

in crystalline form of a substance (I) active for *Leuconostoc citrovorum*, and the chick; furthermore, it competitively reverses the toxicity of 4-aminopteroylglutamic acid (II) for the mouse.

When pteroylglutamic acid (PGA) or its N<sup>10</sup>-formyl derivative was reduced catalytically over platinum in formic acid at 0 to 30°, two moles of hydrogen were absorbed. Isolation of the crystalline substance (I) was accomplished by adsorption of impurities on Magnesol at pH 7, adsorption of activity on Darco G-60 at pH 4, elution, fractional crystallization of the barium salt, and finally chromatographic separation on Magnesol columns. *Anal.* Calcd. for C<sub>20</sub>H<sub>21</sub>N<sub>7</sub>O<sub>7</sub>Ba·5H<sub>2</sub>O: C, 34.4; H, 4.47; N, 14.0; Ba, 19.7; CHO, 4.15. Found: C, 34.7; H, 4.31; N, 14.1; Ba, 20.2; CHO, 3.80. Calcd. for C<sub>20</sub>H<sub>23</sub>N<sub>7</sub>O<sub>7</sub>·3H<sub>2</sub>O: C, 45.5; H, 5.54; N, 18.6; CHO, 5.50; H<sub>2</sub>O, 10.3. Found: C, 45.2; H, 5.67; N, 18.8; CHO, 5.07; H<sub>2</sub>O, 11.2. In 0.1 N sodium hydroxide solution I (10 mg./l.) exhibited a maximum at 282 mμ (%T = 27.0) and a minimum at 243 mμ (%T = 75.3). Although stable in solution at neutral to mildly alkaline pH under aerobic conditions, I rapidly changes at pH 2 with loss of activity for *Leuconostoc citrovorum*, but retains PGA-like activity for *Streptococcus faecalis* R and *Lactobacillus casei*. The primary product of anaerobic acid treatment of I appeared to be a labile derivative of tetrahydropteroylglutamic acid.

In microbiological assays of I (barium salt ·5H<sub>2</sub>O), about 0.15 mγ to 0.20 mγ corresponded to one "unit."<sup>1</sup> Thymidine was not added to the basal culture medium although this addition has been reported to increase the sensitivity of the assay.<sup>4</sup>

In mice I prevented the lethal effects of 4-aminopteroylglutamic acid.<sup>5</sup> Doses were injected three times weekly.<sup>5</sup> With 10 γ of II the average survival time was 6.8 days; with 20 γ, 5.0 days. With 10 γ of II and 15 γ of I injected simultaneously, 9 out of 11 mice survived the 14-day assay period. Average gain was 0.3 g. With 10 γ of II and 30 γ of I, all survived and the gain was 5.3 g.; with 20 γ of II and 30 γ of I, 10 out of 11 survived and the loss was 2.1 g. With 20 γ of II and 60 γ of I all survived and the gain was 4.3 g. The toxic action of 10 γ of II has been shown<sup>6</sup> not to be diminished by 20 γ of PGA.

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RECEIVED JULY 19, 1950

(4) Shive, Paper presented at 117th Meeting, American Chemical Society, Houston, Texas, March, 1950.

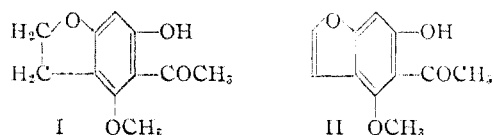
(5) Franklin, *et al.*, *Proc. Soc. Exp. Biol. Med.*, **67**, 398 (1948).

(6) Broquist, *et al.*, *J. Biol. Chem.*, **185**, 399 (1950).

### COUMARONE DEHYDROGENATION WITH N-BROMOSUCCINIMIDE

Sir:

In the course of studies on the synthesis of the furochromones khellin, visnagin and related compounds, we have found that the dehydrogenation of certain coumaranes to coumarones, typified by the conversion of dihydrovisnaginone (I) to visnaginone (II), can be carried out by a halogenation-dehydrohalogenation process involving the use of N-bromosuccinimide.



Since Horning and Reisner<sup>1</sup> have recently described unsuccessful attempts to use this reagent for the dehydrogenation of dihydrofurocoumarins, we wish to describe our findings.

The treatment of the acetate of I with N-bromosuccinimide and a trace of benzoyl peroxide in carbon tetrachloride yielded an oily product which when treated successively with dimethylaniline and alcoholic alkali afforded crude visnaginone (II). After purification there was obtained 59% of pure visnaginone, m. p. and mixed m. p. 108–109°. The synthetic material showed the same color reactions (ferric chloride, concentrated sulfuric acid) as the natural substance,<sup>2</sup> and was converted into an acetate, m. p. 63.5–65.5° which did not depress the melting point of a sample of the acetate prepared from natural visnaginone (calcd. for C<sub>13</sub>H<sub>12</sub>O<sub>5</sub>: C, 62.90; H, 4.87; found, C, 63.07; H, 5.12).

This "dehydrogenation" procedure has been applied to some related compounds; the details will be reported in forthcoming papers.

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RECEIVED JUNE 23, 1950

(1) Horning and Reisner, *This Journal*, **72**, 1514 (1950).

(2) Späth and Gruber, *Ber.*, **74B**, 1492 (1941).

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(4) S. B. Penick and Co. Fellow, 1949–50.

(5) The authors gratefully acknowledge the financial assistance of the Smith, Kline and French Laboratories and S. B. Penick and Co.

### REARRANGEMENTS INVOLVING 2-THENYLMAGNESIUM CHLORIDE

Sir:

When an ethereal solution of 2-thenyl chloride, at once a β-halo-sulfide and an isolog of benzyl chloride, was passed over amalgamated magnesium turnings in the "cyclic reactor,"<sup>1</sup> the Grignard reagent was obtained in 92% yield; hydrolysis of this solution gave an 86% yield of 2-methylthiophene (b. p. 111–113°). When the

(1) Rowlands, Greenlee and Boord, Abstracts of Papers, American Chemical Society meeting, Philadelphia, April 9 to 13, 1950, p. 8L.

reagent was prepared in the usual way, the yield was only 7.3%. Since a Grignard reagent seems never to have been prepared from an  $\alpha$ -(halomethyl)-heterocycle,<sup>2</sup> it seemed of interest to investigate typical reactions.

Carbonation of the reagent solution in the usual way gave a total yield of 45% of two pure crystalline acids, after separation by extensive fractional recrystallization. The normal product, 2-thienylacetic acid,<sup>3</sup> m. p. 61–62.5° (no depression in admixture with an authentic sample; 5.82 g.), predominated over the isomeric 2-methyl-3-thenoic acid<sup>4</sup> (3.13 g.); m. p. 115–117°.

Both products were characterized by conversion to unique derivatives. 2-Thienylacetamide<sup>5</sup> melted at 147–148°; the mixture melting point with an authentic sample was not depressed. 2-Methyl-3-thenoic acid was oxidized by alkaline potassium permanganate to thiophene-2,3-dicarboxylic acid,<sup>5</sup> m. p. 272–274° (dec.), which was converted by boiling acetic anhydride to the anhydride<sup>5</sup>; m. p. 140–141°.

Addition of the 2-thienyl reagent to an excess of ethyl chlorocarbonate in ether, with cooling in a Dry Ice-acetone-bath, followed by saponification, yielded 17.9 g. (72%) of 2-methyl-3-thenoic acid, identical with the minor product of carbonation. None of the normal acetic acid could be detected.

Investigation of other reactions of the 2-thienyl reagent and of the preparation of reagents from other halomethyl heterocycles is in progress. This work was supported by a grant-in-aid from the Graduate School.

(2) See, in this connection, Gilman and Hewlett, *Rec. trav. chim.*, [4] **51**, 93 (1932); Blicke and Burckhalter, *THIS JOURNAL*, **64**, 477 (1942); and Lecocq and Buu-Hoi, *Compt. rend.*, **224**, 658 (1947); and, concerning reagents from  $\beta$ -halomethyl compounds, Campaigne and LeSuer, *THIS JOURNAL*, **70**, 1555 (1948); and Sherman and Amstutz, *ibid.*, **72**, 2195 (1950).

(3) Blicke and Zienty, *ibid.*, **63**, 2945 (1941); Ford, Prescott, and Colingsworth, *ibid.*, **72**, 2109 (1950); Crowe and Nord, *J. Org. Chem.*, **15**, 81 (1950); and Cagniant, *Bull. soc. chim. France*, **847** (1949). Melting points are corrected.

(4) Steinkopf and Jacob, *Ann.*, **515**, 273 (1935).

(5) Linstead, Noble and Wright, *J. Chem. Soc.*, 911 (1937).

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RECEIVED JULY 10, 1950

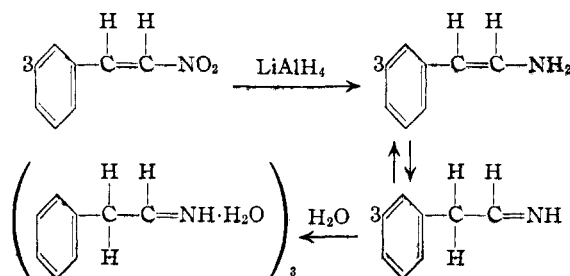
#### REVERSE ADDITION OF LITHIUM ALUMINUM HYDRIDE TO NITRO OLEFINS

Sir:

In an extension of our earlier studies<sup>1</sup> on the reduction of nitro olefins with lithium aluminum hydride, a series of experiments in this laboratory has shown that the nitro groups of  $\omega$ -nitrostyrene and 1-phenyl-2-nitropropene-1 can be selectively reduced by the reverse addition of the calculated amount of lithium aluminum hydride at sub-zero temperatures. When the first compound was treated in this way, hydrolysis of the

intermediate organo-metallic complex with 20% aqueous sodium potassium tartrate led to the isolation of phenylacetaldimine (b. p. 100–102° (4 mm.)), a viscous oil of characteristic odor (yield 45%). On standing in air it formed a white crystalline solid which, after recrystallization from petroleum ether (30–60°), melted at 83–85°. This compound is believed to be identical with the phenylacetaldimine hydrate trimer,  $(C_6H_5CH_2CH=NH \cdot H_2O)_3$ , reported previously.<sup>2</sup> *Anal.* Calcd. for  $C_{24}H_{33}N_3O_3$ : C, 70.04; H, 8.08; N, 10.21. Found: C, 70.12; H, 7.93; N, 10.05.

The probable course of these reactions is, in agreement with earlier observations<sup>3</sup>



Treatment of the aldimine with 2,4-dinitrophenylhydrazine<sup>4</sup> gave the corresponding 2,4-dinitrophenylhydrazone (m. p. 121–121.5°). *Anal.* Calcd. for  $C_{14}H_{12}N_4O_4$ : N, 18.66. Found: N, 18.52.

Benzyl methyl ketimine (b. p. 116–118° (4 mm.)), (yield 60%) obtained by the selective reduction of 1-phenyl-2-nitropropene-1, also formed a hydrate trimer (m. p. 63–65°) but less readily than did phenylacetaldimine. *Anal.* Calcd. for  $C_{27}H_{39}N_3O_3$ : C, 71.42; H, 8.66; N, 9.33. Found: C, 71.50; H, 8.52; N, 9.23. The ketimine also gave the corresponding 2,4-dinitrophenylhydrazone (m. p. 162.5–153.5°). *Anal.* Calcd. for  $C_{16}H_{14}N_4O_4$ : N, 17.83. Found: N, 17.96. The melting points of the 2,4-dinitrophenylhydrazones of the aldimine and ketimine showed no depression when mixed with authentic samples.

Experiments on the acidic hydrolysis of the intermediate organo-metallic complexes, obtained from  $\omega$ -nitrostyrene and 1-phenyl-2-nitropropene-1, have led to the isolation of phenylacetaldehyde (yield 5%). (*Anal.* of methone deriv. Calcd. for  $C_{24}H_{30}O_4$ : C, 75.36; H, 7.91. Found: C, 75.22; H, 7.75) and phenylacetone (yield 75%), respectively (*Anal.* of semicarbazone. Calcd. for  $C_{10}H_{12}N_2O$ : C, 62.80; H, 6.85. Found: C, 62.65; H, 6.58). Thus, the application of the reverse addition of lithium aluminum hydride to nitro olefins could lead to a convenient method of synthesis of higher homologs of carbonyl compounds since nitro olefins of the above type are readily formed by the condensation of aldehydes

(2) Grignard and Escourrou, *Compt. rend.*, **180**, 1883 (1925).

(3) Hochstein and W. G. Brown, *THIS JOURNAL*, **70**, 3484 (1948).

(4) Shriner and Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

(1) Gilsdorf and Nord, *J. Org. Chem.*, **15**, 807 (1950).