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.

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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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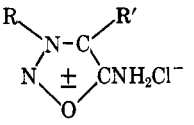
TABLE I

PHARMACOLOGICAL ACTIVITY OF ALKYL-, ARYL-, AND ARALKYLSYDNONIMINES

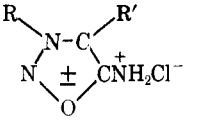


Compd	R	R′	I_{50}, M or inhibition of deamination by 1 mM inhibitor, %: Tyramine	5-HT	Stimulation[c] of central effect of 5-HTP, tryptophan, PEA	Central stimulating action[c]	Peripheral sympathomimetic action[c]	LD_{50} for mice, mg/kg, iv
I	CH_3	H	25	0	0	0	1	>100
II	CH_3	n-C_9H_{19}	88	72	0	0	0	>100
III	$(CH_3)_2CH$	H	18	0				
IV	*sec*-C_4H_9	H	27	13	0	0	1	>100
V	n-C_4H_9	H	9.0×10^{-4}	9.0×10^{-3}[a]				
VI	2-n-C_8H_{17}	H	1.8×10^{-4}	5.9×10^{-4}[b]	1	0	0	42
VII	C_6H_{11}	H	1.0×10^{-5}	3.3×10^{-4}[b]	3	1	2	70
VIII	C_6H_5	H	1.6×10^{-4}	8.0×10^{-5}[a]	1	0	2	75
IX	$C_6H_5CH_2$	H	1.4×10^{-3}	5.4×10^{-3}[b]	2	1	2	100
X	$C_6H_5CH_2$	CH_3	44	24				
XI	$C_6H_5CHCH_3$	H	75	50[b]	0	0	2	>100
XII	$C_6H_5CH_2CH_2$	H	3.3×10^{-5}	1.8×10^{-5}	3	2	3	92
XIII[d]	$C_6H_5CH_2CHCH_3$	H	3.1×10^{-5}	6.6×10^{-5}[a]	3	3	3	51
XIV	$C_6H_5CH_2CHCH_3$	CH_3	0	7	2	0	2	39
XV	$C_6H_5CH_2CHCH_3$	C_6H_5	34.5	27	0	0	2	10
XVI	$(C_6H_5)_2CHCH_2$	H	63	8[b]	0	0	0	>100
XVII	$(C_6H_5CH_2)_2CH$	H	63	30[b]	0	0	0	65
XVIII	$C_6H_5CHOHCHCH_3$	H	2.4×10^{-4}	2.2×10^{-4}	1	0	2	>100

[a] P (statistical probability) <0.01 (for the difference between the degree of inhibition of enzymatic deamination of tyramine and 5-HT). [b] P <0.001. [c] Degree of activity: 3, high; 2, medium; 1, low; 0, no activity. [d] Sydnophen.

TABLE II

MELTING POINTS AND YIELDS FOR THE SYDNONIMINES OBTAINED



Compd	R	R′	Mp, °C (recrystn soln)	Yield, %	Formula	Analyses
II	CH_3	n-C_9H_{19}	121–122 (Me_2CO)	62[b]	$C_{12}H_{23}N_3O \cdot HCl$	C, H
IV	*sec*-C_4H_9	H	116–117 (i-PrOH–Me_2CO, 3:2)	48[a]	$C_6H_{17}N_3O \cdot HCl$	C, H, Cl
VI	2-n-C_8H_{17}	H	81–83 (Et_2O–acetone)	36[b]	$C_{10}H_{19}N_3O \cdot HCl$	C, H, Cl
XIII[d]	$C_6H_5CH_2CH(CH_3)$	H	153–154 (i-PrOH–Me_2CO, 4:1)	51.5[a]	$C_{11}H_{13}N_3O \cdot HCl$	C, H, Cl
XV	$C_6H_5CH_2CH(CH_3)$	C_6H_5	130–132 (EtOH–Me_2CO, 1:10)	60[b]	$C_{17}H_{17}N_3O \cdot HCl$	Cl, N
XVI	$(C_6H_5)_2CHCH_2$	H	188–189 (EtOH–Et_2O)	77[c]	$C_{16}H_{15}N_3O \cdot HCl$	C, H, Cl
XVII	$(C_6H_5CH_2)_2CH$	H	167–168 (EtOH–Et_2O)	30[a]	$C_{17}H_{17}N_3O \cdot HCl$	N, Cl
XVIII	$C_6H_5CHOHCHCH_3$	H	168 (BuOH)	25[a]	$C_{11}H_{13}N_3O_2 \cdot HCl$	C, H, Cl

[a] Yield calcd for amine RNH_2. [b] Yield calcd for nitrile (A). [c] Yield calcd for nitroso deriv (B). [d] Sydnophen.

tioned avoidance.[13] 3-(β-Phenylisopropyl)sydnonimine was used as a drug[14] in some psychiatric and neurological clinics and exhibited properties of a mild stimulator with an antidepressive action.[15]

Chemistry.—Hydrochlorides of sydnonimines (Table II) were synthesised as shown in Scheme I. Some sydnonimines previously synthesized by us are: I,[16] III,[17] V,[16] VII,[17] IX,[18] and XIV.[19] Several compds were synthesized as described in the literature: VIII,[20] X, XI, and XII.[2]

Experimental Section†

Sydnonimine Hydrochlorides (IV, VI, XIII, XVII, XVIII).—To a soln of 0.05 mole of amine·HCl in 10 ml of H_2O[21] a soln of 0.06 mole of KCN in 10 ml of H_2O and then (at 10–15°, dropwise) 4.5 g of 33% HCHO were added; after stirring at this temp for 2 hr the mixt was acidified by 10% HCl (to pH 2) and a soln of 4 g of $NaNO_2$ in 8 ml of H_2O was added at 4–6°. After stirring at this temp for 2 hr the nitroso derivative was extd with Et_2O

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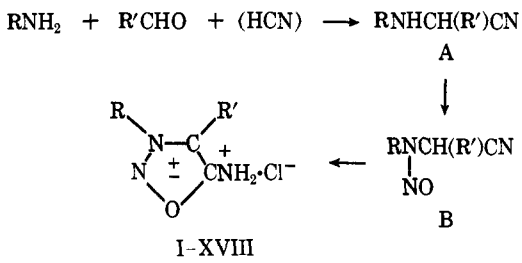
† Where analyses are indicated only by symbols of the elements, anal. results obtained for those elements were within ±0.4% of the theor values.

(21) Cyanomethylation of XVII was carried out in 50% aq EtOH.

SCHEME I



I-XVIII

(3 × 30 ml). The dried ext was treated with stirring with 14 ml of 4 *N* dry HCl soln in Et_2O at −5°. The mixt was kept for 10 hr; the sydnonimine hydrochlorides were then sepd by filtration and crystd from a suitable solvent (Table II).

***N*-Methyl-α-aminoundecanonitrile·HCl (A; R = Me; R′ = *n*-C_9H_{19}).**—To a soln of 0.05 mole of $MeNH_2$·HCl in 10 ml of H_2O 8 ml of decyclic aldehyde and (dropwise, at 10–15°) a soln of 0.055 mole of KCN in 5 ml of H_2O were added; the mixt was kept for 20 hr and acidified by concd HCl (to pH 2), and the ppt formed was sepd by filtration: yield, 2.7 g; mp 121–122° (Me_2CO). *Anal.* ($C_{12}H_{24}N_2$·HCl) C, H, Cl.

3-Methyl-4-*n*-nonylsydnonimine·HCl (II).—To a cooled (2–4°) soln of 0.01 mole of nitrile·HCl (A; R = Me; R′ = *n*-C_9H_{19}) in 10 ml of H_2O a soln of 0.7 g of $NaNO_2$ in 3 ml of H_2O was added. The mixt was kept for 2 hr and then extd with Et_2O. To the dried ext was slowly added a cooled satd soln of dry HCl in abs Et_2O. A ppt of II was sepd by filtration (Table II).

***N*-(β-Phenylisopropyl)-α-aminophenylacetonitrile (A; R = $PhCH_2MeCH$; R′ = Ph).**—To a soln of 34.3 g of β-phenylisopropylamine·HCl in 100 ml of H_2O were added a soln of 13.7 g of KCN in 50 ml of H_2O and (at 10–15°) 22 g of PhCHO. The mixt was kept for 2 hr. A ppt of nitrile (45.4 g, 91%) was sepd by filtration, mp 73–75° ($MeOH-H_2O$, 4:1). *Anal.* ($C_{17}H_{18}N_2$) C, H, N.

3-(β-Phenylisopropyl)-4-phenylsydnonimine·HCl (XV).—The nitrile (43 g) described above was dissolved in 220 ml of HCl (1:10) and added (at 4–6°, dropwise) to 13 g of $NaNO_2$ dissolved in 20 ml of H_2O. After 2 hr the mixt was extd with Et_2O (3 × 50 ml), and after drying ($MgSO_4$) was cooled carefully and treated with 30 ml of a 6 *N* soln of dry HCl in Et_2O. The oil formed was dissolved in abs EtOH and pptd by addn of abs Et_2O (Table II).

***N*-(β,β-Diphenylethyl)-α-aminoacetonitrile (A; R = Ph_2CHCH_2; R′ = H).**—To a soln of 23.3 g of β,β-diphenylethylamine·HCl in 100 ml of EtOH (1:1) were added (at 10–15°) 9 g of 32% HCHO soln and then (dropwise) a soln of 7.8 g of KCN in 40 ml of EtOH (1:1). To the mixt was added 100 ml of dichloroethane; it was stirred during 2.5 hr, the layer of org solvent was removed and evapd *in vacuo* to dryness giving 9.0 g of nitrile, mp 171–172° (dichloroethane–MeOH, 1:1). *Anal.* ($C_{16}H_{16}N_2$) C, H, N.

***N*-Nitroso-*N*-(β,β-diphenylethyl)-α-aminoacetonitrile (B; R = Ph_2CHCH_2; R′ = H).**—Cyanomethylation was carried out as described above. The mixt was kept for 2.5 hr and acidified by concd HCl (using Congo red indicator). Then we added, at 4–6°, a soln of 6.9 g (0.1 mole) of $NaNO_2$ in 35 ml of EtOH (1:1) kept the mixt for 14 hr, removed the dichloroethane layer, dried it, concd it *in vacuo*, and removed the pptg nitroso derivative (14 g, 53%), mp 90–91° (abs Et_2OH). *Anal.* ($C_{16}H_{15}N_3O$) C, H, N.

3-(β,β-Diphenylethyl)sydnonimine·HCl (XVI).—To a soln of 14.2 g of nitroso derivative, prepd as described above, in 100 ml of dry CH_2Cl_2 was added (at 0–2°) 30 ml of satd soln of dry HCl in EtOH. The pptg XVI was sepd by filtration (Table II).

3-(β-Phenylisopropyl)sydnonimine·HCl (XIII).—To a soln contg 425 g of $Me_2C(OH)CN$ were added (at a temp not higher than 18°) 450 ml of 37% HCHO and a soln of 5 g of K_2CO_3 in 25 ml of H_2O. The mixt was stirred at 10–15° during 4 hr. Then 675 g of β-phenylisopropylamine was added (at 0–5°), stirring was continued for another 2 hr, the mixt was kept overnight at 20° and cooled, and 465 ml of concd HCl, dild with H_2O up to 2 l., was added. Then (at 0°, dropwise) a soln of 350 g of $NaNO_2$ in 1 l. of H_2O was added. The mixt was kept for 3 hr. Then 800 ml of EtOAc was added to it, the org layer was sepd, and the aq layer was reextd with EtOAc twice. The extracts were combined, dried, and cooled, after which with constant stirring 2.5 l. of 3 *N* soln of HCl (g) in dry *i*-PrOH was added. The product formed was sepd by filtration (Table II).

Inhibition of MAO.—Lyophilized liver[22] and brain[23] mitochondria from 150- to 200-g white male rats were used for *in vitro* expts. Inhibition of MAO *in vivo* was studied in 50% liver or brain homogenates in 0.1 *M* potassium phosphate buffer (pH 7.4) contg 1.25% of a nonionic detergent (Soviet OP-10 or "Cutscum," Fischer Scientific Co.). Hydrochlorides of tyramine or dopamine and 5-HT creatinine sulfate were used as substrates. Activity of MAO was estimated from the rates of NH_3 liberation at 37° for 50 min in O_2.[24] Content of protein (standard cryst beef serum albumin) was measured as described by Lowry, *et al.*[25]

Polarographic Analysis.—The content in 50% rat liver homogenates of XIII after its iv administration was measured polarographically. In the homogenates pH value was adjusted to 3 by addn of 0.1 *N* HCl. After incubation for 5 min at 100° the ppt was removed by centrifugation (8000*g*, 10 min). To 2.5 ml of the supernatant 2.5 ml of potassium borate–phosphate–acetate buffer (pH 8.75) was added before polarographic measurements (differential polarograms).

Pharmacology.—Central effects of sydnonimines (behavior, potentiation of the action of 5-HTP,[9] tryptamine,[10] and PEA[11]) were studied in white male rats (140–160 g) and mice (18–20 g). The compds (0.33–0.5 of the LD_{50} but not higher than 50 mg/kg) were injected into rats (sc) or mice (ip). Peripheral sympathomimetic effects were evaluated by piloerection and exophthalmia in rats or an increase in blood pressure and potentiation of the pressor action of norepinephrine (10 μg/kg) in narcotized cats (3–5 mg of sydnonimines/kg).

Acute toxicity of sydnonimines (iv) was studied in white mice (16–18 g) of both sexes. For compds which caused death in doses less than 100 mg/kg the LD_{50} values were calculated.[26]

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Quaternary Isothiazolylpyridinium Salts. Oral Hypoglycemic Agents

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A number of quaternary azolylpyridinium salts, including members of the pyrazolyl-,[1a] isoxazolyl-,[1b] 1,2,4-oxadiazolyl-,[1c] thiazolyl-,[1d] oxazolyl-,[1e] and indolylpyridinium[1f] salt families, have been found to display hypoglycemic activity when administered orally to laboratory animals. Pyridinium salts substituted with 1,2,4-triazolyl, 1,3,4-thiadiazolyl, tetrazolyl, and imidazolyl groups did not induce a hypoglycemic response in normal mice.[2] The pharmacological activity of one of the more interesting compds in the active series, 1-methyl-4-(3-methyl-5-isoxazolyl)pyridinium

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