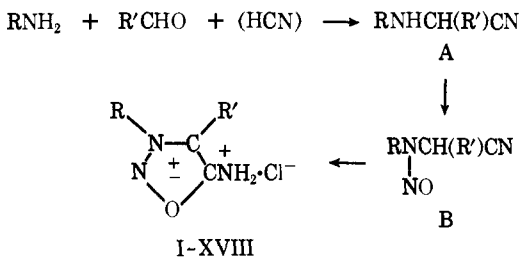
SCHEME I



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 coned 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 coned 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, coned 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 coned 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 30 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]

(22) V. Z. Gorkin and I. V. Veryovkina, *Vop. Med. Khim.*, **9**, 315 (1963).
(23) L. Seiden and J. Westley, *Arch. Int. Pharmacodyn.*, **146**, 145 (1963).
(24) V. Z. Gorkin and R. S. Krivchenkova, *Biokhimiya*, **29**, 992 (1964).
(25) O. H. Lowry, N. J. Rosebrough, A. L. Farr, and R. J. Randall, *J. Biol. Chem.*, **193**, 265 (1951).
(26) J. Körber, *Arch. Exp. Pathol. Pharmakol.*, **162**, 480 (1932).

Quaternary Isothiazolylpyridinium Salts. Oral Hypoglycemic Agents

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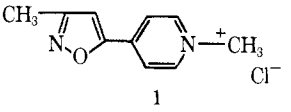
A number of quaternary azolylpyridinium salts, including members of the pyrazolyl-,[1a] isoxazolyl-,[1b] 1,2,4-oxadiazolyl-,[1c] thiazolyl-,[1d] oxazolyl-,[1e] and indolylpyridinium[1f] salt families, have been found to display hypoglycemic activity when administered orally to laboratory animals. Pyridinium 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

(1) (a) V. J. Bauer, H. P. Dalalian, W. J. Fanshawe, S. R. Safir, E. C. Tocus, and C. R. Boshart, *J. Med. Chem.*, **11**, 981 (1968); (b) V. J. Bauer, W. J. Fanshawe, H. P. Dalalian, and S. R. Safir, *ibid.*, **11**, 984 (1968); (c) W. J. Fanshawe, V. J. Bauer, S. R. Safir, D. A. Blickens, and S. J. Riggi, *ibid.*, **12**, 381 (1969); (d) G. E. Wiegand, V. J. Bauer, S. R. Safir, D. A. Blickens, and S. J. Riggi, *ibid.*, **12**, 891 (1969); (e) G. E. Wiegand, V. J. Bauer, S. R. Safir, D. A. Blickens, and S. J. Riggi, *ibid.*, **12**, 943 (1969); (f) W. J. Fanshawe, V. J. Bauer, S. R. Safir, D. A. Blickens, and S. J. Riggi, *ibid.*, **13**, 993 (1970).
(2) V. J. Bauer, G. E. Wiegand, W. J. Fanshawe, and S. R. Safir, *ibid.*, **12**, 944 (1969).

chloride (**1**), has been described.[3a-c] As a further development of this lead, we have synthesized representative isothiazolylpyridinium salt analogs and have investigated the effect of this change in structure on hypoglycemic activity.



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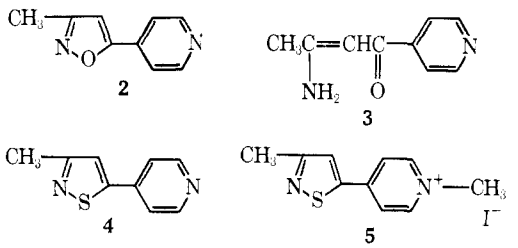
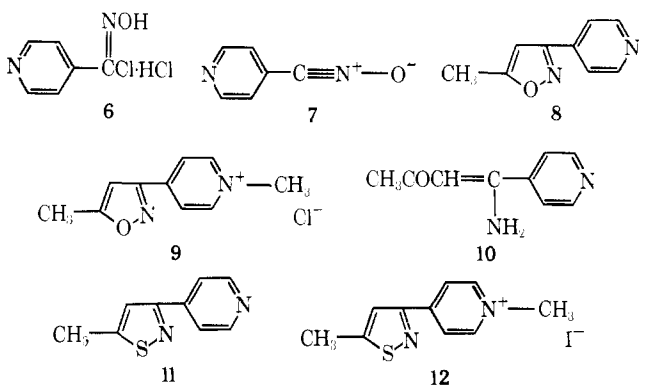
The (3-methyl-5-isothiazolyl)pyridinium salt **5** was prepd by the general method of McGregor, *et al.*[4] Hydrogenolysis of the isoxazolylpyridine **2**[1b] gave the enamino ketone **3**, which was then fused with P_2S_5 to give the isothiazolylpyridine **4**. Alkylation of **4** with



2 **3** **4** **5**

MeI gave the desired quaternary salt **5**.

The isomeric (5-methyl-3-isothiazolyl)pyridium salt **12** was prepd in a similar manner. The requisite isoxazolylpyridine **8** was synthesized by the 1,3-cycloaddition[5] of the nitrile oxide **7**, generated *in situ* from **6**, to propyne. Because two directions of cycloaddition



6 **7** **8** **9** **10** **11** **12**

are possible, the structure of **8** was confirmed by conversion to the methochloride salt **9**, a known[1b] isomer of **1**. Hydrogenolysis of **8** gave the enamino ketone **10**, which was fused with P_2S_5 to give the isothiazolylpyridine **11**. Alkylation of **11** with MeI gave the desired quaternary salt **12**.

Hypoglycemic Activity.[6]—Saline solns (0.1 ml/10 g) of compds were administered by gavage to male CF-1-S mice (Carworth Farms, 25–30 g) which were fasted after dosing. Control animals received an equal vol of vehicle. Blood samples (0.05 ml) of 3–6 surviving mice obtained from retrobulbar plexuses were assayed[3a] for glucose using the method of Hoffman[7] as adapted for the Technicon AutoAnalyzer. Both **5** and **12** were active hypoglycemic agents. Blood glucose was reduced 33±8% 5 hr after dosing with 0.5 mmole/kg and 72±10% after 1.5 mmoles/kg of **5**. Compd **12** induced blood glucose decreases of 65±8% and 90±1% 5 hr after dosing with 0.3 or 0.5 mmole/kg, resp. Blood glucose in controls was increased 4±3% in the experiment with **5** and decreased 21±4% in the **12** study. Predose blood glucose concns of 36 animals were 137±6 mg/100 ml.

Experimental Section[8]

1-(4-Pyridyl)-3-amino-2-buten-1-one (3).—A mixt of 20 g (0.125 mole) of **2**[1b] and 2.5 g of PtO_2 in 300 ml of EtOH was hydrogenated at 2.8 kg/cm² at room temp for 3 hr. The mixt was filtered and the filter cake was washed with large quantities of MeOH. The filtrate was concd under reduced pressure and the solid residue was recrystd (EtOAc) to give 18.6 g (92%) of colorless crysts, mp 211–213°. *Anal.* ($C_9H_{10}N_2O$) C, H, N.

4-(3-Methyl-5-isothiazolyl)pyridine (4).—A mixt of 3.6 g (0.022 mole) of **3** and 6 g (0.027 mole) of P_2S_5 was fused at 140–155° for 1 hr, cooled, warmed with 1 *N* KOH soln, and extd with $CHCl_3$. The $CHCl_3$ exts were dried ($MgSO_4$), decolorized (Darco), and concd *in vacuo* to a brown solid. Sublimation at 85–95° (18 mm) gave 0.40 g (11%) of pale yellow needles. A second sublimation at 88–90° (15 mm) gave colorless needles, mp 59–60°. *Anal.* ($C_9H_8N_2S$) C, H, N; S: calcd, 18.2; found, 17.4.

1-Methyl-4-(3-methyl-5-isothiazolyl)pyridinium Iodide (5).—A soln of 0.40 g (2.3 mmoles) of **4** and 2 ml of MeI in 15 ml of EtOH was heated under reflux for 1.5 hr, cooled, dild with Et_2O, and filtered. The solid residue was recrystd (MeCN) to give 0.60 g (83%) of yellow crysts, mp 172–174° dec. *Anal.* ($C_{10}H_{11}IN_2S$) H, I, N, S; C: calcd, 37.7; found, 37.2.

4-(5-Methyl-3-isoxazolyl)pyridine (8).—To a large excess (75 ml) of freshly condensed propyne, cooled to −40° in a Dry Ice bath and dild with 400 ml of Et_2O, was added 19.3 g (0.10 mole) of isonicotinohydroxamoyl chloride·HCl (**6**) (Aldrich Chemical Co.). At −40 to −50° with stirring, a soln of 28 ml (0.20 mole) of Et_3N in 100 ml of Et_2O was slowly added. The mixt was stirred at −30 to −50° for 5 hr, allowed to come to room temp overnight, treated with 300 ml of H_2O, and made alk with 1 *N* NaOH soln. The aq layer was sepd and extd with Et_2O and $CHCl_3$. The combined organic soln was dried ($MgSO_4$) and concd *in vacuo* to a solid residue. Recrystn (hexane) followed by sublimation at 90–95° (14 mm) gave 6.8 g (42%) of colorless needles, mp 86–87°. *Anal.* ($C_9H_8N_2O$) C, H, N; methochloride salt **9**, mp 221–222°.[1b]

1-Amino-1-(4-pyridyl)-1-butene-3-one (10).—A mixt of 0.48 g (3.0 mmoles) of **8** and 100 mg of PtO_2 in 35 ml of EtOH was hydrogenated at 1 atm for 18 hr and then filtered. The filtrate was concd to dryness, and the residue was recrystd (EtOAc–hexane) to give 0.20 g (41%) of pale yellow crysts: mp 152–153°. *Anal.* ($C_9H_{10}N_2O$) C, H, N.

4-(5-Methyl-3-isothiazolyl)pyridine (11).—A mixt of 1.0 g (6.2 mmoles) of **10** and 1.8 g (8.0 mmoles) of P_2S_5 was fused at 180–195° for 0.5 hr, cooled, dild with H_2O, made alk with 1 *N* KOH soln, and extd with $CHCl_3$. The $CHCl_3$ exts were dried ($MgSO_4$), decolorized (Darco), and concd under reduced pressure. The solid residue was sublimed at 110–115° (15 mm) to give 0.41 g (31%) of colorless needles, mp 49–52°. *Anal.* ($C_9H_8N_2S$) C, H, N; S: calcd, 18.2; found, 17.6.

1-Methyl-4-(5-methyl-3-isothiazolyl)pyridinium Iodide (12).—A soln of 0.25 g (1.5 mmoles) of **11** and 2 ml of MeI in 10 ml of EtOH was heated under reflux for 1.5 hr, cooled, and dild with Et_2O. The solid was collected and recrystd (EtOH–Et_2O) to give 0.38 g (77%) of yellow crysts, mp 110–112° dec. *Anal.* ($C_{10}H_{11}IN_2S \cdot 0.5H_2O$) C, H, I, N; S: calcd, 9.80; found, 9.26.

(3) (a) S. J. Riggi, D. A. Blickens, and C. R. Boshart, *Diabetes*, **17**, 646 (1968); (b) D. A. Blickens and S. J. Riggi, *Toxicol. Appl. Pharmacol.*, **14**, 393 (1969); (c) D. A. Blickens and S. J. Riggi, *Diabetes*, **18**, 612 (1969).

(4) D. N. McGregor, U. Corbin, J. E. Swigor, and L. C. Cheney, *Tetrahedron*, **25**, 389 (1969).

(5) R. Huisgen and W. Mack, *Tetrahedron Lett.*, 583 (1961).

(6) Technical assistance of Mr. E. Locke, Mr. H. Siegriest, and Miss L. Will is greatly appreciated.

(7) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937).

(8) Melting points were determined in a Hershberg apparatus and are uncor. Microanalyses were performed by Mr. L. M. Brancone and staff. Where analyses are indicated only by symbols of the elements, anal. results obtained for those elements were within ±0.4% of the theor values.