

Lack of Anticonvulsant Properties of Orally Administered Creatinine in Mice

Sir:

Cade (1) reported that pentylenetetrazol-induced convulsions in guinea pigs were controlled successfully by intraperitoneal injections of creatinine. Further, creatinine injections to control seizures of epileptic patients were encouraging. Pfeifer and co-workers (2) found creatinine administered subcutaneously in rats to show some protection against pentylenetetrazol-induced convulsions in summer but not winter, to abolish convulsions produced by hydration, and to be ineffective against electrically induced convulsions.

We have evaluated creatinine in male albino Swiss-Webster mice, using standard anticonvulsant procedures (3). Mice (groups of ten each) received daily oral administration of creatinine 100, 200, 400, and 800 mg./Kg./day for 4 days. On the third day, the animals were challenged by electroshock (M.E.S. test) 1 hour after the third dose and on the fourth day they were challenged

with pentylenetetrazol (Met. test) 1 hour after the fourth dose. No protection was observed. However, deaths following electroshock became progressively less as the dose of creatinine became larger (60, 20, 30, and 0%, respectively). In a second experiment, creatinine was mixed in the diets (0, 0.5, 1.0, and 5.0%) and fed for 7 days to groups of 30 mice per diet. The mice were challenged with electroshock on the third and sixth day, and with pentylenetetrazol on the seventh day. No protection was observed. The number dying was almost identical for the four groups. Weight changes were not appreciably different for the four groups.

We were unable to show anticonvulsant properties for creatinine in mice using two standard anticonvulsant laboratory procedures.

- (1) Cade, J. F., *Med. J. Australia*, 2, 621(1947).
(2) Pfeifer, A. K., Patakyi, I., and Hajdu, P., *Acta Physiol. Acad. Sci. Hung.*, 3, 153(1952).
(3) Swinyard, E. A., Brown, W. C., and Goodman, L. S., *J. Pharmacol. Exptl. Therap.*, 106, 319(1952).

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Use of Sulfur Tetrafluoride in Syntheses of Potential Anticancer Agents

Sir:

The recent communication (1) dealing with the synthesis of the trifluoromethyl analog of thymine as a potential anticancer agent has prompted us to report an alternate method of synthesis utilizing sulfur tetrafluoride. Fluoro analogs of many of the naturally occurring pyrimidines have been prepared and tested as potential anticancer agents. Specifically, the trifluoromethyl group has been substituted on the 2, 4, and 6 positions of pyrimidines (2) by classical procedures utilizing a convenient two or four carbon starting material derived from trifluoroacetic acid. For several years we have tried unsuccessfully to prepare 5-trifluoromethyluracil by condensation of ethyl 3,3,3-trifluoro-

propionate, urea, and ethylorthoformate,¹ a modification of the procedure developed by Whitehead (3).

Since sulfur tetrafluoride was introduced as a reagent for the conversion of the carboxyl group to the trifluoromethyl group (4), many reports have appeared on the selective nature of this reagent (5). Raasch (6) noted the protective effect of excess hydrogen fluoride on the fluorination of aliphatic amino acids. The synthesis of 5-trifluoromethyluracil was successfully completed by a convenient one-step synthesis starting with uracil-5-carboxylic acid. Introduction of fluorine at the 5-carboxyl group in preference to attack of the other reactive sites was observed. The selective nature of the reagent under controlled temperature and with excess hydrofluoric acid (generated *in situ* from water and SF₄) demonstrates the versatility and the many applications possible in the synthesis of trifluoro-

¹ Appreciation is expressed to Donald A. Thompson for exhausting methods of synthesis of 5-trifluoromethyluracil by this approach.