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Synthesis and Properties of Some 9,10-Dihydro-7*H*-Imidazo[1,2-*b*]Benz[*d*,*e*]Isoquinolin-7-one Derivatives

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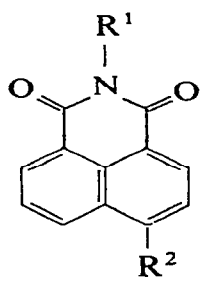
SUMMARY

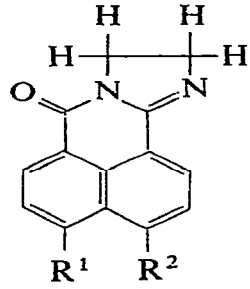
The various routes of synthesis of some methoxy- and acetylamino-9,10-dihydro-7H-imidazo[1,2-b]benz[d,e]isoquinolin-7-one derivatives are described. The mixtures of geometric isomers obtained were separated and the chemical constitution of individual isomers was confirmed by the u.v., i.r., n.m.r. and mass spectroscopy. The fluorescence properties of individual isomers were also determined.

1. INTRODUCTION

A number of known optical brightening agents of the type **1**[1,2] contain the benz[*d*,*e*]isoquinoline system. In the course of the investigation of new potential optical brightening agents for synthetic fibres the synthesis of methoxy- and acetylamino- 9,10-dihydro-7*H*-imidazo[1,2-*b*]benz[*d*,*e*]-isoquinolin-7-one derivatives (**2a–d**) was carried out.



(**1**) R^1 = Alkyl, R^2 = OAlkyl, NHAc



(**2a**) R^1 = H, R^2 = OCH_3
(**2b**) R^1 = OCH_3, R^2 = H
(**2c**) R^1 = H, R^2 = NHAc
(**2d**) R^1 = NHAc, R^2 = H

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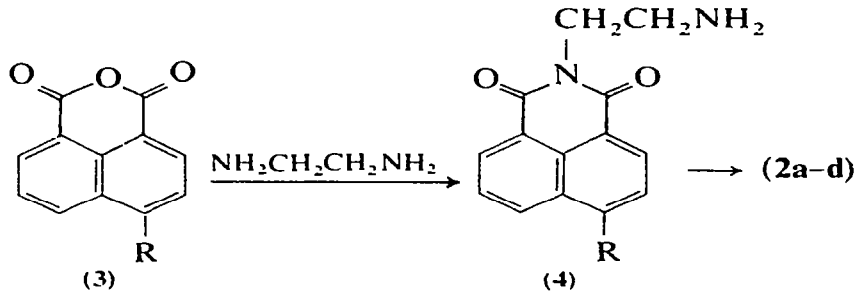
Unsubstituted 9,10-dihydro-7*H*-imidazo[1,2-*b*]benz[*d*,*e*]isoquinolin-7-one had been obtained earlier by thermal cyclisation of *N*-(2-aminoethyl)naphthalimide.[3,4] However, this compound is not of commercial value as an optical brightening agent due to its low emission yield.

2. RESULTS AND DISCUSSION

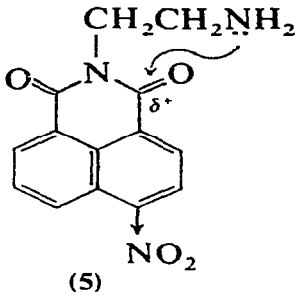
The general synthetic route to the methoxy- and acetylamino- 9,10-dihydro-7*H*-imidazo[1,2-*b*]benz[*d*,*e*]isoquinolin-7-one derivatives, which were expected to possess better fluorescence properties than the unsubstituted compound, is outlined below.



The acylation of ethylenediamine and cyclisation of the *N*-(2-aminoethyl)naphthalimide (**4**) were carried out in one step in water or pyridine. As was expected, the presence of geometric isomers was observed in chromatograms (TLC) of the reaction products. The mixtures of compounds **2a**, **2b** and **2c**, **2d** were obtained by using 4-methoxy- (**3a**) and 4-acetylamino- (**3b**) naphthalic anhydrides respectively. However, the reaction between 4-nitronaphthalic anhydride (**3**; R=NO_2) and ethylenediamine yielded only one isomer, 3-nitro-9,10-dihydro-7*H*-imidazo[1,2-*b*]benz[*d*,*e*]isoquinolin-7-one (**7**). In this case the direction of cyclisation reaction is favoured by the large electron deficiency on the carbonyl carbon atom in the *para* position to the nitro group in intermediate compound **5**.

The formation of by-product **6** was observed in all the reactions described above, as a result of double acylation of ethylenediamine with an appropriate naphthalic anhydride derivative.

In order to confirm the structure of the methoxy- and acetylamino-9,10-dihydro-7*H*-imidazo[1,2-*b*]benz[*d*,*e*]isoquinolin-7-one derivatives



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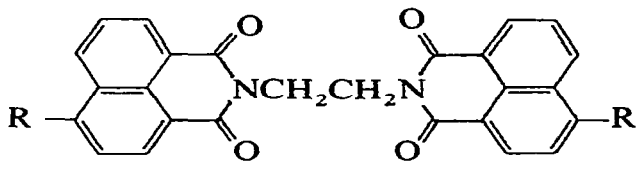
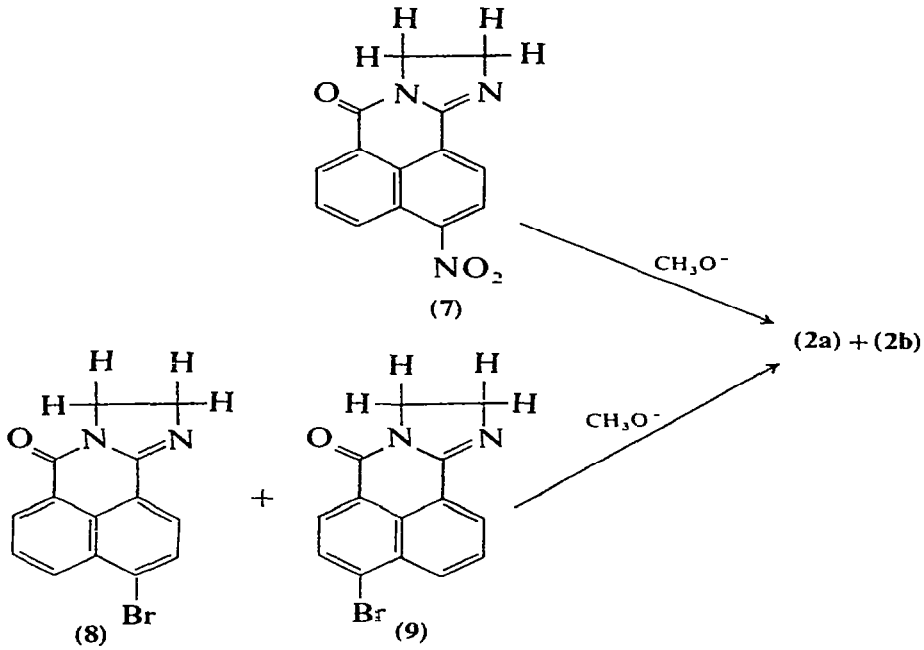


(6)

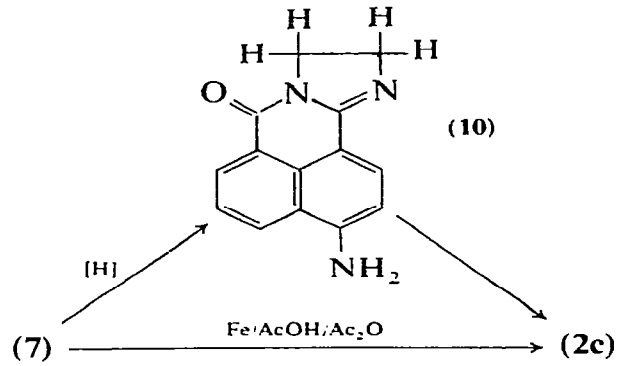
as well as to examine the possibilities of synthetic routes leading to products with different isomer ratios, the synthesis of these compounds was performed by another method. The methoxy derivatives of 9,10-dihydro-7*H*-imidazo[1,2-*b*]benz[*d*,*e*]isoquinolin-7-one were synthesised by nucleophilic substitution of a bromine atom or a nitro group by the method shown below:



It was observed that both reactions shown yielded mixtures of geometric isomers. Formation of isomer mixtures in the substitution reaction of a 3-nitro group can occur via opening of the imidazole ring

in compound 7 or in the intermediate products of the substitution reaction. An attempt to isomerise the pure 3-methoxy isomer (**2a**) under substitution reaction conditions was ineffective.

Reduction of the nitro group in compound 7 followed by acetylation of the amine (**10**), in accordance with the scheme below, gave only one isomer, 3-acetylamino-9,10-dihydro-7*H*-imidazo[1,2-*b*]benz[*d*,*e*]isoquinolin-7-one (**2c**).



(10)

(7) → (2c)

The mixtures of isomers from the reactions described above were separated by column chromatography, and individual compounds were characterised by u.v.–visible, i.r., n.m.r. and mass spectroscopy.

Significant differences in the electronic absorption spectra of the protonated methoxy- and acetylamino- 9,10-dihydro-7*H*-imidazo[1,2-*b*]benz[*d*,*e*]isoquinolin-7-one derivatives (**2a–d**) were found. The 3-methoxy (**2a**) and 3-acetylamino (**2c**) compounds in neutral medium absorbed at slightly longer wavelengths than the corresponding 4-substituted derivatives. Addition of an excess of hydrochloric acid to ethanolic solutions of 3-substituted isomers caused the large bathochromic shift. The absorption spectrum of 4-acetylamino-9,10-dihydro-7*H*-imidazo[1,2-*b*]benz[*d*,*e*]isoquinolin-7-one (**2d**) remained practically unchanged but the absorption band of the 4-methoxy isomer (**2b**) underwent a bathochromic shift.

The differences in u.v.–visible spectra of the protonated compounds allowed the ratio of isomers in reaction products to be estimated using the method of spectral data analysis at two different wavelengths.[5] The results are presented in Table 1.

The carbonyl stretching bands in i.r. spectra of 3-substituted isomers (**2a,c**) are shifted to lower wave numbers as compared with appropriate

TABLE 1
The Ratio of Isomers in the Product Obtained

Products	*Method of synthesis*	*Isomers found (%)*	
		3-substd.	*4-substd.*
Methoxy derivatives	From 4-methoxynaphthalic acid anhydride	7	93
Methoxy derivatives	Substitution of bromine atom	11	89
Methoxy derivatives	Substitution of nitro group	36	64
Acetylamino derivatives	From 4-acetylaminonaphthalic acid anhydride	4	96
Acetylamino derivatives	Reduction of nitro group followed by acetylation	100	0

bands in the spectra of 4-substituted isomers (**2b,d**), due to the mesomeric effect of electron donating groups in the *para* position. The imino group stretching bands were shifted in the opposite direction. In the spectrum of the 3-acetylamino isomer **2c** in the solid state (KBr, Nujol) the acetyl carbonyl group absorption was not observed. On the other hand, an additional band in the region 3250 cm^{-1} appeared. These features are characteristic for the solid state, as the spectrum of a chloroform solution of **2c** showed the appearance of the acetyl carbonyl band together with disappearance of the 3250 cm^{-1} band.

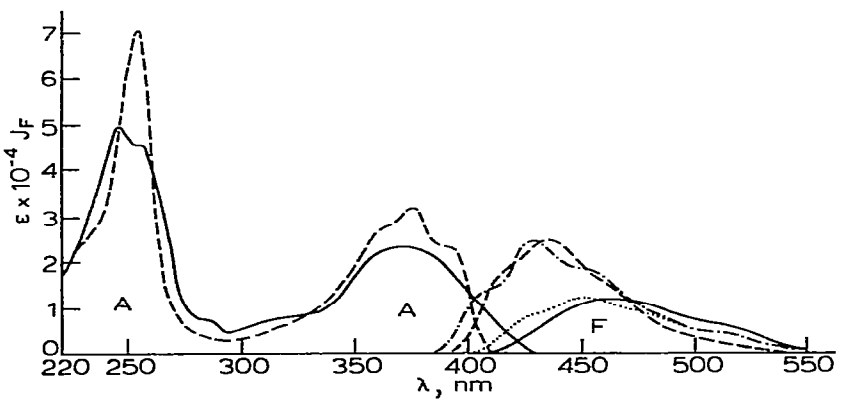


Fig. 1. Electronic spectra of methoxy isomers. *A*, region of absorption spectra; *F*, region of fluorescence spectra. ——— Ethanolic solution of 3-methoxy isomer **2a**; – – – – – – ethanolic solution of 4-methoxy isomer **2b**; · · · · · · · · · · · · dioxane solution of 3-methoxy isomer **2a**; –·–·–·– dioxane solution of 4-methoxy isomer **2b**.

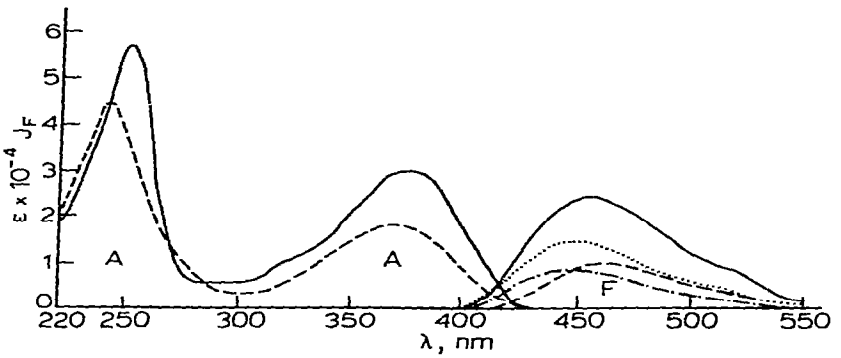


Fig. 2. Electronic spectra of acetylamino isomers. *A*, region of absorption spectra; *F*, region of fluorescence spectra. ——— Ethanolic solution of 3-acetylamino isomer **2c**; – – – – – – ethanolic solution of 4-acetylamino isomer **2d**; · · · · · · · · · · · · dioxane solution of 3-acetylamino isomer **2c**; ·—·—·— dioxane solution of 4-acetylamino isomer **2d**.

In the n.m.r. spectrum (CF_3COOH) of the 3-methoxy isomer **2a** a peak from three protons of the methoxy group appeared at lower fields than in the spectrum of the 4-substituted isomer **2b**. This effect is due to the deshielding of the methoxy protons in compound **2a** caused by the influence of the protonated *para* imino group. The n.m.r. spectra of acetylamino isomers **2c** and **2d** were practically identical. For all compounds integration of signals agreed with the structures.

Mass spectroscopy confirmed the molecular weights of the compounds.

Electronic emission spectra for 1,4-dioxane solutions showed a bathochromic shift of the emission band of the 3-substituted isomers (**2a,c**) relative to the 4-substituted isomers (**2b,d**) (Figs. 1 and 2). The emission band maxima of methoxy- and acetylamino- 9,10-dihydro-7*H*-imidazo-[1,2-*b*]benz[*d*,*e*]isoquinolin-7-one derivatives (**2a–d**) are located

TABLE 2
Fluorescence Properties of the Compounds Obtained Relative to Compound **2b**

Compound	*Fluorescence yield*	*Quantum yield*
2a	0·628	0·90
2b	1·000	1·00
2c	0·907	0·99
2d	0·331	0·74
bis-MSB	1·191	0·72

in the 430–470 nm region which is characteristic of commercial optical brightening agents.

Relative fluorescence yields (F) calculated as $\int J_f d\nu$,[6] where J_f represents the relative fluorescence intensity, and the relative fluorescence quantum yields (Q) are presented in Table 2 for the compounds under consideration.

The fluorescence properties of the isomeric methoxy and acetylamino-9,10-dihydro-7*H*-imidazo[1,2-*b*]benz[*d*,*e*]isoquinolin-7-one derivatives (**2a–d**) are similar and comparable to those of the known fluorescence standard bis-MSB (1,4-di(3-methylstyryl)benzene).

3. EXPERIMENTAL

Melting points (uncorrected) were determined with Boetius PHMK-05 hot-stage apparatus. Infrared spectra were recorded using Jena UR-10 (KBr) and Specord-71 i.r. (chloroform) spectrometers. Ultraviolet–visible (2.10^{-5} mol litre^{-1} in ethanol and ethanol–36% aq. hydrochloric acid solution, 100:1) and emission (2.10^{-5} mol litre^{-1} in ethanol and dioxane solutions; excitation at λ_{max} of absorption band) spectra were determined with the Jena Specord u.v.–visible and the Jobin–Yvonne apparatus respectively. Nuclear magnetic resonance spectra (in trifluoroacetic acid; TMS) were recorded with a Tesla 100 MHz instrument and mass spectra with an LKB 2091 spectrometer. Chromatography of the products was carried out on DC–Karten SI (Riedel de Haen), with pyridine–toluene 1:4 for methoxy-, and ethanol–dioxane 1:1 eluents for acetylamino-, bromo-, and nitro- 9,10-dihydro-7*H*-imidazo[1,2-*b*]benz[*d*,*e*]isoquinolin-7-one derivatives.

4-Nitro-, 4-bromo-, 4-methoxy-, and 4-acetyl-aminonaphthalic acid anhydrides were obtained according to the literature methods.[7–10]

3.1. 3-Nitro-9,10-dihydro-7*H*-imidazo[1,2-*b*]benz[*d*,*e*]isoquinolin-7-one (7)

Finely powdered 4-nitronaphthalic acid anhydride (5·0 g, 0·02 mol) was added over 0·5 h to ethylenediamine (2·4 g, 0·04 mol) in 50% aq. methanol (160 cm^3) in the presence of acetic acid (3·4 g) at 30 °C. The reaction mixture was stirred at 30–35 °C for 2 h. Subsequently 30% aq. sodium hydroxide (1 cm^3, 0·01 mol) was added; the reaction mixture was gradually heated to the boiling point over 2 h, and maintained at this

temperature for 3 h. Then 30 % aq. sodium hydroxide (1 cm^3, 0·01 mol) was added and methanol (100 cm^3) was removed by distillation. The water (100 cm^3) was added and the reaction mixture was refluxed for 5 h. After cooling to room temperature and filtration, the product (5·0 g, 93 %) was obtained, m.p. 240–241 °C (chlorobenzene). Found: N, 15·59; $C_{14}H_9N_3O_3$ requires N, 15·72 %; ν_{max} 1665, 1615, 1525, 1340 cm^{-1}.

3.2. 3-Methoxy- and 4-methoxy- 9,10-dihydro-7*H*-imidazo[1,2-*b*]benz[*d*,*e*]-isoquinolin-7-ones (2a and b)

(*a*) From 3-nitro-9,10-dihydro-7*H*-imidazo[1,2*b*]benz[*d*,*e*]isoquinolin-7-one. A 30 % methanolic solution of sodium methoxide (4·5 g, 0·025 mol) was added to a suspension of the 3-nitro compound (7) (1·5 g, 0·0056 mol) in methanol (100 cm^3) in the presence of pyridine (5 cm^3). The reaction mixture was heated to 50 °C during 0·5 h and stirred at 50–55 °C for 2 h. The resulting solution was evaporated to dryness, and the product mixture of compounds **2a** and **2b** (0·9 g, 67·5 %) was extracted with boiling chlorobenzene (100 cm^3), m.p. 220–232 °C. Found: N, 11·23; $C_{15}H_{12}N_2O_2$ requires N, 11·10 %; λ_{max} 251·0, 374·5 nm (ε 34 000, 14 800); λ_{max} (in presence of HCl) 256·6, 400·0 nm (ε 28 000, 15 200); δ 3·38, 3·44 (3H s, s, 4-OCH_3, 3-OCH_3), 3·52–3·92 (4H m, CH_2—CH_2), 5·76–6·00, 6·20–6·50 and 6·82–7·34 (1H m, 1H m, 3H m, naphthalene).

The product of the above reaction was submitted to separation by means of column chromatography (50 cm, Silica Gel 70–325 mesh (Merck), pyridine–chlorobenzene 2:3) which yielded 4-methoxy isomer (**2b**) (0·35 g, first fraction), m.p. 257–258 °C; λ_{max} 250·8, 374·2 nm (ε 36 000, 15 000); λ_{max} (in presence of HCl) 257·6, 402·2 nm (ε 29 000, 14 000); ν_{max} 1655, 1630, 1405, 1394 cm^{-1}; *m/e* 253 (16), 252 (M^+, 100), 251 (48), 237 (M—CH_3, 9), 222 (1); and 3-methoxy isomer (**2a**) (0·15 g, second fraction), m.p. 224–225 °C; λ_{max} 243·9, 254·8, 375·8 nm (ε 27 000, 22 900, 11 000); λ_{max} (in presence of HCl) 255·2, 384·6, 400·0 nm (ε 26 500, 17 100, 16 100); ν_{max} 1660, 1627, 1387 cm^{-1}; *m/e* 253 (18), 252 (M^+, 100), 251 (57), 237 (M—CH_3, 5), 225 (2).

(*b*) From 4-methoxynaphthalic acid anhydride. This was performed according to the patent specification,[11] m.p. 232–254 °C. Found: N, 11·25; $C_{15}H_{12}N_2O_2$ requires N, 11·10 %; λ_{max} 250·8, 374·2 nm (ε 35 800, 15 000); λ_{max} (in presence of HCl) 257·6, 402·2 nm (ε 28 100, 14 200); δ 3·38 (3H s, OCH_3), 3·52–3·90 (4H m, CH_2—CH_2), 5·76–5·95, 6·22–6·46, 6·96–7·17, 7·18–7·34 (1H d, 1H t, 2H d, 1H d, naphthalene).

(*c*) From 4-bromonaphthalic acid anhydride. The finely powdered 4-bromonaphthalic acid anhydride (5·6 g, 0·019 mol) was added over 0·5 h to a solution of ethylenediamine (1·2 g, 0·02 mol) in pyridine (100 cm^3) at 25–30 °C. The reaction mixture was then gradually heated to 110 °C over 0·5 h and stirred at this temperature for 8 h. After hot filtration and evaporation of the filtrate the product was obtained (3·1 g, 52 %), m.p. 270–271 °C. Found: N, 9·24; $C_{14}H_9N_2OBr$ requires N, 9·30 %; ν_{max} 1680, 1630, 1395 cm^{-1}.

Substitution of the bromine atom with methoxide ion was performed in the same way as substitution of the nitro group. The product was obtained with 80 % yield, m.p. 239–254 °C. Found: N, 11·04; $C_{15}H_{12}N_2O_2$ requires N, 11·10 %; λ_{max} 250·7, 374·2 nm (ε 35 000, 14 800), λ_{max} (in presence of HCl) 257·6, 402·2 nm (ε 28 000, 15 500); other spectral data were the same as for reaction product of 4-methoxynaphthalic acid anhydride with ethylenediamine.

3.3. 3-Acetylamino-9,10-dihydro-7*H*-imidazo[1,2-*b*]benz[*d*,*e*]isoquinolin-7-one (2c)

Anhydrous stannous chloride (13·5 g, 0·07 mol) was slowly added at 60 °C over 1 h to the suspension of the nitro compound (**7**) (5·4 g, 0·02 mol) in 35 % aq. hydrochloric acid solution (50 cm^3). The precipitated stannic salt of the amine **10** (10 g) was filtered off, washed with 35 % aq. hydrochloric acid solution (10 cm^3), dried, and suspended in pyridine (200 cm^3). Acetic anhydride (16 cm^3, 0·16 mol) was added and the reaction mixture was refluxed for 5 h. Mineral salts were then filtered off and the filtrate was evaporated to dryness to yield the product (3·0 g, 54·0 %), m.p. 284·0–285·0 °C. Found: N, 15·11; $C_{16}H_{13}N_3O_2$ requires N, 15·05 %; λ_{max} 274·1, 371·5 nm (ε 28 600, 13 300); λ_{max} (in presence of HCl) 255·9, 400·0 nm (ε 30 150, 15 100); ν_{max} 3265, 1662, 1632, 1392 cm^{-1}; ν_{max} (chloroform) 1705, 1670, 1390 cm^{-1}; δ 2·08 (3H s, CH_3), 3·72–3·90 (4H m, CH_2—CH_2), 5·32–5·68, 5·82–6·17 (2H m, 3H m, naphthalene); *m/e* 280 (19), 279 (M^+, 100), 237 (60), 236 (26).

The TLC analysis of one-step reduction and acetylation of compound 7 (0·1 g) with iron (0·5 g) in acetic acid (10 cm^3) and acetic anhydride (5 cm^3) mixture proved that only one isomer is formed in the reaction described above. This reaction additionally proved the structure of compound **7**, as the product was the same as the first fraction in the separation described below.

3.4. 4-Acetylamino-9,10-dihydro-7*H*-imidazo[1,2-*b*]benz[*d*,*e*]isoquinolin-7-one (2d)

The synthesis of a mixture of isomers from 4-acetylaminonaphthalic acid anhydride and ethylenediamine was performed according to the patent specification:[11] m.p. 210·0–216·0 °C; Found: N, 15·08; $C_{16}H_{13}N_3O_2$ requires N, 15·05%; λ_{max} 238·2, 368·7 nm (ε 26 000, 11 500); λ_{max} (in presence of HCl) 241·8, 370·4 nm (ε 25 000, 16 000); n.m.r. data as above.

The product was submitted to separation by means of column chromatography (0·75 g, 50 cm, Silica Gel 70—325 mesh (Merck), ethanol–dioxane 1:1) which yielded 4-acetylamino isomer **2d** (0·34 g, second fraction), m.p. 220·0–221·0 °C; λ_{max} 238·1, 368·7 nm (ε 25 000, 8600); λ_{max} (in presence of HCl) 239·2, 368·4 nm (ε 23 700, 17 300); ν_{max} 1685, 1652, 1385 cm^{-1}; *m/e* 280 (21), 279 (M^+, 100), 254 (10), 237 (69), 236 (31), 212 (10).

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