BEHAVIOUR OF SOME PERIMIDINES TOWARDS OXIDANTS

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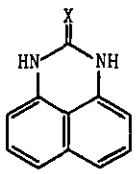
Abstract - The oxidation of some perimidines with 3-chloroperbenzoic acid, trifluoroperacetic acid, and dipotassium nitrosodisulphonate is reported. Perimidine-2-thione is oxidised to perimidine-2-sulphonic acid, while other perimidines are oxidised to give 4- and 6-perimidinones.

Very few oxidation reactions of perimidines have been reported to date. Although the dehydrogenation of 2,3-dihydroperimidines[1] and the formation of both 4- and 6-perimidinones from perimidines by treatment with dipotassium nitrosodisulphonate (Fremy's salt)[2] are well-established processes, most other reactions of perimidines with oxidants result in degradation of the heterocyclic nucleus.[3,4] We have investigated the reactions of some perimidines with 3-chloroperbenzoic acid, with trifluoroperacetic acid, and with dipotassium nitrosodisulphonate.



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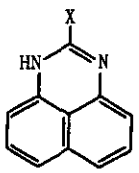
a: X = S

b: X = O



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a: X = SO_3H

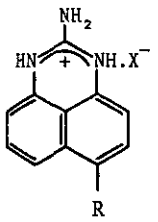
b: X = H

c: X = SMe

d: X = S(O)Me

e: X = $CONHCH_2CH_2NMe_2$

f: X = COOEt



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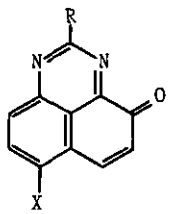
a: R = H; X = Br

b: R = Br; X = $OCOCF_3$

c: R = H; X = $\frac{1}{2}SO_4$



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a: R = NH_2; X = Br

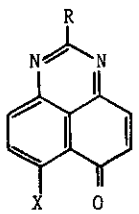
b: R = X = H

c: R = COOEt; X = H

Oxidation of perimidine-2-thione (1a)[3] with 3-chloroperbenzoic acid in dimethylformamide at 0°C gave perimidine-2-sulphonic acid (2a). However, when an aqueous solution of this sulphonic acid was

heated, hydrolysis occurred to give 2-perimidinone (1b). In accord with this observation, treatment of 1a with trifluoroperacetic acid at 0°C gave only 2-perimidinone (1b). Oxidation of 2-(methylthio)perimidine (2c) with 3-chloroperbenzoic acid proceeded in a similar way to that of 1a, giving 2-(methylsulphinyl)perimidine (2d).[5]

In contrast to perimidine-2-thione and 2-methylthioperimidine, salts of 2-perimidinamine underwent oxidation in the naphthalene moiety to form 4- and 6- perimidinones. Thus, treatment of 2-perimidinaminium bromide (3a) with trifluoroperacetic acid in trifluoroacetic acid gave a mixture of products. The major component, 6-bromo-2-perimidinaminium trifluoroacetate (3b) which precipitated from the reaction mixture, is formed in a process analogous to that previously reported for the preparation of 4-bromoaniline from anilinium bromide.[6] The trifluoroacetic acid-soluble fraction of the reaction mixture contained two minor products, identified as 2-amino-7-bromo-4-perimidinone (4a) and 2-amino-7-bromo-6-perimidinone (5a). These perimidinones evidently result from further oxidation of 3b in a carbocyclic ring; similar products are obtained from the oxidation of perimidine derivatives with dipotassium nitrosodisulphonate (Fremy's salt).



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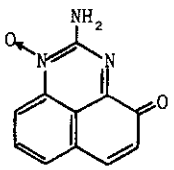

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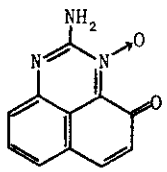

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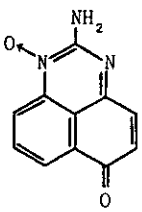

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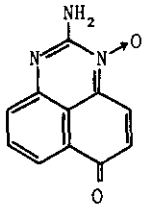
a: R = NH_2; X = Br

b: R = X = H

c: R = COOEt; X = H

Incorporation of a bromine atom into the product was avoided by oxidation of bis(2-perimidinaminium) sulphate (3c) which, under the same conditions, formed 2-amino-4-perimidinone-1(3)-oxide (6 or 7) and 2-amino-6-perimidinone- 1(3)-oxide (8 or 9). Although it is possible that the products isolated may be isomeric mixtures, the spectral data are indicative of single compounds. The similarity in the positions of the carbonyl stretching band in the infrared spectra of the N-oxides to those observed in the infrared spectra of 4-perimidinone (4b) and 6-perimidinone (5b) suggests that the actual structures of the N-oxides are 6 and 8, where the oxidised nitrogen centre is that most remote from the carbonyl group. Moreover, assuming that oxidation in a carbocyclic ring occurs first, N-oxidation should occur at the most electron rich

nitrogen, which is that remote from the carbonyl group. Clearly, oxidation in a carbocyclic ring and subsequently at an annular nitrogen atom occurs in preference to oxidation of the 2-amino substituent; this result stands in direct contrast to the oxidation of perimidine-2-thione described above, which affords the corresponding sulphonic acid in good yield, with no indication of the formation of any ring-oxidised side-products.



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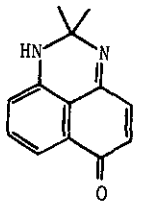

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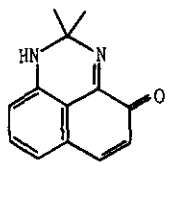

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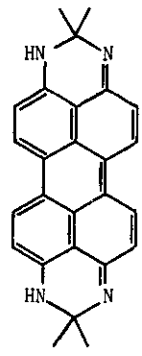

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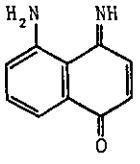

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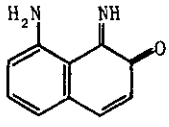

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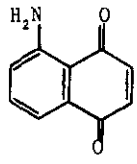

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Oxidation of perimidines in a carbocyclic ring using dipotassium nitrosodisulphonate has been reported as a general synthetic procedure.[2] However, in the present work it was found that although treatment of perimidine (2b) with 2.5 molar equivalents of dipotassium nitrosodisulphonate gave 4-perimidinone (4b, 44%) and 6-perimidinone (5b, 21%) as expected, the action of dipotassium nitrosodisulphonate on the amide 2e and on ethyl perimidine-2-carboxylate (2f) resulted in the formation of some unexpected products. In the simplest case, treatment of a methanolic solution of 2f with an aqueous solution containing 2.5 molar equivalents of Fremy's salt gave a mixture from which the oxidised ester 5c (11%) and 6-perimidinone (5b, 3%) were isolated. The isomeric perimidinones 4c and 4b were formed also, but were unable to be separated chromatographically. That perimidinones 4b and 5b are formed by hydrolysis and decarboxylation of the desired products was shown by the formation of 5b when a solution of 5c in aqueous methanol was heated. When the reaction was repeated on a larger scale, none of the perimidinone 4b, and only a trace of its isomer 5b (3%), was formed. The major product isolated was 1,2-dihydro-2,2-dimethylperimidin-6-one (10, 26%). Small amounts of the isomeric product 11 (2%) and the dimeric compound 12 (2%) were obtained also. Perimidinones 10 and 11 result from cyclisation (with acetone, in which the crude solid was dissolved during work-up) of the quinone imines 13 and 14 respectively. Indeed, when the

reaction was repeated but exposure of the product to acetone was avoided, the only products isolated were 5c (11%) and 5-aminonaphthalene-1,4-dione (15, 8%), the latter being formed by hydrolysis of the intermediate 5-amino-4-imino-1-naphthalenone (13). As ring cleavage of ethyl perimidine-2-carboxylate (2f) has not been observed under other conditions, and as the absence of 1,8-naphthalenediamine as a potential contaminant in the starting ester 2f was established (t.l.c.), it appears that ring cleavage of either ester 2f or 5c may be facilitated by Fremy's salt. The dimer 12 presumably is formed as a result of coupling of radical intermediates in the oxidation process.

N-(2-Dimethylaminoethyl)perimidine-2-carboxamide (2e) [5] was found to be relatively unreactive toward Fremy's salt, a proportion of the starting material (41%) being recovered from chromatography of the crude reaction mixture, which also yielded 6-perimidinone (5b, 5%), 5-aminonaphthalene-1,4-dione (15, 3%) and, somewhat surprisingly, the quinone imine 13 (6%).

EXPERIMENTAL

Perimidine-2-sulphonic Acid (2a)

3-Chloroperbenzoic acid (0.93 g, 4.65 mmol) was added during 1 min to a solution of perimidine-2-thione (310 mg, 1.55 mmol)[3] in dried dimethylformamide (25 ml) at 0°C. The mixture was stirred for 30 min while warming to room temperature, then diluted with water (200 ml) and filtered immediately to give 2a (298 mg, 78%) as yellow needles. These were dissolved in dimethylformamide; addition of water to this solution gave pale yellow needles, mp > 300°C. *Anal.* Calcd. for $C_{11}H_8N_2O_3S$: C, 53.2; H, 3.3; N, 11.3; S, 12.9. Found: C, 53.4; H, 3.1; N, 11.4; S, 12.7%. ν_{max}(KBr) 3200–2850 (NH, OH), 1630 (C=N), 1300–1200 cm^{-1} (OSO_2). δ_H(CD_3SOCD_3) 6.80–7.07 (m, 2H, H4, H9), 7.18–7.37 (m, 4H, H5, H6, H7, H8). *m/z* 248 (M, 10%), 184 (M-SO_2, 84), 168 (M-SO_3, 74), 166 (184-H_2O, 82), 139 (166-HCN, 29), 64 (SO_2, 100).

2-Perimidinone (1b)

A mixture of trifluoroacetic acid (2 ml) and aqueous hydrogen peroxide (2.67 ml of 34%, 26.7 mmol) was stirred at room temperature for 30 min, then cooled to 0°C and perimidine-2-thione (178 mg, 0.89 mmol) was added with stirring. The resulting suspension was stirred for 30 min at 0°, then for 90 min at room temperature, and diluted with water (5 ml). The resulting white precipitate was isolated by filtration, and recrystallised from aqueous ethanol to give 1b (147 mg, 95%) as white

microcrystals, mp 304-305°C (lit.[3] 304-305°C). ν_{max}(KBr) 3400 (NH), 1655 (C=O), 1600 cm^{-1} (C=C). δ_H(CD_3SOCD_3) 6.45-6.66 (m, 2H, H4, H9), 6.98-7.40 (m, 4H, H5, H6, H7, H8), 10.10 (br s, 2H, 2NH). *m/z* 184 (M, 100 %), 166 (M-H_2O, 54).

Oxidation of 2-Perimidinaminium Bromide

A mixture of trifluoroacetic acid (5 ml) and aqueous hydrogen peroxide (0.2 ml of 34%, 2 mmol) was stirred at room temperature for 10 min, then 2-perimidinaminium bromide (178 mg, 0.67 mmol) was added. The mixture was stirred for 30 min, and water (5 ml) was added. The mixture was filtered to give 2-amino-6-bromoperimidinium trifluoroacetate (3b) (90 mg, 36%) as a grey solid, mp *ca.* 245°C. ν_{max}(KBr) 3700-2600 (NH), 1700 cm^{-1} (br, C=O). δ_H(CD_3SOCD_3) 6.75 (d, *J* 8 Hz, 1H, H4), 6.94 (dd, J_o 6 Hz, J_m 3 Hz, 1H, H9), 7.46-7.63 (m, 1H, H8), 7.73 (d, *J* 8 Hz, 1H, H5), 8.34-8.60 (m, 1H, H7). *m/z* 263, 261 (M-CF_3COOH, 99, 100%), 246, 244 (263/261-NH_3, 28, 29), 165 (244-Br , 44), 69 (CF_3, 52). Attempts to convert this material into the free base, by treatment with aqueous ammonia, resulted only in decomposition. The filtrate was neutralised with aqueous ammonia and extracted with ethyl acetate (2 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a dark red solid (129 mg). P.l.c. of this material on alumina in chloroform gave (i) 2-amino-7-bromoperimidin-6-one (5a) (12 mg, 6%) as a red solid, mp 228-230°C. *HRMS* Calcd. for $C_{11}H_6BrN_3O$: $M^{\cdot+}$, 274.9694, 276.9674. Found: $M^{\cdot+}$, 274.9692, 276.9697. ν_{max}(KBr) 3450 (NH), 1640 (C=O), 1615 cm^{-1} (C=N). δ_H($CDCl_3$) 6.81 (d, *J* 10 Hz, 1H, H5), 7.40 (d, *J* 10 Hz, 1H, H4), 7.56 (br s, 2H, NH_2) 7.83 (d, *J* 8 Hz, 1H, H9), 8.24 (d, *J* 8 Hz, 1H, H8). *m/z* 277, 275 (M, 100, 95%), 249, 247 (M-CO, 22, 21), 196 (M-Br, 38), 168 (247-Br, 34), 141 (168-HCN, 44) and (ii) 2-amino-7-bromoperimidin-4-one (4a) (28 mg, 15%) as a red solid, dec. *ca.* 238°. *HRMS* Calcd. for $C_{11}H_6BrN_3O$: $M^{\cdot+}$, 274.9694, 276.9674. Found: $M^{\cdot+}$, 274.9740, 276.9688. ν_{max}(KBr) 3450 (NH), 1635 (C=O), 1615 cm^{-1} (C=N). δ_H(CD_3SOCD_3) 6.96 (d, *J* 10 Hz, 1H, H5), 7.30 (br s, 2H, NH_2), 7.60 (d, *J* 10 Hz, 1H, H6), 7.67 (d, *J* 9 Hz, 1H, H9), 8.06 (d, *J* 9 Hz, 1H, H8). *m/z* 277, 275 (M, 100, 98%), 249, 247 (M-CO, 37, 36), 168 (247-Br, 27), 141 (168-HCN, 36).

Oxidation of Bis(2-perimidinaminium) Sulphate

A mixture of trifluoroacetic acid (5 ml) and aqueous hydrogen peroxide (0.2 ml of 34%, 2 mmol) was stirred at room temperature for 5 min, then bis(2-perimidinaminium) sulphate (130 mg, 0.56 mmol of amine) was added, and the mixture was stirred at room temperature for 5 min. Work-up as above gave (i) 2-aminoperimidin-6-one-1-oxide (8) (8 mg, 7%) as a bright red solid, mp > 300°C. *HRMS* Calcd. for $C_{11}H_7N_3O_2$: $M^{\cdot+}$, 213.0538; M-$O^{\cdot+}$, 197.0689. Found: $M^{\cdot+}$, 213.0584; M-$O^{\cdot+}$, 197.0714. ν_{max}(KBr) 3420,

1655 (NH_2), 1645 (C=O), 1620 (C=N), 1590 cm^{-1} (C=C). $\delta_H(CD_3SOCD_3)$ 6.94 (d, *J* 10 Hz, 1H, H5), 7.20 (2H, br s, NH_2), 7.63 (d, *J* 10 Hz, 1H, H4), 7.75-7.90 (m, 3H, H7, H8, H9). *m/z* 213 (M, 3%), 197 (M-O, 100), 169 (197-CO, 50), 142 (169-HCN, 18) and (ii) 2-aminoperimidin-4-one-1-oxide (6) (8 mg, 7%) as a bright orange solid, m.p. > 300°. *HRMS* Calcd. for $C_{11}H_7N_3O_2$: M^+, 213.0538; $M-O^+$, 197.0689. Found: M^+, 213.0577; $M-O^+$, 197.0716. ν_{max}(KBr) 3450, 1655 (NH_2), 1645 (C=O), 1620 cm^{-1} (C=N). $\delta_H(CD_3SOCD_3)$ 6.54 (d, *J* 10 Hz, 1H, H5) 7.35 (m, 2H, NH_2) 7.52-7.87 (m, 4H, H6, H7, H8, H9). *m/z* 213 (M, 2%), 197 (M-O, 100), 169 (197-CO, 51), 142 (169-HCN, 19).

Oxidation of Ethyl Perimidine-2-carboxylate with Dipotassium Nitrosodisulphonate

(A) A solution of *dipotassium nitrosodisulphonate*[7] (1.07 g, 4.0 mol) in water (50 ml) was added all at once to a solution of ethyl perimidine-2-carboxylate[8] (0.382 g, 1.6 mol) in methanol (50 ml). Methanol was immediately removed under vacuum, and the aqueous mixture was saturated with sodium chloride then extracted with ethyl acetate (2 x 50 ml). The combined extracts were dried (Na_2SO_4) and evaporated. P.l.c. of the residue in benzene on alumina gave (i) 2-ethoxycarbonylperimidin-6-one (5c) (45 mg, 11%), as an ivory solid which was recrystallised from benzene-heptane to give pale yellow needles, mp 191-192.5°C. *Anal*. Calcd. for $C_{14}H_{10}N_2O_3$: C, 66.1; H, 4.0; N, 11.0. Found: C, 66.1; H, 3.7; N, 10.9%. ν_{max}(KBr) 1740 (COO), 1660 (C=O), 1620 (C=N), 1200 cm^{-1} (C-O). $\delta_H(CDCl_3)$ 1.55 (t, *J* 7 Hz, 3H, CH_3) 4.66 (q, *J* 7 Hz, 2H, CH_2) 7.07 (d, *J* 10 Hz, 1H, H5) 7.95 (d, *J* 10 Hz, 1H, H4) 8.16 (dd, J_o 8 Hz, J_m 6 Hz, 1H, H8) 6.74-7.01 (m, 2H, H7, H9). *m/z* 256 (M+2H, 2%), 254 (M, 2), 210 ($M-C_2H_4O$, 9), 182 (210-CO, 100), 155 (182-HCN, 26), 127 (155-CO, 20), (ii) 6-perimidinone (5b) (10 mg, 3%) as a buff-coloured solid, which was recrystallised from heptane to give pale yellow needles, mp 192.5-193.5°C (lit.[2] mp 190°C). ν_{max} 1650 (C=O), 1610 cm^{-1} (C=N). $\delta_H(CDCl_3)$ 7.03 (d, 1H, *J* 10.5 Hz, H5) 7.79 (d, 1H, *J* 10.5 Hz, H4) 8.07 (dd, 1H, J_o 4.5 Hz, J_m 3.5 Hz, H9) 8.23-8.57 (m, 2H, H7, H8) 9.53 (s, 1H, H2). *m/z* 182 (M, 100 %), 154 (M-CO, 74), 127 (154-HCN, 39), and (iii) a mixture (45 mg) of 2-ethoxycarbonylperimidin-4-one (4c) and 4-perimidinone (4b).

(B) A solution of dipotassium nitrosodisulphonate (3.5 g, 10.7 mmol) in water (200 ml) was added all at once to a solution of ethyl perimidine-2-carboxylate (1.25 g, 5.2 mmol) in methanol (200 ml). The mixture was immediately concentrated under reduced pressure to *ca*. 200 ml, then extracted with dichloromethane (2 x 200 ml). The combined extracts were dried (Na_2SO_4) and evaporated to give an intense purple solid (1.1 g). This solid was extracted with boiling acetone, and the resulting extract was again evaporated to dryness. P.l.c. of the residue in benzene-methanol (98:2) on alumina gave (i) 2-ethoxycarbonylperimidin-6-one (5c; 39 mg, 3%), (ii)

1,2-dihydro-2,2-dimethylperimidin-6-one (10) (283 mg, 26%) as intense mauve rhombs, mp 185-189.5°C (lit.[2] mp 192°C). ν_{max}(KBr) 3350 (NH), 1640 (C=O), 1622 (C=N), 1594 cm^{-1} (C=C). $\delta_H(CDCl_3)$ 1.58 (s, 6H, $2CH_3$), 4.07 (br s, 1H, NH), 6.50-6.73 (m, 2H, H4, H5) 6.97-7.32 (m, 3H, H7, H8, H9). *m/z* 214 (M+2H, 3%), 212 (M, 5%), 197 (M-CH_3, 100), 169 (197-CO, 21), (iii) 1,2-dihydro-2,2-dimethylperimidin-4-one (11; 21 mg, 2%) as an intense purple oil. *HRMS* Calcd. for $C_{13}H_{12}N_2O$: $M^{\cdot+}$, 212.0950; $[M+2]^{\cdot+}$, 214.1106. Found: $M^{\cdot+}$, 212.0972; $[M+2]^{\cdot+}$, 214.1122. ν_{max}(KBr) 3300 (NH), 1660 (C=O), 1620 (C=N), 1580 cm^{-1} (C=C). $\delta_H(CD_3SOCD_3)$ 1.46 (s, 6H, $2CH_3$), 6.21 (d, *J* 10 Hz, 1H, H5), 6.44-6.74 (m, 2H, H8, H9), 9.90-7.20 (m, 1H), 7.48 (d, *J* 10 Hz, 1H, H6). *m/z* 214 (M+2H, 11%), 212 (M, 6), 199 (214-CH_3, 34), 198 (199-H, 20), 197 (212-CH_3 100), 169 (197-CO, 28), and (iv) dimeric product 12 (20 mg, 2%) as a very intense purple solid, mp > 300°C. ν_{max}(KBr) 3650-3250 (NH), 1655, 1620 (C=N), 1580 cm^{-1} (C=C). *m/z* 390 (M, 100%).

(C) A solution of dipotassium nitrosodisulphonate (1.34 g, 5.0 mmol) in water (50 ml) was added to a solution of ethyl perimidine-2-carboxylate (0.50 g, 2.0 mmol) in methanol (25 ml). The mixture was extracted immediately with dichloromethane (2 x 50 ml), and the combined extracts were dried (Na_2SO_4) and evaporated to give an intense purple solid. P.l.c. of this material in dichloromethane on alumina gave (i) 5-aminonaphthalene-1,4-dione (15) (33 mg, 8%) as an intense mauve solid, mp 177-179°C (lit.[9] mp 180°C). ν_{max}(KBr) 3450, 3330, 1660 (NH_2), 1635, 1600 cm^{-1} (C=O). $\delta_H(CDCl_3)$ 6.39-7.43 (m, 5H). *m/z* 173 (M, 100%), 172 (M-H, 94), 145 (M-CO or 172-HCN, 50), 117 (145-CO, 68), and (ii) 2-ethoxycarbonylperimidin-6-one (5c) (67 mg, 11%).

Oxidation of N-(2-Dimethylaminoethyl)perimidine-2-carboxamide with Dipotassium Nitrosodisulphonate

A solution of dipotassium nitrosodisulphonate (1.34 g, 5.0 mmol) in water (50 ml) was added all at once to a solution of N-(2-dimethylaminoethyl)perimidine-2-carboxamide[5] (0.56 g, 2.0 mmol) in methanol (25 ml). The mixture was then saturated with sodium chloride and extracted with dichloromethane (3 x 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a brown solid (0.43 g). P.l.c. of this material on alumina in chloroform gave (i) 5-amino-4-imino-1-naphthalenone (13; 21 mg, 6%) as an oily mauve solid. *HRMS* Calcd. for $C_{10}H_8N_2O$: M†, 172.0636. Found: M†, 172.0673. ν_{max}(KBr) 3400 (NH), 1645 (br, NH_2), 1615 (C=O), 1600 (C=N), 1590 (C=C). $\delta_H(CDCl_3)$ 6.53-7.47 (m, 5H). *m/z* 172 (M, 65%), 144 (M-CO, 87), 117 (144-HCN, 100), (ii) 5-aminonaphthalene-1,4-dione (15; 10 mg, 3%), (iii) 6-perimidinone (5b; 19 mg, 5%), and (iv) N-(2-dimethylaminoethyl)perimidine-2-carboxamide (2e; 232 mg, 41%).

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