2c hydrochloride hydrate: mp > 167 °C (95% EtOH). Anal. ($C_{19}H_{17}N_5O_2Cl_2 \cdot HCl \cdot H_2O$) C, H, N, Cl.

2c maleate hemihydrate: mp 97 °C (bubbling) (EtOH). Anal. ($C_{19}H_{17}N_5O_2Cl_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$) C, H, N, C.

2c phosphate: mp 227–230 °C (95% EtOH). Anal. ($C_{19}H_{17}N_5O_2Cl_2 \cdot H_3PO_4$) C, H, N, Cl, P.

Alternate Route to 2c from 6b. A mixture of (2 mmol) of **6b** and 15 mL of 15% NH_3–MeOH was left standing at room temperature for 3 days. The reaction mixture was evaporated in vacuo. The residue was chromatographed on a column of silica gel with MeOH as eluent, affording 0.42 g (51%) of **2c**.

Alternate Route to 2c from 6e. With **6e** as starting material, the reaction was carried out as described for the preparation of **2a** and gave **2c** in 60% yield.

Alternate Route to 2c from 6g. With **6g** as starting material, the reaction was carried out as described for the preparation of **2b** and gave **2c** in 86.4% yield.

5-Chloro-2′-fluoro-2-[3-[(glycylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (2d). A mixture of 2.0 g (3.8 mmol) of **6i** and 0.49 g (9.9 mmol) of $NH_2NH_2 \cdot H_2O$ in 15 mL of EtOH was heated at reflux for 30 min. The precipitated phthalhydrazide was removed with suction, and the filtrate was evaporated in vacuo. The residue was then partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The organic layer was washed with brine, dried, and evaporated to give 1.3 g (85.2%) of **2d**, mp 135-137 °C (AcOEt). Anal. ($C_{19}H_{17}N_5O_2ClF$) C, H, N, F, Cl.

2′,5-Dichloro-2-[3-[(L-phenylalanylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (2e). A suspension of 2.4 g (3.8 mmol) of **6h** and 0.2 g of $NH_2NH_2 \cdot H_2O$ in 20 mL of EtOH was refluxed for 1 h. The precipitate was removed with suction and the filtrate was evaporated in vacuo. The residue was partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was dried and evaporated to give a viscous oil, which upon treatment with 0.4 g (4.4 mmol) of $(CO_2H)_2$ in AcOEt yielded 1.9 g of the oxalate of **2e**: mp > 68 °C (aq CH_3CN). $[\alpha]^{24}_D$ +29.0 ± 0.7° (*c* 1.099, EtOH). Anal. ($C_{26}H_{23}N_5O_2Cl_2 \cdot (CO_2H)_2 \cdot H_2O$) C, H, N, Cl.

2′,5-Dichloro-2-[3-[(glycylamino)methyl]-5-cyclopropyl-4*H*-1,2,4-triazol-4-yl]benzophenone (2f). To a suspension of 0.8 g (1.4 mmol) of **6j** in 30 mL of EtOH was added 0.2 g (3.4 mmol) of $NH_2NH_2 \cdot H_2O$, and the mixture was heated at reflux for 2 h. The precipitated phthalhydrazide was removed with suction, and the filtrate was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was dried and evaporated to give an oily residue, which was chromatographed on a SiO_2 column with MeOH as an eluent, affording 0.4 g (63%) of **2f**: mp 148–151 °C (AcOEt); IR (Nujol) 3300, 1660 (br), 1590 cm^{-1}; NMR ($CDCl_3$) δ 0.67–1.73 (m, 5 H), 1.80 (br m, 2 H), 3.30 (br m, 2 H), 4.0–4.67 (m, 2 H), 8.43 (br m, 1 H), 7.23–7.97 (m, 7 H). Anal. ($C_{21}H_{19}N_5O_2Cl_2$) C, H, N, Cl.

Pharmacology. The experiments were conducted on albino male mice (DS strain, Aburahi Farm, Shionogi, 20–24 g). All compounds were suspended in an aqueous solution of arabic gum and administered orally.

Rotorod Performance Test.[19] Groups of five mice were used. Sixty minutes after a mouse had received a dose of a drug, it was put on a wood rod, 3 cm in diameter, turning at 5 rpm, and the number of animals falling off with 2 min was counted. ED_{50} values were estimated by the up and down method.[20]

Antipentylenetetrazole Activity.[21] The test was performed with a group of ten mice. The animals were challenged with a subcutaneous injection of 125 mg/kg of pentylenetetrazole at 60 min after dosing. The dose required to prevent convulsion and death in 50% of the animals during 2 h of observation was defined, and ED_{50} values were estimated by the probit method.

Spontaneous Motor Activity.[22] Spontaneous motor activities of mice were quantitated with an "Animex" activity meter (Type S, AB Farad, Sweden). Five groups per dose (each group consisting of three mice) were measured for 10 min, beginning at 60 min after dosing. ED_{30} values were defined as the dose of drug required for a 30% reduction of control responses and were estimated by regression analysis.

Taming. A modification of the method of Tedeshi et al.[23] was used. A pair of mice was confined under an inverted circular glass enclosure and given foot shocks (5 Hz, 2 ms, DC 50 V). Five pairs of mice were used for each dose. Pairs showing 15–20 fighting episodes during 3 min were selected, and the number of responses before and at 60 min after dosing was counted. ED_{50} values were defined as those doses causing a 50% inhibition of the response and were calculated by regression analysis.

Thiopental Narcosis. Groups of ten mice pretreated with test drugs were challenged with an intravenous injection of 35 mg/kg of thiopental sodium. ED_{50} values were defined as those doses needed for a 50% increase in the duration of anesthesia and were estimated by regression analysis.

Chlorprothixene Hypnosis.[16] Groups of ten mice were treated with a combination of test drugs and chlorprothixene (2 mg/kg, ip). Sixty minutes later, each animal was placed on its back, and the duration of the loss of the righting reflux was measured. The number of animals remaining in the supine position for more than 30 s was counted, and the ED_{50} values were estimated by probit analysis.

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Synthesis and Pharmacological Activity of 6-Aryl-2-azabicyclo[4.2.1]nonanes

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A series of 6-phenyl-, 6-(*m*-methoxyphenyl)-, and 6-(*m*-hydroxyphenyl)-2-azabicyclo[4.2.1]nonanes was synthesized by a sequence involving alkylation of an appropriate 2-arylcyclopentanone with an aminoalkyl substituent. Subsequent ring closure at the other α position on the cyclopentanone ring and Wolff–Kishner reduction afforded the title compound. Several derivatives of these materials showed activity in an antinociceptive assay comparable to codeine. Most analogues were either inactive or toxic.

For some time we have been interested in developing structure–activity relationships for a series of benzo-fused azabicyclic systems, which are generally thought of as "simplified morphines". The prototype of these systems is benzomorphan (1), but many others are now known, including the benzazocines **2**[1] and **3**[2] and the benazepines

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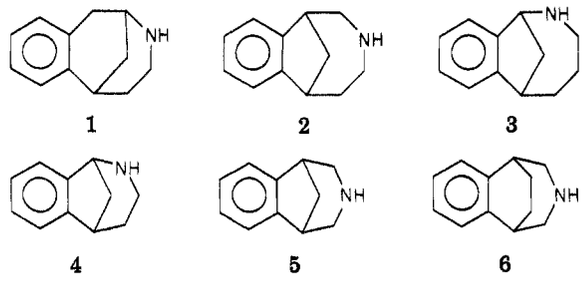
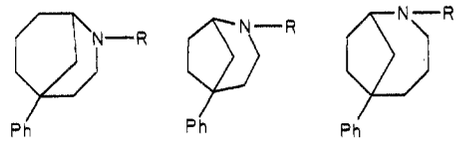


1 2 3 4 5 6

4,[3] 5,[4] and 6.[5] There appears to be growing correlation since all of the known 3-benzazocines (1, 2, and the unbridged parent[6]) show analgesic activity and have been classified as "active",[7] whereas the 2-benzazocine 3 is inactive.[2] A similar correlation seems to be developing with the benzazepines, since 4 and the parent 2-benzazepine show activity,[3,8] but 5, 6, and the parent 3-benzazepine are inactive.[4,5,9]

The non-benzo-fused azabicyclic systems offer another area in which correlations of this type could be developed, and although fewer systems are known, the analgesic activities of 7[10] and 8[11] appear to parallel those of the re-

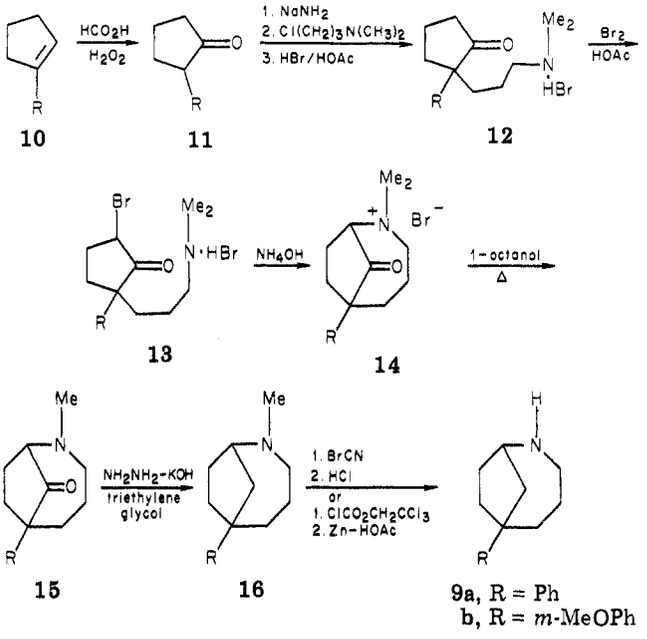


7 8 9

spective benzo-fused analogues 1 and 4. In this paper we report our investigations on the 6-aryl-2-azabicyclo-[4.2.1]nonane system 9, the aryl-substituted analogue of the benzo-fused 3.

Chemistry. The synthesis of 9 is outlined in Scheme I. Alkylation of the 2-arylcyclopentanone 11[12] with *N,N*-dimethylaminopropyl chloride affords the amino ketone 12. Bromination of 12 and subsequent ring closure gave the bicyclic amino ketone 14, which was subsequently dealkylated to 15 by heating in 1-octanol. Wolff–Kishner reduction of 15 gave the *N*-methyl bicyclic amine 16. Demethylation of 16a to 9a was carried out in 40% yield by the conventional von Braun method. Compound 16b was demethylated more efficiently by treatment with 2,2,2-trichloroethyl chloroformate, followed by reductive decarboxylation with zinc[13] to give 9b in 77% overall yield. The overall yields from the arylcyclopentenes were 9% to 16a and 5% to 16b.

Scheme I



10 11 12 13 14 15 16

9a, R = Ph
b, R = *m*-MeOPh

Pharmacology. Analgesic potencies were determined with aqueous solutions of the hydrobromides or oxalates by the Eddy hot plate[14a] or Nilsen[14b] methods. Test results are listed in Table I. The results listed are somewhat ambiguous in that slightly over half of the molecules tested show no activity, but three of them, 9b, 16b, and 19f, show activity in the range of codeine in the same assay. All of these contain an oxygenated aryl substituent. It is clear that these materials (9b, 16b, 19f) show significantly more activity than any of the derivatives of the previously reported benzo-fused analogue 3. At least in the case of the 6-aryl-2-azabicyclo[4.2.1]nonanes, analgesic activity in aryl-substituted bicyclic systems does not parallel that found in the corresponding benzo-fused analogue.

The results in the 6-aryl-2-azabicyclo[4.2.1]nonane system are probably best compared to those found in the 5-aryl-2-azabicyclo[3.2.1]octane (8)[11] system. Thus, in the *N*-methyl-substituted series in the present case, one sees an increase in activity in proceeding from unsubstituted (16a) to methoxy-substituted phenyl (16b), followed by a decrease in activity in the hydroxy analogue (19b). Indeed, Ong and co-workers[11] have found that the *N*-methyl hydroxy compound is less active than the methoxy compound in their system (8) also. We presume this is at least partially due to an increase in water solubility in the hydroxy-substituted case (19b), resulting in inefficient delivery to the active site. In the case of *N*-phenethyl derivatives, Ong and co-workers[11] found a tenfold increase in activity in going from methoxy- to hydroxyphenyl-substituted derivatives. We find an approximately 2.5-fold increase for the same substitution pattern (compare 18d to 19f). We expect that optical resolution and further pharmacological evaluation of the enantiomers of 19f would be useful. We intend to carry out these investigations and will report on them in due course.

Experimental Section

Melting points were taken in capillary tubes and are uncor-

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Table I. Analgetic Potency of 6-Aryl-2-azabicyclo[4.2.1]nonanes

compd	R	Ar	analgetic act.: ED_{50}, mg/kg sc	salt
9a	H	C_6H_5	toxic, inactive	oxalate
9b	H	m-C_6H_4OMe	4.0 (2.9-5.6)	HBr
16a	CH_3	C_6H_5	11.7 (8.4-16.1)	oxalate
16b	CH_3	m-C_6H_4OMe	5.7 (3.9-8.3)	oxalate
17a	$CH_2CH_2CH_3$	C_6H_5	toxic, inactive	oxalate
17b	$CH_2CH=CH_2$	C_6H_5	toxic, inactive	oxalate
17c	$CH_2CH=C(CH_3)_2$	C_6H_5	toxic	oxalate
18a	$CH_2CH_2CH_3$	m-C_6H_4OMe	N/A	oxalate
18b	$CH_2CH=CH_2$	m-C_6H_4OMe	20 (14.4-27.7)	HBr
18c[a]	$CH_2CH=C(CH_3)_3$	m-C_6H_4OMe	inactive	oxalate
18d	$CH_2CH_2C_6H_5$	m-C_6H_4OMe	10.9 (7.3-16.4)	HBr
19a	H	m-C_6H_4OH	inactive	HBr
19b	CH_3	m-C_6H_4OH	16.2 (11.7-22.4)	HBr
19c	$CH_2CH_2CH_3$	m-C_6H_4OH	inactive	HBr
19d	$CH_2CH=CH_2$	m-C_6H_4OH	inactive	HBr
19e[b]	$CH_2CH=C(CH_3)_2$	m-C_6H_4OH	inactive	HBr
19f[c]	$CH_2CH_2C_6H_5$	m-C_6H_4OH	4.5 (3.4-5.9)	HBr
morphine sulfate			1.0 (0.7-1.4)	
codeine phosphate			6.8 (4.5-10.2)	

[a] Nilsen 0/8 at 10, 25% at 20. [b] Nilsen, 0/8 at 25, 1/8 at 50. [c] Nilsen, 5.5 (3.8-7.8).

rected. Elemental analyses (indicated by C, H, and N were within ±0.4% of calculated values) were performed by Dr. Franz Kasler of the University of Maryland. IR spectra were taken on a Perkin-Elmer 281 spectrophotometer, ^1H NMR spectra were taken on a Varian EM-360 or XL-100 spectrophotometer, and chemical shifts are reported in parts per million relative to either tetramethylsilane or sodium silapentanesulfonate as an internal standard.

1-Phenylcyclopentene (10a). To a stirred solution of phenylmagnesium bromide (prepared from 57 g of bromobenzene and 9 g of Mg) in 250 mL of anhydrous ether was added cyclopentanone (30 g, 357 mmol) in 30 mL of anydrous ether with ice cooling over 0.5 h. After removal of the ice bath, 30% H_2SO_4 (180 mL) was added, and the mixture was refluxed for 1 h. The ether layer was separated and the aqueous layer was extracted with ether (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and distilled to give 37.5 g (73%) of 1: bp 65–66 °C (1.2 mm) [lit.[15] bp 133–135 °C (25 mm)]. Compound **10b** was similarly prepared from *m*-bromoanisole in 75% yield, bp 95–97 °C (1.5 mm) [lit.[16] bp 129–131 °C (13 mm)].

2-Phenylcyclopentanone (11a). According to the procedure of Plate et al.,[12] 85% HCOOH (20 mL) and 30% H_2O_2 (4.5 mL) were mixed together and then warmed to 40 °C for 10 min, and **10a** (4.32 g, 30 mmol) was added dropwise at such rate that the reaction temperature remained 30–35 °C. After all the 1-phenylcyclopentene was added, the mixture was stirred for 1 h and left overnight at room temperature. The formic acid and water were distilled, basified with concentrated NaOH to a weak alkaline solution, and extracted with ether. The residue in the distillation flask was diluted with ether (40 mL) and then washed with cooled 10% NaOH and with water. The ether solutions were combined, dried (K_2CO_3), evaporated, and distilled to give 3.15 g (66%) of **11a**: bp 117–120 °C (1.5 mm) [lit.[12] bp 115–117 °C (mm)].

Compound **11b** was similarly prepared from **10a** in 38% yield, by 127–129 °C (0.3 mm) [lit.[11,16] bp 116–117 °C (0.1 mm) and 138–140 °C (0.5 mm)].

2-[3-(Dimethylamino)propyl]-2-phenylcyclopentanone Hydrobromide (12a). To a stirred solution of 2.8 g (17.5 mmol) of **11a** in anhydrous benzene (25 mL) under N_2 was added portionwise 1.6 g (40 mmol) of $NaNH_2$. After the solution was refluxed for 1 h, 2.43 g (20 mmol) of 3-(dimethylamino)propyl chloride in anhydrous benzene (10 mL) was added over 1 h. Refluxing and stirring were continued overnight. Usual workup gave the amine as an oil (1.8 g, 40%), bp 144–147 °C (1.8 mm).

The free amine was converted to the hydrobromide salt with 30% HBr in HOAc, which was recrystallized from acetone, mp 137–139 °C. Anal. ($C_{16}H_{24}NOBr$) C, H, N.

Compound **12b** was prepared from **11b** in a similar manner, bp 156–157 °C (1.2 mm).

The free amine was converted to the hydrobromide and recrystallized from acetone, mp 123.5–124.5 °C. Anal. ($C_{17}H_{26}NO_2Br$) C, H, N.

5-Bromo-2-[3-(dimethylamino)propyl]-2-phenylcyclopentanone Hydrobromide (13a). To a refluxing solution of 26.1 g (80 mmol) of **12a** in HOAc (200 mL) was added 13 g (81 mmol) of bromine in HOAc (30 mL) over 0.5 h. After refluxing for another 0.5 h, the reaction mixture was cooled under N_2, ether (400 mL) was added, and the mixture was kept at −5 °C. Decantation of the liquid layer and removal of the residual HOAc on a vacuum pump overnight gave 28.8 g (89%) of **13a**, which was recrystallized (acetone) to give a white crystalline powder (24.3 g, 75%), mp 117–119 °C. Anal. ($C_{16}H_{23}NOBr_2 \cdot 0.5H_2O$) C, H, N.

Compound **13b** was prepared from **12b** in a similar manner at 60–70 °C, as a white crystalline powder in 85% yield, mp 102–103.5 °C (acetone). Anal. ($C_{17}H_{25}NOBr_2$) C, H, N.

2-Methyl-9-oxo-6-phenyl-2-azabicyclo[4.2.1]nonane Methobromide (14a). A mixture of 15.2 g (36.6 mmol) of **13a**, 75 mL of cold water, 75 mL of ether, and 4.5 mL of ammonium hydroxide was shaken vigorously in a separatory funnel until all the small lumps disappeared. The ethereal layer was separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined ethereal extracts were evaporated and then recrystallized (methanol) to give a white crystalline compound (10.1 g, 98%), mp 219–221 °C. Anal. ($C_{16}H_{22}NOBr \cdot H_2O$) C, H, N.

Compound **14b** was prepared in a similar manner from **13b** in 83% yield, mp 192–193.5 °C (ethanol). Anal. ($C_{17}H_{24}NO_2Br$) C, H, N.

2-Methyl-9-oxo-6-phenyl-2-azabicyclo[4.2.1]nonane (15a). A mixture of 10 g (29.2 mmol) of **14a** and 45 mL of 1-octanol was immersed in a bath preheated to 200 °C and stirred at reflux until solution was complete (ca. 15 min). After cooling under N_2, ether (100 mL) was added and the mixture was extracted with 5% HCl (3 × 30 mL). Ammonium hydroxide was added to the extracts to pH 12, and the aqueous solution was extracted with ether (4 × 40 mL), dried (K_2CO_3), and evaporated to give an oil, which was crystallized at room temperature (4.1 g, 61%). Recrystallization (hexanes) gave white crystals (2.37 g, 36%), mp 59–60 °C. Anal. ($C_{15}H_{19}NO$) C, H, N.

Compound **15b** was prepared in a similar manner from **14b** in 64% yield, bp 176–178 °C (1 mm).

The free amine was converted to the hydrobromide, mp 150–152 °C (acetone). Anal. ($C_{16}H_{21}NO_2 \cdot HBr$) C, H, N.

2-Methyl-6-phenyl-2-azabicyclo[4.2.1]nonane (16a) Oxalate. A mixture of **15a** (8.7 g, 37.9 mmol), 95% NH_2NH_2 (9.3 mL), KOH (9.3 g), and triethylene glycol (70 mL) was heated at 160–165

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°C for 4 h and at 185–190 °C for 5 h. The reaction mixture was poured onto ice and extracted with ether (3 × 30 mL). The ether extracts were washed with water, dried (K_2CO_3), evaporated, and distilled to give **16a** as an oil (6.06 g, 75%), bp 124–127 °C (0.7 mm).

The free amine **16a** was treated with ethereal oxalic acid to give **16a** oxalate, mp 127–129 °C. Anal. ($C_{17}H_{23}NO_4$) C, H, N.

Compound **16b** was prepared in a similar manner from **15b** in 70% yield, bp 144–146 °C (1.2 mm).

The free amine **16b** was treated with ethereal oxalic acid to give **16b** oxalate, mp 196.5–197.5 °C (acetone–methanol). Anal. ($C_{18}H_{25}NO_5$) C, H, N.

2-Cyano-6-phenyl-2-azabicyclo[4.2.1]nonane (16c). A solution of **16a** (8.23 g, 38 mmol) in ahydrous $CHCl_3$ (75 mL) was added dropwise to BrCN (4.43 g, 42 mmol) in anhydrous $CHCl_3$ (35 mL) over 2.5 h with stirring. The reaction mixture was stirred at reflux for 4 h and concentrated in vacuo. Ethanol (50 mL) was added, and the mixture stirred at reflux for 0.5 h and concentrated. Recrystallization (ether–hexane) gave light yellow crystal cyanoamine (**16c**; 4 g, 46%), mp 77–78 °C. Anal. ($C_{15}H_{18}N_2$) C, H, N.

6-Phenyl-2-azabicyclo[4.2.1]nonane (9a) Oxalate. A mixture of 2.5 g (11.4 mmol) of the cyanoamine **16c** and 165 mL of 2 N HCl was stirred at reflux for 24 h, cooled, and extracted with ether to remove neutral materials. The water layer was treated with 40% NaOH, and the liberated oily amine was extracted with ether, dried (K_2CO_3), evaporated, and distilled to give **9a** (1.98 g, 86%), bp 140–142 °C (1.5 mm), which was converted to the oxalate, mp 138–140 °C (methanol–ether). Anal. ($C_{16}H_{21}NO_4 \cdot H_2O$) C, H, N.

6-Phenyl-2-propyl-2-azabicyclo[4.2.1]nonane (17a) Oxalate. To a mixture of **9a** (0.70 g, 3.5 mmol) and anhydrous K_2CO_3 (1.24 g) in 10 mL of dry DMF (distilled from CaH_2) was added 0.46 g (93.7 mmol) of 1-bromopropane. The mixture was stirred at reflux for 4 h, cooled, and filtered. The solid was washed with $CHCl_3$, and the combined filtrates were concentrated in vacuo. The resulting oil was bulb to bulb distilled [185 °C (0.9 mm)], and the oily product was converted to the oxalate (0.71 g, 61%): white powder; mp 174–176 °C (acetone–ether). Anal. ($C_{19}H_{27}NO_4$) C, H, N.

2-Allyl-6-phenyl-2-azabicyclo[4.2.1]nonane (17b) Oxalate. To a mixture of **9a** (0.92 g, 4.6 mmol) and $NaHCO_3$ (1.45 g) in 30 mL of absolute ethanol was added 0.7 g (5.8 mmol) of 3-bromopropene. The mixture was stirred at reflux for 24 h, cooled, and filtered. The filtrate was treated with $CHCl_3$ and again filtered. The filtrate was concentrated, dissolved in absolute ether, and converted to the oxalate (1.23 g, 81%), mp 210–213 °C (MeOH–acetone).). Anal. ($C_{19}H_{25}NO_4 \cdot H_2O$) C, H, N.

2-(3-Methyl-2-butenyl)-6-phenyl-2-azabicyclo[4.2.1]nonane (17c) Oxalate. To a mixture of **9a** (0.77 g, 3.8 mmol) and $NaHCO_3$ (0.50 g) in 30 mL of dry DMF (distilled from CaH_2) was added 0.58 g (5.8 mmol) of 1-bromo-3-methyl-2-butene. The mixture was stirred at reflux for 4 h, and the solids were filtered off. After DMF and excess 1-bromo-3-methyl-2-butene were removed by distillation, the residue was dissolved in ether and converted to the oxalate (1 g, 69%), mp 157–159 °C (MeOH–acetone). Anal. ($C_{21}H_{29}NO_4 \cdot H_2O$) C, H, N.

6-(3-Methoxyphenyl)-2-(2,2,2-trichlorocarbethoxy)-2-azabicyclo[4.2.1]nonane (16d). Compound **16b** (1.25 g, 10 mmol) and anhydrous K_2CO_3 (1.6 g) were placed in dry benzene (30 mL) and heated at reflux for 0.5 h. To this solution was added 3.1 g (13.2 mmol) of trichloroethyl chloroformate, and the mixture was heated at relfux under N_2 for 24 h. The reaction mixture was poured into ice–water, the benzene layer was separated, and the aqueous layer was extracted with methylene chloride (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo to give **16d** as a colorless oil (1.88 g, 91%), essentially pure by TLC analysis [R_f 0.68 (silica gel; $CHCl_3/CH_3OH$, 14:1)].

6-(3-Methoxyphenyl)-2-azabicyclo[4.2.1]nonane (9b) Hydrobromide. Compound **16d** (1.88 g, 4.6 mmol) was dissolved in 25 mL of 95% HOAc, and Zn powder (3.5 g) was added in small portions at room temperature. After stirring for 36 h, the mixture was filtered, and the filtrate was diluted with water (100 mL) and extracted with ether (4 × 30 mL). The combined ether extracts were washed with 5% NaOH (3 × 30 mL) and water (2 × 20 mL), dried ($MgSO_4$), concentrated in vacuo, and bulb to bulb distilled (190 °C, 1.2 mm) to give 0.91 g (85%) of colorless oil **9b**, which was converted to the hydrobromide with 30% HBr in HOAc, mp 222–223 °C (ethanol). Anal. ($C_{15}H_{22}NOBr$) C, H, N.

6-(3-Methoxyphenyl)-2-propyl-2-azabicyclo[4.2.1]nonane (18a) Oxalate. To 0.80 g (3.5 mmol) of **9b** and 1.2 g of K_2CO_3 in 10 mL of dry DMF (distilled from CaH_2) was added 0.46 g (3.7 mmol) of *n*-propyl bromide. The mixture was refluxed for 4 h, cooled, and filtered. Solids were washed with $ChCl_3$, and the combined filtrates were concentrated in vacuo and bulb to bulb distilled (220 °C, 0.9 mm) to give 0.83 g (88%) of colorless **18a**. The free amine was converted to the oxalate, mp 186–187 °C (ethanol–ether). Anal. ($C_{20}H_{29}NO_5$) C, H, N.

2-Allyl-6-(3-methoxyphenyl)-2-azabicyclo[4.2.1]nonane (18b) Hydrobromide. To 0.77 g (3.3 mmol) of **9b** and 1.07 g of $NaHCO_3$ in 25 mL of absolute EtOH was added 0.52 g (4.3 mmol) of 3-bromopropene. The mixture was stirred at reflux for 24 h, cooled, and filtered. Solids were washed with EtOH, and the combined filtrates were concentrated and bulb to bulb distilled (200 °C, 0.8 mm) to give 0.72 g (79%) of **18b**. The free amine was converted to the hydrobromide, mp 160–161 °C (acetone–ether). Anal. ($C_{18}H_{27}NOBr$) C, H, N.

6-(3-Methoxyphenyl)-2-(2-phenylethyl)-2-azabicyclo-[4.2.1]nonane (18d) Hydrobromide. To a solution of 0.72 g (2.7 mmol) of **9b** and 1 g of K_2CO_3 in 15 mL of DMF was added 0.52 g (2.8 mmol) of 2-phenylethyl bromide. The mixture was refluxed overnight and filtered, and the filtrate was concentrated in vacuo and bulb to bulb distilled (220 °C, 0.8 mm) to give 0.95 g (85%) of **18d**. The free amine was converted to the hydrobromide, mp 227.5–228.8 °C (ethanol–ether). Anal. ($C_{23}H_{30}NOBr$) C, H, N.

6-(3-Methoxyphenyl)-2-(3-methyl-2-butenyl)-2-azabicyclo[4.2.1]nonane (18c) Oxalate. To 0.57 g (2.5 mmol) of **9b** and 0.3 of K_2CO_3 in 20 mL of dry DMF was added 0.48 g (2.6 mmol) of 1-bromo-3-methyl-2-butene. The mixture was refluxed for 4 h, cooled, and filtered. The solids were washed with EtOH, and the combined filtrates were concentrated in vacuo to give the free amine (0.59 g, 79%). The free amine was converted to the oxalate (5.36 g, 55%), mp 177–178.5 °C. Anal. ($C_{22}H_{31}NO_5$) C, H, N.

6-(3-Hydroxyphenyl)-2-(2-phenylethyl)-2-azabicyclo-[4.2.1]nonane Hydrobromide (19f). A solution of 0.33 g (0.8 mmol) of **18d**·HBr in 5 mL of 48% aqueous HBr was heated at 100 °C for 2 h and evaporated to dryness. The residue was dissolved in EtOH, treated with decolorizing carbon, and filtered, and the filtrate was concentrated in vacuo and recrystallized from ethanol–ether to give 0.29 g (90%) of **19f**, mp 227.5–228.5 °C. Anal. ($C_{22}H_{28}NOBr$) C, H, N.

Compounds **19a–e** were prepared in a similar manner. **19a**: mp 219–220 °C (ethanol). Anal. ($C_{14}H_{20}NOBr$) C, H, N. **19b**: mp 140–141 °C (acetone–methanol–ether). Anal. ($C_{15}H_{22}NOBr$) C, H, N. **19c**: mp 195–196.5 °C (ethanol–acetone). Anal. ($C_{17}H_{26}NOBr$) C, H, N. **19d**: mp 82–84 °C (ethanol–ether). Anal. ($C_{17}H_{24}NOBr \cdot H_2O$) C, H, N. **19e**: mp 142–145 °C (ethanol–ether). Anal. ($C_{19}H_{28}NOBr \cdot H_2O$) C, H, N.

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