate method (ref 17). [b] 7/10 animals responded, but this was a toxic dose. [c] ED_{50} data from ref 3.

On the other hand, Bentley et al.[19] have demonstrated that ozonolysis of the aromatic ring in the 6,14-*endo*-ethenotetrahydrothebaine series containing bulky groups in the C-7 position gives rise to conjugated unsaturated derivatives with significant analgetic activity. Furthermore, Bentley and Lewis[20] have postulated that molecules of the above type,[19] because of additional binding from bulky C-7 substituents, can remain effective when interacting with only part of the "receptor" even though they are devoid of an aromatic ring. The present study has shown that the replacement of an aromatic ring by a single unsaturation, to give rise to structures even more abbreviated than the benzomorphans, does not result in compounds with significant analgetic activity.

Experimental Section

High-resolution NMR spectra and spin-decoupling experiments were recorded on a Fourier Transform 250-MHz spectrometer at Carnegie Mellon University in $CDCl_3$ or $(CD_3)_2SO$, with Me_4Si as internal standard. Mass spectra were determined on an LKB Model 9000 spectrometer at 70 eV. All gas chromatographic (GC) separations were done on a Varian Aerograph 1860 series gas chromatograph using a $^1/_8$ in. × 6 ft stainless steel column packed with 10% Carbowax 20M + 2% KOH on Supelcoport. Melting points were taken on a Thomas-Hoover instrument and are uncorrected. TLC was carried out with silica gel GF or alumina GF (Analtech, Inc.) and the spots were located with Dragendorff's reagent.[21] All concentrations were done under reduced pressure, after first drying the organic solutions over anhydrous $MgSO_4$ powder. The pyridine used was previously distilled from BaO. The Woelm basic alumina used for chromatography was activity grade V. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and analytical results are within ±0.4% of the theoretical values.

2-Methyl-2-azabicyclo[3.3.1]nonan-7-ol (5). A stirred solution of the ketone **4**[5a] (1.53 g, 10.0 mmol) in 60 mL of methanol was treated portionwise, at ice-bath temperature, with solid $NaBH_4$ (1.5 g, 40 mmol) over a 10-min period. The mixture was stirred for 24 h, allowing the bath to reach room temperature, and concentrated and the residue was dissolved in a minimum amount of water. The aqueous solution was extracted five times with 15-mL portions of CH_2Cl_2 and then concentrated to an oil. The oil was purified by chromatography through a column (2.2 × 25 cm) of Woelm basic alumina (100 g) packed in 1:1 benzene–$CHCl_3$. The amino alcohol **5** was eluted from the column with the same solvent mixture, affording 1.18 g (76%) as a homogeneous oil (determined by TLC and GC). The picrate was formed by standard procedures and recrystallized three times from methanol, mp 273–274 °C dec. Anal. ($C_{15}H_{20}N_4O_8$) C, H, N.

2-Methyl-2-azabicyclo[3.3.1]non-6-ene (3) and 2-Methyl-2-azabicyclo[3.3.1]non-7-ene (6). An ice-cooled solution of **5** (0.315 g, 2.03 mmol) in 4 mL of dry pyridine was treated with 3.2 mL of a freshly prepared solution of distilled methanesulfonyl chloride in pyridine (0.143 g of CH_3SO_2Cl/mL of pyridine) and allowed to react at 4 °C for 24 h. The reaction mixture was diluted with 50 mL of $CHCl_3$ and extracted five times with 10-mL portions of H_2O. The aqueous phase was cooled in ice, basified with 10% NaOH, and then extracted five times with 10-mL portions of CH_2Cl_2. After drying the organic phase, it was titrated with an ethereal solution of picric acid and then concentrated to dryness. The solid residue was dissolved in hot acetone and adsorbed onto 40 g of Woelm basic alumina and air-dried. The resulting powder was then placed onto a 2 × 78 cm column of Woelm basic alumina (300 g) packed in benzene. Benzene (dried by Woelm basic alumina, activity grade I, 50 g per gallon) was passed through the column at a 0.5-mL/min rate. Fractions that were homogeneous on TLC (silica gel, 5% CH_3OH in NH_4OH saturated $CHCl_3$) were combined. The first to elute from the column was olefin **3** and it was converted, in benzene, to its picrate salt[9] and the mixture was concentrated to dryness. The crystalline residue was recrystallized from benzene: mp 276.5–277.5 °C dec; mass spectrum *m/e* (rel intensity) 137 (47, M^+), 122 (19), 96 (15), 91 (18), 70 (100, retro-Diels–Alder followed by allylic cleavage[22]). Anal. ($C_{15}H_{18}N_4O_7$) C, H, N.

The more polar olefin **6** was also converted to its picrate salt[9] directly in the benzene used to elute it from the column. Recrystallization from benzene gave the analytical sample: mp 280–282 °C dec; mass spectrum *m/e* (rel intensity) 137 (49, M^+), 96 (100, retro-Diels–Alder followed by allylic cleavage[22]), 94 (44), 79 (33). Anal. ($C_{15}H_{18}N_4O_7$) C, H, N.

For biological testing purposes the HCl salt of each olefin was formed by diluting the benzene fractions of the respective free amine with 20% CH_3OH, shaking with 1 N HCl solution, and then concentrating the solution to a solid residue. The solid residue of each HCl salt was sublimed at 135–140 °C (0.005 mm), shown to be homogeneous by TLC, and then submitted for biological testing. The average yield of **3** and **6** from three experiments, as their HCl salts, was 31 and 19%, respectively.

2-Methyl-2-azabicyclo[3.3.1]nonane (7). (a) *m*-Nitrophenylacetic acid (Aldrich Chemical Co.) was reduced to *cis*-3-aminocyclohexylacetic acid[16] and cyclized to 2-azabicyclo[3.3.1]nonan-3-one as reported by Ginsburg[16] and Dygos,[16] mp 162–163 °C (lit.[16] 163–165, 165 °C). N-Methylation with NaH–CH_3I gave 2-methyl-2-azabicyclo[3.3.1]nonan-3-one, as described by Dygos.[16] The latter lactam was converted to the desired **7** with $LiAlH_4$ by the method of Dygos[16] and isolated as its picrate salt, mp 262–264 °C dec (lit.[16] 262–263 °C dec).

(b) A solution of 15 mg of the HCl salt of **3** in 2 mL of C_2H_5OH, containing 1 drop of 1 N HCl, was shaken with 15 mg of PtO_2 (Engelhard, 87%) in a Parr hydrogenator at 50–55 psi for 2 h at ambient temperature. The mixture was then passed through a column (0.3 × 10 cm) of Woelm basic alumina packed in ether and eluted with an additional 10 mL of ether. The ethanol–ether eluent containing the free amine **7** was titrated with an ethereal solution of picric acid and concentrated. The crystalline residue was recrystallized from benzene, mp 261–263 °C dec; the mixture melting point with **7** prepared as in part (a) was 262–263 °C dec.

(c) Olefin **6**, hydrogenated as above, gave **7**, which was converted to its picrate salt, mp 262–264 °C dec; the mixture melting point with **7** prepared as in part (a) was 261–264 °C dec. The infrared spectra of **7**, prepared as in parts (b) and (c), were identical with that of **7** from part (a).

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Heterocyclic and Piperonylic Acid Esters of 1-Methyl-4-piperidinol as Analgesics[1]

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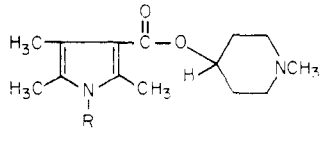
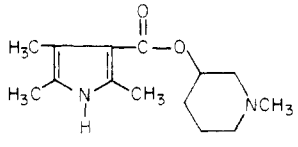
Heterocyclic and piperonylic acid esters of 1-methyl-4-piperidinol were synthesized and evaluated for analgesic activity. 1-Methyl-4-piperidinol 4-piperonylate (14) exhibited activity in the codeine range (mouse hot plate). In monkeys, 14 acted neither as a typical narcotic agonist nor as a typical antagonist and it showed no physical dependence liability of the morphine type. The nonquaternary C-4 piperidinol esters 1a, 4, 8, and 14 exhibited marginal to virtually no binding to the opiate receptor in rat brain homogenates. The interaction of various functional groups of this series with potential binding sites of a nonopiate type receptor is discussed.

In a recent study of pyrrolecarboxylates of various cyclic amino alcohols as potential analgesics, 1-methyl-4-piperidinol 4-(2,4,5-trimethylpyrrole-3-carboxylate) (**1a**) was observed to have activity in the codeine–morphine range in the mouse hot-plate assay.[2] More significantly, **1a** did not exhibit a physical dependence syndrome of the morphine type in monkeys. An important structural feature of **1a** that differs from that of the pethidine or alphaprodine analgesics is that it does not have quaternary phenyl substitution at C-4 of the piperidine ring. Since



1a, R = H
b, R = CH_3



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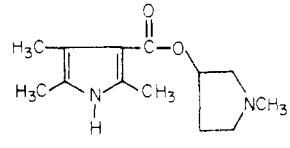

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the heterocyclic moiety of the ester may play an important role in drug–receptor interaction, CNS concentration, and metabolism, it was of interest to replace the 2,4,5-trimethylpyrrole ring of **1a** with other heterocycles that would confer different electronic, steric, and lipophilic properties to this class of compounds.

In this study, nitrogen-, oxygen-, and sulfur-containing heterocyclic esters **4–13**, piperonylic acid esters **14** and **15**, and related 4-piperidinol esters **16–18** were prepared by the acid chloride method (Table I and Experimental Section) and evaluated for analgesic activity (Table II). Selected compounds were assayed for binding affinity to the opiate receptor (Table III) and for physical dependence liability in Rhesus monkeys.

Results and Discussion

Compounds from each of the three groups of heterocyclic carboxylates (N, S, and O) and piperonylates showed activity in the mouse hot-plate assay[3] (Table II). Quinoline carboxylates **4** and **5** were moderately active (ED_{50} 9.3 and 11.2, respectively), whereas the pyridine and quinoxaline derivatives **6** and **7** were only marginally active and inactive, respectively. The 2-thiophene and 2-furan esters (**8** and **10**) exhibited one-half the potency of codeine by the hot-plate assay. Compound **8** was inactive in the Nilsen assay,[4a] whereas morphine and related drugs are nearly equipotent in the two systems.[4a] Esters **9** and **11**, substituted by electron-donating (methyl) and -withdrawing (bromo) groups, were both less active than the parent compounds. 1-Methyl-4-piperidinol 4-piperonylate (**14**) was the most active compound in this study, showing a potency equivalent to that of codeine (hot plate). It was three times more active than piperonylate **15**. Evidently the 4-piperidinol ring system in **14** is preferred over that of the 3-piperidinemethanol in **15**, even though the carbonyl oxygen and piperidine nitrogen atoms are separated by three carbons in both cases. The potential interaction of certain functions in **1a** and **14** with a receptor will be discussed later.

Compound **14** showed no morphine-like dependence liability in monkeys.[5] In single-dose suppression experiments, it caused only a slight increase in the severity of abstinence signs at 6.0 mg/kg. In nonwithdrawn monkeys it produced only very mild abstinence signs and very mild CNS depression at 6.0 mg/kg. At a higher dosage (12 mg/kg), piloerection, tremors, retching, and increased respiration were observed, but it was not a typical morphine withdrawal syndrome.

Quinolinecarboxylate **4**, thiophenecarboxylate **8**, and piperonylate **14** showed very marginal to essentially no binding to the opiate receptor as shown by their inability to reduce [^{3}H]dihydromorphine binding to rat brain homogenates[6] (Table III). The binding affinity of pyrrole