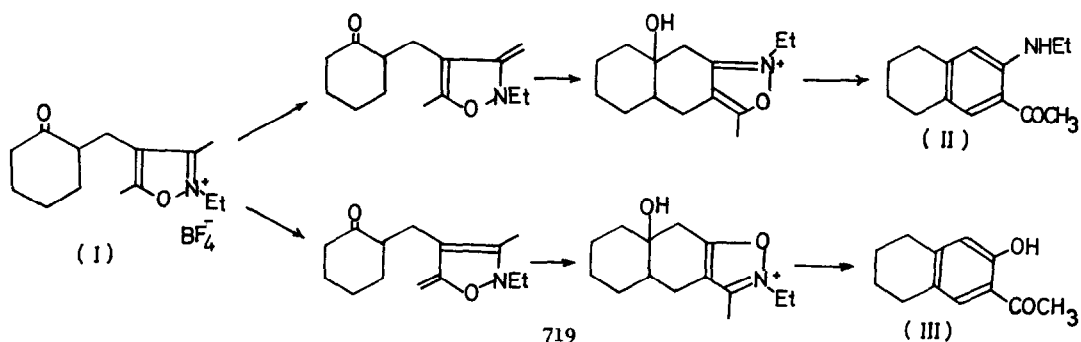


THE ISOXAZOLE AROMATIZATION REACTION.
A SYNTHETIC APPROACH TO DITERPENOID PHENOLS

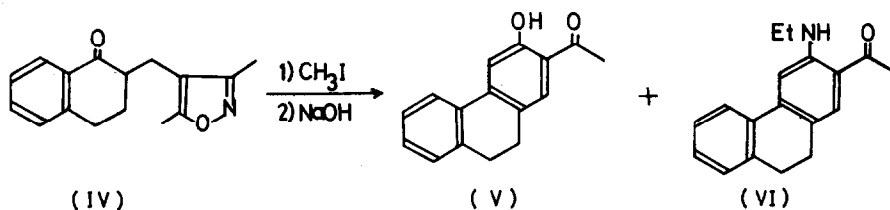
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(Received in Japan 25 October 1967)

During the investigation of isoxazole annelation^{1,2)} it was discovered that the quaternary salts of 4(3-oxoalkyl)isoxazoles were converted into acylphenols upon base treatment²⁾. This finding has drawn our attention to a new general synthetic approach to diterpenoid phenols. However, the reaction turned out to be fairly sensitive to reaction conditions, reflecting the character of isoxazoles. For instance, treatment of I²⁾ with pyrrolidine in benzene afforded 3-acetyl-2-N-ethylamino-5,6,7,8-tetrahydronaphthalene(II), $\lambda_{\text{max}}^{\text{EtOH}}$ 238, 267, 395 μ (log ϵ 4.26, 3.83 and 3.65 respectively), ν neat 3300, 1645, 1575, 1515 cm^{-1} , δ in CDCl_3 1.28(3H, t, J=7 cps) 2.52(3H, s.) 3.22(2H, q, J=7 cps) 6.46(1H, s.) and 7.46(1H, s.) ppm, semicarbazone; m.p. 201-202°, in 25 % yield as a sole aromatic product, while with 1N sodium hydroxide an acetylphenol III^{2,4,8)} became the major product(40-50 %) along with a small amount of II.



Similarly, treatment of the tetralone derivative IV, m.p. 104-105°, prepared in 60 % yield by MMC⁵⁾ alkylation of tetralone with 3,5-dimethyl-4-chloromethylisoxazole³⁾, with methyl iodide followed by reflux in 1N sodium hydroxide furnished a mixture of dihydrophenanthrene derivatives in about 40 % yield which consisted of V⁸⁾, m.p. 119-120°, $\lambda_{\max}^{\text{EtOH}}$ 222, 300 and 354 m μ (log ϵ 4.35, 4.30 and 3.81 respectively), ν_{nujol} 1645 and 1625 cm⁻¹, δ in CDCl₃ 2.68(3H, s.) 2.90(4H, s.) 7.39(1H, s.) 7.60(1H, s.) and 12.18(1H, s.) ppm and VI, m.p. 115-117°, $\lambda_{\max}^{\text{EtOH}}$ 238, 262, 308 and 416 (log ϵ 4.23, 4.32, 4.29 and 3.84 respectively), ν_{nujol} 3300, 1640 and 1560 cm⁻¹, in about 2:1 ratio.

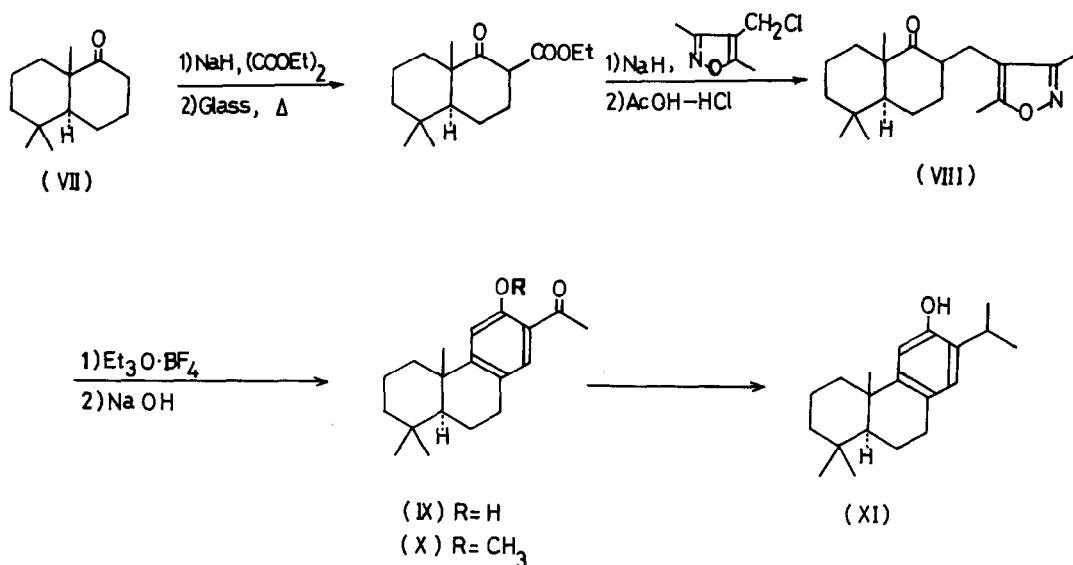


These reactions suggest that there are two ways of aromatization originating from a loss of a proton from either one of active methyl groups present at 3 and 5 positions of isoxazole as shown in the scheme.

Aside from the mechanistic interest, we were encouraged to learn that quaternary salts of 3,5-dimethyl-4(3-oxoalkyl)isoxazoles were transformed into acylphenols in moderate yields and tried to apply this reaction to a synthesis of ferruginol(XI), a typical diterpenoid phenol⁶⁾. Thus 5,5,8a-trimethyl-1-decalone(VII)⁷⁾ was converted in the usual way into a β -ketoester derivative of which alkylation with 3,5-dimethyl-4-chloromethylisoxazole followed by decarboxylation with acid afforded VIII, m.p. 99-100°, $\lambda_{\max}^{\text{EtOH}}$ 224 m μ (log ϵ 3.67), ν_{nujol} 1704, 1638 cm⁻¹, δ in CCl₄ 0.94(6H, s.) 1.11(3H, s.) 2.12(3H, s.) 2.30(3H, s.) ppm. Treatment of VIII with triethyloxonium fluoroborate followed by reflux in 1N sodium hydroxide gave, along with some recovered starting material, an acylphenol IX⁸⁾, m.p. 123-124°, $\lambda_{\max}^{\text{EtOH}}$ 220, 265 and 341 m μ (log ϵ 4.33, 4.15 and 3.66 respectively), ν_{nujol} 1645 and 1621 cm⁻¹, δ in CDCl₃ 0.99(6H, s.)

1.21(3H, s.) 2.60(3H, s.) 6.84(1H, s.) 7.35(1H, s.) and 11.87(1H, s.) ppm, in 36 % yield based on utilized VIII. The acylphenol IX was further characterized by the formation of its methyl ether (X), $\lambda_{\max}^{\text{EtOH}}$ 219, 258 and 321 μ ($\log \epsilon$ 4.12, 3.92 and 3.55 respectively), $\nu_{\text{chf.}}$ 1668 and 1608 cm^{-1} , δ in CDCl_3 3.87 (3H, s.), semicarbazone; m.p. 218–219°¹⁰). Since X had been already converted into dl-ferruginol by King and his co-workers⁹) the isoxazole aromatization mentioned above thus completed a total synthesis of ferruginol¹¹).

Further applications of the method to syntheses of various diterpenoid phenols are in progress.



Acknowledgment: The authors are grateful to Professor Gilbert Stork, Columbia University, whose advice was of vital importance to them in the early stages of this work.

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- 8) With ferric chloride this compound gives deep blue coloration.
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- 10) Although melting point of the semicarbazone is slightly lower than the reported value(222-223°), its spectral properties are all in accord with structure X indubitably.
- 11) All new crystalline compounds gave satisfactory elemental analysis.