p-fluorobenzonitrile in 50 ml of THF, and then refluxed for 12 hr. The cooled mixt was decompd with aq NH_4Cl and extd with Et_2O. The Et_2O soln was extd with cold 1 *N* HCl. The aq exts were washed with Et_2O, made strongly alk with solid K_2CO_3, and extd with Et_2O. The exts were washed with H_2O, dried (K_2CO_3), and added to a soln of maleic acid in Et_2O. The ppt which formed was filtered, washed with Et_2O, and recrystd from $CHCl_3$–Et_2O to provide 1.45 g (17%) of **24** as white needles, mp 143–144°.

Synthesis and Analgetic Activity of 1,5-Methano-3-methyl-1,2,3,4,5,6-hexahydro-3-benzazocines

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The 1,5-methano-3-methyl-1,2,3,4,5,6-hexahydro-3-benzazocines described in Table I were prepared as possible analgetics and because compound **3** was desired for comparison with an amine of unknown structure obtained from another project. To our knowledge the 1,3-dimethyl,[1] the 1,3-dimethyl-11-oxo,[1] and the 2,6-dioxo[2] derivatives are the only published examples of this ring system. No pharmacological studies on these compds have been reported.

In the present synthetic scheme, hydrogenation of the methyl tosylate quaternary of methyl 5-phenyl-nicotinate[3] and subsequent recovery of the bases gave a mixture of the *cis*- and *trans*-nipecotic esters which were separated as their acid maleate and acid fumarate salts, resp. Their probable configurations were assigned by equilibrating each ester with NaOMe. This procedure gave a 7:3 mixture of esters and the cis diequatorial form was considered to be the favored configuration.[4] Each of the isomeric nipecotic acids was cyclized by polyphosphoric acid to the 6-oxo compd **1** (Table I) in excellent yield. The latter was converted to the compds described by procedures given in the Experimental Section.

The reduction of **1** either catalytically or with LAH gave the cis alcohol **4** which was readily isomerized to the trans alcohol **5** by MsOH. The configurations of these compds were assigned from the coupling constants of the benzylic proton at position 6. The configurations of alcohols **9** and **11** are unknown, but, since all attempts to acetylate **9** failed, its Ph group is probably trans to the bridge; the form in which the OH group is most hindered.

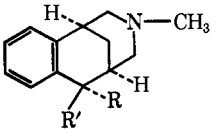
Pharmacology.—Behavioral, neurologic, and autonomic actions were assessed in preliminary dose-ranging studies in mice using the method of Irwin.[5]

Groups of 3 mice were treated orally with the compd dissolved or suspended in 0.4 ml of a 0.5% carboxymethylcellulose vehicle/20-g mouse, and a dose of 100 mg/kg was used for primary screening.

Analgetic activity was determined by the ability of the compds to alter the nociceptive response to pinching the tail with a forcep[6] in the initial dose-ranging studies,

TABLE I

1,5-METHANO-3-METHYL-1,2,3,4,5,6-HEXAHYDRO-3-BENZAZOCINES



No.	R	R1	Salt[a]	Mp, °C	Crystn,[b] solvent	Yield, %	Formula[c]
1		O[d]		61–63	H	87	$C_{13}H_{15}NO$
2		O[d]	HCl	253–256	E–EA		$C_{13}H_{16}ClNO$
3	H	H[e]	HCl	243–245	E–EA	59	$C_{13}H_{18}ClN$
4	H	OH[f,g,h]		78–80	I	80	$C_{13}H_{17}NO$
5	OH	H[i]		88–89	H	75	$C_{13}H_{17}NO$
6	H	C_2H_5COO[h]		85–87	I	60	$C_{16}H_{21}NO_2$
7	H	C_2H_5COO	HCl	211–212	A		$C_{16}H_{22}ClNO_2$
8	C_2H_5COO	H[i,j]	HCl	199–201	E–EA	35	$C_{16}H_{22}ClNO_2$
9	C_6H_5	OH[k,l]	M	180–181	E	75	$C_{23}H_{25}NO_5$
10	C_6H_5	H[i]	HCl	278–280	A–E		$C_{19}H_{22}ClN$
11	$C_6H_5CH_2$	OH[k,m]	HCl	246–248	E	38	$C_{20}H_{24}ClNO$
12	$C_6H_5CH_2$	OAc[k]		134–135	E–I		$C_{22}H_{25}NO_2$

[a] M = acid maleate. [b] A, CH_3CN; E, EtOH; EA, EtOAc; H, hexane; I, *i*-Pr_2O. [c] Analytical results were within ±0.4% for C, H, and N for all compounds listed. [d] R + R1 = 0. [e] Base prepd from **1** by Wolf-Kishner reduction in diethylene glycol 5 hr at 175°. [f] Prepd by LAH reduction of **1** in Et_2O. [g] Prepd by reduction of **1** with Pt in AcOH contg NH_4OAc, yield 60%. [h] Nmr $J_{H_6H_5}$ = 6.5 Hz. [i] Nmr $J_{H_6H_5}$ = 0 Hz. [j] Prepd from **5** as described for **6**. [k] Configuration unknown. [l] Prepd from **1** and PhLi in Et_2O. The free base formed cryst solvates with Et_2O, EtOAc, and with MeCN all melting at 90–120°. [m] Prepd from **1** and PhMgCl in Et_2O.

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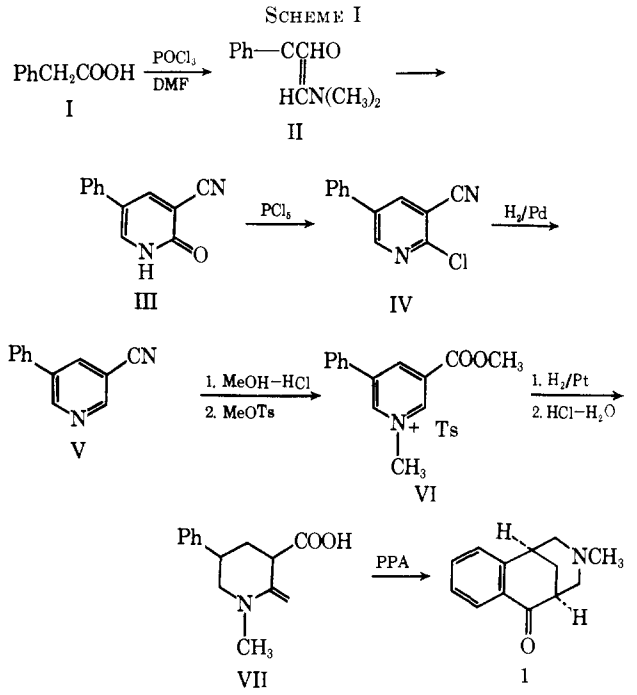
(6) C. Bianchi and J. Francheschini, *Brit. J. Pharmacol.*, **9**, 280 (1954).

and also by their ability to block the stretching response provoked by the administration of 10 ml/kg of 0.6% AcOH, a modification[7] of the method of Hendershot and Forsaith.[8] In this test a dose equivalent to one-third the neurotoxic dose, or a maximum of 100 mg/kg, served for the initial screening in groups of 5 mice.

None of the compds tested (the isomeric nipecotic esters and the compds in Table I) altered the tail-pinch response or had behavioral effects of interest. Compds **3**, **9**, and **12** produced clonic convulsions at 100 mg/kg but only **3** caused deaths. In the AcOH test only **10** reduced the incidence of stretching by more than 50% at 30 mg/kg. Its ED_{50}, 5.0 mg/kg was unaltered by the simultaneous treatment with the narcotic antagonist naloxone and indicated potential nonnarcotic analgetic activity. The ED_{50} for codeine in this test is 5 mg/kg.

SCHEME I



Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncor. Ir spectra and nmr spectra taken on a Varian A-60 (TMS in $CDCl_3$) were consistent for the proposed structures and data are given only when used for the assignment of configuration. All compds were analyzed for C, H, and N and gave results within ±0.4% of the theoretical value.

3-Carbomethoxy-1-methyl-5-phenylpyridinium *p*-Toluenesulfonate.—Methyl 5-phenylnicotinate (21.3 g, 0.1 mole) and 19.6 (0.105 mole) of methyl *p*-toluenesulfonate were heated with stirring on a steam bath for 1 hr. The reaction, once initiated, was vigorous and larger runs were not made. The product from 3 runs in 300 ml of hot EtOH was dild to 1 l. with EtOAc and gave 75.1 g of crystals, mp 140–142°. The residue from the concn of the mother liquor *in vacuo* when dissolved in 125 ml of EtOH and dild with 500 ml of EtOAc gave 29.1 g of crystals, mp 162–165°. A sample recrystd from the same solvents melted at 167–168.5. The lower-melting first crop also melted at 167–169° when recrystd. *Anal.* ($C_{21}H_{21}NO_5S$).

Methyl 1-Methyl-5-phenylnipecotate.—The above quaternary salt, 20 g in 250 ml of EtOH, was hydrogenated with 0.4 g of PtO_2 and hydrogen at 4.2 kg/cm.^{2} The reaction was stopped when the calcd amount of H_2 was absorbed and the catalyst and solvent were removed. The base, recovered with excess Na_2CO_3 and Et_2O, was distd, bp 125–128° (1 mm). Integration of the NCH_3 protons of its nmr spectrum indicated it was a 55:45 mixt of the cis and trans forms; NCH_3 protons; cis s, δ 2.35; trans s, δ 2.28. OCH_3; cis s δ 3.66; trans s, δ 3.72. *Anal.* ($C_{14}H_{19}NO_2$).

***trans*-Methyl 1-Methyl-5-phenylnipecotate Fumarate.**—The cis–trans mixt of esters (26 g) and 13.5 g of fumaric acid were dissolved in 10 ml of EtOH and dild while hot with 100 ml of hot EtOAc. Cooling gave crystals which were filtered, washed with EtOAc, and recrystd from MeCN. The yield was 11.1 g, mp 152–154°. *Anal.* ($C_{18}H_{23}NO_6$).

***cis*-Methyl 1-Methyl-5-phenylnipecotate Maleate.**—The 16.9 g of base recovered from the EtOAc liquors above and 8.5 g of maleic acid were dissolved in 125 ml of EtOAc and kept overnight. The crystals were filtered, washed, and recrystd from EtOAc, yield 12.2 g, mp 108–110°. *Anal.* ($C_{18}H_{23}NO_6$).

***trans*-1-Methyl-5-phenylnipecotic Acid·HCl.**—The ester recovered from the *trans*-fumarate above was refluxed with excess 4 *N* HCl for 3 hr and concd to dryness *in vacuo*. The salt was crystd from EtOH by dilg the hot soln with EtOAc. It melted at 216–218°. *Anal.* ($C_{13}H_{18}ClNO_2$).

***cis*-1-Methyl-5-phenylnipecotic Acid·HCl.**—The cis ester was hydrolyzed as above, mp 222–224°. *Anal.* ($C_{13}H_{18}ClNO_2$).

1,5-Methano-3-methyl-6-oxo-1,2,3,4,5,6-hexahydro-3-benzazocine (1).—*trans*-Nipecotic acid·HCl (10 g) in 410 g of polyphosphoric acid was stirred and heated at 145–155° for 4 hr. The cooled mixt was poured onto ice and H_2O, basified with KOH, and extd with Et_2O. The solvent was distd, and the residue was crystd from hexane; yield 6.85 g (87%). The yield from the corresponding cis compound was 90%.

***trans*-6-Hydroxy-1,5-methano-3-methyl-1,2,3,4,5,6-hexahydro-3-benzazocine (5).**—The corresponding cis compd **4** (5 g) was stirred with 75 ml of MsOH in an ice bath until it dissolved then for 1.5 hr at room temp. The soln was poured onto ice, basified with NaOH, and extd with Et_2O. The dried (K_2CO_3) ext was filtered and evapd, and the residue was triturated with petr ether and filtered.

***cis*-1,5-Methano-3-methyl-6-propionoxy-1,2,3,4,5,6-hexahydro-3-benzazocine (6).**—A soln of 2.5 g of **4** in 30 ml of $(EtCO)_2O$ and 2 drops of pyridine was refluxed for 3 hr. The excess reactants were removed *in vacuo*, and the residue was dissolved in Et_2O and stirred with dil $NaHCO_3$ until free of anhydride. The dried (K_2CO_3) soln was filtered and evapd.

6-Hydroxy-1,5-methano-3-methyl-6-phenyl-1,2,3,4,5,6-hexahydro-3-benzazocine Maleate (9).—PhLi prepd from 15.8 g (0.1 mole) of PhBr and 1.5 g of Li shot in 200 ml of Et_2O was filtered under N_2 and 10.0 g (0.05 mole) of **1** in 125 ml of Et_2O was added. The mixt was refluxed with stirring for 4 hr, cooled, and decompd with 150 ml of 10% NH_4Cl. Addnl Et_2O was added to dissolve pptd product, and the Et_2O was sepd and evapd. The product 14.5 g was an etherate, mp 90–120°, and no solvent suitable for its crystn was found. It was purified as the acid maleate.

1,5-Methano-3-methyl-6-phenyl-1,2,3,4,5,6-hexahydro-3-benzazocine·HCl (10).—Compd **9** (4 g), 2 g of red P, and 4 ml of 47% HI in 50 ml of AcOH were refluxed in an oil bath for 2 hr. The hot mixt was filtered, poured into H_2O, basified, and extd with Et_2O. The dried soln (K_2CO_3) was filtered and treated with dry HCl.

6-Acetoxy-6-benzyl-1,5-methano-3-methyl-1,2,3,4,5,6-hexahydro-3-benzazocine (12).—The Grignard reagent from 2.05 g of Mg and 3.9 ml of $PhCH_2Cl$ in 80 ml of Et_2O was decanted from excess Mg and 4 g of **1** in 50 ml of Et_2O was added. After stirring at room temp for 6 hr, 20 ml of Ac_2O was added dropwise under reflux and heating was contd for 1 hr. The mixt was stirred at room temp overnight and poured onto 10% NaOH at 0°. More Et_2O was added, and the combined Et_2O and emulsion layers were sepd from H_2O and extd with excess 1 *N* HCl. Recovery of the product with cold dil alkali and C_6H_6 again gave an emulsion which was broken by the dropwise addn of AcOH to pH 8. The dried (K_2CO_3) soln, filtered, and evapd, left 4.5 of yellow oil which was a mixt of the alcohol and ester. It was chromatographed on 125 g of silica gel in $CHCl_3$ and eluted with $CHCl_3$ to yield 1.3 g of product.

Equilibration of *cis*- and *trans*-Methyl 1-Methyl-5-phenylnipecotates.—The ester (2.1 g, 0.01 mole) was refluxed under N_2

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with 0.5 g of NaOMe in 50 ml of MeOH for 24 hr. The solvent was removed *in vacuo*, and the esters were recovered with Et_2O and cold H_2O.

Acknowledgment.—We wish to thank Mr. James Morton for aid in interpreting the nmr spectra.

Synthesis and Pharmacological Effects of Some Alkyl-, Aryl-, and Aralkylsydnonimines

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Sydnonimines chemically resemble the sydnones (mesoionic heterocycles). There are reports on antitumor,[1] antiinflammatory,[2] and spasmolytic[3] activity of some sydnonimines and on the stimulation of the CNS[4] and the inhibition[5] of MAO activity by some sydnones. We describe the synthesis of some new 3- and 4-substituted alkyl, aryl, and aralkyl derivatives of sydnonimines, prompted by our previous observations[6,7] on the marked ability of 3-substituted sydnonimines to inhibit reversibly MAO, to stimulate the CNS, and to cause peripheral sympathomimetic effects.

Enzyme Results.—Increase in the length of the side chain of 3-alkylsydnonimines (I, IV, V, VI; Table I) increased the degree of inhibition of deamination of tyramine and 5-HT *in vitro*. Compds that show a higher affinity toward the active sites of MAO than the 3-alkylsydnonimines were obtained by substitution of alkyls in position 3 of sydnonimines for cyclohexyl, aryl, and aralkyl radicals. Inhibitory effects of 3-phenethyl- and 3-(β-phenylisopropyl)sydnonimines on the deamination of tyramine and 5-HT were comparable with the effect of iproniazid which inhibits deamination of tyramine and 5-HT to the same degree[8] ($I_{50} = 3 \times 10^{-5}$ *M*, preincubation with rat liver mitochondria for 60 min). Decrease in the effect on MAO of 3-aralkylsydnonimines was observed when "heavier" substituents were introduced in position 3 (XVI, XVII) or when Me or Ph groups were introduced in position 4 of sydnonimines (X, XIV, XV; Table I).

In vivo, XIII (60 mg/kg—a dose which was not lethal for rats) inhibited by 27–38% deamination of tyramine, 5-HT, and dopamine in rat liver homogenate (in brain homogenate only deamination of tyramine was inhibited by 25–35%) within 1.5–2 hr after a single iv injection. At pharmacologically effective lower doses (20–40 mg/kg) XIII did not inhibit MAO significantly.

Within 2 hr after an iv injection of XIII (60 mg/kg) into rats its concn in 50% liver homogenates, as shown by polarographic analysis, was about 2×10^{-4} *M*. In samples used for estimation of the effect on deamination of tyramine by liver homogenates the final concn of the compd was about 1×10^{-5} *M*. The activity of MAO in these samples was decreased by about 30%. A quantitatively similar inhibitory effect was caused by addn of XIII to a final concn of about 1×10^{-5} *M* to control samples. These data suggest that under our experimental conditions the inhibition of MAO activity was caused by the molecule of 3-(β-phenylisopropyl)sydnonimine but not by products of its metabolism.

Pharmacology.—Compds inhibiting MAO potentiate[9-11] central effects of tryptamine, 5-hydroxytryptophan (5-HTP), and phenethylamine (PEA). Similar effects were caused also by some derivatives of sydnonimine, especially by 3-cyclohexyl-, 3-phenethyl- and 3-(β-phenylisopropyl)sydnonimine. These compds increased the convulsive effect of 5-HTP and revealed the amphetamine-like effect of PEA. Potentiation of the effects of tyramine was manifested mainly in characteristic carriage of rats ("the kangaroo posture") and intensification of dyspnoea. Tremor of head and forepaws was observed only in some cases.

3-Cyclohexyl- or 3-phenylalkylsydnonimines markedly influenced the behavior of animals. After administration of VII, IX, XII, and XIII into mice a weak transitory excitation and then inhibition of motor activity accompanied by auditory and sensory hyperreflexia took place. In rats not only an increase in reflex excitability but also signs of aggressiveness and phenomena of stereotypy resembling those of the amphetamine-induced stereotypy[12] were noted. The most distinct changes in behavior were caused by 3-(β-phenylisopropyl)sydnonimine.

Most of the sydnonimines studied possessed peripheral sympathomimetic activity. Most distinct and reproducible increases in blood pressure (15–30 mm) were caused by 3-benzyl- and 3-phenethylsydnonimines, while exophthalmia and piloerection in rats were caused by 3-(β-phenylisopropyl)sydnonimine. 3-Aralkylsydnonimines, also increased the pressor effect of norepinephrine. Most of the sydnonimines, after a single administration into mice, exhibited a relatively low toxicity.

Further pharmacological studies of 3-(β-phenylisopropyl)sydnonimine confirmed its marked CNS-stimulatory effect. In cats this compd (5–10 mg/kg, sc) caused alertness, fearfulness, sharp increase in reflex excitability, reaction of activation on EEG, and improvement in cortical response to functional tests; in mice it (20–25 mg/kg, sc) prevented sedative and hypothermic effects of reserpine (2 mg/kg, ip); in rats it (2–5 mg/kg, ip) decreased the latent period of condi-

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