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Synthesis and Properties of the 3- and 4-Dimethylamino Derivatives of 7*H*,9*H*-Quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one

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SUMMARY

*The isomeric 3-dimethylamino- and 4-dimethylamino-7*H,9H*-quinazolino[3,2-*b*]benz*[d,e]*isoquinolin-7-ones have been synthesized. The structure of the dyes was confirmed by IR and UV–visible spectroscopy and by use of quantum calculations by the PPP method. Alkalinity constants of the compounds were measured and the positions at which the dimethylamino-7*H,9H*-quinazolino[3,2-*b*]benz*[d,e]*isoquinolin-7-ones are protonated were determined by a number of quantum calculations.*

Emission spectra of the isomeric solutions of the dyes and their protonated forms are reported.

1. INTRODUCTION

In the course of investigations previously described,[1-3] a range of 7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one derivatives were synthesized. It was found that the majority of these compounds possess fluorescence properties. It was anticipated that the 3-dimethylamino- and 4-dimethylamino-7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-ones (**1a** and **1b**) would also display the ability to fluoresce as shown by derivatives of naphthalimide containing an amino group in the 4-position.[4]

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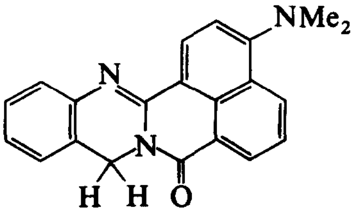
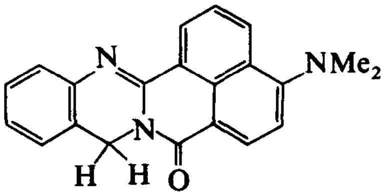
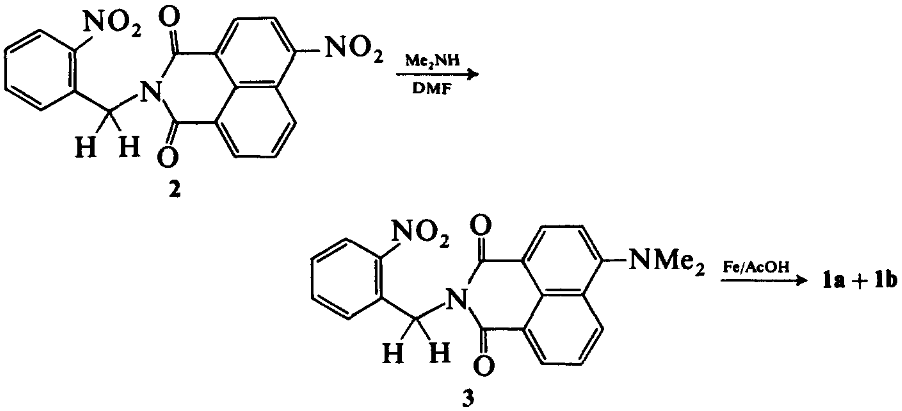


1a



1b

The mixture of the isomeric 3-dimethylamino- and 4-dimethylamino-7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-ones (**1a**, **1b**) was obtained by using the procedure outlined in Scheme 1, i.e. one similar to that used for the synthesis of other 7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one derivatives.[1,3,5]



Scheme 1

2. RESULTS AND DISCUSSION

The synthesis of 7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one derivatives was very facile. Replacement of the nitro group in 4-nitro-*N*-(2-nitrobenzyl)naphthalimide **2** by dimethylamine in dimethylformamide occurred readily, giving a good yield of high-purity product. In nucleophilic replacement reactions in the naphthalimide series, the nitro group is a good leaving group and is much easier to replace than, for example, the bromine atom, the replacement of which requires much more drastic conditions which can result in lower-quality reaction products.

Reduction of the nitro group of compound **3** in boiling 90% acetic acid was accompanied by cyclization, producing a mixture of the isomers **1a** and **1b** in the ratio of *ca.* 1:1, as estimated by chromatography and by the results of separation methods. The mixture of the isomeric dimethylamino derivatives of 7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one was separated into the components by utilizing the differences in the basicity of the nitrogen atoms in the individual isomers. Compound **1a** in *ca.* 10% acetic acid was present almost exclusively in the easily soluble protonated form. Under the same conditions the other isomer, compound **1b**, because of its significantly lower alkalinity, dissolved only to a small extent.

2.1. Structural investigations

The chemical constitution of the isomeric dimethylamino derivatives of 7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one **1a** and **1b** that were obtained was confirmed by elemental analysis and by IR, UV–visible spectroscopy and NMR measurements.

The data for the NMR measurements are shown in the experimental section. However, analysis of the NMR spectra did not enable any distinction between the two isomers to be made.

In the IR spectra, the absorption peak related to the stretching vibration of a C=N bond occurs in the spectrum of **1a** at a lower frequency (1158 cm^{-1}) than for the isomer **1b** (1563 cm^{-1}). It can thus be presumed that in compound **1a** the dimethylamino group is located in the 3-position, since in this isomer there will be a decreased force constant for the C=N bond due to the mesomeric effect of the electron-donor dimethylamino group in the *para*-position. Similarly, in the 4-dimethylamino derivative **1b**, in which the dimethylamino group is in the *para*-position relative to the C=O group, the stretching frequency relatable to the carbonyl group occurs at a lower frequency (1661 cm^{-1}) than for the isomeric 3-dimethylamino derivative **1a** (1665 cm^{-1}).

In addition the electronic spectra that the 3-dimethylamino-7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one absorbs at a longer wavelength (450 nm) than the isomeric 4-dimethylamino derivative **1b** (444 nm), in which the dimethylamino group is more distant from the C=N group. Both compounds **1a** and **1b** have relatively high molar absorptivities (20 300 and 24 900, respectively) when compared with other 7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolinone derivatives (*ca.* 14 000).[3]

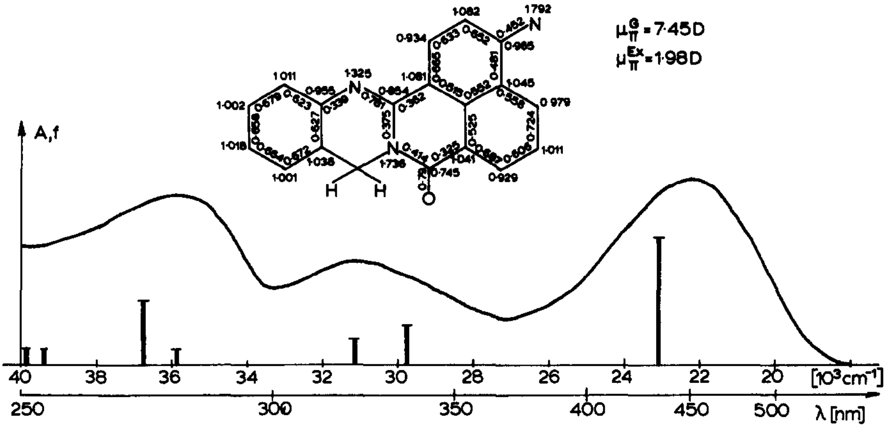


Fig. 1. Comparison of absorption spectrum of 3-dimethylamino-7*H*,9*H*-quinazolino-[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one (**1a**) in 1,2-dichloroethane (1 cm path length, 3·05 × 10^{-5} mol dm^{-3}) with calculated data.

Results of calculations by the PPP method (Figs 1 and 2), performed using the parameterization previously described[6] give an additional proof that the correct constitution has been assigned to the individual isomers **1a** and **1b**.

The π-electron bond orders obtained by the PPP method confirmed earlier assumptions concerning the differences between the force

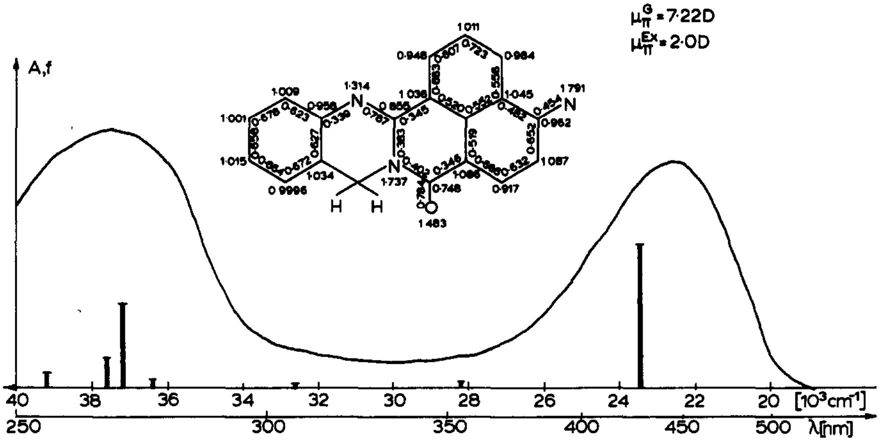


Fig. 2. Comparison of absorption spectrum of 4-dimethylamino-7*H*,9*H*-quinazolino-[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one (**1b**) in 1,2-dichloroethane (1 cm path length, 3·05 × 10^{-5} mol dm^{-3}) with calculated data.

constants of the C=N and the C=O bonds in the isomers **1a** and **1b**, and a good correlation between bond-order changes and the corresponding band position shifts in the IR range was observed.

Similarly, calculations relating to the electronic spectra of the isomers are in good agreement with the experimental data both in the visible and UV spectrum ranges.

2.2. Protonation of the 7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one derivatives

During the synthesis, remarkable differences were observed in the behaviour of compounds **1a** and **1b** in the presence of acids. In addition to the considerable differences in alkalinity, which enabled relatively easy separation of the reaction mixture into the individual isomers to be effected, the compounds showed much deeper colours in acidic medium. The acidity constants, pK'_a of the protonated forms of compounds **1a** and **1b** were determined from the spectrophotometric measurements of their solutions in 50% ethanol containing varying amounts of HCl (Figs 3 and 4).

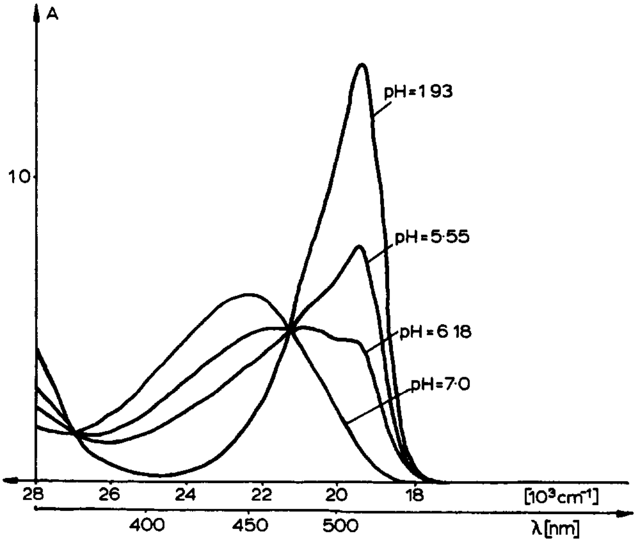


Fig. 3. Effect of hydrochloric acid on absorption spectra of 3-dimethylamino-7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one in 50% ethanol (1 cm path length, $3{\cdot}05 \times 10^{-5}$ mol dm^{-3}).

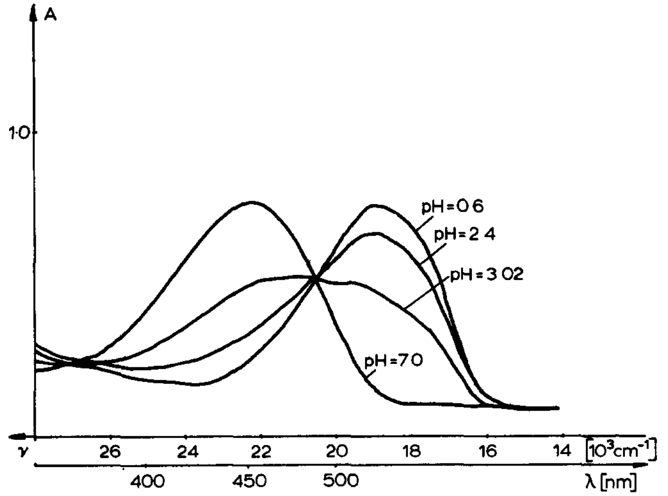
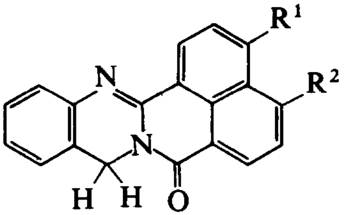


Fig. 4. Effect of hydrochloric acid on absorption spectra of 4-dimethylamino-7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one in 50% ethanol (1 cm path length, 3·05 × 10^{-5} mol dm^{-3}).

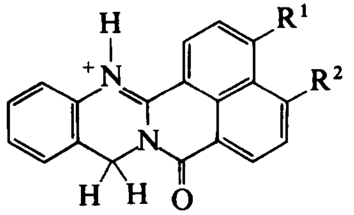
For the 3-dimethylamino derivative the pK'_a value was found to be 5·6 whilst for the 4-dimethylamino derivative it was 3·0. As is shown in Figs 3 and 4, the colour of the derivatives of 7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one becomes much deeper on protonation. With the 3-dimethylamino derivative, the colour shifts from orange to red (λ_{max} = 515 nm in 50% EtOH), and with the isomer substituted in the 4-position, a violet-red hue is obtained (λ_{max} = 529 nm in 50% EtOH). In addition, protonation of the 3-dimethylamino derivative results in a significant hyperchromic shift (λ_{max} = 15 200 in 50% EtOH).

It is difficult to explain such great differences in the behaviour of the isomers **1a**, **1b** using, as a simple model, protonation on the dimethylamino nitrogen atom. With such protonation, a hypsochromic effect should be observed as a result of the loss of conjugation of the lone electron pair of the protonated dimethylamino group with the rest of the molecule. The differences in the alkalinity of compounds **1a** and **1b** are also not explainable by comparison of the electron densities on the dimethylamino nitrogen atoms as determined by the PPP method (Figs 1 and 2). The densities are almost equal.

To explain the effects observed, further estimations were performed, using the PPP method, for a range of protonated forms of compounds **1a** and **1b**. In addition to the model involving dimethylamino group



1c: $R^1 = \overset{+}{N}HMe_2, R^2 = H$
1d: $R^1 = H, R^2 = \overset{+}{N}HMe_2$



4a: $R^1 = NMe_2, R^2 = H$
4b: $R^1 = H, R^2 = NMe_2$

protonation (**1c, 1d**), there is also the possibility of protonation in the ring, on the nitrogen atom at the 14-position, as in structures **4a, 4b**.

The effects resulting from protonation were accounted for by modifying, in the PPP method, the parameters associated with the ionization potentials of the respective atoms. For the carbon atom in the neighbourhood of the amino nitrogen atom, I_p was assumed to be equal to 12·36 eV, whilst for the pyridine nitrogen atom at the 14-position, I_p is 17·62 eV.[7] The results of the calculations of the protonated forms are collated in Table 1.

The results of these calculations clearly indicate that for both the 3- and 4-dimethylamino isomers **1a** and **1b**, protonation occurs at the cyclic nitrogen atom at the 14-position of the molecule. Some differences between the results of the calculation and the experimental spectra have been observed. These discrepancies may be attributable in part to the necessity of using a polar medium in the protonation reaction, which could produce a bathochromic shift of the absorption band. However,

TABLE 1
Calculated and Experimental Values of π–π^* Transition Energy of the Long-Wave Absorption Band of **1a** and **1b**

Compound	*Transition Energy* $S_0 \rightarrow S_1$ *(eV)*	
	Calculated	*Experimental*[a]
1a	2·865	2·752
1c	3·041	2·405
4a	2·743	
1b	2·923	2·790
1d	3·019	2·343
4b	2·675	

[a] In 1,2-dichloroethane.

very good coincidence of both the directions and the degrees of the changes resulting from the protonation has been observed. The monoprotonated compound **4b** in relatively mild conditions ($pK'_a = -0{\cdot}4$ in 50% EtOH) undergoes a second protonation. The spectrum of the salt formed as the result of the reaction is in good agreement with that of the unsubstituted 7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one hydrochloride (Fig. 5).

The nitrogen atom protonation in the 14-position of compounds **1a** and **1b** is also confirmed by the IR spectra of the respective compounds. As a result of the protonation of these compounds, there also appear wide stretching-vibration bands of the N—H bonds in the 3000 cm^{-1} range. As a result of the second protonation of compound **4b**, there appears additionally a band at 2350 cm^{-1}. These bands correspond to those appearing in 7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one hydrochloride (3000 cm^{-1}) and in 4-dimethylamino-*N*-(2-nitrobenzyl)-naphthalimide hydrochloride (2400 cm^{-1}). All observed properties and results of the quantum calculations show that compound **1a** is 3-dimethylamino-7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one and compound **1b** is 4-dimethylamino-7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one.

Emission data of solutions of dyes **1a** and **1b** were recorded and compared with those of *N*-benzyl-4-dimethylamine-naphthalimide (**5**) as reference compound. Results of these measurements and calculations are presented in Table 2.

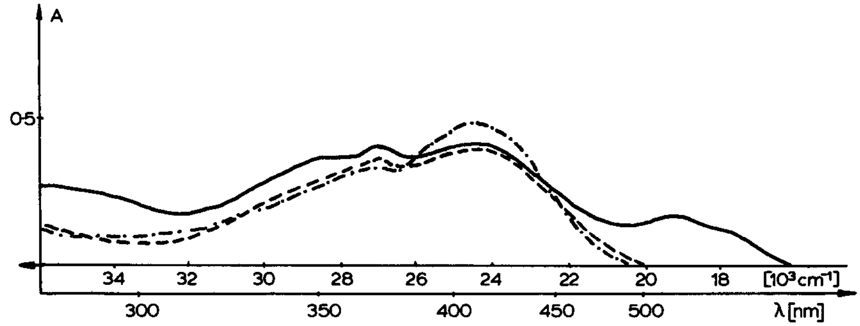


Fig. 5. The result of second-stage protonation of 4-dimethylamino-7*H*,9*H*-quinazolino-[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one (**1b**): ———, spectrum in 3M HCl in 50% ethanol; – – – –, difference spectrum obtained from absorption spectra of **1b** at pH = 7·0 and monoprotonated form **1b**; —·—·—, spectrum of unsubstituted 7*H*,9*H*-quinazolino-[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one in 3M HCl in50% ethanol.

TABLE 2

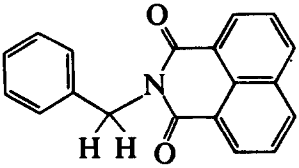
Fluorescence Properties of **1a**, **1b**, **5** at a Concentration of 5×10^{-6} mol dm^{-3} in Different Solvents

Compound	*Solvent*						
	1,2-Dichloroethane			*50% Ethanol*		*50% Ethanol + HCl, pH = 1·8*	
	λ_{max} *(nm)*	F^a	ϕ^b	λ_{max} *(nm)*	F^a	λ_{max} *(nm)*	F^a
1a	550	0·046	0·03	515 540	0·010	522	0·072
1b	512	0·862	0·48	530	0·228	Not fluorescent	
5	498	1·000	1·00	—	—	—	—

[a] F = intensity of fluorescence.

[b] ϕ = relative quantum yield of fluorescence.

There are considerable differences between the 3- and 4-dimethylamino isomers in their fluorescent properties. The 4-dimethylamino isomer **1b** has its fluorescence band bathochromically shifted in relation to the reference compound **5** by 16 nm. It has similar fluorescence, and the quantum yield of fluorescence is reduced by half. The 3-dimethylamino isomer **1a** exhibits a larger bathochromic shift of the fluorescence peak (52 nm) but its intensity and fluorescence quantum yield are 25–30 times smaller than those of the reference compound **5**.



5

Polar solvents cause a proportional decrease in the fluorescence of both **1a** and **1b**. The protonated forms, however, behave differently; the 3-dimethylamino isomer shows an increase in fluorescence, whilst the 4-dimethylamino isomer does not fluoresce under these conditions.

3. EXPERIMENTAL

Melting points were determined on a Boetius 05 apparatus and were not corrected. All reactions were monitored by TLC on Silica Gel 60 (Merck 5553), using 1:4 ethyl acetate–toluene solution as eluent. To verify isomer separation, 1:4:20 acetic acid–ethyl acetate–toluene was used as eluent. Infrared spectra were recorded on a Specord 71-IR (KBr) instrument.

Electronic spectra were recorded on a Specord UV–vis spectrophotometer (Jena), using $3{\cdot}05 \times 10^{-5}$ mol dm^{-3} dye solutions in 1,2-dichloroethane and hydrochloric acid solutions in 50% EtOH.

The ionic strength of the solutions was kept constant (0·05) by adding suitable amounts of KCl. Spectrum calculations by the PPP method were made for 30 single-excited configurations. Emission spectra were recorded on an Aminco–Bowman spectrofluorimeter using 5×10^{-6} mol dm^{-3} solutions in 1,2-dichloroethane at 430 nm light excitation. Nuclear magnetic resonance spectra were recorded in $CDCl_3$ on a Bruker 90 MHz apparatus.

3.1. *N*-(2-Nitrobenzyl)-4-nitronaphthalimide, 2

Finely ground 4-nitronaphthalic anhydride (24·3 g, 0·1 mol), and 2-nitrobenzylamine hydrochloride (21·7 g, 0·11 mol), were heated to 50 °C in 20% aq. ethanol (800 cm^3) and then 10% aq. NaOH (30 cm^3, 0·1 mol) was added over 1 h.

The reaction mixture was stirred at 50–60 °C for 1 h, and 10% aq. Na_2CO_3 (5 cm^3) was then added. The mixture was brought to reflux over 30 min and refluxed for 3 h. After filtering hot, 35·4 g (94%) of product, m.p. 224–226 °C (chlorobenzene) were obtained. ν_{max}(IR): 1720 (C=O), 1675 (C=O), 1535 (NO_2), 1340 (NO_2) cm^{-1}.

3.2. *N*-(2-Nitrobenzyl)-4-dimethylaminonaphthalimide, 3

N-(2-nitrobenzyl)-4-nitronaphthalimide (7·55 g, 0·02 mol), a 23% solution of dimethylamine in DMF (39·1 g, 0·2 mol) and DMF (35 cm^3) were heated gradually for 1 h to 70 °C and stirred at this temperature for a further 1 h. Water (70 cm^3) was then added to the mixture and, after filtering, 6·9 g (92%) of product, m.p. 179–181 °C (dioxane) was obtained. ν_{max} (IR): 2900 (CH_3), 1700 (C=O), 1650 (C=O), 1534 (NO_2), 1345 (NO_2) cm^{-1}.

3.3. 3-Dimethylamino- and 4-dimethylamino-7*H*,9*H*-quinazolino[3,2-*b*]-benz[*d*,*e*]isoquinolin-7-one, 1a and 1b

A mixture of 4-dimethylamino-*N*-(2-nitrobenzyl)naphthalimide (5·0 g, 0·0133 mol), 90% aq. AcOH (60 cm^3) and iron powder (10 g) was refluxed for 3 h. The reaction mixture was then poured onto water (600 cm^3) and left overnight before filtering. The product was twice recrystallized from butanol to give 0·9 g of 4-dimethylamino-7*H*,9*H*-quinazolino[3,2-*b*]-benz[*d*,*e*]isoquinolin-7-one (**1b**), m.p. 182–183 °C. Found: N 12·70%; $C_{21}H_{17}N_3O$ requires N 12·83%. ν_{max} (IR): 2860 (CH_3), 1661 (C=O), 1563 (C=N) cm^{-1}. λ_{max} (1,2-dichloroethane): 444·4 nm, (ε_{max} 24 900 dm^3 mol^{-1} cm^{-1}). NMR: 3·05 (s, 6H) $N(CH_3)_2$; 5·26 (s, 2H) N—CH_2Ar; 7·02–7·31 (m, 5H) 4ArH benzene + 1ArH naphthalene; 7·51–7·68 (t, 1H), 8·23–8·40 (t, 2H), 8·75–8·83 (d, 1H) ArH naphthalene.

30% aq. NaOH (100 cm^3) was added to the filtrate, and the residue was filtered off and twice recrystallized from butanol to give 1·0 g of 3-dimethylamino-7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one (**1a**), m.p. 158–159 °C. Found: N 12·75%. ν_{max} (IR): 2850 (CH_3), 1665 (C=O), 1558 (C=N). λ_{max} (1,2-dichloroethane): 449·6 nm (ε_{max} 20 300 dm^3 mol^{-1} cm^{-1}). NMR: 3·03 (s, 6H) $N(CH_3)_2$; 5·25 (s, 2H) N—CH_2—Ar; 7·09–7·34 (m, 5H) 4ArH benzene + 1ArH naphthalene; 7·50–7·68 (q, 1H), 8·33–8·48 (m, 2H), 8·67–8·76 (d, 1H) ArH naphthalene.

3.4. Hydrochlorides of 1a and 1b

The respective hydrochlorides were obtained by crystallizing the compounds from the aqueous solutions of hydrochloric acid of various concentrations.

4. CONCLUSIONS

The method used for synthesizing isomeric 3-dimethylamino- and 4-dimethylamino-7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-ones can be used as a general process to produce high-purity products relatively easily.

The quantum calculation method used for the interpretation of the structure and properties of heterocyclic dyes of this type has been shown to be a generally applicable one. It permits characterization of the isomer **1a** as 3-dimethylamino-7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]isoquinolin-7-one and of **1b** as 4-dimethylamino-7*H*,9*H*-quinazolino[3,2-*b*]benz[*d*,*e*]-isoquinolin-7-one.

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