Communications TO THE EDITOR

The Free Radical Chemistry of Cyclic Ethers: A Novel Free Radical Rearrangement

Sir:

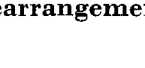
The peroxide and light induced reactions of cyclic and acyclic aliphatic amines with olefins have been studied to some extent in the past.[1,2] The reaction mechanism involves alpha hydrogen atom abstraction from the amine in the chain-propagating step. The resulting alpha amino radical adds to the olefin in question to give a beta amino alkyl radical which then reacts with more amine in the chain transfer step to give the product. Thus, in the *tert*-butyl peroxide induced reaction of piperidine with 1-octene the 1:1 addition product is 2-octylpiperidine. However, no rearrangement products were reported.

As a logical extension of the above work we have investigated the *tert*-butyl peroxide induced reaction of 4-, 5-, and 6-membered cyclic ethers with 1-octene. The respective products were 3-undecanone, 4-dodecanone, and 5-tridecanone. This indicates that the alpha ethereal radical, initially formed by the abstraction of a hydrogen atom, undergoes a rearrangement before adding to the olefin. Apparently, an intramolecular hydrogen atom shift occurs simultaneously with the opening of each ring.

In a typical experiment, 1.32 moles of tetrahydrofuran (95 g.), 0.25 moles of 1-octene (28 g.), and 0.03 mole of *tert*-butyl peroxide (5 ml.) were heated in a Parr bomb under an inert atmosphere for 2 hr. at 150°. Atmospheric distillation removed the peroxide decomposition products and unreacted starting material. Further distillation under reduced pressure removed the unreacted 1-octene. The remainder was distilled to give 18.7 g. of 4-dodecanone (40.6% yield based on 1-octene). An infrared spectrum of the ketone displayed a strong carbonyl band at 5.85 μ. Product indentification was further established by gas chromatography and isolation of a solid derivative. A gas chromatogram of the product and an authentic sample of 4-dodecanone on a 10-ft. silicone column had the same retention time at 195°, and a mixture yielded a single peak. A hydantoin melted at 114–115° (reported[3] m.p. 114–115°). A mixture melting point with an authentic sample showed no depression.

The following mechanistic path seems most plausible for the formation of the ketone:

$$(CH_3)_3CO{-}OC(CH_3)_3 \longrightarrow 2(CH_3)_3CO\cdot$$

$$(CH_3)_3CO\cdot + \text{  } \longrightarrow \text{} + (CH_3)_3COH$$

$$\text{} \longrightarrow \cdot CH_2CH_2CH_2CHO$$

$$\cdot CH_2CH_2CH_2CHO \longrightarrow CH_3CH_2CH_2CO\cdot$$

$$CH_3CH_2CH_2CO\cdot + C_6H_{13}CH{=}CH_2 \longrightarrow CH_3CH_2CH_2COCH_2\dot{C}HC_6H_{13}$$

$$CH_3CH_2CH_2COCH\dot{C}HC_6H_{13} + RH \longrightarrow CH_3CH_2CH_2COCH_2CH_2C_6H_{13} + R\cdot$$

These results have prompted us to investigate morpholine which is both a cyclic amine and a cyclic ether in order to ascertain what mechanism predominates in this system.

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The Structure of Fervenulin, a New Antibiotic[1]

Sir:

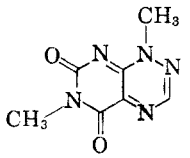
Fervenulin, a new crystalline antibiotic isolated by Eble and co-workers[2] from culture filtrates of an actinomycete (from a California soil), *Streptomyces fervens* n. sp., has demonstrated broad-spectrum antibacterial, antifungal, antiparasitic, and antitumor cell activity *in vitro*.[3] No structure for fervenulin has been proposed. Its empirical formula has been reported as $C_7H_7N_5O_2$, and its infrared spectrum was interpreted[2] to indicate the presence of a six-membered enol lactone.

This antibiotic is of interest since the proposed empirical formula, $C_7H_7N_5O_2$, is identical with that of toxoflavin (I), an antibiotic recently synthesized in our laboratory.[4] The ultraviolet absorption spectrum of fervenulin is not identical, but strikingly similar, to that of toxoflavin; furthermore,

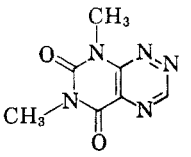
(1) This investigation was supported by research contract SA-43-ph-3025 from the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service.

fervenulin, like toxoflavin, is readily reduced electrolytically.[2]

These facts strongly suggested that fervenulin is isomeric with toxoflavin. Consideration of the structural requirements necessary to explain the ease of hydrogenation exhibited by fervenulin resulted in the formulation of several possible structures with the basic pyrimido(5,4-e)-*as*-triazine ring system. These derivatives have been synthesized in our laboratory. Among these compounds the 6,8-dimethyl isomer II,[5] m.p. 178–179°, prepared by the method of Pfleiderer and Schündehütte,[5] by the reductive cyclization of 1,3-dimethyl-2,4 - dioxo - 5 - nitroso - 6 - formylhydrazino-1,2,3,4-tetrahydropyrimidine with sodium hydrosulfite in the presence of formic acid and formamide, was found to be identical to fervenulin[6] in every respect.



I
Toxoflavin



II
Fervenulin

The ultraviolet absorption [$\lambda_{max}^{ethanol}$ 238 mμ (ε 18,500), 275 mμ (ε 1600), and 340 mμ (ε 4200)] and the infrared absorption [λ_{max}^{Nujol} (μ) 3.0 (w), 3.4 (s), 3.8 (w), 5.8 (s), 6.0 (s), 6.4 (s), 6.55 (s), 6.8 (s), 7.0 (s), 7.1 (m), 7.2 (w), 7.4 (s), 7.8 (s), 8.0 (w), 8.25 (s), 8.75 (w), 9.0 (w), 9.2 (s), 9.6 (s), 10.05 (m), 10.4 (w), 10.7 (m), 11.3 (m), 12.2 (m), 12.45 (w), 13.4 (s), 13.55 (m), and 13.9 (s)] of the synthetic compound and those of the authentic sample of fervenulin[6] proved to be identical. There was no depression in the mixed melting point determination. The R_f values (at 25°, descending) of the synthetic and the natural product in 96% water–4% 1-butanol are 0.82 and 0.81, respectively; and in 25% acetic acid–50% 1-butanol–25% water are 0.81 and 0.81, respectively.

Thus the structure of the new antibiotic, fervenulin, is established as 6,8-dimethyl-5,7-dioxo-5,6,7,8-tetrahydropyrimido(5,4-e)-*as*-triazine (II). The structure of fervenulin and that of toxoflavin have provided a new class of antibiotics with pyrimido(5,4-e)-*as*-triazine as their basic ring system. Further studies in this interesting area are in progress.

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(6) This comparison was made possible by a generous gift of fervenulin (Lot No. 4234-DMW-74-7) kindly provided by Dr. T. E. Eble of the Upjohn Co., Kalamazoo, Mich., to whom sincere thanks are due.

Acylation of a Carbonium Ion by the Action of a Reissert Compound

Sir:

Although many base-catalyzed condensation reactions of Reissert compounds are known,[1] the only reports of acid-catalyzed condensation reactions have been those describing the formation in relatively low yield of benzoin and some related compounds in the acid-catalyzed hydrolysis reactions of 1-benzoyl-1,2-dihydroquinaldonitrile and 2-benzoyl-1,2-dihydroisoquinaldonitrile (I).[2,3] However, on the basis of a mechanism for the acid-catalyzed hydrolysis of Reissert compounds proposed several years ago,[3] we reasoned that such compounds might function as acylating agents towards carbonium ions. We now wish to report the results of two remarkably different types of acid-catalyzed condensation reactions, the first between I and benzhydrol which illustrates the anticipated acylation reaction, and the other between I and 1,1-diphenylethylene (or 1,1-diphenylethanol) which is best described as a complex rearrangement-condensation reaction.

Treatment of 2-benzoyl-1,2-dihydroisoquinaldonitrile (I) with benzhydrol and concentrated sulfuric acid in dioxane solution gave isoquinaldamide bisulfate (VII) and α,α-diphenylacetophenone (VI),[4] the latter compound being obtained in 76% yield. In accord with the mechanism of acid-catalyzed hydrolysis of I proposed previously,[3] it is visualized that the reaction of I with sulfuric acid first gives the cyclic intermediate II. Condensation of II with the benzhydryl cation, which is formed by the action of concentrated sulfuric acid on benzhydrol,[5] gives IV. Perhaps the mesoionic compound III is also formed as an intermediate

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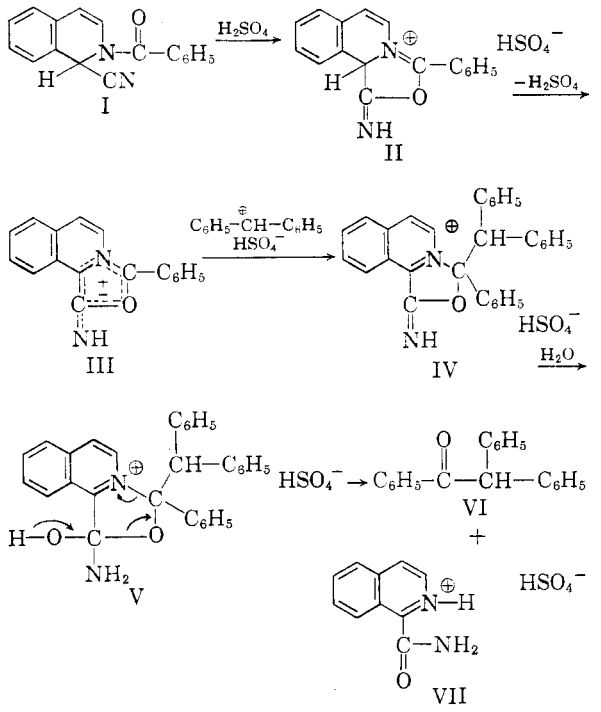
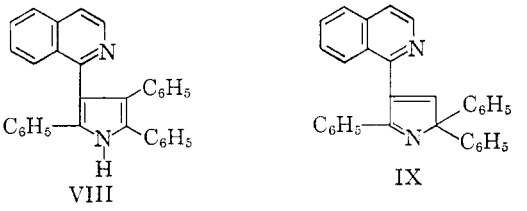
but this has not been demonstrated to be the case. Addition of water to IV affords V, which then collapses to give VI and VII.



The sulfuric acid-catalyzed condensation of I with 1,1-diphenylethylene (or 1,1-diphenylethanol) in dioxane solution gave two isomeric compounds of molecular formula $C_{31}H_{22}N_2$. The first, a colorless substance, m.p. 194.0–194.5°, was obtained in 19–26% yield; it showed no infrared absorption peak in the NH stretching region and did not form an acetyl derivative. The second, a yellow solid, m.p. 262.5–263.5°, obtained in 6–17% yield, had a sharp infrared absorption peak at about 2.9 μ and gave an *N*-acetyl derivative, m.p. 230.0–231.5°, on treatment with hot acetic anhydride in the presence of sodium acetate. Prolonged hydrolysis of either of the isomeric compounds, $C_{31}H_{22}N_2$, in 3.6*N* sulfuric acid solution gave equimolar amounts of 1-hydroxyisoquinoline[6] and 2,3,5-triphenylpyrrole.[7] The compound of m.p. 194.0–194.5° was readily converted to its isomer by the action of hot 12*N* sulfuric acid or by potassium hydroxide fusion. Thus, it can be inferred that the compound of m.p. 262.5–263.5° is 2,3,5-triphenyl-4-(1-isoquinolyl)-pyrrole (VIII). On the basis of mechanistic concepts which will be explained more fully in a forthcoming paper, the compound of m.p. 194.0–194.5° is tentatively assigned the structure of 2,2,5-triphenyl-4-(1-isoquinolyl)-pyrrolenine (IX).[8]



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(8) Complete and satisfactory analyses were obtained for all of the compounds reported in this communication. The known compounds were identified by mixed melting point tests and infrared spectral comparisons with samples synthesized according to the methods given in the literature.