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A NOVEL REARRANGEMENT CATALYZED BY A GRIGNARD REAGENT

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A previous communication (1) from these laboratories reported the product, m.p. 219-220°, from the reaction between 11-keto-6, 11-dihydrodibenzo[b,e] oxepine (I) and 3-dimethylaminopropylmagnesium chloride to be 11-hydroxy-11-(3-dimethylaminopropyl)-6,11-dihydrodibenzo [b,e] oxepine (II). On heating this product in refluxing acetic anhydride, an anthracene derivative (IV) resulted instead of the expected 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[b,e] oxepine. Stach and Bickelhaupt (2) have also carried out this reaction but under somewhat different conditions. In contrast to our results these workers have reported a product melting at 120-121°, which under various dehydrating conditions always gave the expected olefin and no significant amounts of anthracene-like compounds.[1] These apparent discrepancies prompted a closer examination of the identity of the higher-melting product and of the reaction conditions.

When ketone (I) was heated at 40° for three hours in tetrahydrofuran with the Grignard reagent prepared from two equivalents of 3-dimethylaminopropylchloride[2] the compound reported by Stach and Bickelhaupt (2) resulted in 55% yield. [M.p. 119-120° from isopropanol; Calcd. for $C_{19}H_{23}NO_2$: C,76.73, H,7.79, N,4.70. Found C,76.45, H,7.98

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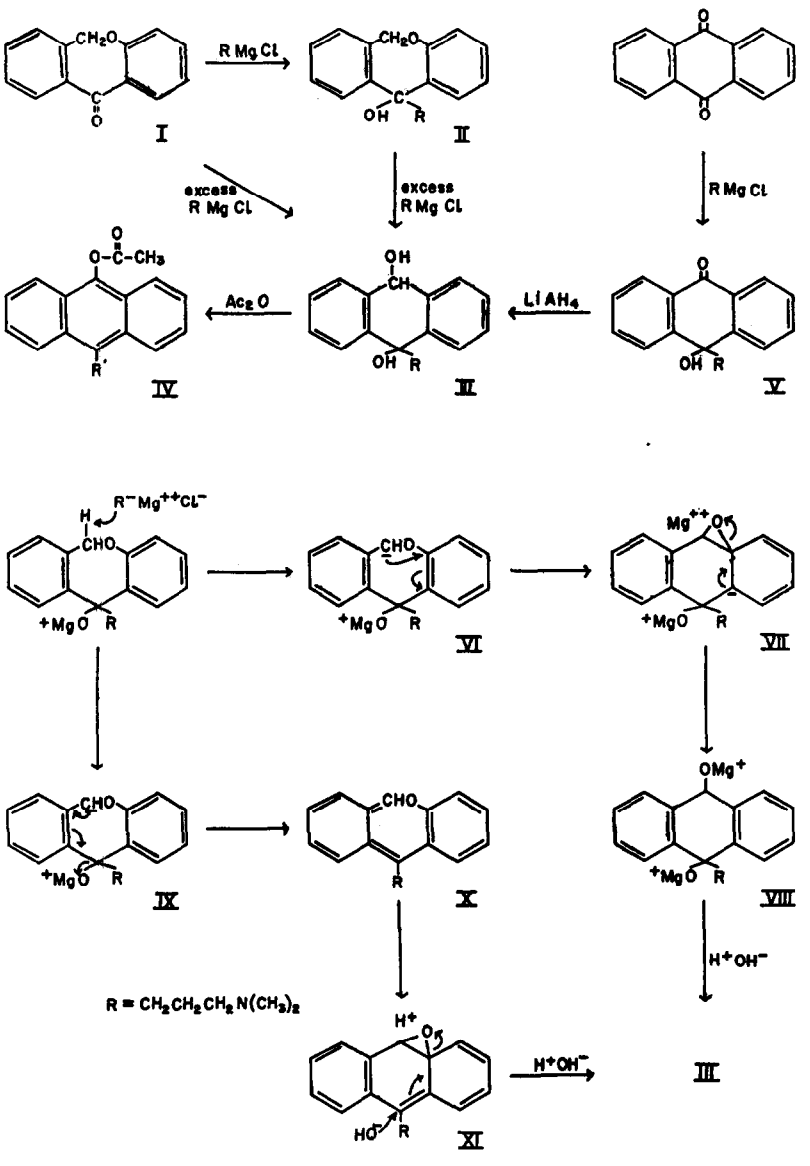
1 Personal communication from K. Stach.

2 The conversion of this compound to the Grignard reagent is assumed to be 60-70%.


R Mg Cl
excess R Mg Cl
excess R Mg Cl
R Mg Cl
Ac2 O
LiAlH4
R = CH2CH2CH2N(CH3)2
H+OH-
H+OH-

N,4.60. λ_{max}(ethanol), 263,269 (ϵ=880, 857); ν_{max}(nujol) 2800 (associated OH); τ^{3}_{max}(CD_3OD), 2.72, 2.84, 2.89, 2.94, 5.07, 7.52, 7.74, 7.91, 8.62, 8.74]. The chemical and physical properties clearly indicated the structure of the expected product, 11-hydroxy-11-(3-dimethylaminopropyl)-6,11-dihydrodibenzo[b,e] oxepine (II). The reaction was repeated using the same ratio of Grignard reagent to ketone but with heating for 16 hrs. under reflux. In this case, the yield of compound II fell to 47% and a byproduct, m.p. 219-220°, was produced in 10% yield which, because of its insolubility in chloroform, was easily separated from the major product. This higher melting product was produced exclusively and in 89% when ketone (I) was treated with a larger excess of Grignard reagent (prepared from three equivalents of 3-dimethylaminopropylchloride)for 16 hours in refluxing tetrahydrofuran. [M.p. 219-220° from acetone-methanol; Calcd. for $C_{19}H_{23}NO_2$: C,76.73; H,7.79; N,4.70. Found: C,76.65; H,7.65, N,4.83. λ_{max}(ethanol) 260,269 (ϵ=595,444) ν_{max}(nujol) 2800 (associated OH) 3320 (free OH)]. These data suggested that the compound could be 9-(3-dimethylaminopropyl)-9,10-dihydroxy-9,10-dihydroanthracene (III) and that a rearrangement of the dibenzo[b,e] oxepine ring system catalyzed by the excess Grignard reagent may have taken place.

Since the higher melting product was not sufficiently soluble for an N.M.R. spectral determination an attempt was made to convert it to a monoacetate by treatment with acetic anhydride in pyridine at room temperature. The acetylation product was isolated as a viscous oil and resisted attempts at crystallization. As would be expected from its proposed structure, it was heat-sensitive and easily underwent dehydration to form the anthracene derivative (IV).

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[3] Run at 60 mc/sec and using tetramethylsilane as standard.

The oil was used without further purification for determination of its ultraviolet, infrared and N.M.R. spectra. [λ_{max} (ethanol) 251, 257, 261 (s) 269 (s), 335, 355, 373, 394. (ε=930,1390, 760, 412, 10, 15, 24,25); ν_{max}($CHCl_3$) 2900 (associated OH), 1730 (carbonyl); τ^{3}_{max}($CDCl_3$) 2.22, 2.30, 2.54, 2.73, 2.81, 3.04, 3.24, 7.60, 7.67, 7.96, 8.07, 8.86]. The presence of approximately 0.3% of the anthracene derivative (IV) was clearly indicated by the ultraviolet spectrum. This amount was sufficient to distort the normal spectrum of the dihydroanthracene so that the expected twin peaks at 261 and 269 appeared only as shoulders. The formation of a monoacetate was confirmed by the disappearance of the free hydroxyl band and the appearance of the ester carbonyl band in the infrared spectrum. The N.M.R. spectral data on the monoacetate furthar corroborated the proposed structure (III) for the higher melting product. All of the expected peaks were present with the exception of a peak for the benzylic proton. Since this proton is considerably deshielded by the acetoxy group and the two benzene rings its peak may have shifted downfield to the extent that it was masked by the aromatic proton region.

The structure of the higher melting compound was finally demonstrated unequivocally by a comparison with 9-(3-dimethylaminopropyl)-9,10-dihydroxy-9,10-dihydroanthracene (III) which had been synthesized by an independent and unambiguous route. The Grignard reagent prepared from two equivalents of 3-dimethylaminopropylchloride was added dropwise to a refluxing solution of anthraquinone in tetrahydrofuran containing 10% benzene to give a 56% yield of 10-(3-dimethylaminopropyl)-10-hydroxy-anthrone (V). [M.p. 148-149° from isopropanol; Calcd. for $C_{19}H_{21}NO_2$: C,77.26; H,7.17, N,4.74: Found C,77.13; H,7.38; N, 4.67. λ_{max}(ethanol)273 (ε=15,190); ν_{max}(nujol) 2800 (associated OH), 1664 (carbonyl)]. The reduction of the hydroxy ketone (V) was carried out with lithium aluminum

hydride in ether at room temperature for two hours giving a 40% yield of III which was identical in every respect with the higher melting product resulting from the reaction of the ketone (I) with an excess of 3-dimethylaminopropylmagnesium chloride.

The catalytic role of the excess Grignard reagent in promoting the rearrangement of the dibenzo[b,e] oxepine ring was shown by the successful conversion of the low melting product (II) into the isomeric higher melting product (III). A solution of II in tetrahydrofuran when heated under reflux for 16 hours in the presence of the Grignard reagent prepared from three equivalents of 3-dimethylaminopropylchloride gave III in 80% yield.

Two possible mechanisms for the conversion of II into III are suggested by the fact that this rearrangement is base catalyzed. Both require the initial attack of the Grignard anion for removal of a benzylic proton to produce a carbanion at position six of the dibenzo[b,e] oxepine ring. This carbanion can then be transformed in a concerted manner as depicted in structures VI and VII to the more stable alkoxide anion VIII which on hydrolysis would give III. Another possible mechanism involves the vinylogous beta elimination of the hydroxyl group shown in structure IX, to produce a compound represented by X. A valence tautomerism can then produce the epoxy compound XI which on hydrolysis would also give III.

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