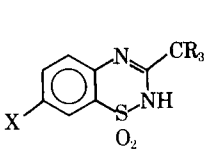
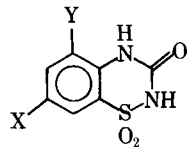
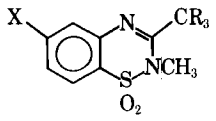


I: R = alkyl, X = H
II: R = alkyl, X = Cl



III: X = H, Y = H
IIIa: X = Cl, Y = H
IIIb: X = Cl, Y = Cl



IV: R = H, X = H
IVa: R = Cl, X = H
V: R = H, X = Cl
Va: R = Cl, X = Cl

was removed and the dark-yellow solution was allowed to stand for 0.5 hr. The reaction mixture was then poured into crushed ice and the solid material was collected and washed several times with water. Recrystallization from methanol gave crystals, mp 135–137°. NMR analysis in acetone-d_6 gave a proton count of seven, showing the four protons for the benzene ring at 8 ppm and a singlet (three protons) at 3.75 ppm for the methyl group in the 2-position.

Anal.—Calc. for $C_9H_7Cl_3N_2O_2S$: C, 34.47; H, 2.25; N, 8.93. Found: C, 34.86; H, 2.21; N, 8.95.

6-Chloro-2-methyl-3-trichloromethyl-1,2,4-benzothiadiazine 1,1-Dioxide (Va)—Compound V (16 g) was chlorinated in 50 ml of dimethylformamide at 55–80° with 16 g of chlorine. Recrystallization of the crude substance from benzene–hexane gave Va, mp 145–146°. NMR analysis in acetone-d_6 showed a singlet at 3.75 ppm for the methyl group and three protons for the ring at 7.75–8.20 ppm.

Anal.—Calc. for $C_9H_6Cl_4N_2O_2S$: C, 31.06; H, 1.74; N, 8.05. Found: C, 31.23; H, 1.92; N, 7.81.

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COMMUNICATIONS

Hydroxymethylfuraldimines: Possible Intermediates in Maillard Reaction

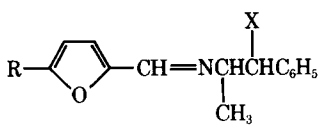
Keyphrases □ Hydroxymethylfuraldimines—possible intermediates in Maillard reaction, relationship to browning of dextroamphetamine sulfate □ Dextroamphetamine sulfate—hydroxymethylfuraldimines as possible intermediates in Maillard reaction □ Maillard reaction—hydroxymethylfuraldimines as possible intermediates, relationship to browning of dextroamphetamine sulfate

To the Editor:

Recently, Blaug and Huang (1) reported that dextroamphetamine sulfate yields a brown precipitate when heated with dextrates in solution. This brown precipitate was postulated as the imine (Ia) resulting from condensation of amphetamine with 5-hydroxymethylfurfural on the basis of elemental analysis, a strong band at 1650 cm^{-1} in the IR spectrum, and TLC.

During investigations conducted in this laboratory, it became of interest to prepare Ia and a few other 2-furanecarboxaldimines (Ib–Id) for spectral and reactivity comparisons. These compounds were readily prepared by warming benzene (Ib–Id) or ethanol (Ia) solutions of the amine and the furfural and were unambiguously characterized by their IR, UV (Table I), and NMR spectra[1] (Figs. 1a–1d). Compounds Ib–Id were readily purified by either vacuum distillation (Ic) or crystallization (Ib and Id).

Since extensive decomposition of Ia occurred on attempted distillation, the method of choice for its preparation involved employing a slight excess of



	R	X
Ia:	CH_2OH	H
Ib:	CH_2OH	OH
Ic:	H	H
Id:	H	OH

[1] Determined on a Varian T-60 or Varian XL-100.

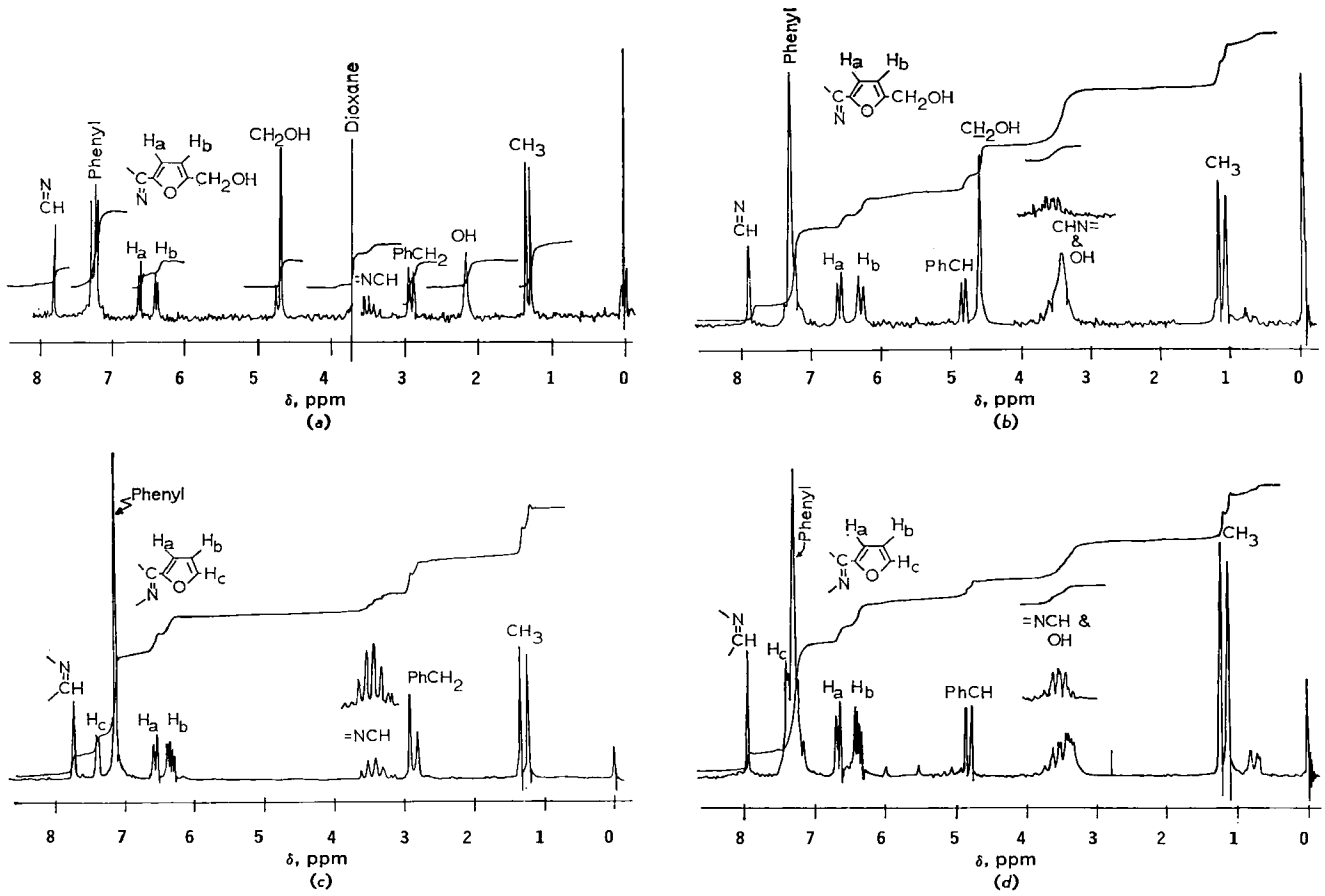


Figure 1—*Proton magnetic resonance spectra of furaldimines. Key:* a, *Ia at 100 MHz;* b, *Ib at 60 MHz (insert: D_2O added);* c, *Ic at 60 MHz; and* d, *Id at 60 MHz (insert: D_2O added).*

dextroamphetamine. Separation of I*a* from excess amphetamine was then obtained by dry column chromatography on silica gel employing dioxane as the eluant. Satisfactory elemental analyses were obtained for I*b*–I*d*; however, the elemental analysis and NMR spectroscopy indicated significant traces of dioxane in I*a*. A GC–mass spectrum of I*a* is shown in Fig. 2.

Several discrepancies were observed in comparing I*a* and the brown precipitate, which was prepared at pH 8 by heating an aqueous solution of 1% dextroamphetamine sulfate and 10% dextrose for 5 days at 60°. The brown precipitate was solid, while I*a* was a pale-yellow oil; the IR and UV spectra (Fig. 3) were different; and TLC confirmed the nonidentity of these substances (Fig. 4).

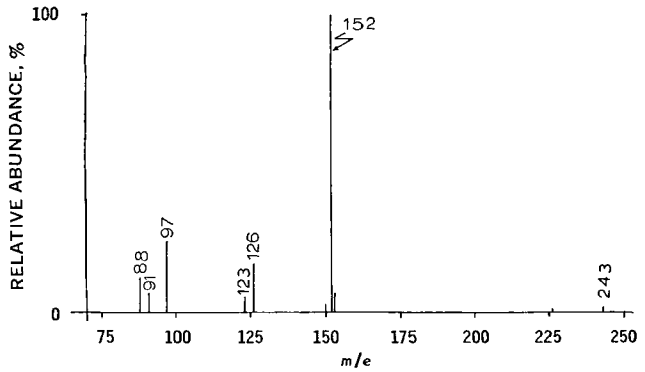


Figure 2—*GC–mass spectrum of* I*a*.

The UV spectrum of I*a* closely approximated that of 5-hydroxymethylfurfural (Table I). Indeed, the UV spectra of all Schiff bases prepared closely resembled those of the corresponding furfural, a result which is expected with Schiff bases unless the C=N is involved in transmitting conjugation between the portions of the molecule derived from the carbonyl and amine.

Blaug and Huang (1) also reported a peak of maximum absorbance at 298 nm, which apparently behaves in a manner similar to the 320-nm band reported by Duvall *et al.* (2). An aqueous solution of I*a* showed maximum absorbance at 282 nm, which may be due either to intact I*a* or to the hydroxymethylfurfural resulting from hydrolysis of I*a*. Consequently, it appears that the 298-nm band is not due to I*a*. One

Table I—Significant Spectrometric Features of Furfural Derivatives

Compound	λ_{max}[a] ($\epsilon \times 10^{-3}$)	υC=N
5-Hydroxymethylfurfural	280 (15.5)	—
I*a*	277 (18.7)	1640[b]
I*b*	277 (18.3)	1640[c]
2-Furaldehyde	270 (14.6)	—
I*c*	268 (18.8)	1645[b]
I*d*	269 (17.7)	1640[c]

[a] UV spectra were recorded in ethanol with about 5.0×10^{-5} *M* solutions. Wavelengths are reported in nanometers. [b] Determined on a neat film. [c] Determined on a mineral oil mull.

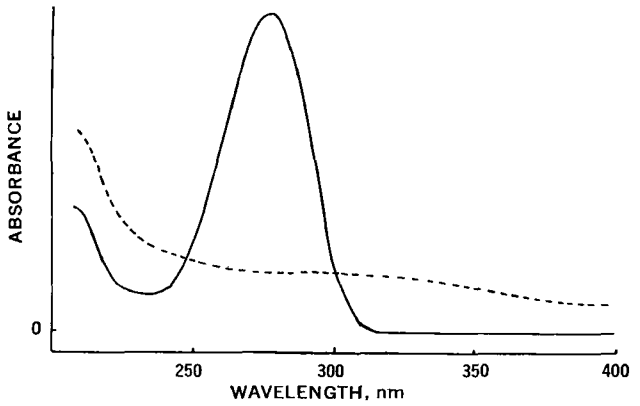


Figure 3—*Absorption spectrum of Ia* (—) *and brown precipitate obtained by heating 1% dextroamphetamine sulfate and 10% dextrose for 5 days at 60°* (- - - -). *Both spectra were determined in ethanol solution.*

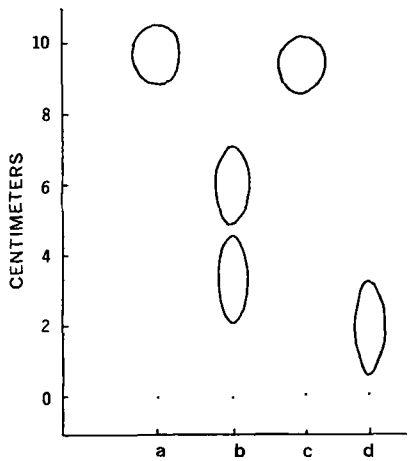


Figure 4—*Thin-layer chromatogram of dextroamphetamine sulfate–dextrose and Schiff-base solutions, developed in the lower phase of a mixture of ethyl acetate–pyridine–water (2:1:2) (see Ref. 1). Key: a, fresh 5-hydroxymethylfurfural; b, ethanol solution of precipitate from 1% dextroamphetamine sulfate and 10% dextrose solution heated at 60° for 5 days; c, Ia; and d, amphetamine base.*

would also expect Ia to absorb at longer wavelength than an amphetamine–sugar Schiff base (3). Consequently, it appears that neither the 298-nm band (1) nor the 320-nm band (2) is due to either Ia or the amphetamine–sugar Schiff base, although either of these may be *intermediates* involved in the browning reaction.

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Effect of Vehicles on Reduction of Brain Norepinephrine by α-Methyltyrosine

Keyphrases □ Methylcellulose—vehicle effect on α-methyl-*p*-tyrosine reduction of brain norepinephrine, compared to polysorbate 80 □ α-Methyl-*p*-tyrosine reduction of brain norepinephrine—vehicle effect, methylcellulose, polysorbate 80 □ Norepinephrine reduction by α-methyl-*p*-tyrosine—vehicle effect, methylcellulose, polysorbate 80

To the Editor:

Investigators seeking to elucidate the functional significance of brain norepinephrine have been aided by the development of the specific enzyme inhibitor, α-methyl-*p*-tyrosine (1). Spector *et al.* (2) demonstrated that α-methyl-*p*-tyrosine selectively inhibits tyrosine hydroxylase, the rate-limiting enzyme in the biosynthesis of the catecholamines, and thereby depletes these amines from the brain. α-Methyl-*p*-tyrosine has been employed to estimate the turnover rate and the turnover time of the catecholamines (3) in various body tissues including brain.

Bernard and Paolino (4), employing 80 mg/kg α-methyl-*p*-tyrosine suspended in 5% polysorbate 80, were able to lower the brain norepinephrine levels of adult male mice (C57BL/6J) by 52%, 4 hr following intraperitoneal injection. Similar results were obtained in wild rats (5) when using 250 mg/kg α-methyl-*p*-tyrosine. These depleted levels are similar to those obtained by other investigators employing other vehicles or acidification of aqueous solutions to increase the solubility of this enzyme inhibitor (6–9). The purpose of our experiment was to determine if a suspending agent such as 1% methylcellulose 400

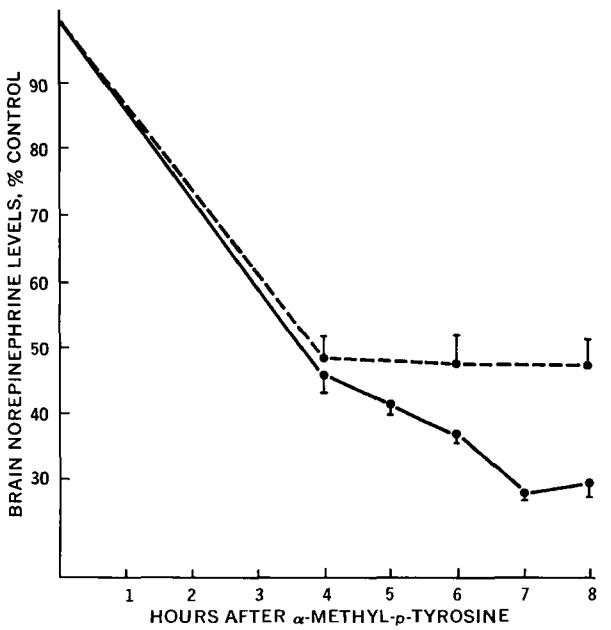

Figure 1—*Adult male mice were injected with α-methyl-p-tyrosine (80 mg/kg ip) in either 5% polysorbate 80* (- - - -) *or 1% methylcellulose 400* (—). *At various time intervals following injection, the animals were decapitated and their brains were removed and assayed for norepinephrine. Each data point represents the mean ± standard error* ($3 \leq n \leq 8$).