

Photochemical Reductive Acylation and Oxidative Acyl Activation on Phenazine and Related Nitrogen Heterocycles¹⁾

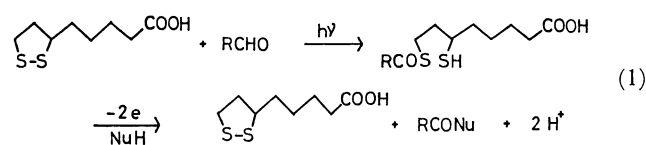
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(Received December 17, 1979)

Synopsis. Irradiation of phenazine in acetaldehyde or propionaldehyde solution gave an *N*-acylated 5,10-dihydrophenazine. Acridine similarly gave 9-acyl-9,10-dihydroacridine, and 10-methylacridinium salt gave 9-acyl-10-methyl-9,10-dihydroacridine. In methanol *N*-acylated dihydrophenazines reacted with *N*-bromosuccinimide to give phenazine and methyl carboxylates in quantitative yield.

p-Benzoquinones are known to undergo reductive acylation with aldehydes under photo-irradiation.²⁾ When the resultant hydroquinone monocarboxylates are oxidized in the presence of appropriate nucleophiles, oxidative acyl activation takes place, and the acyl group is transferred to the nucleophile with a concurrent reproduction of *p*-benzoquinones.³⁾ The entire process, the reductive acylation followed by the oxidative acyl transfer, constitutes a cycle which converts aldehydes into activated acyl compounds by means of a quinone-hydroquinone redox pair as an acyl carrier. A similar process has been disclosed recently by us for a 1,2-dithiolane-1,3-dithiol redox pair, and a formal resemblance of the process to the reaction of coenzyme lipoic acid in pyruvate dehydrogenase has been pointed out (Eq. 1).⁴⁻⁷⁾ In living organisms there are several redox coenzymes which contain nitrogen heterocycles, *e.g.*, flavin and nicotinamide, and it would be interesting to study nitrogen heterocycles for the reaction similar to quinones and 1,2-dithiolanes.

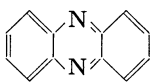
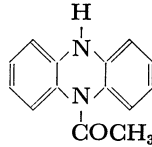
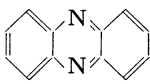
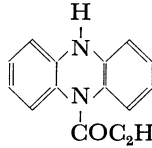
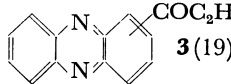
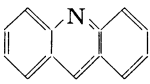
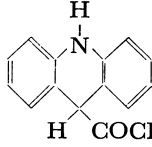
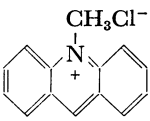
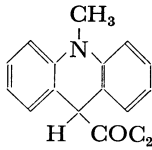


Results and Discussion

The results of photo-reactions are summarized in Table 1. Besides the heterocycles in Table 1, 1,10-phenanthroline, quinoxaline, quinoline, and benzothiazole were subjected to photo-irradiation in propionaldehyde solution, but the starting heterocycles were recovered unreacted. *N*-alkylated quinolinium and 1-benzyl-3-carbamoylpyridinium chlorides gave intractable complex mixtures. The reactions in Table 1 generally gave complicated mixtures, and the isolation of the products was attained by recrystallization and column chromatography.

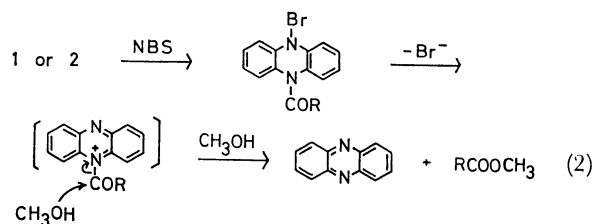
The mechanism of the present photochemical reductive acylation is yet to be studied. In contrast to the reaction of 1,2-dithiolanes which was effected under both photochemical and thermal (in the presence of AIBN as radical initiator) conditions,⁷⁾ the reaction of phenazine proceeded only under photo-irradiation. The photo-reduction of acridine⁸⁾ and phenazine⁹⁾ has

TABLE 1. PHOTO-REACTION OF NITROGEN HETEROCYCLES WITH ALDEHYDES

Heterocycle	Aldehyde	Irradiation time/h	Product (yield/%)
	CH ₃ CHO	6	 1 (35)
	C ₂ H ₅ CHO	5	 2 (20)
	C ₂ H ₅ CHO	5	 3 (19)
	CH ₃ CHO	2	 4 (36)
	C ₂ H ₅ CHO	3	 5 (52)

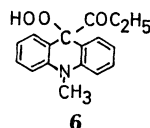
been reported. The reductive photo-alkylation of acridine by aliphatic carboxylic acid has also been described.¹⁰⁾ The present reaction may be related to these reactions in mechanism. The acylation reaction will find a synthetic use for the preparation of acyl-phenazines, since the synthesis of acetyl- and propionyl-phenazine has not been described in the literature reflecting the difficulty of the direct acylation of the phenazine nucleus.

The 5-acyl-5,10-dihydrophenazines **1** and **2** in methanol were allowed to react with *N*-bromosuccinimide (NBS) at room temperature. The oxidation proceeded in a few minutes to give a quantitative yield of methyl carboxylates and phenazine. The plausible mechanism is formulated in Eq. 2. Thus, it is concluded that phenazine undergoes the same type of reductive acylation and oxidative acyl transfer reactions as those



of quinones and 1,2-dithiolanes.

The oxidation of **4** or **5** did not bring about such an acyl activation. The compound **5** was found to be gradually oxidized in the air, even in the isolated crystalline state, to give 10-methyl-9(10*H*)-acridinone. The reaction most probably involved the formation of a 9-hydroperoxy derivative **6** by air oxidation and its subsequent decomposition to propionic acid and 10-methyl-9(10*H*)-acridinone.



Experimental

Photo-reaction of Phenazine with Acetaldehyde. Phenazine (0.40 g) was dissolved in acetaldehyde (200 ml), and the mixture was irradiated under nitrogen at $\leq 10^\circ\text{C}$ by a 100W immersion type high pressure mercury lamp.^{4,6)} The light shorter than 330 nm in wavelength was eliminated by a liquid filter (NaBr-Pb(NO₃)₂-H₂O).⁶⁾ After 6 h irradiation, the red reaction mixture was evaporated, the residue was digested in 5 ml of benzene, and the insoluble red solid was collected. Recrystallization from ethanol gave reddish crystals, 0.22 g (**1**, 35%). For further purification, the product dissolved in chloroform was passed through a short column of silica gel. Another recrystallization from ethanol gave white granular crystals. mp 258–260 °C (254–255 °C¹¹⁾); IR (Nujol) 3280 (NH) and 1650 cm⁻¹ (CO); NMR (CF₃CO₂H) δ =2.58 (3H, s, CH₃), 7.0–7.6 (8H, m, aromatic H). Found: C, 74.90; H, 5.46; N, 12.48%. Calcd for C₁₄H₁₂N₂O: C, 74.98; H, 5.39; N, 12.49%.

Photo-reaction of Phenazine with Propionaldehyde. The reaction was carried out in a similar manner to the above procedure using 0.55 g of phenazine in 150 ml of propionaldehyde. After 5 h photo-irradiation, the mixture was concentrated. The solid product was filtered and recrystallized from ethanol. Yellow needles (**3**). Yield, 0.14 g, 19%; mp 123–123.5 °C; IR (Nujol) 1685 cm⁻¹ (CO); NMR (CCl₄) δ =1.29 (3H, t, J =7.0 Hz, CH₃), 3.43 (2H, q, CH₂), 7.6–8.4 (7H, m, aromatic H); MS (m/e) 236 (M⁺), 179 (M⁺-C₂H₅-CO). Found: C, 75.88; H, 5.14; N, 11.82%. Calcd for C₁₅H₁₂N₂O: C, 76.25; H, 5.12; N, 11.85%. The filtrate from the concentrated reaction mixture was further evaporated to dryness, and the residue was dissolved in a small amount of ethanol. The addition of hexane produced precipitates, which were recrystallized from ethanol to give reddish crystals. **2**. Yield, 0.15 g, 20%. Another recrystallization from ethanol after passing through a short column of silica gel in chloroform gave white granular crystals. mp 193–194 °C; IR (Nujol) 3250 (NH) and 1650 cm⁻¹ (CO); NMR (CDCl₃) δ =1.10 (3H, t, J =7.0 Hz, CH₃), 2.52 (2H, q, CH₂), 6.12 (1H, s, NH, D-exchange), 6.6–7.5 (8H, m, aromatic H); MS (m/e) 238 (M⁺), 181 (M⁺-C₂H₅CO). Found: C, 75.49; H, 5.97; N, 11.72%. Calcd for C₁₅H₁₄N₂O: C, 75.61; H, 5.92; N, 11.75%.

Photo-reaction of Acridine with Acetaldehyde. Acridine (2.01 g) dissolved in acetaldehyde (200 ml) was irradiated for 2 h. The white precipitates formed (9,9',10,10'-tetrahydro-9,9'-biacridine,¹²⁾ 0.12 g, 12%) were filtered off, and the filtrate was concentrated to dryness. The residue was

subjected to column chromatography (silica gel, benzene) to yield **4** as colorless crystals. Yield, 0.45 g, 36%; mp 92–93 °C (benzene); IR (KBr) 3350 (NH) and 1687 cm⁻¹ (CO); NMR (CDCl₃) δ =1.98 (3H, s, CH₃), 4.90 (1H, s, HC←), 6.27 (1H, s, NH) 7.5–8.4 (8H, m, aromatic H). Found: C, 80.93; H, 5.86; N, 6.45%. Calcd for C₁₅H₁₃NO: C, 80.69; H, 5.87; N, 6.27%.

Photo-reaction of 10-Methylacridinium Chloride with Propionaldehyde.

10-Methylacridinium chloride (1.02 g) in propionaldehyde (100 ml) was irradiated for 3 h. A part of the salt remained undissolved. The reaction mixture was filtered and concentrated to dryness. The residue was taken in chloroform and subjected to column chromatography (silica gel, chloroform) to give pale yellow crystals of **5**. Yield, 0.36 g, 52%; mp 60–63 °C; IR (Nujol) 1710 cm⁻¹ (CO); NMR (CDCl₃) δ =0.83 (3H, t, J =7.0 Hz, CH₂CH₃), 2.35 (2H, q, CH₂), 3.37 (3H, s, NCH₃), 4.85 (1H, s, HC←), 6.7–7.4 (8H, m, aromatic H). Found: C, 81.10; H, 6.87; N, 5.58%. Calcd for C₁₇H₁₇NO: C, 81.24; H, 6.82; N, 5.57%. The sample stored in the dark in a desiccator turned to high-melting yellow crystals in a year. A recrystallization from ethanol gave yellow needles, mp 202–204 °C, which proved to be 10-methyl-9(10*H*)-acridinone (mp 199 °C¹³⁾ by comparing with an authentic sample.¹³⁾

Oxidation of 1 by NBS. **1** was dissolved in 5–10 mmol/dm³ concentration in 10 ml methanol. The methanol contained hexane as internal standard for the subsequent GLC analysis. NBS was added in twice molar excess of **1**, and the mixture was stirred at room temperature (–20 °C). UV spectra showed the formation of phenazine to be complete in 5 min according to Eq. 2. The GLC analysis on 10% tetraethyleneglycol on Celite at room temperature indicated 80–100% formation of methyl acetate. Both hexane and methyl acetate peaks appeared before the solvent (methanol) peak under these GLC conditions. The oxidation of **2** similarly confirmed the reaction in Eq. 2.

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