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PHOTOCHEMICAL SYNTHESIS OF PHENANTHRENES. SYNTHESIS OF ARISTOLOCHIC ACID

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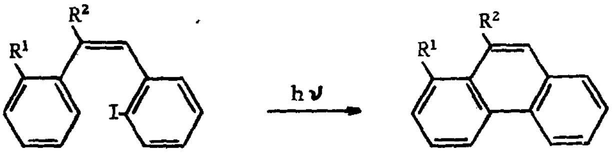
A new general synthesis of substituted phenanthrene derivatives, involving photocyclization of substituted 2-iodostilbenes, is presented herewith. The usefulness of the method for the synthesis of nitrophenanthrenes, not readily accessible by other approaches, is illustrated in an efficient synthesis of the naturally-occurring tumor inhibitor, aristolochic acid (V, R^1=H, R^2=OCH_3) (1,2).

N. Kharasch and co-workers have shown that photolysis of iodoaromatic compounds in an aromatic solvent, particularly benzene, by essentially monochromatic light (2537 A°), is useful for the preparation of biphenyl and polyphenyl derivatives (3). Photolysis in cyclohexane,methanol, or ethanol results in reductive de-iodination (4).

In this study, the photolysis of iodoaromatic compounds was used in an intramolecular reaction, to effect photocyclization. Thus, 2-iodo-*cis*-stilbene (I, R^1=R^2=H), b.p. 125-127°/0.5 mm., λ_{max}^{EtOH} 271.5 mμ (ε 16,900), photolyzed in cyclohexane for 3 hr. at room temperature with a Nester/Faust NFUV-300 ultraviolet source, afforded phenanthrene, m.p. 95-97°, in 90% yield (isolated product). The progress of the reaction was followed by ultraviolet spectral analysis after appropriate time intervals. Similarly, 2-methyl-2'-iodo-*cis*-stilbene (I, R^1=CH_3, R^2=H), b.p. 104-105°/0.07 mm., λ_{max}^{EtOH} 265 mμ (ε 23,400), photolyzed for 4 hr., afforded a 96% yield of 1-methylphenanthrene (II, R^1=CH_3, R^2=H), m.p. 122-124° (lit. 123° (5)), undepressed upon admixture with an authentic sample.

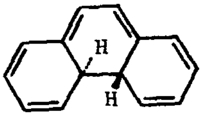


I II

The methyl ester of 2'-iodo-*cis*-stilbene-α-carboxylic acid (I, R^1=H, R^2=$COOCH_3$), $C_{16}H_{13}IO_3$, m.p. 98-100°, λ_{max}^{EtOH} 286 mμ (ε 11,000), afforded (71%) 9-phenanthroic acid methyl ester (II, R^1=H, R^2=$COOCH_3$), m.p. 118-119° (lit. 116° (6)). The methyl ester of 2-methyl-2'-iodo-*cis*-stilbene-α-carboxylic acid (I, R^1=CH_3, R^2=$COOCH_3$), $C_{17}H_{15}IO_2$, m.p. 92-94°, λ_{max}^{EtOH} 273 mμ (ε 6,400), gave (62%) 1-methyl-10-phenanthroic acid methyl ester (II, R^1=CH_3, R^2=$COOCH_3$), $C_{17}H_{14}O_2$, m.p. 94-95°, undepressed upon admixture with material (m.p. 94-95°) prepared by diazomethane methylation of the corresponding acid, prepared as in (5).

α-Nitro-2'-iodo-*cis*-stilbene (I, R^1=H, R^2=NO_2) (7), $C_{14}H_{10}INO_2$, m.p. 64-65°, λ_{max}^{EtOH} 314 mμ (ε 7,600), photolyzed for 2.5 hr., gave a 40% yield of 9-nitrophenanthrene, m.p. 114-116° (lit., 118° (8)). A closer model for the synthesis of aristolochic acid was the preparation of 1-carbomethoxy-10-nitrophenanthrene (II, R^1=$COOCH_3$, R^2=NO_2) by photolysis of 2-carbomethoxy-2'-iodo-α-nitrostilbene, $C_{16}H_{12}INO_4$, m.p. 144-145°, λ_{max}^{EtOH} 306 mμ (ε 9,000). II, R^1=$COOCH_3$, R^2=NO_2, $C_{16}H_{11}NO_4$, m.p. 152-153°, λ_{max}^{EtOH} 257.5 mμ (ε 36,800), was obtained in 45% yield.

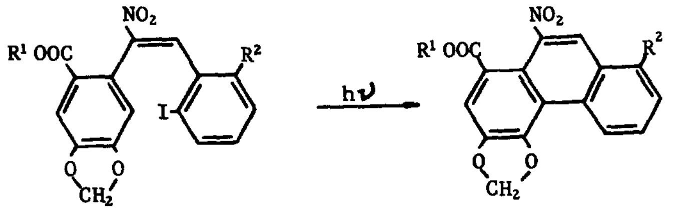
Irradiation with ultraviolet light of solutions containing *cis*-stilbenes in the presence of a suitable oxidant such as molecular oxygen or iodine has been demonstrated to lead to formation of phenanthrene derivatives (9). Evidence which strongly indicates that the latter reaction proceeds *via* the dihydrophenanthrene, III, has recently been presented (10,11). It is highly improbable that the photocyclization of 2-iodo-



III

stilbenes proceeds via a similar intermediate. Photolysis of 2-carbomethoxy-α-nitrostilbene, $C_{16}H_{13}NO_4$, m.p. 94-96°, λ^{EtOH}_{max} 315 mμ (ε 14,500), in the presence of added iodine or dissolved molecular oxygen failed to yield any of the corresponding phenanthrene. The failure of stilbenes having nitro substituents to undergo photoconversion to the corresponding phenanthrenes has been noted previously (9). In the present work, 2-carbomethoxy-2'-chloro-α-nitrostilbene, $C_{16}H_{12}ClNO_4$, m.p. 117-118°, λ^{EtOH}_{max} 308 mμ (ε 10,300), when subjected to irradiation at 2537A°, failed to undergo cyclization, and the latter observation militates strongly against the intermediacy of an unorthodox dihydrophenanthrene such as III in the photocyclization of 2-iodo-stilbenes. A recent electron spin resonance study of the photolysis of iodobenzene at 77°K yielded results which support the occurrence of the "free" phenyl radical as the active intermediate in the photoconversion of iodobenzene to biphenyl (12). It is suggested that the photocyclization of 2-iodostilbenes may likewise proceed via a free radical pathway.

Photolysis of 2-carbomethoxy-4,5-methylenedioxy-2'-iodo-α-nitrostilbene (IV, $R^1=CH_3$, $R^2=H$), $C_{17}H_{12}INO_6$, m.p. 131-133°, yielded (26%) aristolochic acid II methyl ester (V, $R^1=CH_3$, $R^2=H$), m.p. 274-275° (lit. 274° (13)). Photolysis of 2-carbomethoxy-4,5-methylenedioxy-2'-iodo-6'-methoxy-α-nitrostilbene (IV, $R^1=CH_3$, $R^2=OCH_3$), $C_{18}H_{14}INO_7$, m.p. 154-155°, λ^{EtOH}_{max} 304 mμ (ε 9,400), afforded, in 54% yield, aristolochic acid methyl ester (V, $R^1=CH_3$, $R^2=OCH_3$), m.p. 280-283°. Hydrolysis of the ester yielded aristolochic acid



IV V

(V, R^1=H, R^2=OCH_3), m.p. 275-277° dec., λ_{max}^{EtOH} 390 mμ (ε 6,500), 318 mμ (ε 12,000), 250 mμ (ε 27,000), m.p. undepressed by admixture with an authentic sample (2). The infrared spectrum (KBr pellet) was superimposable upon that of the authentic sample.

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