A New Route to 1H-Pyrido[1,2-a]quinazolines

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Bis-2,4,6-trichlorophenyl Malonates, 2-Methyl-4-quinazolinones, 1H-Pyrido[1,2-a]quinazoline-1,6-diones

The synthesis of 2,5-disubstituted 5,6-dihydro-1H-pyrido[1,2-a]quinazoline-1,6-diones (**3**) by reacting monosubstituted bis 2,4,6-trichlorophenyl malonates (**1**) with 3-aryl-3,4-dihydro-2-methyl-4-quinazolinones (**2**) is described. Allylation of the pyridoquinazoline **3e** with allylbromide afforded the corresponding 3-allyloxy derivative **4**. Certain generalizations of the cleavage processes of this series in the MS are reported.

An important feature of C-2 or C-4 methylquinazolines is the high reactivity of the methyl group, which is comparable in its C–H acidity with activated methylene compounds. Aldehydes or phthalic anhydride are reported to condense with 2-methyl-4-quinazolones to give the corresponding styryl derivatives or phthalones, respectively [1]. Acetylation of 2-methyl-1-phenyl-4-quinazolinone produced the 2-acetyliden compound [2]. Although the 3-unsubstituted 2-methyl-4-quinazolinone failed to react with diethyl oxalate in the presence of sodium ethoxide, the 2,3-dimethyl derivative yielded 2-ethoxalylmethyl-3-methyl-4-quinazolinone [3]. On the other hand, the 2-methyl group in 3-aryl-2-methyl-4-quinazolones was shown to be mono- or dibrominated depending on the experimental conditions [4].

In order to investigate further the reactivity of the C-2 methyl group in 4-quinazolones, we have tried the reaction of some monosubstituted bis 2,4,6-trichlorophenyl malonates (**1**) with 3-aryl-2-methyl-4-quinazolones (**2**) at the fusion point of the mixtures. This furnished 2,5-disubstituted 5,6-dihydro-3-hydroxy-1H-pyrido[1,2-a]quinazoline-1,6-diones (**3**) in yields ranging from 30 to 50% (Table I). The cyclization is similar to those previously occurred in analogous reactions of 2-alkylpyridines [5, 6], 2-alkylquinolines [7], 1-methylisoquinoline [7], 1-alkyl-3,4-dihydroisoquinolines [8], 6-alkylphen-

anthridines [7], 1,2,3,4-tetrahydrophenazine [9], 3-methyl- and 2,3-dimethylquinoxalines [9] and 3-alkyl-2-quinoxalones [9] with active malonates **1**. Mechanistically, the reaction is conceived to involve an intermediate keten-carboxylate derivative which is generated *in situ* from **1** [10].

Only two routes leading to the few known derivatives of 1H-pyrido[1,2-a]quinazoline have been described in the literature. In one method, 4a-methyl- and 4a-phenyl-3,4,4a,5-tetrahydro-1H-pyrido[1,2-a]quinazoline-1,6(2H)-diones were prepared by condensing anthranilamide with 5-oxohexanoic acid or 4-benzoylbenzoic acid, respectively [11]. Whereas, in the other method, 3,5-disubstituted 6-oxo-2,3,4,5-tetrahydro-1H-pyrido[1,2-a]quinazoline-1,2-dicarboxylic acids were either obtained by the Diels-Alder reaction of 2-styryl-4-quinazolones with maleic acid or from the alkaline hydrolysis of the intermediate cycloadducts prepared from 2-styryl-4-quinazolones and maleic anhydride or N-phenylmaleimide [12].

Of the different structural isomeric pyridoquinazoline ring systems, certain derivatives of

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Table I. 2,5-Disubstituted 5,6-dihydro-3-hydroxy-1H-pyrido[1,2-a]quinazoline-1,6-diones (**3**).

Com-pound	R ¹	R ²	Yield [%]	M.p. [°C]	Molecular formula	Analysis [%]		IR (KBr)
						Calcd	Found	
3a	C ₆ H ₅ CH ₂	C ₆ H ₅	41	273–274	C ₂₅ H ₁₈ N ₂ O ₃ (394.4)	C 76.13 H 4.60 N 7.10	76.28 4.69 7.06	3300–3000 b (OH), 1660 s, b (CO), 1615 s, 1555 cm ⁻¹ s.
3b	C ₂ H ₅	C ₆ H ₅	33	290 dec.	C ₂₀ H ₁₆ N ₂ O ₃ (332.4)	C 72.28 H 4.85 N 8.43	72.19 4.99 8.37	3200–2980 s, b (OH and CH), 1710 s, 1690 s (CO), 1665 s (CO); 1610 s, 1550 s, 1530 cm ⁻¹ sh.
3c	C ₆ H ₅	C ₆ H ₅	43	255–257	C ₂₄ H ₁₆ N ₂ O ₃ (380.4)	N 7.36	6.77	3560 s, 3200–2900 b (OH), 1700 s (CO), 1665 s, b (CO), 1610 s, 1555 s, 1500 cm ⁻¹ m.
3d	C ₆ H ₅ CH ₂	<i>p</i> -Br-C ₆ H ₄	45	298–300	C ₂₅ H ₁₇ BrN ₂ O ₃ (473.3)	C 63.44 H 3.62 Br 16.88 N 5.92	63.50 3.63 16.55 5.84	3300–3000 b (OH), 1700 s (CO), 1650 s (CO), 1615 s, 1550 cm ⁻¹ s.
3e	(CH ₃) ₂ CH	<i>p</i> -Br-C ₆ H ₄	35	283–285	C ₂₁ H ₁₇ BrN ₂ O ₃ (425.3)	C 59.30 H 4.03 Br 18.79 N 6.59	59.36 4.20 18.59 6.55	3500–3100 b (OH), 2980 w (CH), 2900 sh, 1675 s (CO), 1650 m (CO), 1630 s, 1605 m, 1545 cm ⁻¹ s.
3f	(CH ₃) ₂ CH	<i>o</i> -Cl-C ₆ H ₄	29	285–288	C ₂₁ H ₁₇ ClN ₂ O ₃ (380.8)	C 66.23 H 4.50 N 7.36	66.20 4.51 7.40	32440–3020 s (OH), 2980 s (CH), 1710 sh, 1690 s (CO), 1650 s, b (CO), 1605 s, 1550 sh, 1530 cm ⁻¹ s.
3g	CH ₃ (CH ₂) ₂ CH ₂	<i>o</i> -Cl-C ₆ H ₄	42	248–250	C ₂₂ H ₁₉ ClN ₂ O ₃ (394.9)	C 66.92 H 4.85 Cl 8.98 N 7.09	66.80 4.88 9.20 7.11	3250–3040 b (OH), 3000–2900 m (CH), 2700 w, 1700 m (CO), 1655 s, b (CO), 1610 s, 1550 cm ⁻¹ s.
3h	C ₆ H ₅	<i>o</i> -Cl-C ₆ H ₄	27	282–284	C ₂₄ H ₁₅ ClN ₂ O ₃ (414.9)	C 69.48 H 3.64 Cl 8.55 N 6.75	69.43 3.42 8.86 6.79	3100 w (OH), 2980 w, 2720 w, 1710 s, 1690 s (CO), 1660 s (CO), 1610 s, 1565 sh, 1550 cm ⁻¹ s.
3i	C ₆ H ₅ CH ₂	<i>o</i> -CH ₃ -C ₆ H ₄	42	275–277	C ₂₆ H ₂₀ N ₂ O ₃ (408.3)	C 76.48 H 4.90 N 6.86	76.29 5.00 6.80	3230 m (OH), 1660 s, 1610 m, 1595 w, 1555 cm ⁻¹ s.
3j	C ₂ H ₅	<i>o</i> -CH ₃ -C ₆ H ₄	51	280–285 dec.	C ₂₁ H ₁₈ N ₂ O ₃ (346.4)	C 72.82 H 5.24 N 8.09	73.15 5.48 8.17	3300–2900 m, b (OH and CH), 1700 s (CO), 1665 s, b (CO), 1610 s, 1550 cm ⁻¹ s.
3k	CH ₃ (CH ₂) ₂ CH ₂	<i>o</i> -CH ₃ -C ₆ H ₄	30	253–255	C ₂₃ H ₂₂ N ₂ O ₃ (374.4)	C 73.78 H 5.92 N 7.48	74.02 6.10 7.42	3200–2900 s, b (OH and CH), 1700 s (CO), 1665 s, b (CO), 1615 s, 1550 cm ⁻¹ s.

¹H NMR (DMSO-d₆) of **3f**: δ = 1.25 (d, *J* = 7 Hz, two CH₃-isopropyl); 3.3 (q, CH-isopropyl), 5.05 (s, H at C-4); 7.3–8.0 (m, 6 aromatic H); 8.2 (dd, *J* = 2 and 7 Hz, H at C-7); 9.9 (dd, *J* = 2 and 7 Hz, H at C-10); 10.9 (s, OH).

¹H NMR (DMSO-d₆) of **3i**: δ = 2.4 (t, *J* = 16 Hz, CH₃-tolyl); 3.8 (t, *J* = 14 Hz, CH₂-benzyl); 5.1 (t, *J* = 13, H at C-4); 6.8–8.1 (m, 13 aromatic H); 9.2 (dd, *J* = 2 and 7 Hz, H at C-10); 10.4 (s, OH).

¹H NMR (DMSO-d₆) of **3j**: δ = 1.05 (t, *J* = 7 Hz, CH₃-ethyl); 2.1 (s, CH₃-tolyl); 2.45 (q, *J* = 7 Hz, CH₂-ethyl); 5.1 (s, H at C-4); 7.3–8.0 (m, 6 aromatic H); 8.15 (dd, *J* = 2 and 7 Hz, H at C-7); 9.45 (dd, *J* = 2 and 7 Hz, H at C-10); 10.35 (s, OH).

pyrido[2,1-b]quinazoline showed antiallergic, anti-inflammatory and analgesic effects [13–16]. As part of our interest was directed towards the synthesis of compounds with useful biological activities, the choice of the 4-quinazolones (**2**) utilized was based on their sedative-hypnotic and anticonvulsant potencies.

The desired quinazolones **2** were prepared by condensing N-acetyl-anthranilic acid with the appropriate aromatic amine in the absence of a catalyst as previously reported [17, 18]. Treatment of the pyridoquinazoline **3c** with allyl bromide in dimethylformamide at a temperature not exceeding 80 °C and in the presence of potassium carbonate

yielded the corresponding 3-allyloxy derivative 4.

Rising the temperature to 90–100 °C causes partial decomposition of the allyloxy derivative 4. Attempts to effect the Claisen rearrangement of 4 in DMF yielded a brownish oil, which comprised a number of new compounds; however, neither recrystallization nor separation by column chromatography (Merk silica gel G 60) was successful in getting compounds. When 4 was heated in boiling N,N-dimethylaniline, an alkaline insoluble product of unknown structure was isolated, which was also obtained when the oil from the DMF rearrangement reaction was heated in boiling HCl.

Efforts to chlorinate 3 with sulfuryl chloride in dioxane were unsuccessful, too. Keeping the reaction temperature below 50 °C, no reaction took place, whereas at 70–100 °C only a number of decomposition products of the pyridoquinazolines 3 were observed.

The MS data of 3 and 4 are recorded in Table II and a common decomposition mode of 3 is illustrated in Scheme 3. The spectra of 3 are characterized by the loss of $R^1-C^+=C=O$ (A) associated with hydrogen transfer giving the ion B which is the base peak

Table II. Mass spectral data.

Compound	<i>m/e</i> Values (relative abundance %)
3a	396 (9, $M + 2$); 395 (39, $M + 1$); 394 (100, M^+), 364 (6); 339 (6); 317 (5, $M-C_6H_5$); 290 (12); 289 (39, $M-C_6H_5CO$); 264 (6); 263 (33, $M-C_6H_5CH_2C=C=O$); 262 (5); 236 (27); 235 (57); 234 (30); 221 (7); 146 (18); 144 (29); 132 (9); 131 (36, $C_6H_5CH_2C=C=O$); 127 (12); 126 (13); 125 (11); 103 (15); 91 (42, $C_6H_5CH_2$); 77 (24, C_6H_5).
3b	333 (24, $M + 1$); 332 (64, M^+); 318 (30); 317 (100, $M-CH_3$); 303 (10, $M-C_2H_5$); 289 (12); 263 (26, $M-C_2H_5C=C=O$); 235 (25); 234 (24); 146 (29); 144 (27); 77 (60, C_6H_5).
3c	381 (22, $M + 1$); 380 (56, M^+); 352 (7, $M-CO$); 264 (24); 263 (100, $M-C_6H_5C=C=O$); 234 (6); 144 (13); 117 (5, $C_6H_5C=C=O$); 116 (5); 102 (5); 90 (6); 89 (7); 77 (18, C_6H_5); 51 (5).
3d	475 (33); 474 (76, M^+ of Br^{81}); 473 (35); 472 (70, M^+ of Br^{79}); 367 (22); 365 (21); 341 (14, $M-C_6H_5C=C=O$); 339 (15); 315 (20); 314 (26); 312 (24); 261 (15); 234 (43); 233 (24); 224 (12); 222 (11); 205 (12); 160 (13); 157 (17, $C_6H_4Br^{81}$); 155 (18, $C_6H_4Br^{79}$); 146 (38); 144 (24); 131 (82, $C_6H_5CH_2C=C=O$); 119 (9); 118 (18); 116 (15); 115 (34); 114 (12); 104 (15); 103 (35); 102 (20); 92 (27); 91 (100, $C_6H_5CH_2$); 77 (41, C_6H_5); 76 (46); 75 (27); 69 (21); 65 (29); 63 (22); 55 (20).
3e	427 (8); 426 (18, M^+ of Br^{81}); 425 (7); 424 (18, M^+ of Br^{79}); 412 (22); 411 (54, $M-CH_3$); 409 (51, $M-CH_3$); 343 (32); 342 (14); 341 (30); 315 (28); 314 (26); 313 (28); 312 (14); 301 (19); 262 (61); 260 (30); 235 (37); 234 (100); 233 (49); 231 (24); 223 (32); 205 (30); 150 (71); 147 (56); 141 (54); 115 (90); 105 (47, C_6H_5CO); 101 (46); 95 (64); 91 (78, $C_6H_5CH_2$).
3f	382 (12); 381 (13); 380 (36, M^+ of Cl^{35}); 367 (32); 366 (28); 365 (100, $M-CH_3$); 348 (8); 297 (12, $M-(CH_3)_2CHC=C=O$); 261 (6); 235 (5); 111 (6, C_6H_4Cl); 91 (8); 69 (16); 57 (20); 55 (48).
3g	397 (5); 396 (15); 395 (12); 394 (31, M^+ of Cl^{35}); 365 (6); 354 (16); 353 (44); 352 (37); 351 (100, $M-C_3H_7$); 323 (6); 297 (9, $M-C_4H_5C=C=O$); 269 (9); 261 (14); 235 (22); 234 (12); 180 (10); 178 (21); 150 (10); 146 (46); 144 (18); 111 (10, C_6H_4Cl); 90 (9); 77 (8, C_6H_5); 57 (9, C_4H_9).
3h	417 (7); 416 (19); 415 (21); 414 (43, M^+ of Cl^{35}); 386 (6, $M-CO$); 397 (7); 300 (12); 299 (37);

Table II (continued).

Compound	<i>m/e</i> Values (relative abundance %)
	297 (100, M-C ₆ H ₅ C=C=O); 262 (8); 261 (12); 255 (11); 234 (12); 207 (7); 205 (7); 196 (9); 180 (10); 179 (7); 178 (23); 166 (7); 161 (6); 152 (11); 151 (10); 150 (13); 146 (15); 145 (27); 144 (17); 120 (15); 111 (16, C ₆ H ₄ Cl); 102 (13); 92 (12); 91 (36); 90 (19); 89 (25); 77 (26); 76 (17).
3i	409 (34, M + 1); 408 (100, M ⁺); 380 (8, M-CO); 363 (2); 352 (12); 351 (10); 331 (5, M-C ₆ H ₅); 304 (8); 303 (28); 277 (20, C ₂ H ₅ C=C=O); 276 (8); 275 (6); 250 (20); 249 (38); 248 (17); 165 (12); 131 (22); 112 (28); 91 (24, <i>o</i> -CH ₃ -C ₆ H ₄); 77 (19, C ₆ H ₅); 44 (41).
3j	347 (20, M + 1); 346 (72, M ⁺); 332 (28); 331 (76, M-15); 318 (6); 317 (8, M-C ₂ H ₅); 301 (9); 300 (25); 278 (8); 277 (20, M-C ₂ H ₅ C=C=O); 250 (9); 249 (19); 248 (14); 247 (15); 236 (22); 235 (100); 234 (24); 233 (9); 200 (4); 158 (6); 146 (12); 144 (6); 130 (5); 91 (5, <i>o</i> -CH ₃ -C ₆ H ₄); 65 (6).
3k	375 (15, M + 1); 374 (35, M ⁺); 332 (49); 331 (100, M-C ₃ H ₇); 277 (15, M-C ₄ H ₉ C=C=O); 256 (10); 249 (10); 235 (24); 146 (22); 144 (14); 130 (16); 91 (66, <i>o</i> -CH ₃ -C ₆ H ₄); 70 (20); 69 (21); 57 (20, C ₄ H ₉); 55 (20); 47 (19); 45 (18).
4	421 (23, M + 1); 420 (46, M ⁺); 392 (5, M-CO); 379 (5, M-CH ₂ =CH-CH ₂); 353 (25); 352 (60); 323 (22); 275 (10); 263 (24); 262 (59); 235 (14); 234 (52); 233 (20); 221 (17); 213 (14); 205 (16); 204 (43); 165 (10); 159 (14); 158 (100); 146 (13); 145 (22); 144 (17); 130 (54); 129 (26); 117 (16); 115 (20); 103 (13); 102 (15); 90 (20); 89 (31); 77 (95, C ₆ H ₅); 51 (13).

of the spectra of 3e and 3h. B is then degraded to C by loss of CO and/or to D by release of CH₂=C=O⁺. Although D constitutes the base peak of the spectrum of 3j, it is not apparant in the spectra of 3b-3d, 3f, 3g and 3i. Further fragmentation of C and D would lead to the radical cations E at *m/e* 144 and F at *m/e* 234, respectively. However, E is absent from the spectra of 3e, 3f and 3i and F which forms the base peak of the spectrum of 3e is insignificant for 3f, 3i and 3k. Other fragmentations of some importance depend on the nature of the substituent R¹. Thus when R¹ is benzyl, ethyl, isopropyl or butyl, intense ions corresponding to M-C₆H₅,

M-C₂H₅, M-CH₃ or M-C₃H₇ were observed (Table II). Compound 4 behaves in a similar way; its spectrum showed a prominent peak at *m/e* 262 originated by the elimination of the fragment C₆H₅-C≡C-O-CH₂-CH=CH₂. This latter fragment (*m/e* 158) is the base peak of the spectrum and the former ion, *m/e* 262, corresponds to the species B-H in the spectra of 3. In addition the spectrum revealed the ion B at *m/e* 263.

Experimental

Melting points are uncorrected. IR spectra: Perkin Elmer 421. ¹H-NMR spectra: Varian A 60A or Varian EM 360 with TMS as internal standard. MS spectra: Organic MS 20 AEI (70 eV) and Varian MAT 111 (80 eV).

1. Substituted bis-2,4,6-trichlorophenyl malonates (1)

The substituted active malonic esters utilized in this investigation were prepared according to the reported method [5].

2. 3-Aryl-3,4-dihydro-2-methyl-4-quinazolinones (2)

2-Methyl-3-phenyl-4-quinazolinone (2a), 3-(*o*-chlorophenyl)-2-methyl-4-quinazolinone (2c) and 2-methyl-3-(*o*-tolyl)-4-quinazolinone (2d) were prepared by heating equimolar quantities of N-acetyl-anthranilic acid and the appropriate amine in bromobenzene as previously described [17].

3. 3-(*p*-Bromophenyl)-3,4-dihydro-2-methyl-4-quinazolinone (2b)

An intimate mixture of N-acetyl-anthranilic acid (1.79 g; 0.01 mole) and *p*-bromoaniline (1.81 g; 0.0105 mole) was heated at 160 °C for 2 h. Subsequently, the dark brown reaction mixture was cooled and the solidified product crystallized from ethanol, m.p. 171-172 °C (lit.: 165-167 °C [19]; 171-172 °C [20]); yield 1.4 g (44%).

IR (KBr): 1680 s (C=O) and a band splitted at 1600 s and 1570 cm⁻¹ m.

¹H NMR (DMSO-d₆): δ = 2.11 (s, CH₃); 7.2-8.12 (m, 8 aromatic H).

C₁₅H₁₁BrN₂O (315.2)

Calcd	C 57.16	H 3.52	N 8.89,
Found	C 57.30	H 3.50	N 9.00.

4. 2,5-Disubstituted 5,6-dihydro-3-hydroxy-1H-pyrido[1,2-a]quinazoline-1,6-diones (3a-k)

A mixture of 1 (0.001 mole) and 2 (0.001 mole) was placed in an oil bath previously heated to 250 °C for 30 min. After cooling the dark brown reaction mixture was mixed with benzene and the deposited solid was filtered, washed with benzene, dried and recrystallized from ethanol or aqueous

ethanol. In this way the following compounds were prepared (for characteristic data see Table I):

- 2-Benzyl-5,6-dihydro-3-hydroxy-5-phenyl-1H-pyrido[1,2-a]quinazoline-1,6-dione (**3a**);
 5,6-Dihydro-2-ethyl-3-hydroxy-5-phenyl-1H-pyrido[1,2-a]quinazoline-1,6-dione (**3b**);
 5,6-Dihydro-2,5-diphenyl-3-hydroxy-1H-pyrido[1,2-a]quinazoline-1,6-dione (**3c**);
 2-Benzyl-5-(4-bromophenyl)-5,6-dihydro-3-hydroxy-1H-pyrido[1,2-a]quinazoline-1,6-dione (**3d**);
 5-(4-Bromophenyl)-5,6-dihydro-3-hydroxy-2-(2-propyl)-1H-pyrido[1,2-a]quinazoline-1,6-dione (**3e**);
 5-(2-Chlorophenyl)-5,6-dihydro-3-hydroxy-2-(2-propyl)-1H-pyrido[1,2-a]quinazoline-1,6-dione (**3f**);
 2-(1-Butyl)-5-(2-chlorophenyl)-5,6-dihydro-3-hydroxy-1H-pyrido[1,2-a]quinazoline-1,6-dione (**3g**);
 5-(2-Chlorophenyl)-5,6-dihydro-3-hydroxy-2-phenyl-1H-pyrido[1,2-a]quinazoline-1,6-dione (**3h**);
 2-Benzyl-5,6-dihydro-3-hydroxy-5-(2-methylphenyl)-1H-pyrido[1,2-a]quinazoline-1,6-dione (**3i**);
 5,6-Dihydro-2-ethyl-3-hydroxy-5-(2-methylphenyl)-1H-pyrido[1,2-a]quinazoline-1,6-dione (**3j**);

2-(1-Butyl)-5,6-dihydro-3-hydroxy-5-(2-methylphenyl)-1H-pyrido[1,2-a]quinazoline-1,6-dione (**3k**).

5. 3-Allyloxy-5,6-dihydro-2,5-diphenyl-1H-pyrido[1,2-a]quinazoline-1,6-dione (**4**)

To a stirred mixture of **3c** (1.8 g; 0.0047 mole) and potassium carbonate (5.6 g; 0.04 mole) in DMF (10 ml) was added allyl bromide (0.7 ml; 0.008 mole) dropwise at 80 °C. After the addition was complete, the mixture was stirred for a further 3 h, then cooled. Inorganic material was filtered off and washed with cold DMF and the combined filtrate and washings were evaporated in vacuo below 70 °C. The resulting crude product was dissolved in benzene/chloroform (200 ml) and the solution was washed successively with 1 N cold sodium hydroxide and water, dried and evaporated in vacuo below 70 °C. The residue was recrystallized from aqueous ethanol. Yellow prisms, m.p. 132 °C; yield 1.2 g (60%).

IR (KBr): 3100 w, 1695 s (C=O), 1610 m, 1595 m, 1545 cm⁻¹ s.

¹H NMR (DMSO-d₆): δ = 4.2 (d, *J* = 7 Hz, -OCH₂-), 4.95 (d, *J* = 7 Hz, =CH₂), 5.1 (s, H at C-4), 5.35–5.7 (m, *J* = 7 Hz, -CH= allyl), 7.2–8.2 (m, 13 aromatic H), 9.2 (dd, *J* = 2 and 7 Hz, H at C-10).

C₂₇H₂₀N₂O₃ (420.5)

Calcd	C 77.13	H 4.79	N 6.66,
Found	C 77.44	H 4.86	N 6.77.

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