# REVISION OF THE SCHEME FOR THE FORMATION OF HETEROCYCLIC QUINONES UPON THE PHOTOLYSIS OF 3-AMINO-2-CYCLOALKYLAMINO-1,4-NAPHTHOQUINONES

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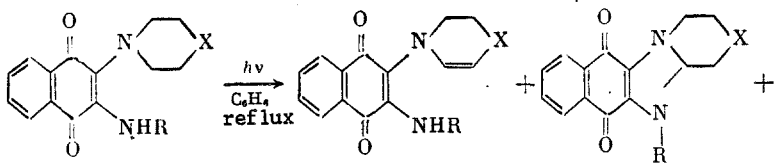
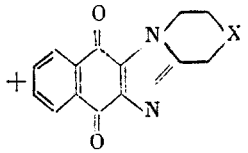
The formation of heterocyclic naphthimidazole quinones from 2-cycloalkylamino-1,4-naphthoquinones was observed as a result of thermal transformations of the corresponding 3-azido derivatives [1, 2]. In the thermolysis of 2-piperazino-3-azido-1,4-naphthoquinones, we have shown that the enaminoquinone products of the dehydrogenation of the heterocyclic ring are precursors to naphthimidazoles [2]. Naphthimidazole derivatives were also obtained in the photolysis of 2-piperidino- and 2-morpholino-3-amino-1,4-naphthoquinones [3]. On the other hand, the photolysis of 2-cycloalkylaminonaphthoquinones lacking an amino group at $C^3$ gave enaminoquinones [4]. Gritsan and Bazhin [5] established that the initial step in the photolysis of 2-morpholinonaphthoquinone, for example, is analogous to the initial step in the photolysis of 2-N,N-dialkylamino-1,4-naphthoquinones and leads to the formation of naphthodihydrooxazoles. In this regard, it was of interest to determine whether the formation of naphthimidazoles in the photolysis of 3-amino-2-cycloalkylamino-1,4-naphthoquinones is the result of a photochemical reaction or of subsequent dark transformations of unstable enaminoquinones. 2-(4'-Benzoylpiperazino)-3-aminonaphthoquinone (Ia) was taken as a model compound in order to detect such unstable enaminoquinones since, as shown in our previous work [2], the corresponding enaminoquinone (IIa) is a rather stable compound.

The photolysis of (Ia) at 20°C in ether or benzene, as in the case of (Ib) and (Ic) [3], leads to the formation of unstable blue dihydronaphthimidazole (IIIa), which is especialy unstable in contact with air. Dihydronaphthimidazole (IIIa) converts to naphthimidazole (IVa) [2]. In order to take the PMR spectrum, the photolysis of (Ia) and (Ic) in $C_6D_6$ was carried out in an NMR tube. The separation of the signals in (IIIc) was carried out using the double resonance technique (Table 1). The aliphatic protons in the PMR spectrum of (IIIa) are poorly resolved. This poor resolution is probably related to hindrance to rotation of the COPh group about the C–N bond.




(Ia–f) (IIa, d-f) (IIIa-f)



(IVa–c)

X = NCOPh, R = H (Ia)–(IVa); X = $CH_2$, R = H (Ib)–(IVb); X = O, R = H (Ic)–(IVc). X = NCOPh, R = Ac (Id)–(III d) X = $CH_2$, R = Ac (Ie)–(III e) X = O, R = Ac (If)–(III f)

The irradiation of 3-amino derivative (Ia) in benzene at 80°C, as in the photolysis of 2-piperidino- and 2-morpholino-1,4-naphthoquinones [4], which lack an amino group at

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TABLE 1. Characteristics of the Compounds Obtained

| Compound | Mp, °C | Mol. mass, m/z, found/calculated | Chemical formula | IR spectrum ν, $cm^{-1}$ | UV spectrum $\lambda_{max}$, nm (log ε) | PMR spectrum (δ, ppm, J, Hz) |
|---|---|---|---|---|---|---|
| (I d) | 113–116 [a] | 403.1511/ /403.1132 | $C_{23}H_{21}N_3O_4$ | 3390(NH), 1705, 1680, 1650(C=O) | 240(4.28) 282(4,28), 494(3,60) | |
| (II d) | 118–122 [b] | 401.1356/ /401.1375 | $C_{23}H_{19}N_3O_4$ | 3390(NH), 1670(C=O) | 246(4,33), 298(4.31), 571(3,70) | 2.11 s (3H, $CH_3$), 3,78–4.14 m (4H, $H^{5,6}$), 5.57 d(1H, $H^6$), 5,97 d (1H, $H^2$, $J_{H^2H^3}$=2,6), 7.36–7,54 m (5H, Harom. 7,56–7,64 m (2H, $H_\beta$), 7,88 br.s (1H, NH), 2,92–8,04 m (2H, $H_\alpha$) |
| (II f) | 134–137 [b] | 298.0944/ /298,0954 | $C_{16}H_{14}N_2O_4$ | 3395(NH), 1680, 1650 (C=O) | 244(4.17), 286(4.18), 571(3.59) | 2.14 s (3H, $CH_3$), 3.94 t (2H, $H^6$), 4,20 t (2H, $H^5$, $J_{H^5H^6}$=5), 5,77 d(1H, $H^2$), 6,36 d (1H, $H^3$, $J_{H^2H^3}$=5), 7,40 br.s (1H, NH), 7,60–7,70 m (2H, $H_\beta$), 7.94–8.06 m (2H, $H_\alpha$) |
| (III a) | 130 [b] (dec.) | 359 [c]/359 | $C_{21}H_{17}N_3O_3$ | 3420(NH), 1650 br (C=O) | 250(4,43), [d] 280(4,20), 308(4,05), 622(2,80) | |
| (III c) | 140 [b] (dec.) | 256.0820/ /256,0848 | $C_{14}H_{12}N_2O_3$ | 3310(NH), 1680, 1660, 1625(C=O) | 250(4.30), [d] 277 sh(4,02), 286(4,05), 316(4.01) 683(2,88) | 2,80 t.d(1H, $H^{1a}$, $J_{H^{1a}H^{1e}}$ = 12, $J_{H^{1a}H^{2a}}$ = 12, $J_{H^{1e}H^{2e}}$ = 3), 2,86 m(1H, $H^{1a}$), 3,05 t.d (1H, $H^{2a}$, $J_{H^{2a}H^{2e}}$ = 12, $J_{H^{1a}H^{2a}}$ = 12, $J_{H^{1e}H^{2a}}$ = 3), 3,14 d.d (1H, $H^{1e}$, $J_{H^{4a}H^{4e}}$ =11, $J_{H^{4e}H^{5aa}}$ = 3), 3,26 d.d (1H, $H^{2e}$, $J_{H^{2a}H^{2e}}$ = 12, $J_{H^{1e}H^{2e}}$ = 3), 3,67 br.s (1H, NH), 4,39 d.d(1H, $H^{1e}$, $J_{H^{1a}H^{1e}}$ = 12, $J_{H^{1e}H^{2e}}$ = 3), 4,41 d (1H, $H^{5aa}$, $J_{H^{4a}H^{5aa}}$ = 12), 6,96 m(2H, $H_\beta$), 7,90 d.d (1H, $H_\alpha$), 7.97 d.d(1H, $H_\alpha$) |
| (III d) | 133–135 [b] | 401.1360/ /401.1375 | $C_{23}H_{19}N_3O_4$ | 1770, 1720 (N–C=O), 1665, 1640 (C=O) | 240 sh(4.19), 296(4,26), 587(3,31) | 2,31 s (3H, $CH_3$), 3.01 m (2H, $H^{2,4}$), 3,45 m (1H, $H^{1e}$), 3,88–4,84 m (2H, $H^{2,4}$), 5.06 d (1H, $H^{1a}$), 5,83 d (1H, $H^{5aa}$), 7.44 br.s (5H, Harom), 7,52–7,74 m (2H, $H_\beta$), 7,90–8,04 m (2H, $H_\alpha$) |

TABLE 1 (continued)

| Compound | Mp, °C | Mol. mass, m/z, found/calculated | Chemical formula | IR spectrum, ν, $cm^{-1}$ | UV spectrum, $\lambda_{max}$, nm (log ε) | PMR spectrum (δ, ppm, J, Hz) |
|---|---|---|---|---|---|---|
| (IIIe) | 173–175[b] | 296.1147/ /296.1161 | $C_{17}H_{16}N_2O_2$ | 1685 sh, 1670, 1640 (C=O) | 239 sh(4.05), 293(4.38), 603(3.45) | 1.60m (4H, $H^{2,3,3',4'}$), 1.92m (2H, $H^{2,4}$), 2.31s (3H, $CH_3$), 3.20t.d (1H, $H^{1a}$), 5.04d (1H, $H^{1e}$), 5.73d.d (1H, $H^{5aa}$), 7.50–7.72m (2H, $H_\beta$), 7.89–8.02m (2H, $H_\alpha$) |
| (IIIf) | 185–187[b] | 298.0964/ /298.0954 | $C_{16}H_{14}N_2O_4$ | 1780, 1730 (N–C=O), 1670, 1640 (C=O) | 248 sh(4.11), 296(4.24), 598(3.57) | 2.38s (3H, $CH_3$), 3.50d (1H, $H^{1a}$), 3.64d (2H, $H^{2,4}$), 3.94d (1H, $H^{1}$), 4.03d.d (1H, $H^{5}$), 4.94d (1H, $H^{1e}$), 5.97d.d (1H, $H^{5aa}$), 7.56–7.78m (2H, $H_\beta$), 7.92–8.06m (2H, $H_\alpha$) |

[a]From $C_6H_6$.
[b]Precipitated by petroleum ether from benzene.
[c]A weak peak with m/z 359 was seen upon recording the mass spectrum, which rapidly disappears in a narrow temperature range with the appearance of naphthimidazole (IVa) with m/z 357 (found: 357.1105; calculated; 357.1113).

$C^3$, gave good yields of the enaminoquinone, (3-amino-1,4-naphthoquinonyl-2)-4-benzoyl-1,4,5,6-tetrahydropyrazine (IIa), which is identical to the product obtained upon the thermolysis of the 3-azido derivative [2]. The formation of enaminoquinones (II) was also observed in the photolysis of piperidino and morpholino derivatives (Ib) and (Ic), which may be stabilized for some time by the addition of acetic acid as described for 2-morpholino-1,4-naphthoquinone [5]. An attempt to separate enamines (IIb) and (IIc) proved unsuccessful since any treatment led to the corresponding dihydronaphthimidazoles (IIIb) and (IIIc), which then rapidly convert to naphthimidazoles (IVb) and (IVc).

The formation of derivative (IId) with an acetyl group at the primary amino group adjacent to the enamino group occurs upon the acetylation of rather stable enaminoquinone (IIa). Under the reaction conditions, (IId) readily converts to 1,2,5a,5-tetrahydro-4H-3-benzoylpyrazino[1,2-a]naphth[2,3-d]-5-acetylimidazole-6,11-dione (IIId). Apparently, enaminoquinones with an acetylamino group at $C^3$, similar to the derivatives with a primary amino group [2], are capable of cyclizing to give imidazole derivatives of naphthoquinone.

In order to obtain such enaminoquinones and support the proposed hypothesis, we synthesized and irradiated 3-acetylamino derivatives of 2-(4'-benzoylpiperazino)-, 2-piperidino-, and 2-morpholino-1,4-naphthoquinones (Id-f). The photolysis of (Id-f) in benzene at 80°C gives products with an identical elemental composition (IId-f) and (IIId-f), which were identified on the basis of the spectral data as enaminoquinones with an acetylamino group at $C^3$ and N-acetyldihydroimidazoles, respectively. Thus, the IR spectra of (IId-f) have NH stretching bands at 3390 $cm^{-1}$, while the IR spectra of (IIId-f) do not display this band. The PMR spectra of (IId-f) have two doublets for the methine protons at 5.5-6.4 ppm in addition to the signals for the aromatic protons, heterocyclic ring methylene protons, and $CH_3$ group protons. The PMR spectra of (IIId-f) have a more complex structure (Table 1).

As in the case of enaminoquinones with a primary amino group at $C^3$ (IIa-c), the stability of enamines with an acetylamino group (IId-f) depends on the electron-withdrawing capacity of substituent X in the heterocyclic ring, which was previously noted for naphthoquinone enamines without a functional group at $C^3$ [6]. Thus, while enamine (IIe, X = $CH_2$) was detected only chromatographically, the conversion of (IIf, X = O) to acetyldihydroimidazole (IIIf) occurs upon chromatographic separation and upon storage in the dark (50% conversion over 20 days). (3-Acetylamino-1,4-naphthoquinonyl-2)-4-benzoyl-1,4,5,6-tetrahydropyrazine

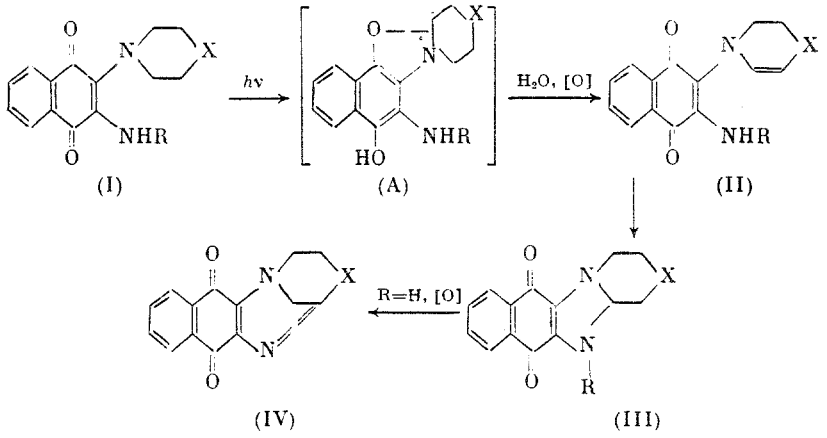
TABLE 2. The Photolysis of 2-N⟨ ⟩X-3-NHR-1,4-naphthoquinones in Benzene at 80°C

| Compound | Substituent | | Reaction time, h | Product yields, % | | |
|---|---|---|---|---|---|---|
| | R | X | | (II) | (III) | (IV) |
| (Ia) | H | NCOPh | 1.5 | 83 * | – | – |
| (Ib) | H | $CH_2$ | 1,5 | traces | – | 72 |
| (Id) | Ac | NCOPh | 16 | 64 | 15 | – |
| (Ie) | Ac | $CH_2$ | 16 | traces | 61 | 8 ** |
| (If) | Ac | O | 41 | 31 | 30 | – |

*Without chromatography. Precipitated from benzene by the addition of hexane.
**Formed upon chromatography.

(IId) is stable upon prolonged storage and cyclizes to N-acetyldihydroimidazole (IIId) upon heating at reflux in benzene over 16 h in 7% yield. The conversion of (IId) to (IIId) upon photolysis is 14%. These findings indicate that the formation of dihydroimidazoles (IIIa-f) upon the irradiation of 2-cycloalkylamino-3-amino-1,4-naphthoquinones (Ia-f) is the result of a dark reaction of enaminoquinones (IIa-f).

In the case of (Ia) and (Id), retention of the isobestic points was observed during the course of the photolysis, which indicates the formation of a single photolysis product. Apparently, as in the case of 2-dialkylaminonaphthoquinones unsubstituted at $C^3$ [5], naphthodihydrooxazoles (A) are the initial products of the photolysis of 3-amino-2-cycloalkylamino-1,4-naphthoquinones. The subsequent hydrolysis of (A) leads to the products of the dehydrogenation of the heterocyclic ring (II). The presence of an amino group adjacent to the unsaturated heterocyclic ring in (II) facilitates intramolecular cyclization with the formation of more stable naphthimidazole derivatives (III) and (IV).




## EXPERIMENTAL

The electronic absorption spectra were taken on a Specord UV-VIS spectrometer in ethanol and chloroform. The IR spectra were taken on a UR-20 spectrometer in $CHCl_3$ and KBr pellets. The PMR spectra in $CDCl_3$ were taken on a Bruker WP-200SY spectrometer, while the spectrum of (IIIc) in $C_6D_6$ was taken on a Bruker AM-400 spectrometer. The molecular mass and elemental composition of these compounds were determined relative to the precise mass number of the molecular ions on a Finnigan MAT-8200 mass spectrometer. The elemental analysis corresponded to the calculated values. The thin-layer chromatography was carried out on Silufol plates with benzene as the eluent. The synthesis and indices of (Ia) and (IIa) were described in our previous work [2], while data for (Ib), (Ic), (If), (IIIb), (IVb), and (IVc) were given in our earlier work [3].

2-Acetylamino-3-(4'-benzoylpiperazino)-1,4-naphthoquinone (Id). A sample of 1.0 g 2-acetylamino-3-chloro-1,4-naphthoquinone was added to a freshly prepared solution of N-benzoylpiperazine (from 0.32 g NaOH and 1.81 g benzoylpiperazine hydrochloride in 45 ml ethanol) and maintained for 24 h at 20°C. The NaCl precipitate was filtered off. The filtrate was diluted with water, extracted with chloroform, concentrated at reduced pressure, and subjected to chromatography on grade-II alumina with benzene as the eluent to give 1.41 g (87%) (Id).

Photolysis Procedure. At 20°C. 1. A sample of 2 mg (Ia) or (Ic) in 1 ml $C_6D_6$ in an ampul was irradiated with a DRSh-500 lamp through a BS-7 light filter for 10 min and the PMR spectrum was recorded.

2. A solution of 0.5 mmole (Ia) or (Ic) in 500 ml abs. benzene was irradiated using light with $\lambda > 400$ nm for about 2 h. The blue solution was concentrated at reduced pressure. Products (IIIa) and (IIIc) were precipitated by the addition of petroleum ether. The yields were 50-60%.

At 80°C. A solution of 0.5 mmole aminoquinone (Ia-f) in 500 ml absolute benzene was irradiated at reflux using a 300-W incandescent lamp until the starting quinone disappeared and concentrated at reduced pressure. The residue was subjected to chromatography on an alumina column in the case of (Ib) and on a silica gel column in the case of (Id-f) with benzene and $CHCl_3$ as the eluent. The yields of the secondary photolysis products are given in Table 2.

Cyclization of 1-(3-Acetylamino-1,4-naphthoquinonyl-2)-4-benzoyl-1,4,5,6-tetrahydropyrazine (IId). a. A solution of 0.20 g (IId) in 30 ml benzene was heated at reflux for 16 h, concentrated at reduced pressure, and subjected to chromatography on Silufol plates using benzene as the eluent. The yields were 0.015 g (7%) (IIId) and 0.17 g (85%) (IId).

b. A solution of 0.20 g (IId) in 30 ml benzene was irradiated for 16 h to give 0.028 g (14%) (IIId) and 0.17 g (85%) (IId).

## CONCLUSIONS

The formation of naphthimidazole derivatives in the photolysis of 3-amino- and 3-acetylamino-2-cycloalkylamino-1,4-naphthoquinones is the result of the dark intramolecular cyclization of the corresponding 3-aminoenaminoquinones.

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