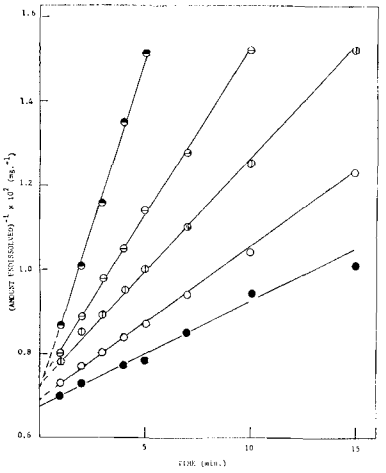

Fig. 2—Second-order plot of reserpine dissolution data assuming dissolution was apparent first order under nonsink conditions. Key: ●, reserpine–DCA, 1:0; ○, 1:4; ◑ 1:8; ⊖, 1:16; ◓, 1:32.

The apparent second-order rate constants were calculated and these are reported in Table I together with the corresponding ratios. A rank correlation is noted between the apparent second-order dissolution rate constants and the biologic activities of the various reserpine preparations. The sole exception is the 1:32 reserpine–DCA dispersion which is significantly less biologically active than would be predicted by the dissolution data.

The use of organic solvents in correlation studies between *in vitro* and *in vivo* data is rarely desirable or logical. However, as noted by Levy (8) dissolution in organic solvents does reflect adequately the particle size of the drug. Furthermore, dissolution in an organic solvent may reflect changes in crystal structure. To explore the latter possibility, diffraction spectra were obtained for reserpine and DCA, separately precipitated from the solvent system, and for various dispersions, using a General Electric XRD-6 diffractometer.[3] All samples appeared to be noncrystalline. In view of the absence of solution interaction between DCA and reserpine in ethyl acetate, and the lack of change in crystal form, it is concluded that the physical state of reserpine (*i.e.*, an extremely fine particle size attained by co-precipitation with DCA) is responsible for the increased dissolution rates observed with the reserpine-DCA dispersions.

(1) Goldberg, A. H., Gibaldi, M., and Kanig, J. L., *J. Pharm. Sci.*, **54**, 1145(1965).
(2) *Ibid.*, **55**, 482(1966).
(3) *Ibid.*, **55**, 487(1966).
(4) Goldberg, A. H., Gibaldi, M., Kanig, J. L., and Mayersohn, M., *ibid.*, **55**, 581(1966).
(5) Mayersohn, M., and Gibaldi, M., *ibid.*, **55**, 1323 (1966).
(6) Malone, M., Hochman, H. I., and Nieforth, K. A., *ibid.*, **55**, 972(1966).
(7) Gibaldi, M., and Feldman, S., *ibid.*, **56**, 1238(1967).
(8) Levy, G., paper presented to the Industrial Pharmacy Section, APhA Academy of Pharmaceutical Sciences, Dallas meeting, April 1966.

MILO GIBALDI
STUART FELDMAN
THEODORE R. BATES*

Department of Pharmaceutics
School of Pharmacy
State University of New York at Buffalo
Buffalo, NY 14214

Received January 2, 1968.
Accepted for publication February 9, 1968.
*Present address: Pharmaceutics Department, Pharmacy Research Institute, University of Connecticut, Storrs, CT 06268

[3] The authors thank Dr. Eli Shefter for providing the diffraction data.

Keyphrases

Reserpine–desoxycholic acid dispersions—solid state
Solid state dispersions—pharmacologic activity effect
Dissolution rate–reserpine–desoxycholic acid dispersion

Antidepressive Effect of N-3,4,5-Trimethoxybenzoyl Heptamethylenimine

Sir:

It was Luts *et al.* (1) who reported on the synthesis and preliminary pharmacological investigation of *N*-3,4,5-trimethoxybenzoyl heptamethylenimine. As stated by these authors, unlike other amines containing trimethoxybenzoyl group the compound is void of depressant and analgesic action; moreover, it exerts a mild stimulating effect.

In a series of studies concerned with a large number of derivatives of heptamethylenimine substituted by benzoic acid the above-mentioned compound has also been synthesized and subjected to close pharmacological investigation.

Synthesis was carried out principally by the method reported by Luts *et al.* (1).

In mice the LD_{50} was 170 ± 5.15 i.p. 200 ± 21.52 s.c.

Investigated after Zetler's (2) cataleptic method, in i.p. doses of 20 mg./Kg., the compound was found to be a strong antagonist of catalepsy caused by reserpine or chlorpromazine. It has furthermore strongly antagonized the toxicity of reserpine under acute and subacute conditions. Alone it gave rise to slight hyperthermia. In doses of 40 mg./Kg. it has reversed hyperthermia due to reserpine. In rotarod test (3) the compound alone failed to exert any effect in doses of 10–80 mg./Kg. i.p., but doses from 10 mg./Kg. have antagonized incoordination caused by 2.5 mg./Kg. reserpine. In doses of 10 mg./Kg. the compound has intensified the hypertensive effect of epinephrine in cats. After preliminary treatment for 5 days, the effect of epinephrine and norepinephrine on blood pressure has been greatly enhanced. As shown by Knoll's motimeter (4), the compound induced minimal hypermotility when administered in i.p. doses of 20 mg./Kg.

Hypermotility caused by amphetamine has been inhibited in the first 60 min., but in the period from 60–210 min. it has been increased in an extraordinary measure. When administered simultaneously with hexobarbital, the compound has slightly prolonged the narcosis time. However, after premedication over 24 hr., anaesthesia was considerably shortened. The compound has exerted practically no influence on pentylenetetrazol,[1] strychnine, and electroconvulsions.

No analgesic effect could be demonstrated. Monoamino oxidase has not been inhibited either *in vitro* or *in vivo* after premedication for 1 week The compound has shown no noteworthy harmful effect in subacute toxicity tests.

Upon due consideration of the obtained findings, the compound would seem to display an extraordinary likeness in pharmacological properties to tricyclic antidepressants, and as such it may be denoted as a potential antidepressive drug of new chemical type.

A report on detailed pharmacological results is to be published later.

[1] Metrazol, Knoll Pharmaceutical Co., Orange, N.J.

(1) Luts, H. A., Zucarello, W. A., Nobles, W. L., and Grattan, J. F., *J. Pharm. Sci.*, **55**, 1459(1966).
(2) Zetler, G., *Arzneimittel-Forsch.*, **13**, 103(1963).
(3) Dunham, N. W., and Miya, T. S., *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 208(1957).
(4) Knoll, J., and Vajnovszki, B., *Arch. Intern. Pharmacodyn.*, **146**, 10(1963).

Eva Pálosi
L. Szporny
K. Nádor

Pharmacological Laboratory of
Chemical Works Gedeon Richter Ltd.
Budapest, Hungary

Received July 31, 1967.
Accepted for publication January 19, 1968.

Keyphrases

N–3,4,5–Trimethoxybenzoyl heptamethylenimine—antidepressive activity
Reserpine activity—antagonism
Epinephrine hypertensive effect—increased
Amphetamine hypermotility effect—antagonism

Validity of the Doty Reaction as a Stability-Indicating Assay for Isoproterenol in an Aerosol Preparation

Sir:

The sensitivity, accuracy, precision, and manipulative simplicity of the ferro-citrate color reaction described by Doty (1) have led to its wide use for assay of preparations containing isoproterenol, epinephrine, and other catecholamine drugs. The reaction is selective for the catechol function, and it will therefore be stability indicating where the degradation reaction involves the catechol group. Higuchi, Sokoloski, and Schroeter (2) assayed known mixtures of epinephrine and its oxidative degradation products by four procedures; they reported close correspondence between the result obtained by the Doty reaction and the true value, indicating that the reaction is stability indicating where degradation occurs by oxidation. Schroeter, Higuchi, and Schuler (3) described a nonoxidative degradation reaction of epinephrine with bisulfite, used as an antioxidant, where a physiologically inactive substituted benzylsulfonic acid is formed. A similar reaction occurs between bisulfite and isoproterenol (4). The epinephrine-bisulfite reaction product was prepared by the literature method (5). As expected, this product was found to give a color with the Doty reagent, vitiating this assay method for catecholamines in solutions preserved by bisulfite. The Doty method would have obvious limitations in following the stability of those catecholamines subject to racemization in solution (6); however this limitation does not exist with the racemic isoproterenol salts official in the compendia.