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Formation and Destruction of Diazine Ring under Conditions of the Vilsmeier–Haack Formylation of 4-Dialkylaminonaphthalic Acid Derivatives

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Abstract—The quaternized 1,3-diazine ring formation qualified as a particular case of the *t*-amino effect has been found under conditions of the Vilsmeier–Haack formylation of 4-dialkylaminonaphthalic acid derivatives. The diazinium ring is hydrolyzed in alkaline media with dealkylation, and 3-dimethylamino-4-alkylamino derivatives are formed.

Introduction

Naphthalic acid derivatives are of considerable interest because many effective organic dyes and luminophores have been found among these compounds.[1] In the course of our systematic studies on the structure modification of such compounds, the behavior of some 4-dialkylaminonaphthalic acid derivatives under Vilsmeier–Haack reaction conditions is studied in this paper. Using semi-empirical quantum chemical simulations an electrophilic substitution in the 4-dimethylaminonaphthalic acid derivatives has been found to occur *ortho* to the dimethylamino group.[2]

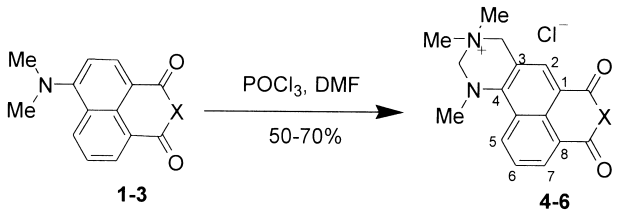
The Vilsmeier reaction is a suitable method for formylating active aromatic and heteroaromatic substrates. However, when the reaction is directed adjacent to *tert*-amino groups it can lead to cyclization of the intermediate iminium salt instead of formylation. Such cyclizations—the *t*-amino effect processes—were previously reviewed and classified with viewpoint of the nature of the reacting X=Y bond and of the size of ring formed.[3]

Results and Discussion

We have found that some 4-dimethylaminonaphthalic acid derivatives, namely, the anhydride (**1**), *N*-methyl- (**2**) and *N*-arylimides (**3**), when being heated with $POCl_3$ in DMF at 100–130°C, give with good yield the water-soluble quaternary salts **4**–**6** instead of expected carboxaldehydes (Scheme 1). These compounds contain a 1,3-diazinium ring annelated to the 3,4-positions of the naphthalic nucleus. Structures of compounds **4**–**6** were determined by ^{1}H NMR data. Besides this, the **6a** structure was confirmed using X-ray diffraction analysis (Fig. 1). The independent part of the unit cell consists of two organic cations, two chloride ions and one water molecule. The expected carboxaldehydes were not found among reaction products.

This reaction seems to be similar as described previously for 4-dimethylaminotoluene.[4] Attempts to formylate it using $POCl_3$ in DMF or *N*-formylmorpholine gave the quinazolinium salts (Scheme 2).

The Vilsmeier–Haack formylation is known to proceed via some intermediates.[5,6] So, the reaction under consideration could be associated with cyclization in the Vilsmeier adduct **A** (Scheme 3). Mechanistically, it can run as one-step (Pathway ***a***) or two-step (Pathway ***b***) process. The PM3[7] quantum chemical simulations for the **1→4** reaction show enthalpy of activation ($\Delta H^{\#}$) 33 and 5 kcal/mol for the first and second stages of the two-step transformation **A→B→4** correspondingly, while the 110 kcal/mol is calculated for the one-step mechanism. At the same time,



Scheme 1.

Keywords: diazine ring; Vilsmeier–Haack formylation; 4-dialkylaminonaphthalic acid derivatives.

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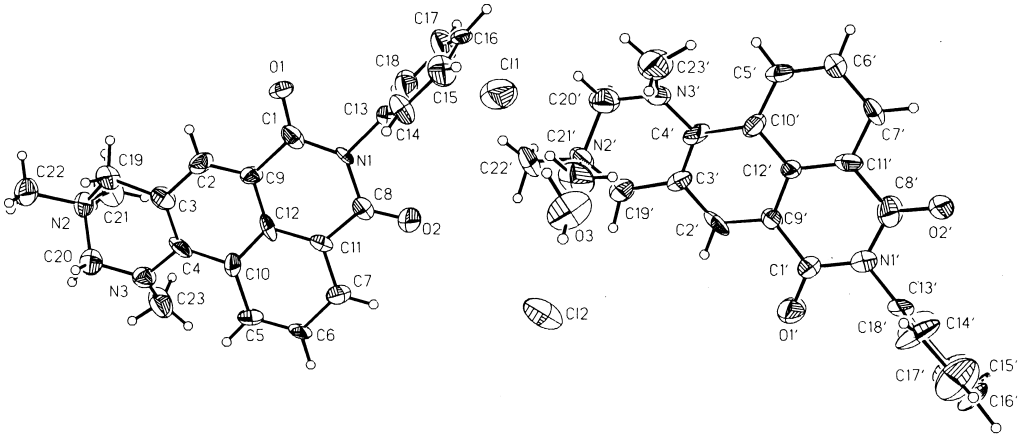
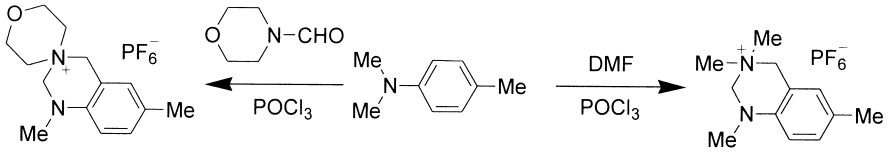
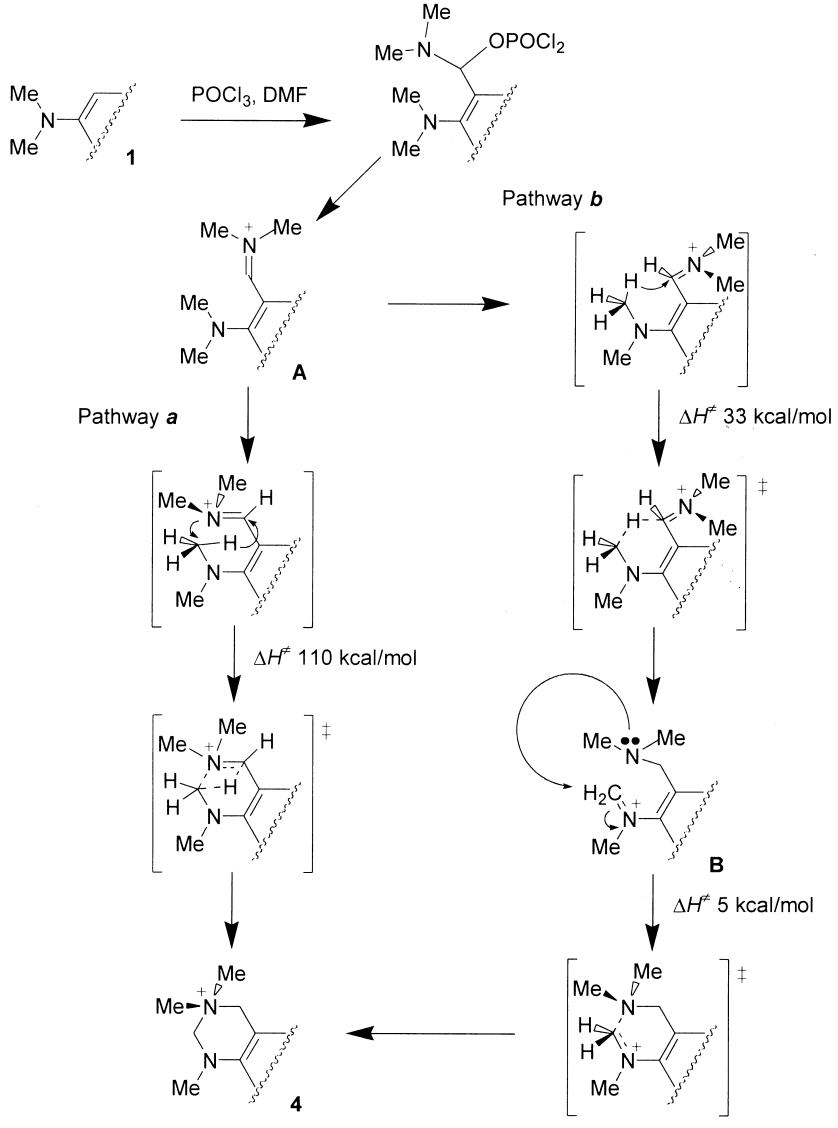


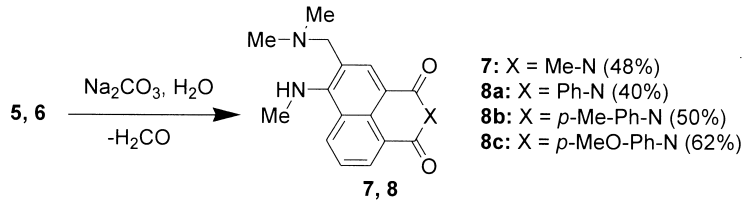
Figure 1. X-Ray structure of quaternary salt **6a**.



Scheme 2.



Scheme 3.



Scheme 4.

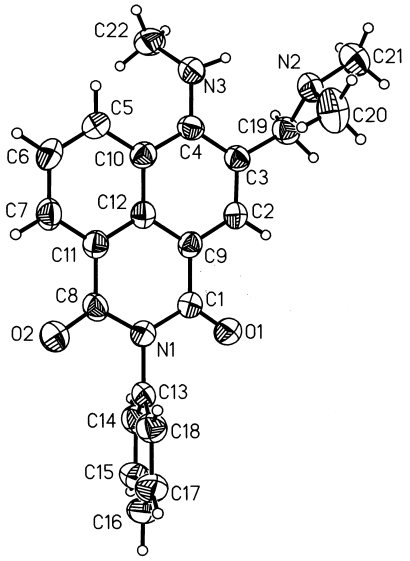


Figure 2. X-Ray structure of phenylimide **8a**.

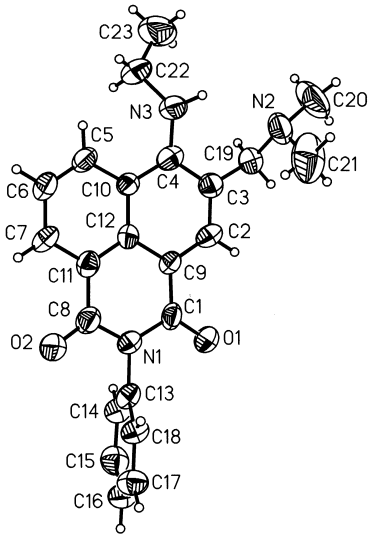


Figure 3. X-Ray structure of phenylimide **11**.

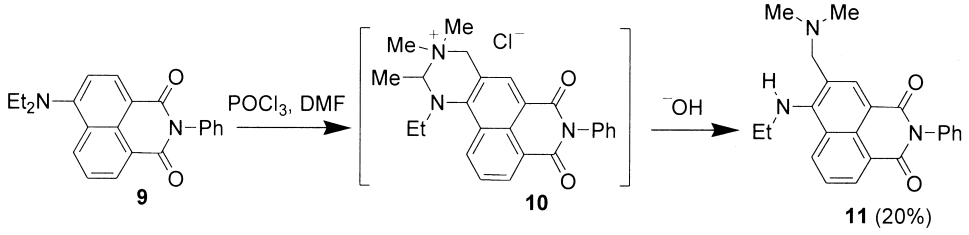
a molecular dynamics simulation shows kinetic energy of 45–50 kcal/mol at 100–130°C. Taking into account this data it is suspected that the reaction proceeds by the two-step pathway via isomeric intermediate **B**. Besides, the $\Delta H^{\#}$ value for the second stage is much less than for the first one. Therefore, just the first stage is a rate-determining step and intermediate **B** cannot be isolated.

Also, it has been found that the quaternized diazine ring in the salts **5** and **6** is hydrolyzed in alkaline media, and water insoluble 3-dimethylaminomethyl-4-methylamino derivatives **7** and **8** are formed (Scheme 4). Methylene group of diazinium salt is eliminated giving formaldehyde, which is discovered by fuchsin sulfurous acid[8] (Schiff's reagent for aldehydes, standard Fluka®). Structures of methylamines **7** and **8** were determined by ^{1}H NMR data, and the **8a** was confirmed also using X-ray diffraction analysis (Fig. 2).

The quaternary diazinium ring formation seems to be a typical feature for naphthalic acid derivatives containing not only 4-dimethylamino group, but perhaps some other 4-dialkylamino groups. So, 4-diethylaminonaphthalic acid phenylimide **9** reacts at the same conditions giving the diazinium salt **10** (Scheme 5). Unfortunately, the latter was failed to be isolated. At the same time in alkaline media the water-soluble product **10** is transformed into **11** under elimination of acetaldehyde molecule. The structure of ethylamine **11** was confirmed by X-ray diffraction analysis (Fig. 3) and ^{1}H NMR data, while that of the salt **10** is determined only hypothetically, taking into account the structure of product **11** and by analogy with quaternary salts **4**–**6**.

Conclusions

The quaternized 1,3-diazinium ring formation instead of formylation is observed in the Vilsmeier–Haack reaction of 4-dialkylaminonaphthalic acid derivatives. The reaction can be associated with the two-step heterocyclization in the



Scheme 5.

intermediate Vilsmeier adduct. Diazinium ring is hydrolyzed in alkaline media with dealkylation, and 3-dimethylamino-4-alkylamino derivatives are formed.

Experimental

General

The reaction run and the purity of products were monitored by TLC (Silica gel 60 TLC Plates, Merck). IR spectra were measured on a Specord 75-IR spectrophotometer. ^{1}H NMR spectra were measured on a Varian VXP-300 (300 MHz) spectrometer in DMSO-d_6 with HMDS as an internal standard. The crystals for X-ray diffraction analyses were grown in DMF by slow solvent evaporation. X-Ray diffraction study of **6a**, **8a** and **11** was carried out using a four-circle automated diffractometer Siemens P3/PC equipped with graphite monochromator (MoKα for **6a**, **11**, and CuKα for **8a**), $2\theta/\theta$ scan technique was used. Crystals used were a nearly isotropic polyhedrons with cross section ca. 0.2–0.3 mm. All computations on these structures were carried out using SHELX-97 program package.

9,9,11-Trimethyl-4,6-dioxo-8,9,10,11-tetrahydro-4*H*,6*H*-isochromeno[4,5-*g*,*h*]quinazolin-9-ium chloride (4). Compound **1** (0.96 g, 4 mmol) was dissolved in DMF (5 mL, 65 mmol), and $POCl_3$ (1.7 mL, 18 mmol) was added dropwise at 60–70°C. The mixture was heated under stirring at 100°C for 10 min, cooled to RT and poured into ice water. The precipitate obtained was collected to give the crude product (1.2 g, 91%). The product was recrystallized from ethanol to give the *title compound* **4** (0.27 g, 20%) as a yellow solid, mp 253°C; [Found: C, 61.2; H, 5.1; Cl, 10.9; N, 8.1. $C_{17}H_{17}ClN_2O_3$ requires C, 61.36; H, 5.15; Cl, 10.65; N, 8.42%]; ν_{max}(KBr) 1768, 1720, 1602, 1570, 1455, 1405, 1375, 1315, 1255 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.27 (6H, s, $^+$N(C*H*$_3$)$_2$), 3.69 (3H, s, 4-NC*H*$_3$), 4.98 (2H, s, C*H*$_2$), 5.18 (2H, s, C*H*$_2$), 7.89–8.67 (4H, m, arom H).

5,9,9,11-Tetramethyl-4,6-dioxo-5,6,8,9,10,11-hexahydro-4*H*-isoquino[4,5-*g*,*h*]quinazolin-9-ium chloride (5). Compound **2** (1.02 g, 4 mmol) was dissolved in DMF (5 mL, 65 mmol), and $POCl_3$ (1.7 mL, 18 mmol) was added dropwise at 60–70°C. The mixture was heated with stirring at 100°C for 10 min, cooled to RT and treated with 98% ethanol. The product was precipitated with acetone and purified by column chromatography on Silochrom C-120 (ethanol) to give the *title compound* **5** (0.70 g, 51%) as a yellow solid, mp 235°C; [Found: C, 62.6; H, 5.9; Cl, 10.2; N, 12.2. $C_{18}H_{20}ClN_3O_2$ requires C, 62.52; H, 5.83; Cl, 10.25; N, 12.15%]; ν_{max}(KBr) 1687, 1640, 1612, 1600, 1565, 1460, 1395, 1365, 1340, 1285 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.33 (6H, s, $^+$N(C*H*$_3$)$_2$), 3.42 (3H, s, *Me*), 3.70 (3H, s, 4-NC*H*$_3$), 5.01 (2H, s, C*H*$_2$), 5.22 (2H, s, C*H*$_2$), 7.84–8.55 (4H, m, arom H).

9,9,11-Trimethyl-4,6-dioxo-5-phenyl-5,6,8,9,10,11-hexahydro-4*H*-isoquino[4,5-*g*,*h*]quinazolin-9-ium chloride (6a). Compound **3a** (1.26 g, 4 mmol) was dissolved in DMF (5 mL, 65 mmol), and $POCl_3$ (1.7 mL, 18 mmol) was added dropwise at 60–70°C. The mixture was heated with stirring at 100°C for 25 min, cooled to RT and poured into ice water. The crude product was recrystallized from ethanol to give the *title compound* **6a** (0.86 g, 53%) as a yellow solid, mp 235°C; [Found: C, 66.3; H, 5.5; Cl, 8.7; N, 10.4. $C_{23}H_{22}ClN_3O_2\cdot 0.5H_2O$ requires C, 66.26; H, 5.56; Cl, 8.50; N, 10.08%]; ν_{max}(KBr) 1695, 1650, 1600, 1565, 1450, 1400, 1375, 1340 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.42 (6H, s, $^+$N(C*H*$_3$)$_2$), 3.88 (3H, s, 4-NC*H*$_3$), 5.00 (2H, s, C*H*$_2$), 5.16 (2H, s, C*H*$_2$), 7.42–8.86 (9H, m, arom H). Crystal data: MW=416.89, $C_{23}H_{23}ClN_3O_{2.5}$, triclinic, sp. gr. $P\bar{1}$, a=9.456(2), b=15.912(4), c=15.939(3) Å, α=114.674(16), β=98.073(18), γ=103.001(18)°, V=2047.7(8) Å^3, Z=4, D_{calc}=1.352 g/cm^3, F_{000}=876, μ(MoKα)=0.214 mm^{-1}, R=0.0496, wR=0.0685 for 1977 observed reflections ($I>2\sigma_I$) and R=0.1161, wR=0.0815 over all 7138 measured reflections.

9,9,11-Trimethyl-4,6-dioxo-5-(4-methylphenyl)-5,6,8,9,10,11-hexahydro-4*H*-isoquino[4,5-*g*,*h*]quinazolin-9-ium chloride (6b). The *title compound* **6b** (1.15 g, 68%, a yellow solid, mp 214–217°C) was obtained by the same procedure as **6a**, except using **3b** (1.32 g, 4 mmol) instead of **3a**. [Found: C, 68.3; H, 5.6; Cl, 8.2; N, 10.0. $C_{24}H_{24}ClN_3O_2$ requires C, 68.32; H, 5.73; Cl, 8.40; N, 9.96%]; ν_{max}(KBr) 1710, 1660, 1600, 1570, 1512, 1455, 1407, 1378, 1340 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.45 (3H, s, *Me*), 3.32 (6H, s, $^+$N(C*H*$_3$)$_2$), 3.73 (3H, s, 4-NC*H*$_3$), 5.04 (2H, s, C*H*$_2$), 5.25 (2H, s, C*H*$_2$), 7.27–8.70 (8H, m, arom H).

5-(4-Methoxyphenyl)-9,9,11-trimethyl-4,6-dioxo-5,6,8,9,10,11-hexahydro-4*H*-isoquino[4,5-*g*,*h*]quinazolin-9-ium chloride (6c). The *title compound* **6c** (1.22 g, 70%, a yellow solid, mp 231–232°C) was obtained by the same procedure as **6a**, except using **3c** (1.38 g, 4 mmol) instead of **3a**. [Found: C, 65.9; H, 5.5; Cl, 8.1; N, 9.7. $C_{24}H_{24}ClN_3O_3$ requires C, 65.82; H, 5.52; Cl, 8.10; N, 9.60%]; ν_{max}(KBr) 1700, 1660, 1600, 1578, 1515, 1465, 1410, 1390, 1350, 1315, 1260 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.44 (6H, s, $^+$N(C*H*$_3$)$_2$), 3.88 (3H, s, 4-NC*H*$_3$), 4.06 (3H, s, O*Me*), 5.00 (2H, s, C*H*$_2$), 5.13 (2H, s, C*H*$_2$), 7.21–8.84 (8H, m, arom H).

5-(4-Carboxyphenyl)-9,9,11-trimethyl-4,6-dioxo-5,6,8,9,10,11-hexahydro-4*H*-isoquino[4,5-*g*,*h*]quinazolin-9-ium chloride (6d). The *title compound* **6d** (0.92 g, 51%, a yellow solid, mp 255–258°C) was obtained by the same procedure as **6a**, except using **3d** (1.44 g, 4 mmol) instead of **3a**. [Found: C, 63.9; H, 4.8; Cl, 7.8; N, 9.4. $C_{24}H_{21}ClN_3O_4$ requires C, 63.93; H, 4.69; Cl, 7.86; N, 9.32%]; ν_{max}(KBr) 1715, 1695, 1660, 1600, 1570, 1465, 1404, 1380, 1350, 1280, 1240 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.32 (6H, s, $^+$N(C*H*$_3$)$_2$), 3.73 (3H, s, 4-NC*H*$_3$), 5.01 (2H, s, C*H*$_2$), 5.25 (2H, s, C*H*$_2$), 7.38–8.67 (8H, m, arom H).

5-Dimethylaminomethyl-2-methyl-6-methylamino-2,3-dihydro-1*H*-benzo[*d*,*e*]isoquinoline-1,3-dione (7). Quaternary salt **5** (0.27 g, 0.8 mmol) was refluxed with 20 mL of 1% aq. Na_2CO_3 for 1.5 h. The precipitate formed was filtered off, water-washed and dried. After neutral Al_2O_3 column chromatography ($CHCl_3$), the *title compound* **7** was obtained (0.11 g, 48%) as a yellow solid, mp 139–142°C; [Found: C, 68.8; H, 6.5; N, 13.8. $C_{17}H_{19}N_3O_2$ requires C, 68.67; H, 6.44; N, 14.13%]; ν_{max}(KBr) 1690, 1640, 1580, 1510, 1460, 1360, 1305, 1245 cm^{-1}; δ_H (300 MHz,

DMSO-d_6) 2.20 (6H, s, N(CH_3)$_2$), 3.34 (3H, s, *Me*), 3.41 (3H, s, 4-NCH_3), 3.64 (2H, s, 3-CH_2), 7.63–8.74 (4H, m, arom H).

5-Dimethylaminomethyl-6-methylamino-2-phenyl-2,3-dihydro-1*H*-benzo[*d,e*]isoquinoline-1,3-dione (8a). The *title compound* **8a** (0.12 g, 40%, a yellow solid, mp 222–223°C) was obtained by the same procedure as **7**, except using **6a** (0.30 g, 0.8 mmol) instead of **5**, and recrystallized from toluene instead of column chromatography. [Found: C, 73.7; H, 5.9; N, 11.2. $C_{22}H_{21}N_3O_2$ requires C, 73.52; H, 5.89; N, 11.69%]; ν_{max}(KBr) 1690, 1640, 1590, 1570, 1500, 1455, 1370, 1295, 1210 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.20 (6H, s, N(CH_3)$_2$), 3.43 (3H, s, 4-NCH_3), 3.64 (2H, s, 3-CH_2), 7.30–8.78 (9H, m, arom H). Crystal data: MW=359.42, $C_{22}H_{21}N_3O_2$, monoclinic, sp. gr. $P2_1/c$, a=5.3290(6), b=12.8360(14), c=26.495(3) Å, β=94.933(9)°, V=1805.6(3) Å^3, Z=4, D_{calc}=1.322 g/cm^3, F_{000}=760, μ(CuKα)=0.691 mm^{-1}, R=0.0303, wR=0.0795 for 1755 observed reflections ($I>2\sigma_I$), and R=0.0330, wR=0.0812 over all 2068 measured reflections, number of parameters refined is 251.

5-Dimethylaminomethyl-6-methylamino-2-(4-methylphenyl)-2,3-dihydro-1*H*-benzo[*d,e*]isoquinoline-1,3-dione (8b). The *title compound* **8b** (0.15 g, 50%, a yellow solid, mp 214–216°C) was obtained by the same procedure as **7**, except using **6b** (0.33 g, 0.8 mmol) instead of **5**, and toluene as an eluant for column chromatography. [Found: C, 74.2; H, 6.1; N, 10.5. $C_{23}H_{23}N_3O_2$ requires C, 73.97; H, 6.21; N, 11.25%]; ν_{max}(KBr) 1690, 1640, 1580, 1510, 1475, 1357, 1287, 1233 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.20 (6H, s, N(CH_3)$_2$), 2.39 (3H, s, *Me*), 3.43 (3H, s, 4-NCH_3), 3.64 (2H, s, 3-CH_2), 7.16–8.79 (8H, m, arom H).

5-Dimethylaminomethyl-2-(4-methoxyphenyl)-6-methylamino-2,3-dihydro-1*H*-benzo[*d,e*]isoquinoline-1,3-dione (8c). The *title compound* **8c** (0.16 g, 62%, a yellow solid, mp 214–215°C) was obtained by the same procedure as **7**, except using **6c** (0.35 g, 0.8 mmol) instead of **5**. [Found: C, 70.8; H, 6.0; N, 10.6. $C_{23}H_{23}N_3O_3$ requires C, 70.93; H, 5.95; N, 10.79%]; ν_{max}(KBr) 1690, 1640, 1580, 1570, 1460, 1392, 1363, 1298, 1248 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.20 (6H, s, N(CH_3)$_2$), 3.42 (3H, s, 4-NCH_3), 3.64 (2H, s, 3-CH_2), 3.82 (3H, s, O*Me*), 7.05–8.77 (8H, m, arom H).

5-Dimethylaminomethyl-6-ethylamino-2-phenyl-2,3-dihydro-1*H*-benzo[*d,e*]isoquinoline-1,3-dione (11). Imide **9** (0.70 g, 2 mmol) was dissolved in DMF (2.8 mL, 36 mmol), and $POCl_3$ (1.0 mL, 11 mmol) was added dropwise at 60–70°C. The mixture was stirred at 100°C for 3 h, cooled and treated with ice water. 5% aq. NaOH was added until pH 5–6. The precipitate formed was filtered and purified by column chromatography on Al_2O_3 (benzene) to give the *title compound* **11** (0.15 g, 20%) as a yellow solid, mp 215–218°C (benzene); [Found C, 74.1; H, 6.3; N, 10.9. $C_{23}H_{23}N_3O_2$ requires C, 73.97; H, 6.21; N, 11.25%]; ν_{max}(KBr) 1690, 1640, 1622, 1495, 1460, 1360, 1340, 1290 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.30 (3H, t, J=7.1 Hz, *Me*), 2.22 (6H, s, NMe_2), 3.66 (2H, s, 3-CH_2), 3.77 (2H, q, J=6.6 Hz, 4-NCH_2), 7.31–8.69 (9H, m, aromatic). Crystal data: MW=373.44, $C_{23}H_{23}N_3O_2$, monoclinic, sp. gr. *Cc*, a=18.209(8), b=5.422(2), c=21.175(10) Å, β=91.12(4)°, V=2090(2) Å^3, Z=4, D_{calc}=1.187 g/cm^3, F_{000}=792, μ(MoKα)=0.691 mm^{-1}, R=0.0416, wR=0.0533 for 1204 observed reflections ($I>2\sigma_I$) and R=0.0783, wR=0.0597 over all 3456 measured reflections; number of parameters refined is 254.

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