lesions of which one or more are larger than 5 mm. in diameter) and four were graded 3 on the rating scale. The remaining six stomachs were normal.

These observations indicate that the Mongolian gerbil is less susceptible to the induction of gastric lesions by aspirin than the Holtzman albino rat. The biological basis for the observed difference in resistance is not revealed by the present study. It is, however, clear that a dose level of aspirin causing gastric mucosal erosion in all of the male albino rats that received it did not cause such erosion in those male Mongolian gerbils to which it was administered. Higher dose levels do result in lesion formation in the gerbil, with a direct relationship between incidence and dose. However, even at a dose level fourfold higher than that causing lesions in all rats that received it, only 5 of 11 gerbils exhibited lesions, the severity of which was slight to moderate.

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Isolation and Identification of 8-(2-Diphenylmethoxy-*N*-methylethylamine)-1,3-dimethylxanthine from Dimenhydrinate

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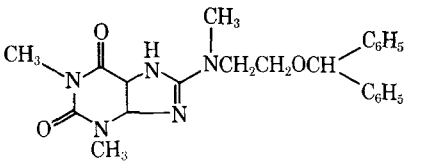
Abstract □ Differences in solubility and in rate of solubility from previously tested chemical lots were observed in a dimenhydrinate chemical evaluated by the tests and specifications in the official monograph. An impurity was isolated from the lot in question and was identified as 8-(2-diphenylmethoxy-*N*-methylethylamine)-1,3-dimethylxanthine based on spectral and elemental data.

Keyphrases □ 8-(2-Diphenylmethoxy-*N*-methylethylamine)-1,3-dimethylxanthine—isolation, identification from dimenhydrinate □ Dimenhydrinate—isolation, identification of 8-(2-diphenylmethoxy-*N*-methylethylamine)-1,3-dimethylxanthine □ Impurity of dimenhydrinate—isolation, identification of 8-(2-diphenylmethoxy-*N*-methylethylamine)-1,3-dimethylxanthine

In a routine analysis of dimenhydrinate chemical according to the tests and specifications in the USP XVII monograph, it was observed that one lot did not completely dissolve in alcohol. Also, its solubility in water, which is the first step in the diphenhydramine assay, was less than complete. In both instances, a hazy solution resulted. However, except for these slight discrepancies, the chemical met the requirements detailed in the monograph. Previous lots dissolved rapidly in the solvents mentioned, while this lot had a poor rate of solubility.



I

Differential thermal analysis revealed one major endotherm at 105° which was identical to previous lots tested. The X-ray diffraction pattern was also the same as previous lots, ruling out polymorphism as a possible explanation for the solubility difference. The thin-layer chromatogram had spots corresponding to the diphenhydramine and 8-chlorotheophylline moieties and a

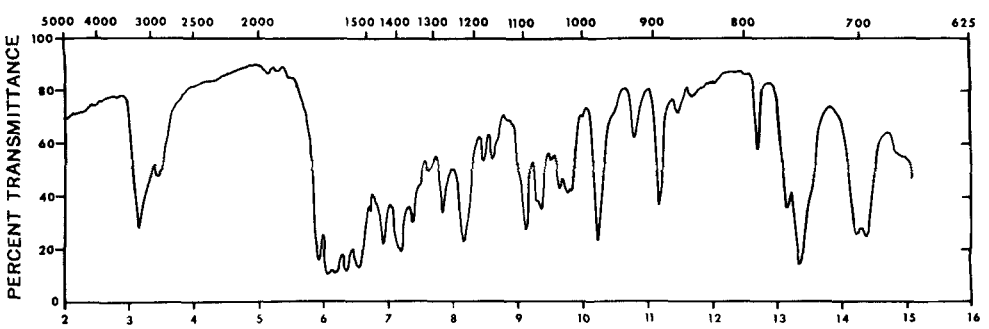


Figure 1—*IR spectrum o unknown.*

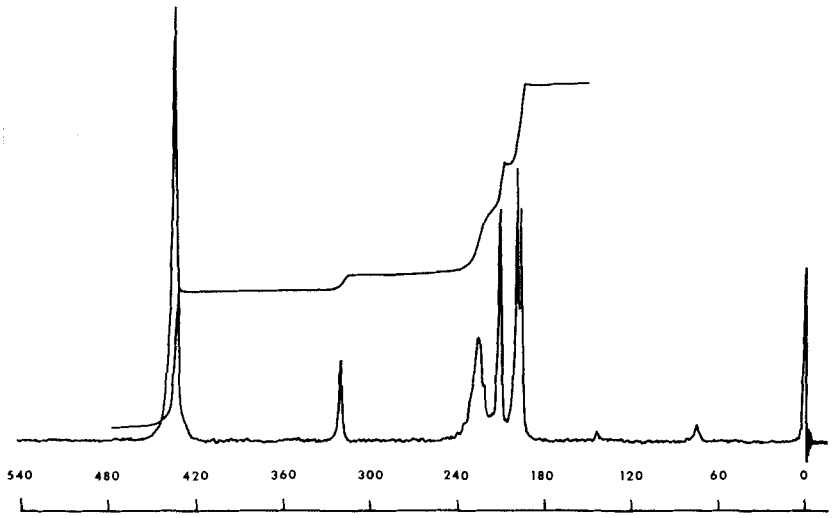


Figure 2—*NMR spectrum of unknown.*

third unknown constituent. This paper describes the isolation of the unknown constituent from dimenhydrinate chemical and its identification as 8-(2-diphenylmethoxy - *N* - methylethylamine) - 1,3 - dimethylxanthine (*I*).

RESULTS AND DISCUSSION

Isolation of the Unknown—Five grams of chemical was weighed into a 250-ml. separator and shaken with 75 ml. of water. The solution was made basic with 5 ml. of 0.1 *N* sodium hydroxide and extracted with 4 × 75-ml. portions of chloroform. The chloroform extracts were passed through a cotton pledget and combined, and the solvent was evaporated with nitrogen gas. The oily residue was transferred to a 12-ml. centrifuge tube with the aid of chloroform, and the chloroform was evaporated with nitrogen gas. The residue was mixed with 5 ml. of ethanol; the tube was capped and allowed to sit for 24 hr. The white precipitate was compacted by centrifugation, the supernatant was decanted, and the residue was washed several times with ethanol. Residual ethanol was evaporated with nitrogen gas. The residue, a white crystalline powder, weighed 35 mg., which represented 0.7% of the starting material.

Anal.—Calcd. for $C_{23}H_{25}N_5O_3$: C, 65.86; H, 6.01; N, 16.70. Found: C, 65.68; H, 6.01; N, 16.57.

TLC—One hundred micrograms was spotted from a chloroform solution of the unknown containing 10 mg./ml. onto a silica gel GF plate activated for 1 hr. at 100°. The plate was equilibrated in a tank for 15 min. before development in the presence of the developing solution. The developing solution was a mixture of chloroform–methanol–formic acid mixed in the proportions of 90 : 10 : 3, respectively. Authenticated dimenhydrinate was run under the same conditions.

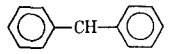
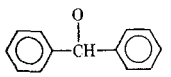
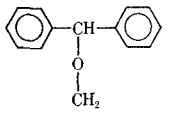
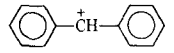
The developed chromatograms were made visible with UV light (254 nm.), iodine vapors, and iodoplatinate reagent. The following spots, along with the R_f values, were visible under UV light and in the presence of iodine vapors: diphenhydramine, origin; 8-chlorotheophylline, 0.36; and unknown, 0.50. With the use of iodoplatinate reagent, diphenhydramine at the origin and the unknown at 0.50 were visible. The chromatogram of the isolated material contained a single spot at R_f 0.50. The starting material contained three spots: diphenhydramine, origin; 8-chlorotheophylline, 0.36; and unknown, 0.50.

Spectroscopy—The IR spectrum of the unknown (Fig. 1) showed the presence of the theophylline moiety as indicated by absorption peaks at 3.15 (NH), 5.90, and 6.05 (C=O) μ. The presence of the amine side chain was shown by absorptions at 8.15 (CH_2—O—CH) and 13.25, 13.35, 14.20, and 14.39 μ. (monosubstituted phenyl groups).

The UV spectrum had a $\lambda_{max.}$ at 300 nm. which is compatible with the structure proposed.

The NMR spectrum (Fig. 2) revealed aromatic protons at 7.3 p.p.m., CH adjacent to aromatics at 5.35 p.p.m., and two methylene and two methyl groups at 3.0–4.0 p.p.m. Integration of the spectrum showed that the protons were presented in a ratio of 10 : 1 : 13, which is consistent with the proposed structure.

The mass spectrum gave a molecular weight of 419. The spectrum supports the proposed structure, and the major peaks may be interpreted as follows:

m/e Value	Fragment Ion Structure
419	molecular ion peak
252	M— 
236	M— 
222	M— 
167	

Conclusion—An impurity isolated from dimenhydrinate chemical was insoluble in water and ethanol. The spectral and elemental data on the unknown are compatible with the structure 8-(2-diphenylmethoxy-*N*-methylethylamine)-1,3-dimethylxanthine.

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