A New Synthesis of Pyrazolo[3,4-*b*]quinoline Derivatives†

D. C. Holla and S. Seshadri*

Dyes Research Laboratory, University Department of Chemical Technology, Matunga, Bombay 400019, India

(Received August 29, 1983)

A new synthesis of pyrazolo[3,4-b]quinoline-4-carboxylic acid derivatives is described. This involves the Pfitzinger reaction of pyrazolone derivatives with isatic acid under controlled conditions. The pyrazoloquinolinecarboxylic acids were converted to their corresponding amides and nitriles, and their absorption and emission characteristics are recorded.

The use of pyrazolo[3,4-*b*]quinoline derivatives as fluorescent brighteners is well known.[1] The major synthetic approach has been the cyclization of appropriately substituted *N*-(1-alkyl-5-pyrazolyl)anthranilic acids by phosphoryl chloride. 5-Chloro-4-formylpyrazoles and substituted aromatic amines on heating form respective 1-phenylpyrazolo[3,4-*b*]-quinoline derivatives which are reported[2,3] to be optical brightening agents.

An obvious alternate synthetic route would be the reaction of pyrazolone derivatives with isatin under the Pfitzinger conditions which would yield the pyrazolo [3,4-*b*]quinoline-4-carboxylic acid. Rather surprisingly, this simple synthetic scheme has not been previously described in the literature. This synthetic scheme has the advantage that different pyrazolones can be employed and further the resultant carboxylic acid could also be further converted to different derivatives such as amide or nitrile.

The Pfitzinger reaction on 3-methyl-1-phenyl-5-pyrazolone (**IIb**) was carried out under normal conditions, employing isatin (**I**) in 40% sodium hydroxide solution. Under these conditions the reaction did not occur even when the reaction mixture was heated for several hours. It was thought that the failure of the reaction might be due to the existence of the pyrazolone in the enolic form in the alkaline conditions, tending to make the pyrazolone inactive for the reaction with isatic acid (2-aminophenylglyoxylic acid). We, therefore carried out the reaction at a certain level of basicity (pH 10—11) so that the enolization would not be complete and the active methylene group would be able to react with isatic acid. Indeed, under these conditions the reaction did take place and on work-up by acidification a yellow product was obtained which was characterized as the expected 3-methyl-1-phenyl-pyrazolo[3,4-*b*]quinoline-4-carboxylic acid (**IIIb**). The structure of this product was established by its acidic character, infrared spectrum (carboxylic acid at 1695 cm^{-1}) and elemental analysis and also by conversion into its derivatives like amide (**IVb**) and nitrile (**Vb**).

Rather surprisingly, the fluorescence of this acid was weak and we therefore wished to study the fluorescence of the derivatives of this acid. Thus the amide (**IVb**) was prepared by the usual method and the amide (**IVb**) was converted to nitrile (**Vb**). The nitrile (**Vb**) was expected to show enhanced fluorescence compared to the carboxylic acid (**IIIb**) but we found that there was no improvement in the fluorescence intensity.

We then proceeded to synthesise other pyrazolo [3,4-*b*]quinoline derivatives by this route. Thus, 3-methyl-5-pyrazolone (**IIa**) was reacted with isatin and 1-unsubstituted pyrazoloquinolinecarboxylic acid (**IIIa**) was obtained. This was further alkylated by dimethyl sulfate to yield the *N*-methyl derivative (**VIa**) and by acrylonitrile to yield *N*-(2-cyanoethyl) derivative (**VIb**). The alkylation products have been given the structures as indicated since there was only a slight bathochromic shift on alkylation. Alkylation on the 2-nitrogen atom would have yielded a quinonoid structure, which would have given a larger bathochromic shift. Thus the compounds (**IIIa, VIa, VIb, IIIb**) showed absorption maxima 382, 386, 392, and 386 nm respectively whereas 2-phenyl derivative (**X**) prepared by us earlier[4] had maximum at 420 nm (Chart 2).

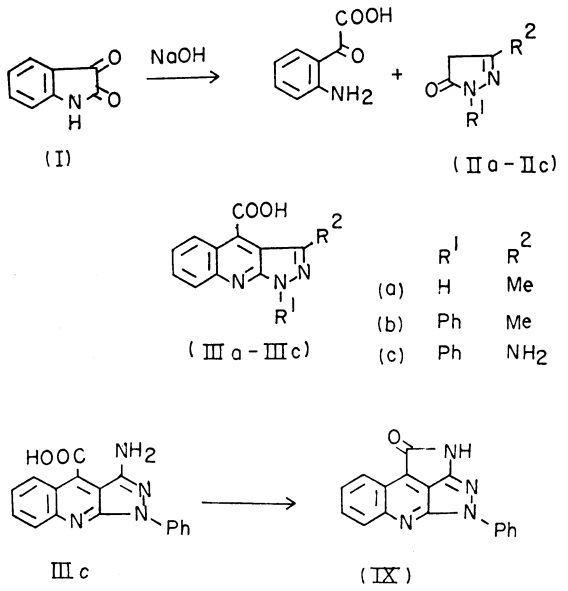

Chart 1.

We found to our satisfaction that the *N*-alkyl derivatives showed much stronger fluorescence and even the *N*-unsubstituted derivative (**IIIa**) showed stronger fluorescence than the *N*-phenyl derivative (**IIIb**). The N-unsubstituted pyrazoloquinolinecarboxylic acid and the two *N*-alkyl derivatives were also converted into the corresponding amides (**VIIa** and **VIIb**) and nitriles (**VIIIa** and **VIIIb**). The absorption and fluorescence efficiencies of these compounds were also studied (Table 1)

From our studies, it can be seen that the *N*-alkylpyrazolo[3,4-*b*]quinoline derivatives are strong

† Abstracted in part from the Ph. D. thesis of D. C. Holla, University of Bombay, 1976.

Table 1. Physical data of various pyraxazolo[3,4-*b*]quinoline-4-carboxylic acids and derivatives

Compound	Yield %	Mp θ_m/°C	Recrystallization solvent	λ_{max} absorption/nm	log E	λ_{max} emission/nm
Carboxylic acid						
IIIa	65	>300	EtOH	382	3.74	425
IIIb	62	188—190	EtOH	386	3.81	480
IIIc	58	214—215	EtOH			
Amides						
IVa	78	276—280	EtOH	388	3.74	434
IVb	80	>300	EtOH	394	3.54	494
VIIa (*N*-CH_3)	80	226—228	EtOH	394	3.93	456
VIIb (*N*-CH_2CH_2CN)	82	246—248	EtOH	392	3.86	434
Nitriles						
Va	86	180—182	C_6H_6	418	3.69	470
Vb	84	>300	EtOH	428	3.36	494
VIIIa (*N*-CH_3)	79	260—262	EtOH	396	3.59	490
VIIIb (*N*-CH_2CH_2CN)	83	166—168	EtOH	400	3.50	472

fluorophores but comparison with a commercial fluorescent brightener (7-diethylamino-4-methylcoumarin) showed them to be very much inferior. These compounds were also evaluated by application to polyester fibre but they did not produce significant brightening.

We also carried out the Pfitzinger reaction on 3-amino-1-phenyl-5-pyrazolone (**IIc**) and the product obtained was the expected 3-aminopyrazolo[3,4-*b*]-quinoline-4-carboxylic acid (**IIIc**) as shown by its amphoteric properties, infrared spectrum (doublet for the amino group at 3200 and 3100 cm^{-1} and carboxyl carbonyl at 1650 cm^{-1}) and elemental analysis. This compound could be converted to the lactam (**IX**) by treatment with conc. hydrochloric acid. The structure of the lactam (**IX**) was established by elemental analysis and infrared spectrum (lactam carbonyl at 1720 cm^{-1}). The amino acid (**IIIc**) and the lactam (**IX**) were strongly colored and did not show any fluorescence (Chart 1).

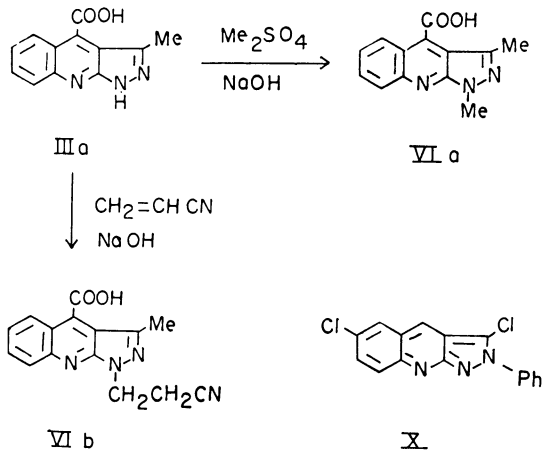

Chart 2.

Experimental

All melting points are uncorrected. The IR spectra were recorded on different spectrophotometers as Nujol mull and the UV spectra were recorded on Pye-Unicam SP8000.

General Procedure for the Synthesis of Pyrazolo[3,4-b]quinoline Derivatives. To a clear solution of isatin (6.8 mmol) in NaOH (10 ml, 10%) pyrazolone derivative (**IIa—IIc**) (7 mmol) was added and stirred till a homogeneous solution was obtained. The pH of the solution was adjusted between 10 and 11 by adding a few drops of HOAc. The solution was refluxed for 5 to 6 h and cooled . On acidification (with HCl 1:1 in the case of 3-Methyl-1-phenyl-5-pyrazolone and 3-methyl-5-pyrazolone and with HOAc to pH 6 in the case of 3-amino-1-phenyl-5-pyrazolone). The products separated were isolated. The yield, mp, recrystallization solvent and molecular formula are given in the Table.

*1,3-Dimethylpyrazolo[3,4-b]quinoline-4-carboxylic Acid (**VIa**).* To the solution of **IIIa** (4.4 mmol) in NaOH (20 ml, 5%) dimethyl sulfate (5.3 mmol) was added and the reaction mixture was heated in a water bath at 60—70 °C for 2 h. The resulting yellow solution was cooled and acidified with dil. HCl (2M). A yellow precipitate of **VIa** was obtained in 86% yield and was recrystallized from ethanol as yellow crystals mp >300° (Found: C, 65.1; H, 4.9; N, 17.1%, Calcd for $C_{13}H_{11}N_3O_2$: C, 65.0, H, 4.6, N, 17.5%).

*1-(2-Cyanoethyl)-3-methylpyrazolo[3,4-b]quinoline-4-carboxylic Acid (**VIb**).* To the solution of **IIIa** (4.4 mmol) in NaOH (20 ml, 5%) containing 0.1 g of Triton B as the catalyst acrylonitrile (5.3 mmol) was added and the reaction mixture was stirred at room temperature for 3 h. The sodium salt that separated was acidified with dil. HCl (2M (1M=1 mol dm^{-3})) and the product **VIb** was obtained in 89% yield. This was recrystallized from ethanol mp >236—237 °C (Found: N, 19.7%, Calcd for $C_{15}H_{12}N_4O_2$: N, 20.0%).

*Synthesis of the Lactam (**IX**).* The acid **IIIc** (3.2 mmol) was taken in concd HCl (10 ml) and kept at room temperature for 3 to 4 h. It was diluted with water, when a brown-colored solid **IX** was obtained in 74% and was recrystallized from EtOAc mp >300 °C (Found: N. 19.1%, Calcd for $C_{17}H_{10}N_4O$: N, 19.6%).

General Procedure for the Synthesis of Pyrazolo[3,4-b]quinoline-4-carboxamides. A mixture of the acid (1 g), dry benzene (5 ml), and freshly-distilled thionyl chloride (10 ml) was refluxed for 2 to 3 h. The acid chloride, obtained after removing excess thionyl chloride and benzene, was

treated with liquid ammonia and kept overnight at room temperature. The amide obtained was filtered. The yield, mp, recrystallization solvent, molecular formula of the various amides prepared are given in the Table.

General Procedure for the Synthesis of Pyrazolo[3,4-b]quinoline-4-carbonitriles. These were prepared by refluxing the amide (1 g) with $POCl_3$ (6 ml) in an oil bath at 110—115 °C for 2 h. After the usual work-up, the product separated was isolated. The yield, mp, recrystallization solvent, molecular formula of the various nitriles prepared are given in the Table.

We are thankful to Prof. M.R. Padhye for recording the IR and UV spectra and to the Microanalytical section of our department for the analyses. One of us (D.C.H.) is thankful to C.S.I.R., New Delhi for the award of a junior research fellowship.

References

1) H, Gold, "The Chemistry of Synthetic Dyes", ed by K. Venkatraman, Academic Press, New York and London 1971, Vol. V, Page 659.

2) A. Brack (Farben fabriken Bayer A. G.) Belg. Pat. 617180, *Chem. Abstr.* **59**, 636 (1963).

3) A. Brack (Farben fabriken Bayer, Laver Kusa Ger) *Ann. Chem.*, **681**, 105—110 (1965) *Chem. Abstr.*, **62**, 11799 (1965).

4) V. Purnaprajna and S, Seshadri, *Ind. J. Chem. Sect. B*, **14B**, 971—2 (1976).