Quinoline Alkaloids. Synthesis of Khaplofoline, Ribalinine, and Flindersine

M. Subramanian, P. S. Mohan, P. Shanmugam, and K. J. Rajendra Prasad*
Department of Chemistry, Bharathiar University, Coimbatore – 641046, India

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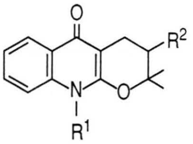
Pyranoquinoline Alkaloids, Khaplofoline, Ribalinine, Flindersine

Reaction of 4-hydroxy-3-prenylquinolin-2(1H)one (**5a**) with iodine and silver acetate gave a iodopyranoquinoline (**6a**), which was then converted into the alkaloids khaplofoline (**1**) and ribalinine (**2**). Reaction of **5a** with iodine and mercuric oxide afforded a mixture of **6a** and its angular isomer **7a**; the coversion of latter into flindersine (**10**) is described.

Pyranoquinoline alkaloids, which possess interesting pharmacological properties are known [1, 2] to occur in the plant family *Rutaceae*. The alkaloids, khaplofoline (**1**) and ribalinine (**2**), isolated respectively from *Haplophyllum foliosum* (Vved) [3] and *Balfourodendron riedelianum* [4], members of the rutaceae, are structurally proven to be of pyrano [2,3-b]quinoline systems. Several reports have appeared in the literature for the synthesis of **1** [3,5–9] and **2** [10–12], but the yields of **1** and **2** in these attempts were not quite appreciable and are often attended by the formation of their isomeric products.



1: $R^1 = R^2 = H$
2: $R^1 = CH_3$; $R^2 = OH$

In this communication, we wish to present an alternative but elegant methodology for deriving the titled alkaloids from **5**, which in turn was prepared [13] from 4-hydroxyquinolin-2(1H)one **3**. Reaction of **5a** with iodine, in the presence of silver acetate in glacial acetic acid at room temperature gave a single product (m.p. 176–177 °C) in 80% yield. It was identified to be 3-iodo-3,4-dihydro-5-oxo-2,2-dimethyl-2H-pyrano[2,3-b]quionoline (**6a**). In its IR spectrum two bands at 3420 cm^{-1} and 1620 cm^{-1} were ascribable to a NH stretching and a 4-quinolinone [14] moiety respectively. In its ^1H NMR spectrum; the six proton singlet at δ 1.58 ppm was characteristic of a gem-dimethyl group, two double doublets with J = 17.4 and 6.6 Hz and a single proton triplet at δ 4.68 ppm were ascribable to methylene and methine protons forming ABX system and a singlet at δ 11.83 ppm assignable to NH proton. The molecular ion peak (M^+) at *m/e:* 355 (55%) in its mass spectrum and elemental analysis C 47.30, H 4.05 and I 35.80% are well agreed to the molecular formula $C_{14}H_{14}NO_2I$. Thus we realized the preparation of iodopyranoquinoline in high yield and it has proven to be a utility in heterocyclic synthesis. **6a** on alkaline hydrolysis using 0.1% aqueous sodium hydroxide yielded 3-hydroxykhaplofoline (**8**); which on heating with methyl iodide furnished the alkaloid ribalinine **2** [4] in 90% yield. With the view to adducing further attestation of the iodopyranoquinoline structure assigned for the product **6a,** it was dehydroiodinated by refluxing in pyridine to chromenoquinoline **9.** Further reduction of **9** with H_2, Pd–C(5)% gave the alkaloid khaplofoline (**1**), which was confirmed with authentic sample [3] (m.p. CoTLC, undepressed m.m.p., superimposable IR spectra) (Scheme 1).

Similar treatment when extended to 6-methyl-4-hydroxy-3-prenylquinolin-2(1H)one (**5b**) gave the corresponding iodopyrano[2,3-b]quinoline (**6b**) exclusively. It is of relevance to note that the diprenylquinolinone (**4b**) used here is not hitherto reported, which was prepared by treating the **3b** with prenyl bromide in 1N sodium hydroxide. The intermediate **4b** on partial deprenylation using sodium hydrogen telluride [13] yielded **5b.**

In another approach, when **5a** was stirred with other Prevost reagent, iodine and yellow mercuric oxide in glacial acetic acid gave a mixture of the iodopyrano[2,3-b]quinoline (**6a**) (10%) and its angular isomer, 3-iodo-3,4,5,6-tetrahydro-5-oxo-2,2-dimethyl-2H-pyrano[3,2-c]quinoline (**7a**) (70%). The two products were most easily distinguished

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* Reprint requests to Dr. K. J. Rajendra Prasad.

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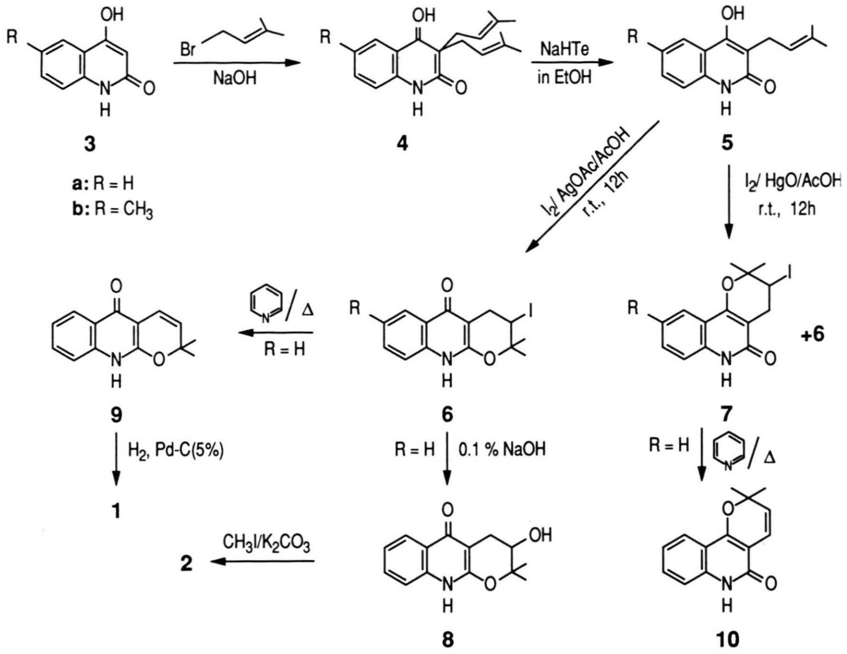

by their m.p., IR and ^{1}H NMR spectral data. Both the products had the same molecular formula $C_{14}H_{14}NO_2I$ derived from their elemental analyses and mass spectra. The structure of the angular isomer **7a** was further attested by its ready conversion into the alkaloid flindersine (**10**) [15] by heating with pyridine.

Extention of the technique to **5b** afforded a mixture of the corresponding linear iodopyranoquinoline (**6b**) and its angular isomer **7b.** The characteristic [16, 17] low-field absorption of the C_5-proton of quinolin-4-(1 H)one system is discernable in the ^{1}H NMR spectra of **6, 8** and **9.**

Experimental

Melting points were determined on Boetius microheating table and Mettler FP 5 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 597 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM 360 (90 MHz) and General Electric QE-300 (300 MHz) spectrometers using TMS as an internal standard. ^{13}C NMR were obtained on General Electric QE-300 (300 MHz) spectrometer. Microanalysis were performed on Carlo Erba 1106 and Perkin Elmer-model 240 CHN analyser. Petroleum ether was used of boiling range 60–80 °C.

4-Hydroxyquinolin-2(1H)one (**3**)

General procedure

A mixture of aniline (2 mmol) and diethylmalonate (1 mmol) was heated on an oil bath at 160 °C for 5 h, so that the ethanol allowed to escape. The solid dianilide formed was washed with pet. ether to remove excess of aniline if any and dried. N,N'-diphenyl malondiamide: Yield (98.5%), m.p. 226–227 °C (EtOH) (lit. [13] m.p. 226–227°).
N,N'-Di-(4-methylphenyl)malondiamide: yield (98%), m.p. 259–260 °C (EtOH), IR(KBr) ν_{max}: 3250 (NH), 1650 (NHCO) cm^{-1}.

The above dianilide (10 mmol) mixed separately with 5–7 times its weight of polyphosphoric acid was heated on an oil bath at 140 °C for 6 h. The reaction mixture was cooled, poured into crushed ice, left over night and filtered to furnish **3. 3a:** yield (95%), m.p. > 300 °C (EtOH–CH_3COOH), (lit. [18] m.p. > 300 °C). **3b:** yield (90%) m.p. > 300 °C (EtOH–CH_3COOH), IR(KBr) ν_{max}: 3450–2900 (br, NH, OH), 1660 (NHCO), 1600, 1510, 1440, 1320, 1240, 820 cm^{-1}.

3,3-Diprenyl-1,2,3,4-tetrahydroquinolin-2,4-dione (**4**)

General procedure

Prenylbromide (18.2 ml, 156 mmol) was added dropwise with stirring to **3** (50 mmol) dissolved in sodium hydroxide (1 N, 100 ml). The mixture was kept stirred at 45 °C for 24 h, after which it was made alkaline with sodium hydroxide solution. The reaction mixture was then extracted with chloroform. The extract was dried over anhydrous sodium sulphate, filtered and evaporated. The residue obtained was chromatographed over a column of silica gel with pet. ether-ethyl acetate (20:1) mixture to give the diprenylquinolindione (**4**).

4b: Yield: (70%), m.p. 123−125 °C (pet. ether) (lit. [6] m.p. 126 °C). IR(KBr) ν_{max}: 3200 (NH), 1690 ($C_4{=}O$), 1660 ($C_2{=}O$) cm^{-1}.

4b: Yield: (75%), m.p. 130−131 °C (pet. ether-C_6H_6), IR(KBr) ν_{max}: 3260 (NH), 2990, 1680 ($C_4{=}O$), 1650 ($C_2{=}O$), 1610, 1500, 1410, 1370, 1280, 1220, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.49, 1.59 (2 s, 12 H, $2(CH_3)_2$), 2.35 (s, 3 H, 6-CH_3), 2.74 (quintet, 4 H, $2\times\underline{CH_2}-CH{=}$, J = 6.6 Hz), 4.91 (t, 2 H, $2\times CH_2-\underline{CH}{=}$, J = 6.6 Hz), 6.90 (d, 1 H, H-7, J = 8.4 Hz), 7.33 (d, 1 H, H-8, J = 8.1 Hz), 7.70 (s, 1 H, H-5), 10.56 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$) δ: 17.855 (C-4′ and C-4″), 20.503 (6-CH_3), 25.604 (C-5′ and C-5″), 37.408 (C-1′ and C-1″), 61.602 (C-3), 116.167 (C-8), 118.001 (C-2′ and C-2″), 119.829 (C-5a), 126.774 (C-5), 132.709 (C-6), 135.458 (C-7), 136.637 (C-3′ and C-3″), 139.113 (C-8a), 175.364 ($C_2{=}O$), 197.785 ($C_4{=}O$). Mass *m/e*: 311 (M^+), 243, 242, 226, 200, 188, 104, 77, 69.

Analysis for $C_{20}H_{25}NO_2$ *(311.40)*

Calcd	C 77.13	H 8.09,
Found	C 77.20	H 8.15.

4-Hydroxy-3-prenylquinolin-2(1 H)one (5)

General procedure

Diprenylquinolinone (**4**) (10 mmol) was added to a solution of sodium hydrogen telluride, formed *in situ* from tellurium powder (2.5 g) and sodium borohydride (2.0 g) in absolute ethanol and the mixture refluxed for 12 h in nitrogen atmosphere. The reaction mixture was then cooled and filtered. The residue obtained on evaporation of filtrate was dissolved in water and extracted with chloroform (to remove traces of **4** if any). The aqueous layer was then acidified with acetic acid, when **5** precipitated out. It was filtered, washed with water, dried and recrystallised.

5a: yield (90%), m.p. 182−183 °C (C_6H_6−EtOH) (lit. [15] m.p. 180−182 °C). IR(KBr) ν_{max}: 3200 (OH), 2900 (NH), 1640 (NHCO), 1590 cm^{-1}.

5b: yield (90%), m.p. 165−166 °C (C_6H_6−EtOH), IR(KBr) ν_{max}: 3250 (OH), 2950 (NH), 1640 (NHCO), 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$+DMSO-d_6), 1.64, 1.74 (2 s, 6 H, $(CH_3)_2$), 2.37 (s, 3 H, CH_3), 3.30 (d, 2 H $\mathbf{CH_2}-CH{=}$, J = 6.3 Hz), 5.17 (t, 1 H, $-CH_2-\mathbf{CH}{=}$, J = 6.3 Hz), 7.18 (m, 2 H, H-7 and H-8), 7.70 (s, 1 H, H-5), 11.14 (s, 1 H, NH). Mass *m/e*: 243 (M^+).

Analysis for $C_{15}H_{17}NO_2$ *(243.29)*

Calcd	C 74.04	H 7.04,
Found	C 74.10	H 7.10.

3-Iodo-3,4-dihydro-5-oxo-2,2-dimethyl-2 H-pyrano[2,3-b]quinoline (6a)

4-Hydroxy-3-prenylquinolin-2(1 H)one (**5a**, 229 mg, 1 mmol), was dissolved in glacial acetic acid (15 ml) and silver acetate (167 mg, 1 mmol) was added to it. The suspension was stirred well at room temperature. To the stirred mixture was added portionwise, well powdered iodine (254 mg, 1 mmol) during a period of 1 h and stirring was continued for 12 h. The precipitated silver iodide was filtered and washed with chloroform. The combined filtrate and the washings were diluted with water and extracted with chloroform. The extract was successively washed with dilute solutions of sodium bicarbonate, sodium thiosulphate and finally with water. It was dried over anhydrous Na_2SO_4 and evaporated. The residue obtained was placed over a column of neutral alumina and eluted with benzene-ethyl acetate (10:1) to give **6a** as colourless needles. Yield: 284 mg (80%), m.p. 176−177 °C (pet. ether-ethyl acetate).

IR(KBr) ν_{max}: 3420 (br. NH), 3050, 2900, 1620 (4-quinolinone carbonyl), 1560, 1500, 1380, 1280, 1180, 1100 cm^{-1}.

^{1}H NMR (DMSO-d_6) δ: 1.58 (s, 6 H, $(CH_3)_2$), 3.10 (dd, 1 H, H_{eq}-4, J = 17.4 and 6.6 Hz), 3.27 (dd, 1 H, H_{ax}-4, J = 17.4 and 5.2 Hz), 4.68 (t, 1 H, H-3, J = 5 Hz), 7.20 (t, 1 H, H-7 or H-8, J = 7.5 Hz), 7.41 (d, 1 H, H-9, J = 8.1 Hz), 7.52 (t, 1 H, H-8 or H-7, J = 7.5 Hz), 8.05 (d, 1 H, H-6, J = 7.8 Hz), 11.83 (s, 1 H, NH). Mass *m/e*: 355 (M^+), 254, 229, 228, 212, 186, 174, 127, 92, 77.

Analysis for $C_{14}H_{14}NO_2I$ *(355.15)*

Calcd	C 47.34	H 3.97	I 35.73,
Found	C 47.30	H 4.05	I 35.80.

3-Iodo-3,4-dihydro-5-oxo-2,2,7-trimethyl-2 H-pyrano[2,3-b]quinoline (6b)

4-Hydroxy-6-methyl-3-prenylquinolin-2(1 H)one (**5b**, 243 mg, 1 mmol) dissolved in glacial acetic acid (15 ml) was reacted with silver acetate (167 mg, 1 mmol) and iodine (254 mg, 1 mmol) in the same manner as described for the preparation of **6a.** Chromatographic purification on neutral alumina in 10:1 benzene-ethyl acetate mixture afforded **6b.** Yield: 276 mg (75%), m.p. 195–196 °C (pet. ether-EtOAc).

IR(KBr) ν_{max}: 3400 (br, NH), 3050, 2995, 1620 (4-quinolinone carbonyl), 1560, 1510, 1340, 1289 cm^{-1}.

^{1}H NMR ($CDCl_3$+DMSO-d_6) δ: 1.60 (s, 6H, $(CH_3)_2$), 2.42 (s, 3H, CH_3), 3.23 (dd, 1H, H_{eq}-4, J = 17.4 and 6.6 Hz), 3.46 (dd, 1H, H_{ax}-4, J = 17.4 and 5.1 Hz), 4.46 (t, 1H, H-3, J = 5.2 Hz), 7.30 (d, 1H, H-8, J = 8.1 Hz), 7.58 (d, 1H, H-9, J = 8.1 Hz), 7.99 (s, 1H, H-6), 11.34 (s, 1H, NH). Mass *m/e*: 369 (M^+).

Analysis for $C_{15}H_{16}NO_2I$ *(369.18)*

Calcd	C 48.79	H 4.36	I 34.37,
Found	C 48.70	H 4.40	I 34.30.

4-Hydroxy-3-prenylquinolin-2(1H)one (**5a**) *with* I_2*-HgO*

To a solution of 4-hydroxy-3(3-methylbut-2-enyl)-2-quinolinone (**5a,** 229 mg, 1 mmol) in glacial acetic acid (15 ml), yellow mercuric oxide (217 mg, 1 mmol) was added and the suspension was stirred well at room temperature. To the stirred mixture powdered iodine (254 mg, 1 mmol) was added in portions over a period of 1 h. After the addition, the stirring was continue for 12 h. The precipitated mercuric iodide was filtered off, and the filtrate was diluted with water and extracted with chloroform. The extract was successively washed with dilute solutions of $NaHCO_3$, $Na_2S_2O_3$ and finally with water and dried. The residue obtained on evaporation of the solvent was placed over a column of neutral alumina and eluted with benzene-ethyl acetate (10:1) to afford **6a.** Yield: 35 mg (10%).

Further elution of the column with benzene-ethyl acetate (10:3) afforded 3-iodo-3,4,5,6-tetrahydro-5-oxo-2,2-dimethyl-2H-pyrano[3,2-c]quinoline (**7a**). Yield: 248 mg (70%), m.p. 234–235 °C (pet. ether-EtOAc).

IR(KBr) ν_{max}: 3150 (br. NH), 3000, 2990, 1640 (2-quinolinone carbonyl), 1600, 1580, 1400, 1320, 1260, 1150 cm^{-1}.

^{1}H NMR ($CDCl_3$+DMSO-d_6) δ: 1.57 (s, 6H, $(CH_3)_2$), 3.08 (dd, 1H, H_{eq}-4, J = 18.3 and 6.6 Hz), 3.27 (dd, 1H, H_{ax}-4, J = 18.3 and 5.1 Hz), 4.65 (t, 1H, H-3, J = 5.2 Hz), 7.14 (t, 1H, H-8 or H-9, J = 7.5 Hz), 7.29 (d, 1H, H-7, J = 8.4 Hz), 7.44 (t, 1H, H-9 or H-8, J = 7.5 Hz), 7.75 (d, 1H, H-10, J = 8.4 Hz), 11.50 (s, 1H, NH). Mass *m/e*: 355 (M^+).

Analysis for $C_{14}H_{14}NO_2I$ *(355.15)*

Calcd	C 47.34	H 3.97	I 35.73,
Found	C 47.36	H 4.04	I 35.68.

4-Hydroxy-6-methyl-3-prenylquinolin-2(1H)one (**5b**) *with* I_2*-HgO*

Yellow mercuric oxide (217 mg, 1 mmol) was added to a solution of 4-hydroxy-6-methyl-3(3-methylbut-2-enyl)-2-quinolinone (**5b,** 243 mg, 1 mmol) in glacial acetic acid (15 ml). The suspension was stirred well at room temperature, powdered iodine (254 mg, 1 mmol) was added in portions over a period of 1 h, and stirring was continued for 12 h. It was then worked up as mentioned in the preparation of **7a.** The residue obtained was placed over a column of neutral alumina and eluted with benzene-ethyl acetate (12:1) to furnish **6b.** Yield: 55 mg (15%).

Further elution of the column with benzene-ethyl acetate (10:2) afforded 3-iodo-3,4,5,6-tetrahydro-5-oxo-2,2,9-trimethyl-2H-pyrano[3,2-c]quinoline (**7b**). Yield: 276 mg (75%), m.p. 240–241 °C (pet. ether-EtOAc).

IR (KBr) ν_{max}: 3200 (br, NH), 3050, 1640 (2-quinolinone carbonyl), 1580, 1400, 1380, 1260, 1100 cm^{-1}.

^{1}H NMR ($CDCl_3$+DMSO-d_6) δ: 1.44 (s, 6H, $(CH_3)_2$), 2.64 (s, 3H, CH_3), 3.01 (dd, 1H, H_{eq}-4, J = 18.3 and 6.7 Hz), 3.19 (dd, 1H, H_{ax}-4, J = 18.3 and 5.4 Hz), 4.25 (t, 1H, H-3, J = 5.2 Hz), 7.0–7.13 (m, 2H, H-7 and H-8), 7.42 (s, 1H, H-10), 10.95 (s, 1H, NH).

Analysis for $C_{15}H_{16}NO_2I$ *(369.18)*

Calcd	C 48.79	H 4.36	I 34.37,
Found	C 48.75	H 4.40	I 34.32.

3-Hydroxy-3,4-dihydro-5-oxo-2,2-dimethyl-2H-pyrano[2,3-b]quinoline (**8**)

Iodopyranoquinoline (**6a,** 355 mg, 1 mmol) was heated with aqueous sodium hydroxide solution (0.1%, 10 ml) at 60 °C for 20 min and then neutralising the clear filtrate with dil. hydrochloric acid. 3-Hydroxykhaplofoline (**8a**) was separated out as white crystalline solid, filtered and dried. Yield: 173 mg (75%) m.p. 273–275 °C (dec) (EtOH), Ir(KBr) ν_{max}: 3350–2950 (br, NH, OH), 1625 (4-quinolinone carbonyl), 1600 cm^{-1}. ^{1}H NMR δ: 1.48, 1.50 (2s, 6H $(CH_3)_2$), 3.20 (dd, 2H, H-4, J = 16.5 and 5.4 Hz), 3.95 (br. peak, 2H, H-3 and 3-OH), 7.20–7.80 (m, 3H, H-7, H-8 and H-9), 8.15 (d, 1H, H-6, J = 8.5 Hz), 11.73 (s, 1H, NH). Mass *m/e*: 231 (M^+).

Analysis for $C_{14}H_{15}NO_3$ *(231.15)*

Calcd	C 72.74	H 6.54,
Found	C 72.80	H 6.47.

Ribalinine (**2**)

A mixture of **8** (150 mg) and methyl iodide (10 ml) was heated under reflux for 7 h. Evaporation of the excess reagent furnished **2** as an amorphous solid. It was recrystallised from benezene-ethanol as colourless crystals. Yield: 143 mg (90%), m.p. 232–233° (dec.) (lit. [4] m.p. 233–234 °C). IR(KBr): ν_{max} 3200 and 1620 (C_5=O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.35, 1.50 (2s, 6H, $(CH_3)_2$), 2.96 (dd, 2H, H-4, J = 16.5 and 5.0 Hz), 3.58 (s, 3H, N–CH_3), 3.92 (br. peak, 2H, H-3 and 3-OH), 7.2–7.9 (m, 3H, H-7, H-8 and H-9), 8.20 (d, 1H, H-6, J = 9 Hz).

5-Oxo-2,2-dimethyl-2H-pyrano[2,3-b]quinoline (**9**)

A solution of the iodopyranoquinoline (**6a,** 178 mg, 0.5 mmol) in dry pyridine (10 ml) was refluxed under nitrogen atmosphere for 8 h. The reaction mixture was then poured in to water (50 ml) and extracted with chloroform (2×20 ml). The chloroform extract was washed with dil. HCl and water and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by crystallisation of the residue obtained with pet. ether-ethyl acetate mixture furnished **9** as colourless crystals. Yield: 100 mg (82%), m.p. 148–150 °C. IR(KBr) ν_{max}: 3350 (br. NH), 3050, 2995, 1620 (C=O), 1555, 1490 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.55 (s, 6H, $(CH_3)_2$), 5.90 (d, 1H, H-3, J = 10 Hz), 6.88 (d, 1H, H-4, J = 10 Hz), 7.20–8.10 (m, 4H, aromatic-H), 11.80 (s, 1H, NH).

Analysis for $C_{14}H_{13}NO_2$ *(227.25)*

Calcd	C 73.79	H 5.76,
Found	C 74.68	H 5.80.

Khaplofoline (**1**)

To a solution of **9** (80 mg, 0.35 mmol) in glacial acetic acid (10 ml) was added Pd–C (5%) (15 mg) and shaken with hydrogen at 60 lb in a Parr hydrogenator for 3 h. The catalyst was filtered off. The filtrate was diluted with water, neutralised with aqueous ammonia and extracted with chloroform. The residue obtained on evaporation of the solvent was recrystallised from ethyl acetate, to give **1** as fine crystals. Yield: 73 mg (90%), m.p. 272–274 °C (dec.) (lit. [3] m.p. 272–274 °C (dec.)). IR(KBr) ν_{max}: 3340 (NH), 2995, 1635 (C=O) cm^{-1}.

Flindersine (**10**)

Iodopyranoquinoline (**7a,** 100 mg) in dry pyridine (10 ml) was dehydroiodinated as described for the preparation of **9.** Evaporation of the solvent and preparative TLC of the residue on silica gel with pet. ether-ethyl acetate (10:1) gave **10** as a colourless crystals. Yield: 80 mg (80%), m.p. 196–197 (CH_3OH) (lit. [15] m.p. 196–197 °C). IR(KBr) ν_{max}: 3390 (NH), 1655 (NH$\underline{CO}$), 1615 cm^{-1}.

^1H NMR ($CDCl_3$) δ: 1.45 (s, 6H, $(CH_3)_2$), 5.25 (d, 1H, H-3, J = 9 Hz), 6.70 (d, 1H, H-4, J = 9 Hz), 6.90–7.50 (m, 4H, aromatic-H), 11.50 (s, 1H, NH).

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