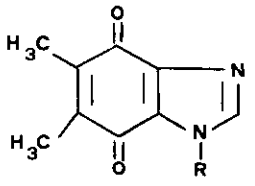
HETEROCYCLIC QUINONES WITH POTENTIAL ANTITUMOR ACTIVITY
A CONVENIENT SYNTHESIS OF 5,6-DIMETHYL-4,7-BENZIMIDAZOLEDIONES

Ippolito Antonini, Gloria Cristalli, Palmarisa Franchetti, Mario Grifantini and Sante Martelli*

Department of Chemical Sciences, University of Camerino, Italy

Abstract - Simple syntheses of 1-substituted 5,6-dimethyl-4,7-benzimidazolediones (Ia-c) are described. The commercially available 5,6-dimethylbenzimidazole was alkylated and nitrated. The corresponding 4,7-dinitro derivatives were reduced to diamines and subsequently oxidized to quinones.

It is well known that many quinone derivatives have anticancer activity [1] and some of them, such as streptonigrin or mitomycins, have the quinone moiety fused to a heterocyclic ring. Several heterocyclic quinones recently reported in the literature [2-6] have significant antitumor activity. As part of an ongoing research program directed to the synthesis of new antitumor compounds, in which a quinone ring is condensed with a five-membered heterocyclic nucleus, we required an efficient and simple synthetic method for large quantities of 5,6-dimethyl-4,7-benzimidazoledione (Ia) as parent compound of a novel class of alkylating agents. Compound Ia was obtained by Talaty [7] as by-product in the oxidation of 5,6-dimethyl-benzimidazole with ceric ammonium nitrate. Although this is a direct method and



I a - c

a R = H

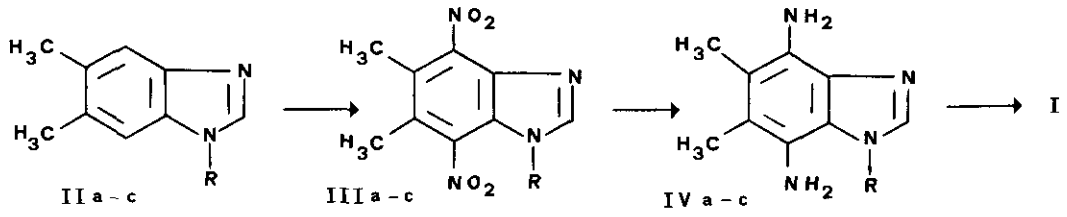
b R = CH_3

c R = C_2H_5

requires only one step, it is not suitable for convenient large scale preparations because it produces inconsistent yields of the desired compound. On the other hand Day's synthesis [8], involving hydrolysis of 4,7-dimethoxybenzimidazole and the oxidation of the corresponding 4,7-dihydroxy derivative with ferric chloride or chromic anhydride, is scarcely useful because of the difficulty in obtaining the required 2,3-dimethyl-1,4-dimethoxybenzene as starting compound.

In fact, in the few cases reported in the literature, the 4,7-benzimidazolediones substituted at position 5- and 6- are usually obtained through 1,4-nucleophilic additions to 4,7-benzimidazoledione or nucleophilic substitutions on 5-chloro-4,7-benzimidazoledione [9].

We describe in this paper a convenient synthesis of Ia and its adaptation to the preparation of other 1-substituted 5,6-dimethyl-4,7-benzimidazolediones with conventional methods in three steps as depicted in the following scheme:



IIa-c IIIa-c IVa-c

a R = H

b R = CH_3

c R = C_2H_5

1,5,6-Trimethylbenzimidazole (IIb) and 1-ethyl-5,6-dimethylbenzimidazole (IIc) were prepared from the commercially available 5,6-dimethylbenzimidazole (IIa) by N-alkylation [10]. However we obtained IIb in nearly quantitative yields by N-alkylation of IIa with methyl iodide via phase-transfer catalysis [11-13].

Treatment of IIa-c with concentrated nitric and sulphuric acids gave a mixture of mononitro and dinitro derivatives from which the 4,7-dinitro-5,6-dimethyl-benzimidazoles IIIa-c were separated by column chromatography. Reduction of IIIa with hydrogen and palladium as catalyst gave 4,7-diamino-5,6-dimethylbenzimidazole (IVa). In the case of IIIb, a similar procedure gave impure IVb partially complexed with palladium while, in the case of IIIc it produced a complex mixture of partially reduced and partially dealkylated compounds. Reduction of IIIb-c with hydrazine and Raney Nickel as catalyst in methanol [14,15] yielded the diamines IVb-c in excellent yields. Treatment of IVa-c in acidic medium with ferric chloride gave Ia-c in high yields.

The present method provides a very convenient route to 5,6-dimethyl-4,7-benzimidazolediones on account of simplicity, availability of starting materials and yields. Application of this procedure to the synthesis of differently substituted 4,7-benzimidazolediones is currently in progress.

Compounds Ia-c submitted for preliminary in vitro tests showed interesting antitumor activity; more detailed results will be reported elsewhere in the near future.

EXPERIMENTAL

The melting points were determined with a Büchi apparatus and are uncorrected. A Perkin-Elmer model 575 spectrophotometer was used for UV spectral determinations. NMR spectra were obtained using a Varian EM-390 90 MHz spectrometer, using TMS as internal standard. Elemental analyses were performed with a Perkin-Elmer 240 CHN analyzer and determined values are within 0.4% of the theoretical values. Silica gel 60, F-254 (E. Merck no. 5729), and silica gel 60 (E. Merck 7734, 70-230 mesh) were used for thin-layer and column chromatography, respectively.

1,5,6-Trimethylbenzimidazole (IIb)

To a suspension of 5,6-dimethylbenzimidazole (1 g, 6.0 mmole) and 5N aqueous potassium hydroxide (10 ml) was added a solution of methyl iodide (0.41 ml, 6.6 mmole) and 18-Crown-6 (50 mg) in carbon tetrachloride (200 ml) and the mixture was shaken at room temperature for 30 h. The organic layer was separated, washed with water and dried on magnesium sulphate. The solvent was removed by evaporation under reduced pressure and the residue was recrystallized.

5,6-Dimethyl-4,7-dinitrobenzimidazoles (IIIa-c); General Procedure

A solution of IIa-c (0.025 mole) in conc. sulfuric acid (20 ml) was added dropwise, with stirring, to a cold mixture of nitric acid (90%) (1.5 ml) and conc. sulfuric acid (8 ml) at 0-7°C and then allowed to stand at room temperature for 12 h. The reaction mixture was poured into cracked ice and neutralized with conc. ammonium hydroxide. The crude precipitate was filtered, washed with water, dried and chromatographed on a silica gel column eluting with ethyl acetate (IIIa) or ethyl acetate/cyclohexane (60:40) (IIIb,c).
The first eluted fraction was recovered and evaporated; the residue was recrystallized from a suitable solvent.

4,7-Diamino-5,6-dimethylbenzimidazoles (IVa-c)

Method A: A solution of III (0.008 mole) in warm ethanol (400 ml) and 5% palladium on charcoal (0.15 g) was hydrogenated in a Parr apparatus at 30 psi until the theoretical amount of hydrogen was consumed. The ethanolic solution, filtered from the catalyst and evaporated, gave a residue which was recrystallized from a suitable solvent.
Method B: A solution of III (0.008 mole) in methanol (50 ml) was added dropwise over a period of 15 min to a refluxing mixture of methanol (10 ml), hydrazine hydrate (5 ml) and Raney Ni (200 mg). After addition was completed, reflux was maintained for 10 min. The catalyst was separated by filtration over celite, the solvent was evaporated and the residue was recrystallized. Acidification of the alcoholic solution of IV with anhydrous hydrochloric acid gave the corresponding

Table. Preparation of compounds II, III, IV and I

Compound	Yield [%]	Method	mp [°C] (solvent)	Molecular formula[a] or lit.mp [°C]	U.V. (95% ethanol) λmax [nm] (log ε)	^{1}H-NMR (TMS)[b] δ [ppm]
IIb	95		143-145 benzene	142-143		2.92 and 2.32 (two s, 6H); 3.75 (s, 3H); 7.30 and 7.44 (two s, 2H); 8.02 (s, 1H).
IIIa	43		216-217 ethanol	$C_9H_8N_4O_4$ (236.2)	290(3.75); 305(3.73); shoulder 360(3.66)	2.42 (s, 6H); 8.46 (s, 1H); 13.52 (broad s, 1H).
IIIb	48		174-176 ethyl acetate	$C_{10}H_{10}N_4O_4$ (250.2)	290(3.54)	2.37 and 2.40 (two s, 6H); 3.74 (s, 3H); 7.91 (s, 1H).
IIIc	47		125-127 ethyl acetate	$C_{11}H_{12}N_4O_4$ (264.2)	289(3.55)	1.43 (t, 3H); 2.38 (s, 6H); 4.14 (q, 2H); 8.02 (s, 1H).
IVa	90	A	255-257(dec) ethyl acetate	$C_9H_{12}N_4$ (176.2)	279(4.22); 335(3.03)	2.0 (s, 6H); 2.5 (broad signal, 5H); 8.11 (s, 1H).
IVb	86	B	202-204 ethyl acetate	$C_{10}H_{14}N_4$ (190.2)	228(4.37); 279(3.80) shoulder 300 (3.54)	2.06 and 2.09 (two s, 6H); 3.35 (broad s, 4H); 4.02 (s, 3H); 7.71 (s, 1H).
IVc	90	B	175-177 ethanol	$C_{11}H_{16}N_4$ (204.3)	232(4.14); 276(3.82) shoulder 302 (3.64)	1.31 (t, 3H); 2.15 and 2.30 (two s, 6H); 4.23 (q, 2H); 9.05 (very broad s, 4H); 9.47 (s, 1H).
Ia	85		247-250(dec) ethanol/water	245° (dec)[7]		
Ib	75		247-249 ethanol	$C_{10}H_{10}N_2O_2$ (190.2)	273 (4.19)	1.99 (s, 6H); 3.90 (s, 3H); 8.06 (s, 1H).
Ic	70		160-162 ethanol	$C_{11}H_{12}N_2O_2$ (204.2)	274 (4.16)	1.38 (t, 3H); 1.99 (s, 6H); 4.34 (q, 2H); 8.16 (s, 1H).

[a] Satisfactory microanalyses obtained: C ± 0.36; H ± 0.36; N ± 0.22.

[b] The ^{1}H-nmr spectra for IIb, IIIa, IVa, IVb, IVc, Ib, Ic were obtained in DMSO-d_6; those for IIIb and IIIc were obtained in $CDCl_3$.

hydrochloride as white precipitate.

5,6-Dimethyl-4,7-benzimidazolediones (Ia-c); General Procedure

To 5,6-Dimethyl-4,7-diaminobenzimidazoles (0.5 g) dissolved in water (50 ml) an excess of ferric chloride (1 g) was added. The resulting solution was made slightly acidic by adding hydrochloric acid and was stirred overnight at room temperature. The yellow precipitate was recovered by filtration, washed with water and recrystallized. The mother solution, neutralized with ammonium hydroxide and extracted with ethyl acetate gave an additional amount of Ia-c.

ACKNOWLEDGEMENT. Financial support of this work by a grant from the Ministry of Public Education, Italy, is gratefully acknowledged.

REFERENCES

1. J. S. Driscoll, G. F. Hazard Jr., H. B. Wood Jr. and A. Goldin, Cancer Chemother. Rep., part 2, 1974, 4 (2), 1.
2. G. Alonso, G. Garcia-Munoz, F. G. De Las Heras, R. Madronero and M. Stud, J. Carbohydr., Nucleosides, Nucleotides, 1974, 1, 381.
3. M. V. Pickering, P. Dea, D. G. Streeter and J. T. Witkowski, J. Med. Chem., 1977, 20, 818.
4. G. Alonso, A. Contreras, M. Fuertes, J. M. Infante, F. S. De Las Heras and M. Stud, Eur. J. Med. Chem., 1978, 13, 155.
5. G. Alonso, A. Contreras, M. Fuertes, J. M. Infante, F. S. De Las Heras and M. Stud , J. Med. Chem., 1978, 21, 578.
6. M. T. Garcia-Lopez, F. G. De Las Heras, M. Mendrand, E. Sanchez and M. Stud, Eur. J. Med. Chem., 1979, 14, 151.
7. C. N. Talaty, N. Zenker and P. S. Callery, J. Heterocyclic Chem., 1976, 13, 1121.
8. L. Weinberger and A. R. Day, J. Org. Chem., 1959, 24, 1451.
9. L. C. March and M. M. Joullie, J. Heterocyclic Chem., 1970, 7, 249.
10. A. M. Simonov, A. E. Pozharskii and V. M. Marianovskii, Indian J. Chem., 1967, 5, 81.
11. C. M. Starks and C. Liotta, "Phase-Transfer Catalysis: Principles and Techniques", Academic Press, New York, 1978.
12. W. P. Weber and G. W. Gokel, "Phase-Transfer Catalysis in Organic Synthesis" Springer Verlag, Berlin, 1977.
13. L. J. Mathias and D. Burkett, Tetrahedron Letters, 1979, 4709.
14. A. Furst, R. C. Berlo and S. Hooton, Chem. Rev., 1965, 65, 51.
15. F. Yuste, M. Saldana and F. Walls, Tetrahedron Letters, 1982, 147.

Received, 9th June, 1982