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.

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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-trifluoropropionate, 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 SF_4) demonstrates the versatility and the many applications possible in the synthesis of trifluoro-

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

methyl substituted heterocycles containing oxygen.

Uracil-5-carboxylic acid[2] (1.00 Gm., 0.0064 mole) and 0.5 ml. of water (0.028 mole) were placed in a steel bomb which was sealed. After cooling the bomb in dry ice-acetone, approximately 45 Gm. of sulfur tetrafluoride[3] (0.41 mole) was introduced. This was heated to 100°, agitated for 16 hours and subsequently allowed to cool to room temperature. The volatile material was vented and decomposed in 10% potassium hydroxide solution and the residue was recrystallized several times from water and sublimed giving 0.883 Gm. (77%, m.p. 247–249° dec., reported (1) m.p. 239–241°).

Anal.[4]—Calcd. for $C_5H_3F_3N_2O_2$: C, 33.35; H, 1.68; F, 31.65; N, 15.55. Found: C, 33.49; H, 1.61; F, 31.87; N, 15.69.

The following ultraviolet absorption spectra were recorded: 0.1 *N* HCl, λmax. 257 mμ, εmolar 8150; pH 7, λmax. 257 mμ εmolar 7210; pH 12.2, λmax. 279 mμ, εmolar 6500.

The pharmacological results and the synthesis of this and other analogs will be published in full detail in the future.

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Note added in proof: Preliminary examination of 5-trifluoromethyluracil (NSC-73757) against Sarcoma-180 showed a lack of significant activity. Toxicity was evident at 500 mg./Kg. (2 of six survivors). At 200 mg./Kg. the tumor/control weight ratio was 0.63 (five of six survivors).

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[2] Nutritional Biochemicals Corp.

[3] Organic Chemicals Dept., E. I. duPont de Nemours & Co., Inc.

[4] Appreciation is expressed to Dr. Earl M. Chamberlin, Merck & Co., Inc., for the analytical data.

Synthesis of Dehydrocycloheximide

Sir:

In addition to our interest in the stereochemistry of cycloheximide (1, 2), we have been concerned with the development of a method for the synthesis of cycloheximide and certain of its degradation products. Recently, Lawes has described the synthesis of anhydrocycloheximide (3); the present communication describes the total synthesis of dehydrocycloheximide.

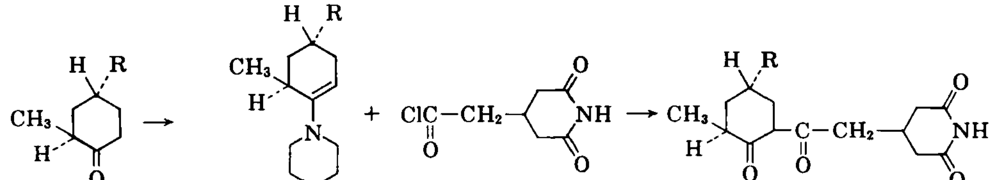
The method which we selected for the synthesis of dehydrocycloheximide employs the combination of the two fragments, 2,4-dimethylcyclohexanone and glutarimide-β-acetyl chloride. The preparation of (+)-*trans*-2,4-dimethylcyclohexanone (I) was accomplished by thermal degradation of cycloheximide (4). When I was allowed to react with piperidine in benzene solution according to the general procedure of Stork (5), a 47% yield of the enamine (II) was obtained; b.p. 79–82°/2.0 mm., $[\alpha]_D^{26} = +44.5°$ (c = 5.66% in ethanol).

Anal.—Calcd. for $C_{13}H_{23}N$: C, 80.76; H, 11.99; N, 7.24. Found: C, 80.58; H, 12.02; N, 7.16.

Condensation of the enamine (II) with glutarimide-β-acetyl chloride (III) (6) in dioxane solution gave, after hydrolysis, a 19% yield of dehydrocycloheximide (IV), m.p. 177–179°, $[\alpha]_D^{20} = -30.9°$ (c = 1.00% in $CHCl_3$).

Anal.—Calcd. for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.02. Found: C, 64.30; H, 7.37; N, 5.22.

Comparison of the optical rotation, the ultraviolet and infrared spectra, the R_f on thin-layer



(I) R = CH_3
(V) R = H

(II) R = CH_3
(VI) R = H

(III)

(IV) R = CH_3
(VII) R = H