absorption of the mixture was monitored at 265 nm on a Cary Model 14 recording spectrophotometer for 2 h.

After filtration through membrane cones (Amicon Centriflo F 25, Amicon Corp.) and concentration, the mixtures were analyzed for substrate and product by HPLC using the conditions described above. Control reactions were conducted with adenosine and ara-A.

(b) 5′-Adenylic Acid Deaminase (Rabbit Muscle). A spectrophotometric assay, similar to that described for adenosine deaminase, above, was used.

The enzyme (0.1 mL, 10.0 units/mL), in 0.05 M phosphate buffer (pH 7.5), was added at room temperature to a solution of **1c** and **1d** (0.130 μmol) in 0.05 M phosphate buffer (pH 7.5, 2.9 mL). The absorption of the mixture was monitored at 265 nm for 2 h. Control reactions were conducted with AMP and ara-AMP.

3. Cytochrome P-450 Dependent Mixed-Function Oxidases. BDF_1 mice were injected intraperitoneally with sodium phenobarbital (75 mg/kg) for 4 consecutive days. The animals were killed 24 h after the last injection, and the livers were excised. A 33% liver homogenate in 0.05 M Tris-HCl–0.15 M KCl–0.01 M $MgCl_2$ buffer (pH 7.4) was centrifuged at 10000*g* for 20 min at 4 °C. The supernatant fraction was aspirated and centrifuged at 105000*g* for 60 min at 4 °C. The microsomal pellet was washed by resuspension in the original volume of buffer containing 0.01 M EDTA and was then resedimented at 105000*g* for 30 min. The final pellet was reconstituted in the Tris–KCl–$MgCl_2$ buffer such that each mL of suspension contained microsomes from 0.33-g wet weight of liver. Each incubation mixture contained cyclic 5′-nucleotide (1 mM), NADH (0.4 mM), glucose 6-phosphate (5.0 mM), glucose 6-phosphate dehydrogenase (0.6 unit/mL), and 0.25 mL of microsomal suspension in a total volume of 1.25 mL. After 1 h at 37 °C, the incubates were transferred to Amicon Centriflo CF 25 membrane cones (Amicon Corp., Lexington, MA) and centrifuged at 2000 rpm (<1000*g*) in a swinging-bucket centrifuge for 75 min at 4 °C. The filtrates were analyzed by HPLC on a μ-Bondapak C-18 column using 0.05 M Tris buffer (pH 7.0)–methanol (85:15) as eluent or on a Partisil 10-SAX column (25 cm × 4.6 mm i.d., Whatman) using 0.01 M $(NH_4)_2HPO_4$ buffer (pH 6.6).

Antitumor Screening. Mice weighing 18–20 g were obtained from Jackson Laboratories, Madison, WI. Murine leukemia P-388 was maintained by weekly intraperitoneal passage in female DBA/2 mice. For antitumor screening, 10^6 cells were inoculated intraperitoneally into male BDF_1 mice. The test compounds, dissolved in sterile 0.9% saline, were administered intraperitoneally daily for 9 consecutive days beginning 24 h after tumor implantation. Control animals were injected on the same schedule with saline only. Animals were observed for 60 days or until the time of death. Antitumor activity was determined by comparing the median survival time of treated animals (*T*) with that of controls (*C*) and was expressed as the percentage increase in life span (% ILS), where % ILS = $(T/C - 1) \times 100$.

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Aminotetralone Analogues of Ketamine: Synthesis and Evaluation of Hypnotic and Locomotor Properties in Mice

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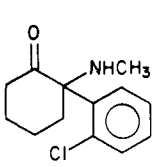
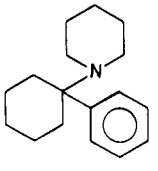
Ketamine and phencyclidine are structurally similar compounds that share many pharmacological actions, some of which are similar to the phenethylamines amphetamine and cathione. In order to integrate structural features of ketamine and cathinone, two groups of analogues, which are more conformationally restricted compared to the parent compounds, were synthesized for biological evaluation. These included 1-amino-1-methyl-2-tetralone and 2-amino-2-methyl-1-tetralone was well as several N-substituted derivatives of these molecules. Locomotor activity testing in mice revealed that 2-amino-2-methyl-1-tetralone caused an increase in locomotor activity while 1-amino-1-methyl-2-tetralone depressed spontaneous locomotor activity. None of the compounds produced hypnosis or profound ataxia.

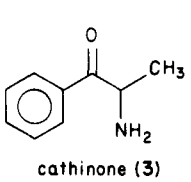
Ketamine, 2-(*o*-chlorophenyl)-2-(methylamino)cyclohexanone (**1**), a dissociative anesthetic agent, is a phencyclidine (**2**) derivative that produces a profound analgesia



ketamine (1)



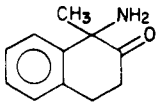
phencyclidine (2)



cathinone (3)

characterized by a trancelike, cataleptic state with mild hypertonus, cardiovascular stimulation, and a lack of respiratory depression at subhypnotic doses.[1,2] While reports have appeared regarding the influence of ring conformation upon the biological activity of phencyclidine, no similar data are available for ketamine.[3,4] The present study describes the syntheses and preliminary biological evaluations of a new group of ketamine analogues that are conformationally more rigid than the parent molecule.

These compounds can be visualized as having structures whose benzene rings are fused to a cyclohexanone ring, restricting conformational flexibility. The first group of prototypes that were prepared included derivatives of 1-amino-1-methyl-2-tetralone (**4**), and the second group



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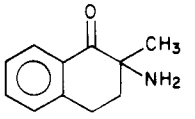

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consisted of analogues of the isomeric 2-amino-2-methyl-1-tetralone (**5**). Compound 4 was chosen because of its

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(1) Domino, E. F.; Corrsen, G. *Anesth. Analg. (N.Y.)* **1966**, *45*, 30.
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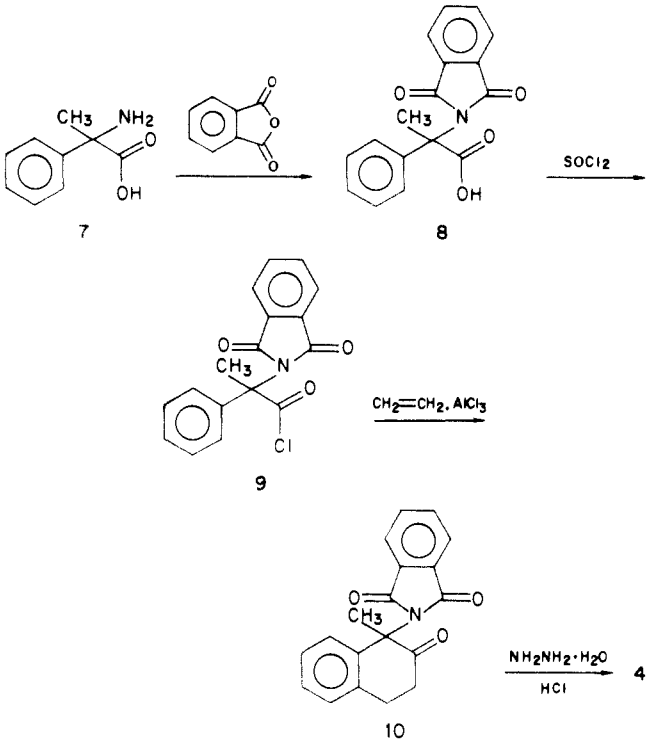
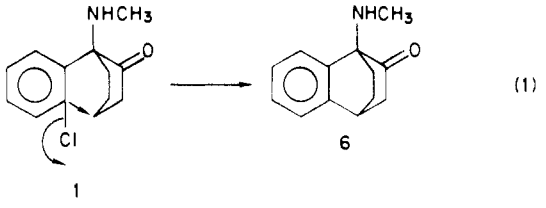
Scheme I



structural similarity to ketamine. For example, removing the chlorine atom and connecting the benzene ring through this position to the five position of the cyclohexanone ring result in the formation of a benzobicyclo[2.2.2]octanone (6) (eq 1). This, in turn, can be simplified to give 4 by

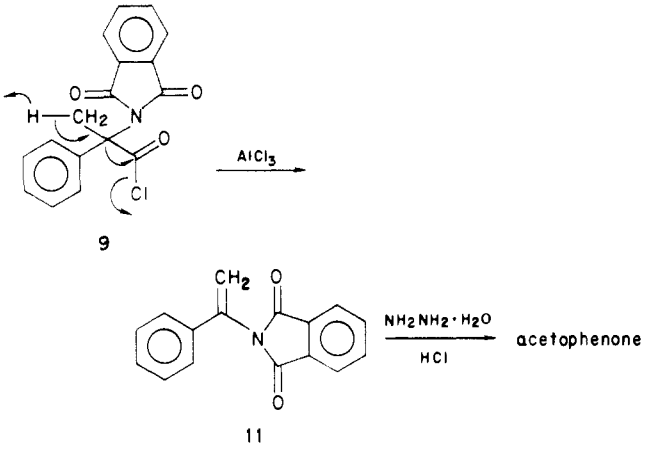


(1)

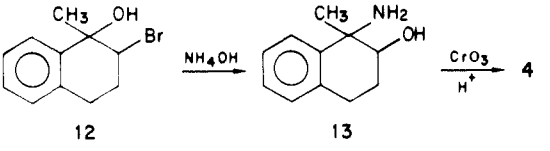
replacing the ethylene bridge with a methyl group. Compound 4, rather than 6, was chosen as a first approach for developing new compounds because of synthetic considerations and because the size, shape, and overall chemical properties of the two compounds should be similar. Compound 5 not only is an isomer of 4 but also bears a close resemblance to cathinone (3), a psychoactive agent with properties similar to amphetamine.[5-9] Some of ketamine's CNS actions also have been compared to amphetamine.[10-12] Therefore, it was decided to include 5 in the present study.

Chemistry. Compound 4 was prepared by two different methods: First, following a previously described synthesis for 2-tetralone,[13] treatment of 2-amino-2-phenylpropionic acid (7)[14] with phthalic anhydride gave the N-protected phthalimide analogue (8). The acid chloride (9), obtained by reacting 8 with either thionyl chloride or phosphorus pentachloride, was treated with ethylene in the presence of aluminum chloride to give the expected N-protected aminotetralone (10) (Scheme I). While the first two reactions gave satisfactory yields, the cyclization step netted only a 15% yield of 10. No improvement was achieved by changing reaction time, temperature, or the sequence of addition of reagents. The phthalimide was then hydrolyzed by using standard methods with hydrazine hydrate.

Scheme II



Scheme III



In all cases a very high yield, approximately 75% of α-phthalimidostyrene (11) was obtained as the major product. The lack of a ketone band in the infrared and the presence of only aromatic and vinylic protons in the NMR spectra supported the structural assignment. The mass spectrum indicated a molecular weight of 249, which was confirmed by the empirical formula obtained from elemental analysis data. As expected, hydrazinolysis of the product resulted in acetophenone, identified as its 2,4-dinitrophenylhydrazone. Thus, under the conditions employed for the synthesis of 10, the acid chloride (9) readily underwent dehydrohalogenation with the concomitant loss of carbon monoxide in preference to cyclization (Scheme II).

In an effort to improve the yield of 4, an alternative method was developed for its synthesis. Treatment of the bromohydrin (12)[15] with ammonium hydroxide solution gave the corresponding amino alcohol (13), which was then oxidized to 4 with Jones reagent[16] (Scheme III). This method gave superior yields compared to the one described above.

N-alkyl analogues of 1-amino-1-methyl-2-tetralone (4) were synthesized by using two different methods: First, treatment of the bromohydrin (12) with aqueous ammonia, methylamine, dimethylamine, or piperidine followed by

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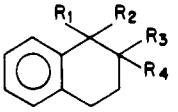
(16) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; p 142.

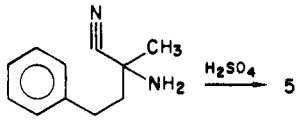
Table I. Locomotor Activity of Substituted Tetrahydronaphthalenes[a]



compd	R^1	R^2	R^3	R^4	counts/min[b,d]
2 (ketamine)					94.3 ± 10.2[e]
4	CH_3	NH_2		=O	27.2 ± 11.1
5		=O	CH_3	NH_2	60.6 ± 3.8[e]
13	CH_3	NH_2	H	OH	16.2 ± 4.2
14	CH_3	$NHCH_3$	H	OH	20.2 ± 2.9
15	CH_3	$NHCH_3$		=O	25.8 ± 3.3
16	CH_3	$N(CH_3)_2$	H	OH	37.5 ± 5.8
17	CH_3	$N(CH_3)_2$		=O	22.9 ± 4.5
18	CH_3	$N(CH_2)_5$	H	OH	21.6 ± 4.8
19	CH_3	$N(CH_2)_5$		=O	4.4 ± 0.8[e]
21		=O	CH_3	$N(CH_3)_2$	67.1 ± 14.8[e]
normal saline[c]					26.9 ± 5.8

[a] Following intraperitoneal injection (100 mg kg^{-1}), animals were placed on an activity monitor and the number of counts for each animal was recorded for a total of 90 min. Counts per minute were calculated by dividing the total number of counts by 90. [b] Mean ± SEM for six animals. [c] Control animals received 0.2 mL. [d] Duncan's multiple-range test was used to compare the treatment groups. [e] $p < 0.05$ compared to normal saline.

Scheme IV



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Jones oxidation of the resultant amino alcohols gave compounds **4**, **15**, **17**, and **19**, respectively (Table I). Second, compound **17** also was obtained by Eschweiler–Clarke methylation[17] of the primary amino alcohol (**13**) followed by oxidation to the ketone. Likewise, compound **13** was treated with 1,5-dibromopentane in the presence of sodium carbonate prior to oxidation to yield the piperidine analogue **19**. In general, treatment of the bromohydrin (**12**) with the appropriate amine followed by oxidation of the amino alcohol product resulted in higher yields of N-alkylated ketones than did direct alkylation of the primary amine (**13**) prior to oxidation.

The synthesis of compound **5** was accomplished by a two-step process (Scheme IV). Benzylacetone was treated with an equimolar mixture of sodium cyanide, ammonium chloride, and ammonium hydroxide to give the corresponding amino nitrile (**22**).[18] This product was then cyclized with sulfuric acid to give compound **5**. Eschweiler–Clarke methylation gave the dimethylated product, compound **21** (Table I).

Pharmacological Results and Discussion

The ability of ketamine to cause a loss of righting reflex has been employed to quantitate the hypnotic/anesthetic properties of the drug.[12] In the present study, none of the compounds, except ketamine, caused a regainable loss of righting reflex in doses ranging from 50–200 mg kg^{-1}. At these doses ketamine caused mean losses ranging from 5.6 ± 1.3 to 47.2 ± 5.1 min, consistent with previous studies.[20] Significant lethality was noted for most of the new compounds at the higher doses tested, and while LD_{50} values were not determined, it would appear they probably would be in the 150–200 mg kg^{-1} range. As a result it was concluded that these compounds do not have potential as hypnotic agents, and the data suggest the need for preserving the relative stereochemical relationship between the phenyl and cyclohexanone rings present in ketamine.

Likewise, increases in spontaneous locomotor activity (SLA) have been utilized to quantitate excitatory respones of laboratory animals to ketamine.[12] In relatively low doses ketamine causes an increase in SLA without inducing loss of righting reflex, and at dose levels that induce loss of righting reflex, animals display posthypnotic stimulation characterized by enhanced SLA. The effects of the ketamine analogues upon spontaneous locomotor activity in mice are shown in Table I. When the isomeric ketones 1-amino-1-methyl-2-tetralone (**4**) and 2-amino-2-methyl-1-tetralone (**5**) were compared, it was seen that the latter caused an increase whereas the former caused no change in SLA compared to control animals. Of the various N-substituted analogues, the piperidyl derivative (**19**) was the only one to cause a significant decrease in locomotor activity, but as noted previously no loss of righting reflex was observed in nonfatal doses. Compounds **5** and **21** appeared to make the animals irritable and induced mild tremors, but no attempts were made to quantitate these observations. The irritability was detected as an apparent increase sensitivity of the animals to environmental stimuli such as noise and rapid movements near the testing cages. Consequently, all SLA testing was conducted in an area as free from extraneous noise and movement as possible.

The SLA data presented in Table I are for doses of 100 mg kg^{-1}, but doses ranging from 50 to 200 mg kg^{-1} also were evaluated. At 50 mg kg^{-1}, qualitatively similar results were noted, with **2**, **5**, and **21** causing increases and **19** a decrease in SLA while the remaining compounds did not differ from saline. At 200 mg kg^{-1}, significant lethality was noted for all compounds (except ketamine); as a result, no attempts were made to quantitate SLA at this dose.

Although the ketones were the primary target compounds of this study, the SLA induced by the alcohol precursors also was measured and compared with the other agents. The lack of hypnotic properties was mentioned earlier, and as can be seen (Table I) nothing of significance was noted in SLA testing except for the piperidyl alcohol (**18**), which caused no change whereas its ketone oxidation product (**4**) lowered SLA compared to controls. Since **19** was the only ketone that suppressed SLA and since it has

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the greatest hydrocarbon content, it might be concluded that this action was related to a higher partition coefficient. However, the fact that the corresponding alcohol (18) lacked the ability to suppress SLA compared to the other alcohol precursors suggests that additional factors may be involved.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and reported as corrected values. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA 30366. Infrared spectral data were obtained on a Perkin-Elmer Model 257 or 710A grating infrared spectrophotometer. NMR spectral data were obtained on a Hitachi Perkin-Elmer Model R-24A high-resolution proton NMR spectrometer at a sweep width of 600 Hz with Me_4Si as the internal reference. GC/MS data were determined on a Du Pont Instruments Dimaspec 321 GC/MS interfaced with a Du Pont Instruments 320 GC/MS data system. Molecular ions and major fragment ions are listed.

2-Phenyl-2-phthalimidopropionic Acid (8). An intimate mixture of 2-amino-2-phenylpropionic acid (7)[13] (16.5 g, 0.10 mol) and finely ground phthalic anhydride (14.8 g, 0.10 mol) was heated for 30 min with stiring at 145–150 °C. After cooling, the solid material was filtered and recrystallized from methanol/water (4:1): yield 13.9 g (46.8%); mp 122–124 °C; IR (KBr) 3300 (OH), 1650 cm^{-1} (C=O) NMR (NaOD and D_2O) δ 1.90 (s, 3, CH_3), 7.20–7.39 (m, 9, aromatic); NMR ($CDCl_3$) δ 2.20 (s, 3, CH_3), 7.15–7.65 (m, 9, aromatic); MS m/z 295 (M^+), 249, 104, 76 (base).

2-Methyl-2-phthalimidophenylacetyl Chloride (9). A mixture of 2-phenyl-2-phthalimidopropionic acid (8) (11 g, 0.037 mol) and thionyl chloride (10 mL) in 140 mL of benzene was heated at 60 °C for 48 h. The solvent was removed in vacuo, leaving a brown oil: yield 7.8 g (66.7%); IR (neat) 1720–1785 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.35 (s, 3, CH_3), 7.30 (s, 5, aromatic), 7.70 (m, 4, aromatic). This material was used without further purification.

1-Methyl-1-phthalimido-2-tetralone (10). A solution of 2-methyl-2-phthalimidophenylacetyl chloride (9) (2.2 g, 7.0 mmol) in methylene chloride (100 mL) was added dropwise with stirring to a suspension of anhydrous aluminum chloride (0.9 g, 7.0 mmol) in methylene chloride (200 mL) at 5 °C. Ethylene gas was introduced below the surface of the solution for a period of 30 min. The mixture was stirred overnight at room temperature and poured into ice. The solution was extracted with methylene chlorided (3 × 50 mL), the combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo, leaving a tan solid. This was recrystallized from acetonitrile to give a granular white solid: yield 0.31 g (14.3%); mp 194–195 °C; IR (KBr) 1710–1770 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.10 (s, 3, 1-CH_3), 2.70–2.95 (m, 2, 3-CH_2), 3.10–3.50 (m, 2, 4-CH_2), 7.10–7.30 (m, 4, aromatic), 7.65–7.80 (m, 4, aromatic); MS m/z 305 (M^+), 158, 130, 115 (base), 76. Anal. ($C_{19}H_{15}NO_3$) C, H, N.

Isolation of α-Phthalimidostyrene (11). The acetonitrile mother liquor from the purification of 1-methyl-1-phrhalimido-2-tetralone (10) was evaporated to dryness. The residue was recrystallized from a mixture of hexanes to give a fine, white, needlelike solid: yield 1.3 g (74.7%); mp 97–98 °C; IR (KBr) 1710–1780 cm^{-1} (C=O); NMR ($CDCl_3$) δ 5.40 (s, 1, vinylic), 5.95 (s, 1, vinylic), 7.30 (s, 5, aromatic), 7.70–7.85 (m, 4, aromatic); MS m/z 249 (M^+), 104, 76 (base). Anal. ($C_{16}H_{11}NO_2$) C, H, N.

1-Amino-2-hydroxy-1-methyl-1,2,3,4-tetrahydronaphthalene (13). A mixture of 2-bromo-1-hydroxy-1-methyl-1,2,3,4-tetrahydronaphthalene (12)[15] (16 g, 0.067 mol) and ammonium hydroxide (400 mL) was heated to 50 °C for 14 h. After cooling, the mixture was extracted with ether (3 × 100 mL), which was then extracted with 1.0 M HCl (3 × 100 mL). The resulting acidic aqueous solution was basified with 2.5 M NaOH and extracted with chloroform (3 × 100 mL). The chloroform extracts were dried ($MgSO_4$) and the solvent removed in vacuo, leaving a thick oil: yield 6 g (50.2%); IR (neat) 3180–3480 cm^{-1} (OH and NH_2); NMR ($CDCl_3$) δ 1.29 (s, 3, 1-CH_3), 1.75–2.20 (m, 2, 3-CH_2), 2.45–2.60 (s, 3, OH and NH_2, exchangeable with D_2O), 2.75–3.10 (m, 2, 4-CH_2), 3.55–3.90 (m, 1, 2-CH), 7.10–7.65 (m, 4, aromatic); MS m/z 177 (M^+), 133 (base), 116.

The hydrochloride was obtained by standard methods and recrystallized from acetone, resulting in a fine, white, needlelike solid, mp 221–223 °C. Anal. ($C_{11}H_{16}ClNO$) C, H, N, Cl.

1-Amino-1-methyl-2-tetralone (4). Method A. A solution of Jones reagent[16] (40 mL) was added dropwise to a stirred solution of 1-amino-2-hydroxy-1-methyl-1,2,3,4-tetrahydronaphthalene (13) (6.3 g, 0.036 mol) in acetone (500 mL) over a period of 1 h. The mixture was filtered, and the solvent was removed in vacuo. The residue was made basic with 2 M NaOH and extracted with ether (3 × 100 mL). The ether extract was dried ($MgSO_4$) and the solvent removed in vacuo, leaving a brown oil: yield 2 g (32.1%); IR (neat) 3300–3360 (NH_2), 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.45 (s, 3, 1-CH_3), 1.90–2.45 (m, 2, 3-CH_2), 2.50–3.35 (m, 4, 4-CH_2 and NH_2, exchangeable with D_2O), 7.01–7.45 (m, 4, aromatic); MS m/z 175 (M^+), 132 (base), 115, 77. Hydrochloride: mp 161–161 °C (ethanol). Anal. ($C_{11}H_{14}ClNO$) C, H, N, Cl.

Method B. A solution of 1-methyl-1-phthalimido-2-tetralone (10) (50 mg, 0.164 mmol) in 95% ethanol (3 mL) was heated to reflux. Hydrazine hydrate (16.4 mg, 0.328 mmol) was added in one portion, and the reflux was continued for 30 min. Hydrochloric acid (6 N, 0.5 mL) was added and the refluxing continued for an additional 1 h. After cooling to room temperature, the solution was made basic with 2 M NaOH and extracted with ether (3 × 10 mL). The ether layer was dried ($MgSO_4$) and subjected to gas chromatographic analysis. The GC/MS data were the same as for the product obtained in method A. Because of the difficulty in obtaining sufficient starting material for this method it was not used for large-scale synthesis.

2-Hydroxy-1-methyl-1-(methylamino)-1,2,3,4-tetrahydronaphthalene (14). Compound 12 was treated with 40% aqueous methylamine as described for the synthesis of 13. A 71% yield of 14 was obtained: IR (neat) 3260–3420 cm^{-1} (OH and NH_2); NMR ($CDCl_3$) δ 1.21 (s, 3, 1-CH_3), 1.98–2.30 (m, 5, 3-CH_2 and 1-CH_3), 2.72–3.10 (m, 4, 4-CH_2, 2-OH, and 1-NH, the latter two protons were exchangeable with D_2O), 3.90–4.18 (m, 1, 2-CH), 7.10-7.30 (m, 4, aromatic); MS m/z 191 (M^+), 131 (base), 116. Hydrochloride: mp 225–226 °C (ethanol). Anal. ($C_{12}H_{18}ClNO$) C, H, N, Cl.

1-Methyl-1-(methylamino)-2-tetralone (15). By the procedure described for the synthesis of 4 (method A) a 55% yield of 15 was obtained from the oxidation of 14: IR (neat) 3340 ($NHCH_3$), 1715 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.35 (s, 3, 1-CH_3), 1.95 (s, 3, 1-NCH_3), 2.15 (s, 1, 1-NH, exchangeable with D_2O), 2.40–3.10 (m, 4, 3-CH_2 and 4-CH_2), 7.15–7.70 (m, 4, aromatic); MS m/z 189 (M^+), 158, 146 (base), 131. Hydrochloride: mp 179–180 °C (ethanol). Anal. ($C_{12}H_{16}ClNO$) C, H, N, Cl.

1-(Dimethylamino)-2-hydroxy-1-methyl-1,2,3,4-tetrahydronaphthalene (16). Compound 12 was treated with 40% aqueous dimethylamine as described for the synthesis of 13. An 81% yield of 16 was obtained: IR (neat) 3420 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.27 (s, 3, 1-CH_3), 2.10 (s, 6, 2-$N(CH_3)_2$), 2.21–3.10 (m, 5, 3-CH_2, 4-CH_2, and 2-OH, exchangeable with D_2O), 3.21–3.60 (m, 1, 2-CH), 6.89–7.30 (m, 4, aromatic); MS m/z 205 (M^+), 160 (base), 146, 137, 117, 91. Hydrochloride: mp 203–204 °C (ethanol). Anal. ($C_{13}H_{20}ClNO$) C, H, N, Cl.

Alternatively, Eschweiler–Clarke methylation[17] of 1-amino-2-hydroxy-1-methyl-1,2,3,4-tetrahydronaphthalene (13) resulted in a 66% yield of 16.

1-(Dimethylamino)-1-methyl-2-tetralone (17). By the procedure descried for the synthesis of 4 (method A) a 52% yield of 17 was obtained from the oxidation of 16: IR (neat) 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.40 (s, 3, 1-CH_3), 2.11 (s, 6, 1-$N(CH_3)_2$), 2.50–3.10 (m, 4, 3-CH_2 and 4-CH_2), 7.11–7.60 (m, 4, aromatic); MS m/z 203 (M^+), 160, 132 (base), 115, 91. Hydrochloride: mp 129–130 °C (ethanol). Anal. ($C_{13}H_{18}ClNO$) C, H, N, Cl.

2-Hydroxy-1-methyl-1-piperidyl-1,2,3,4-tetrahydronaphthalene (18). Method A. A piperidine solution (250 mL) of 2-bromo-1-hydroxy-1,2,3,4-tetrahydronaphthalene (12) (44.4 g, 0.18 mol) was heated to 60 °C for 10 h and then cooled. The product was isolated as described for the synthesis of 13. An 83% yield of 18 was obtained: IR (neat) 3430 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.30 (s, 3, 1-CH_3), 1.45 (m, 6, 1-piperidyl (3-, 4-, and 5-CH_2)), 1.80–2.15 (m, 2, 3-CH_2), 2.35–2.95 (m, 7, 4-CH_2 and 1-piperidyl (2-CH_2 and 6-CH_2), 2-OH, exchangeable with D_2O), 3.95–4.20 (m, 1, 2-CH), 7.01–7.60 (m, 4, aromatic); MS m/z 245 (M^+), 200, 160, 131, 117, 86 (base). Hydrochloride: 206–207 °C (ethanol). Anal.

($C_{16}H_{25}ClNO_2$) (monohydrate) C, H, N, Cl.

Method B. An acetone solution (150 mL) of 1-amino-2-hydroxy-1-methyl-1,2,3,4-tetrahydronaphthalene (**14**) (2.5 g, 0.014 mol) and 1,5-dibromopentane (3.22 g, 0.014 mol) was refluxed for 48 h. After cooling, sodium carbonate (1.5 g, 0.014 mol) was added and the mixture was refluxed for an additional 48 h. The mixture was cooled and filtered and the solvent removed in vacuo. Water (20 mL) was added, and the solution was acidified with 4 M HCl. After washing with ether (3 × 50 mL), the remaining aqueous phase was basified (4 M NaOH) and extracted with chloroform (3 × 100 mL). The combined chloroform layers were dried ($MgSO_4$), and the solvent was removed in vacuo, leaving an oil, yield 1.4 g (41.3%).

1-Methyl-1-piperidyl-2-tetralone (19). By the same procedure described for the synthesis of **4** (method A), a 37% yield of **19** was obtained from the oxidation of 2-hydroxy-1-methyl-1-piperidyl-1,2,3,4-tetrahydronaphthalene (**18**): IR (neat) 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.40 (m, 9, 1-CH_3 and piperidyl (3-, 4-, and 5-CH_2)), 2.15–3.15 (m, 8, 3-CH_2, 4-CH_2, and piperidyl (2- and 6-CH_2)), 7.11–7.60 (m, 4, aromatic); MS m/z 243 (M^+), 215, 200, 131 (base), 84. Hydrochloride: mp 246–268 °C. (ethanol). Anal. ($C_{16}H_{22}ClNO$) C, H, N, Cl.

2-Amino-2-methyl-1-tetralone (5). Concentrated sulfuric acid (25 mL) was added dropwise over a period of 1 h to 2-amino-2-cyano-4-phenylbutane[18] (22.0 g, 0.13 mol). The mixture was stirred at room temperature for 24 h and then cautiously poured into water (200 mL). The solution was neutralized with sodium hydroxide pellets and extracted with ether (3 × 100 mL). The ether was dried ($MgSO_4$) and removed in vacuo, leaving a yellow oil: yield 3.5 g (15.8%); IR (neat) 3290–3350 (NH_2), 1680 cm^{-1} (C=O); NMR ($CHCl_3$) δ 1.30 (s, 3, 2-CH_3), 1.85–2.35 (m, 4, 3-CH_2 and NH_2, exchangeable with D_2O), 3.05 (t, J = 2 2 Hz, 2, 4-CH_2), 7.15–7.50 (m, 3, aromatic), 7.90–8.10 (m, 1, aromatic 8-CH); MS m/z 175 (M^+), 148 (base). Hydrochloride: mp 256–257 °C (ethanol). Anal. ($C_{11}H_{14}ClNO$) C, H, N, Cl.

2-(Dimethylamino)-2-methyl-1-tetralone (21). Eschweiler–Clarke methylation[17] of **19** resulted in an 83% yield of **20**: IR (neat) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.20 (s, 3, 2-CH_3), 1.60–2.80 (m, 10, 3-CH_2, 4-CH_2, and 2-$N(CH_3)_2$), 7.20–8.05 (m, 4, aromatic); MS m/z 203 (M^+), 148 (base).

Evaluation of Spontaneous Locomotor Activity and Loss of Righting Reflex. Male, Swiss–Webster mice (25–35 g) were provided Purina rodent laboratory chow and water ad libitum. Temperature was maintained at 20–24 °C with a light period from 06.00 to 18.00 h. Animals were housed in wire mesh cages (16 × 18 × 24 cm) containing five mice each. Drug solutions were prepared in distilled water such that all doses were given in a volume of 20 mg/mL. All compounds were administered intraperitoneally in 50, 100, 150, and 200 mg kg^{-1} doses. Control animals received a comparable volume of normal saline. Spontaneous locomotor activity was measured with a Stoelting electronic activity monitor system (Stoelting Instruments, Chicago, IL). The average number of activity counts was measured for 5-min intervals up to a total time of 90 min following injection. All animal experiments were conducted between 13.00 and 17.00 h. Comparison of treatment groups by Duncan's multiple-range test was used to test the significance of the results.[19] Following injection, animals were observed for loss of righting reflex which was determined to occur when an animal could not right itself when placed on its back. Righting reflex was judged to be regained when an animal was able to turn over three times in a 10-s period.

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Registry No. **4**, 96866-37-4; **4**·HCl, 96866-38-5; **5**, 96866-39-6; **5**·HCl, 75834-65-0; **7**, 565-07-1; **8**, 24539-99-9; **9**, 24540-00-9; **10**, 96866-40-9; **11**, 3480-56-6; **12**, 91335-38-5; **13**, 96866-41-0; **13**·HCl, 96866-42-1; **14**, 96866-43-2; **14**·HCl, 96866-44-3; **15**, 96866-45-4; **15**·HCl, 96866-46-5; **16**, 96866-47-6; **16**·HCl, 96866-48-7; **17**, 96866-49-8; **17**·HCl, 96866-50-1; **18**, 96866-51-2; **18**·HCl, 96866-52-3; **19**, 96866-53-4; **19**·HCl, 96866-54-5; **21**, 96866-56-7; 2-amino-2-cyano-4-phenylbutane, 96866-55-6; phthalic anhydride, 85-44-9; 1,5-dibromopentane, 111-24-0.

Analogues of Platelet Activating Factor. 3.[1] Replacement of the Phosphate Moiety with a Sulfonylbismethylene Group

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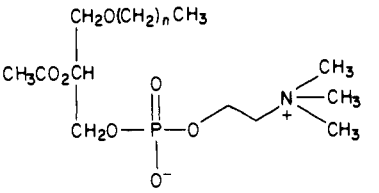
An analogue of platelet activating factor (PAF) in which the phosphate moiety has been replaced with a sulfonylbismethylene group (**8**) has been prepared. A key step in the synthetic sequence is the preparation of 4-[[3-(dimethylamino)propyl]thio]-1-(hexadecyloxy)-2-butanol (**5**) via a one-pot reaction involving a sequential Michael addition and reduction. In comparison to racemic C_{16}-PAF, **8** showed no platelet aggregating activity and substantially reduced hypotensive activity.

Platelet activating factor (PAF), a phospholipid of structure **1** composed primarily of the C_{16} and C_{18} homologues,[2] has a variety of interesting biological properties, among which is its potent ability to aggregate platelets and to lower blood pressure.[3] In a continuation of our study[1]



1, n = 15 or 17

of the structure–activity profile of analogues of this important substance, we have prepared a number of compounds in which the phosphocholine portion of the mol-

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