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Reactivity of 4-Bromomethylquinoline Derivatives Towards Glycine and Thioglycolic Acid. A New Ring System

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Condensation of 4-bromomethylquinoline derivatives **1a-1c** with glycine and thioglycolic acid gave the corresponding quinolylmethylglycine and quinolylmethylthioacetic acid derivatives **2a-2c** and **2d-2f**, respectively. Cyclization of **2a-2f** was affected either by polyphosphoric acid or concentrated sulphuric acid to give **3a-3f**. Chlorination of **2a-2f** and **3a-3f** were also accomplished.

(Keywords: Benzo[c]-2,6-naphthyridine; Bromomethylquinoline; Nitrogen heterocycles; Thiopyrano[4,3—c]quinoline)

Die Reaktivität von 4-Brommethylchinolin-Derivaten gegenüber Glycin und Thioglycolsäure. Ein neues Ringsystem

Die Reaktion von 4-Brommethylchinolin-Derivaten **1a—c** mit Glycin und Thioglycolsäure gab die entsprechenden Kondensationsprodukte **2a—c** und **2d—f**. **2a—f** konnten mit Polyphosphorsäure bzw. mit konzentrierter Schwefelsäure zu Benzo[*c*]-2,6-naphthyridinen **3a—f** zyklisiert werden. **2a—f** und **3a—f** waren einer Chlorierung ($POCl_3$) zugängig.

Certain substituted benzonaphthyridine derivatives are known to possess antimalarial activity[1]. This prompted us to endeavour the synthesis of some benzo[*c*]-2,6-naphthyridines (known till 1970 as benzo[*b*]-2,6-naphthyridine) and its thia-analogue, 1*H*-thiopyrano[4,3—c]-quinolines, since there is only limited knowledge concerning these isomers.

The first observation concerning the isomer, benzo[*c*]-2,6-naphthyridine was made during degradation of the alkaloid "calycanthine" which affords dibenzo[*c,f*]-2,6-naphthyridine (calycanine)[2–4].

The parent 2,6-naphthyridine was first synthesized by a long reaction sequence[5,6] whereas in the present work the naphthyridine derivatives **3a—3f** and **4a-4f** were synthesized by only two steps.

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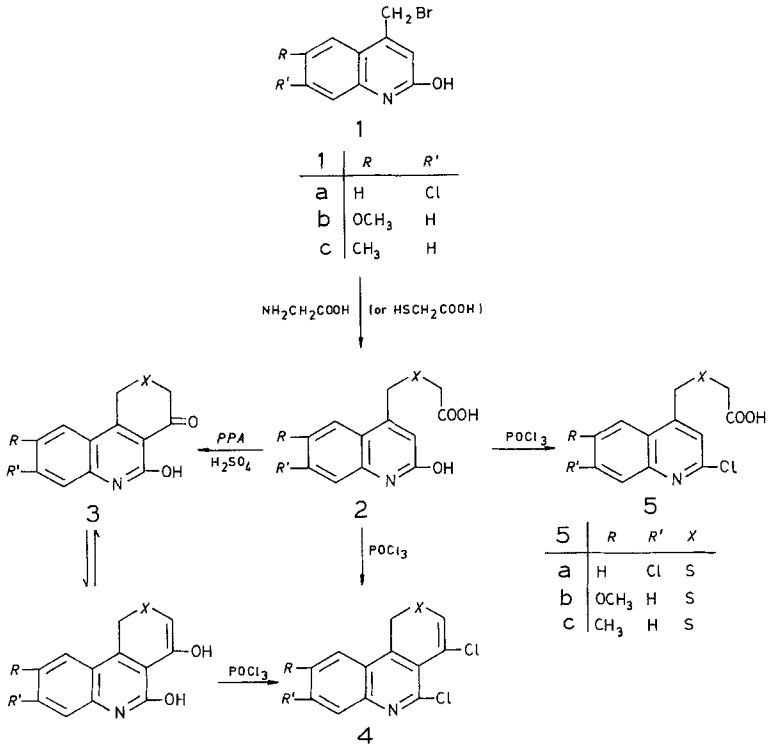
Thus the 4-bromomethylquinoline derivatives[7] **1a–1c** reacted with glycine or thioglycolic acid in alkaline medium to give the corresponding quinolylmethylglycine derivatives **2a–2c** and quinolylmethylthioacetic acid derivatives **2d–2f**, respectively, whereas an attempted



1	R	R'
a	H	Cl
b	OCH_3	H
c	CH_3	H

5	R	R'	X
a	H	Cl	S
b	OCH_3	H	S
c	CH_3	H	S

2,3 and 4	R	R'	X
a	H	Cl	NH
b	OCH_3	H	NH
c	CH_3	H	NH
d	H	Cl	S
e	OCH_3	H	S
f	CH_3	H	S

condensation of **1a–1c** with glycolic acid under different conditions was unsuccessful. The IR spectrum of **2e** shows signals at 1,715 (C=O carboxylic), 1,610 (C=N) and at 750 cm^{-1} (—C—S—). The characteristic feature of the IR spectrum of **2b** is the presence of a signal at 3,340 cm^{-1} (NH stretching).

Cyclization of **2a–2f** either by concentrated sulphuric acid or polyphosphoric acid afforded the desired dihydro[*c*]-2,6-naphthyridin-

4(1*H*)-one derivatives **3a–3c**[8] and the new ring system, 1*H*-thiopyrano[4,3—*c*]quinolin-4(3*H*)-one derivatives **3d–3f**, respectively. These derivatives **3a–3f** are present almost entirely in the enol form as revealed by spectroscopic data.

Thus the IR spectrum for **3a** shows absorption bands at 3,250 (NH), 1,660 (C=O), 1,610, 1,550 cm^{-1} (C=N, C=C aromatic) and at 790 cm^{-1} (C—Cl aromatic). The NMR spectrum of **3a** (CF_3COOD) shows the presence of absorption signals at δ 2.15 (2 H, CH_2 group protons in position-1, singlet), δ 5.25 (1 H, **OH** proton, singlet) and at δ 7.40-8.25 ppm (4 H, aromatic protons, multiplet), as main characteristic features. Also, the NMR spectrum of **3d** (CF_3COOD) shows signals at δ 2.18 (1 H, **CH** proton of the heterocyclic sulphur ring, singlet), δ 2.55 (3 H, CH_3 group protons, singlet), δ 4.25 (2 H, CH_2 group protons of the heterocyclic sulphur ring, singlet), δ 7.25 (1 H, **OH** proton, singlet) and a multiplet centered at δ 7.90 ppm (3 H, aromatic protons).

Treatment of either **2a–2c** or **3a–3c** with phosphorous oxychloride gave the corresponding 4,5-dichloro-2-hydro(1*H*)-benzo[*c*]-2,6-naphthyridine derivatives **4a–4c**, respectively. But if **2d–2f** was treated with phosphorous oxychloride, a mixture of the corresponding 2-chloroquinolylmethylthioacetic acid derivatives **5a–5c** and 4,5-dichloro-1*H*-thiopyrano[4,3—*c*]quinoline derivatives **4d–4f** was obtained. Separation of the mixture was achieved by treatment with alkali. Furthermore, **4d–4f** were obtained through chlorination of **3d–3f** with phosphorous oxychloride. The IR spectrum of **5b** shows a peak at 1,705 cm^{-1} (COOH).

Because of the known biological activity of the *N*,*N*-diethylaminoethylamino group[9] we have also prepared the diamino derivatives **6a** and **6b** by condensation of **4a** and **4d** with *N*,*N*-diethylaminoethylamine. The IR spectrum of **6b** shows absorption bands at 3,350 (NH), 1,610, 1,550 (C=N, C=C aromatic) and at 785 cm^{-1} (C—Cl aromatic).

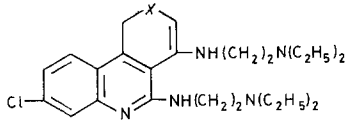
Experimental

All melting points (°C) were uncorrected and were taken in a Gallenkamp electric melting point apparatus and Boëtius melting point microscope. IR spectra were performed on a Carl-Zeiss Jena Infracord Spectrophotometer model "UR 10" using KBr. NMR spectra were obtained in deuterotrifluoroacetic acid solution with a Varian model "A-60". Elementary analyses (C, H, N) of **2a–f**, **3a–f**, **5a–c** and **6a**, **b** were in good agreement with the proposed structures.

N[(7-Chloro-2-hydroxy-4-quinolyl)methyl]glycine (**2a**)
N[(2-Hydroxy-6-methoxy-4-quinolyl)methyl]glycine (**2b**) *and*
N[(2-Hydroxy-6-methyl-4-quinolyl)methyl]glycine (**2c**)

To a mixture of glycine (37.5 g; 0.5 mol) and 4-bromomethylquinoline derivatives **1a–1c** (0.1 mol) were added 200 ml of a 5*N*-NaOH solution portionwise over a period of 2 h, with stirring, then refluxed for further 10 h

and filtered. The filtrate was neutralized with dilute hydrochloric acid and filtered again. The white precipitate was washed with water and recrystallized from dilute acetic acid to give **2a**–**2c** in 30-33% yield. M. p. 274° (**2a**), 227° (**2b**), 218° (**2c**).



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6a : X = NH
6b : X = S

8-Chloro-2,3-dihydro-5-hydroxybenzo[c]-2,6-naphthyridine-4(1H)-one (**3a**), *2,3-dihydro-5-hydroxy-9-methoxybenzo[c]-2,6-naphthyridine-4-(1H)-one* (**3b**) *2,3-dihydro-5-hydroxy-9-methylbenzo[c]-2,6-naphthyridine-4-(1H)-one* (**3c**)

Method (A)

The glycine derivatives **2a**–**2c** (5 g) were dissolved in 25 ml concentrated sulphuric acid heated on a steam bath for 2 h, cooled, poured into 250 ml ice water and filtered. The yellow precipitate was washed with dilute ammonia then with water, dried and recrystallized from acetic acid to give **3a**–**3c** in 75-80% yield.

Method (B)

2a–**2c** (2 g) were refluxed in 25 g of polyphosphoric acid at 140° for 6 h, cooled, poured into 200 ml ice water, neutralized with dilute ammonia and filtered. The precipitate was washed with water, dried and recrystallized from acetic to give **3a**–**3c** in ca. 85% yield. M. p. 223° (**3a**), 270° (**3b**), 312° (**3c**).

2-Hydroxy-4,5,8-trichloro-1H-benzo[c]-2,6-naphthyridine (**4a**).
4,5-Dichloro-2-hydro-9-methoxy-1H-benzo[c]-2,6-naphthyridine (**4b**) *and*
4,5-Dichloro-2-hydro-9-methyl-1H-benzo[c]-2,6-naphthyridine (**4c**)

2a–**2c** (1 g) were refluxed gently in $POCl_3$ (10 ml) under dry conditions for 6 h, cooled, poured carefully into 500 ml icecold ammonia solution (5%) and filtered. The precipitate was washed thoroughly with water, dried in a vacuum desiccator over P_2O_5. The yield was 80-85%. Crude melting points were 184-186° (**4a**), 128° (**4b**) and 155-157° (**4c**). These chloro derivatives were soluble in most organic solvents, but easily hydrolyzed to the corresponding hydroxy derivatives **3a**–**3c** during crystallization. Thus, they were identified from their reactions with diethylaminoethylamine. Treatment of **3a**–**3c** with $POCl_3$, gave identical products (**4a**–**4c**) in 70-75% yield.

8-Chloro-4,5-bis{[2-(diethylamino)ethyl]amino}-2-hydro-1H-benzo[c]-2,6-naphthyridine (**6a**)

A mixture of **4a** (0.3 g; 0.001 mol) and 1 g of phenol was refluxed for 2 h on a water bath. Diethylaminoethylamine (0.32 g; 0.003 mol) was added, refluxing continued for 3 h, then cooled, poured into cold dilute NaOH solution and filtered. The precipitate was washed thoroughly with water, dried and

recrystallized from ethanol. Pale yellow crystals of **6a** were obtained in 55% yield. M.p. 238°.

Thioglycolic acid (13.8g; 0.15mol) was added to a solution of 4-bromomethylquinoline derivatives **1a-1c** in ethanol (400ml); a solution of NaOH (100ml; 12%) was then portionwise added over a period of 4h while stirring on a steam bath. The reaction mixture was then cooled, diluted with water and filtered. The filtrate was neutralized with dilute hydrochloric acid and filtered again. The yellow precipitate was washed with water, dried and recrystallized from acetic acid to give **2d-2f** in 85-90% yield. M.p. 315° (decomp.; **2d**), 293° (**2e**), 304° (**2f**).

8-Chloro-5-hydroxy-1H-thiopyrano[4,3-c]quinoline-4-(3H)-one (**3d**), *5-Hydroxy-9-methoxy-1H-thiopyrano[4,3-c]quinoline-4-(3H)-one* (**3e**) *and 5-Hydroxy-9-methyl-1H-thiopyrano[4,3-c]quinoline-4-(3H)-one* (**3f**)

Method (A)

2d-2f (5g) were heated in concentrated sulphuric acid (25ml) on a steam bath for 2h, cooled, poured into ice cold water and filtered. The yellow precipitate was washed with dilute ammonia and water, dried and recrystallized from acetic acid giving **3d-3f** in a quantitative yield.

Method (B)

2d-2f (2g) was heated in polyphosphoric acid (25g) at 140° for 6h, cooled, poured into ice cold water (200ml), neutralized with dilute ammonia and filtered. The precipitate was washed with water, dried and recrystallized from acetic acid to give **3d-3f** in about 90% yield. M.p. 284° (**3d**), 325° (**3e**), 298° (**3f**).

Chlorination of **2d-2f**

2d-2f (2g) were refluxed in $POCl_3$ (10ml) under anhydrous conditions for 2h, cooled, poured carefully into 250ml ice water and filtered. The precipitate contains both **5a-5c** and **4d-4f**. It was treated with dilute sodium bicarbonate solution and filtered again. The precipitate contains **4d-4f**. The filtrate was washed with water, dried and recrystallized from benzene [yield 26% for **5a** and **5c**, 35% for **5b**; m.p. 149° (**5a**), 156° (**5b**), 144° (**5c**)].

Treatment of **3d-3f** with $POCl_3$ gave identical products (**4d-4f**).

8-Chloro-4,5-bis{[(2-diethylamino)ethyl]amino}-1H-thiopyrano-[4,3-c]quinoline (**6b**)

A mixture of **4d** (0.3g; 0.001mol) and 1g of phenol was refluxed for 2h on a steam bath. Diethylaminoethylamine (0.32g; 0.003mol) was added, reflux was continued for 3h, cooled, poured into cold dilute sodium hydroxide solution, amd filtered. The precipitate was washed thoroughly with water, dried and recrystallized from ethanol. Pale yellow crystals of **6b** were obtained in 45% yield. M.p. 265°.

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