(relative intensity) 264 (5), 134 (48), 130 (14), 81 (100). Anal. Calcd for C_8H_6STe: C, 36.70; H, 2.31; S, 12.25; Te, 48.74. Found: C, 36.47; H, 2.43; S, 12.42; Te, 48.60.

Acknowledgment. This work was supported by a grant from the National Science Foundation (CHE 79-25017). Partial financial support (to L. Engman) from Stiftelsen Blanceflor-Boncompagnie-Ludovisi and Signeuls Fond is also gratefully acknowledged.

Registry No. **1c**, 78482-05-0; **2a**, 7115-90-4; **2b**, 40819-28-1; **5a**, 78763-90-3; **5b**, 78763-91-4; **5c**, 78763-92-5; **6**, 69246-89-5; **7**, 88-95-9; **8**, 78763-93-6; **9**, 7115-91-5; **10a**, 78763-94-7; **10b**, 78763-95-8; **13**, 19172-47-5; **14**, 78763-96-9.

Extension of the Nenitzescu Reaction to a Cyclic Enamino Ketone. One-Step Synthesis of 6-Hydroxy-9*H*-pyrimido[4,5-*b*]indole-2,4-dione

Jean-Luc Bernier and Jean-Pierre Hénichart*

INSERM U-16, 59045 Lille, Cédex, France

Received May 27, 1981

A new one-step synthesis of the 6-hydroxypyrimido[4,5-*b*]indole ring involving the condensation of *p*-benzoquinone with 1,3-dimethyl-6-aminouracil has been reported. This procedure, an extension of the Nenitzescu reaction, was compared to a more classical Fischer-type cyclization. In both reactions, intermediates have provided useful mechanistic information. When nitromethane was used as a solvent, this new Nenitzescu-type synthesis conclusively appeared to present some advantages, including simplicity and a relatively good yield.

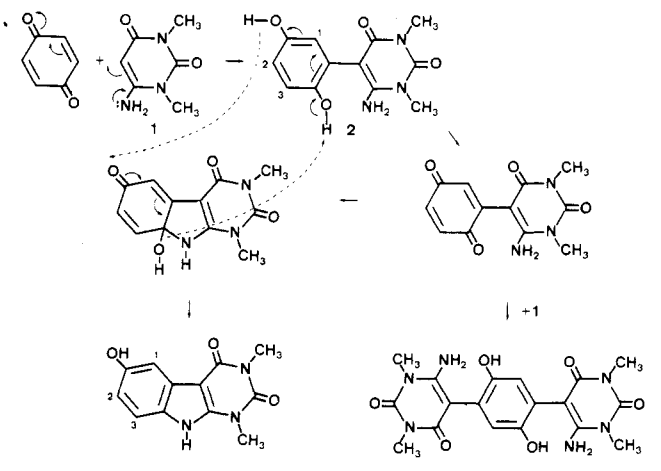
The study of polycyclic DNA-intercalative drugs has been a matter of significant interest for several years. Recently, we have described an approach to a number of 6-hydroxycarbazoles[1] related to the well-known antileukemic 9-hydroxyellipticine.[2] We have also investigated the biological properties of 5-acyl-6-aminouracil derivatives in relation to their structural features.[3]

These initial findings prompted us to include the pyrimidine moiety in a tricyclic system in order to enhance both intercalative and antitumor properties. For this purpose, we have carried out a one-step synthesis of 6-hydroxy-9*H*-pyrimido[4,5-*b*]indole-2,4-dione starting from 1,3-dimethyl-6-aminouracil (1) and *p*-benzoquinone (PBQ) and using either acetic acid or nitromethane as the solvent. In fact, three compounds have been isolated: the hydroquinone **2**, the expected product **3**, and the diadduct **4** (see Scheme I).

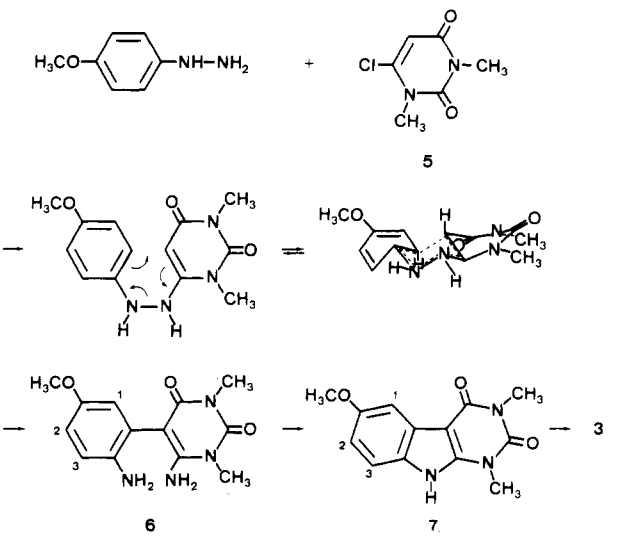
This reaction could be presented as a novel application to the cyclic enamine **1** of the Nenitzescu reaction[4] whose extension to aromatic amines has been recently described.[1a] As demonstrated for classical hydroxyindole synthesis, the reaction presumably proceeds via a Michael addition followed by several steps including an internal oxidation–reduction.[5]

The initial carbon–carbon attack has been clearly demonstrated by the formation of a stable intermediate **2** and

Scheme I



Scheme II



of the diadduct **4**, which is in accordance with previously proposed mechanisms.[6] Furthermore, it is noteworthy

(1) (a) Bernier, J. L.; Hénichart, J. P.; Vaccher, C.; Houssin, R. *J. Org. Chem.* **1980**, *45*, 1493. (b) Hénichart, J. P.; Bernier, J. L.; Vaccher, C.; Houssin, R.; Warin, V.; Baert, F. *Tetrahedron Lett.* **1979**, 945. (c) Hénichart, J. P.; Bernier, J. L.; Vaccher, C.; Houssin, R.; Warin, V.; Baert, F. *Tetrahedron* **1980**, *36*, 3535.

(2) Le Pecq, J. B.; Dat-Xuong, N.; Gosse, C.; Paoletti, C. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 5078.

(3) (a) Bernier, J. L.; Hénichart, J. P. *J. Heterocycl. Chem.* **1979**, *16*, 717. (b) Warin, V.; Foulon, M.; Baert, F.; Bernier, J. L.; Hénichart, J. P. *Acta Crystallogr., Sect. B* **1980**, *B36*, 1721. (c) Bernier, J. L.; Hénichart, J. P. *Tetrahedron Lett.* **1981**, 1243.

(4) Nenitzescu, C. D. *Bull. Soc. Chim. Rom.* **1929**, *11*, 37.

(5) (a) Allen, G. R., Jr.; Pidackes, C.; Weiss, M. J. *J. Am. Chem. Soc.* **1966**, *88*, 2536. (b) Monti, S. A. *J. Org. Chem.* **1966**, *31*, 2669. (c) Allen, G. R., Jr.; Weiss, M. J. *Ibid.* **1968**, *33*, 198. (d) Littel, R.; Allen, G. R., Jr. *Ibid.* **1968**, 2064. (e) Littel, R.; Morton, G. O.; Allen, G. R., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 3740. (f) Kuckländer, U. *Arch. Pharm.* **1971**, *304*, 602. (g) Kuckländer, U. *Tetrahedron Lett.* **1971**, 2093. (h) Kuckländer, U. *Tetrahedron* **1972**, *28*, 5251. (i) *Ibid.* **1973**, *29*, 921. (j) Patrick, J. B.; Saunders, E. K. *Tetrahedron Lett.* **1979**, 4009.

0022-3263/81/1946-4197$01.25/0

that better yields of carbazole (41%) have been obtained by refluxing in nitromethane as described by Patrick and Saunders.[5j]

The structures of the products were assigned on the basis of their spectral properties, and the nature of pyrimido[4,5-*b*]indole **3** was further confirmed by comparison with an independently synthesized sample. For this purpose, the pyrimido[4,5-*b*]indole ring could be obtained either by photolysis or thermolysis of 5-diaza-6-anilinouracils[1c,7] or by thermal catalyzed conversion of 6-phenylhydrazinouracils.[8] This latter Fischer-type cyclization was chosen. Thus, the reaction of 1,3-dimethyl-6-chlorouracil (**5**) with *p*-methoxyphenylhydrazine in the presence of sodium carbonate led to the diamine **6**. The obtention of such a C–C adduct during the course of the Fischer indole synthesis was initially presented as a nucleophilic attack on the C-5 site of the uracil ring by a ortho phenyl carbon, after N-protonation.[9] The formation of **6** most likely proceeds via a [3,3] sigmatropic shift (Scheme II). Such a concerted mechanism seems favored by the electron-donating effect of the methoxy group.

Cyclization of **6** to **7** readily occurred by refluxing either in 98% formic acid or in dimethylaniline. Heating the 9*H*-pyrimido[4,5-*b*]indole **7** at 200 °C with pyridinium chloride afforded **3** in an overall yield of 30%.

The facility with which this new one-step cyclization to 6-hydroxy-9*H*-pyrimido[4,5-*b*]indole-2,4-diones occurs makes this type of approach particularly attractive for the synthesis of some polycyclic rings including dioxopyrimidine and hydroxyindole moieties, with a view toward making new molecules with potential biological activity.

Experimental Section

Standard Techniques. Infrared spectra were recorded with a Perkin-Elmer 177 infrared spectrometer using a potassium bromide pellet. NMR spectra were recorded on a JEOL JNM-FX100 spectrometer with tetramethylsilane as an internal standard. Electron-impact mass spectra were obtained with a quadrupole mass spectrometer (Ribermag R10-10, combined with Riber 400 data system) at 70 eV by using direct insertion. Chemical-ionization mass spectrum was taken by using methane as the reagent gas. High-pressure liquid chromatography (HPLC) was carried out on a Waters 6000A solvent delivery system equipped with a U6K injector and a dual detector system (UV at 2537 Å and a refractive index detector). A reverse-phase Nucleosil 7 C_{18} column was used. Combustion analyses were performed on a Perkin-Elmer CHN240 apparatus. All new compounds exhibited consistent spectral data and elemental analyses.

Nenitzescu-Type Synthesis. Refluxing 15.5 g of 1,3-dimethyl-6-aminouracil (**1**) and 10.8 g of *p*-benzoquinone in acetic acid (route A) or in nitromethane (route B) for 12 h yielded **2** (A, 25%; B, traces), **4** (A, 15%; B, 17%), and **3** (A, 8%; B, 41%).

The compounds were separated through fractional crystallizations or better by preparative HPLC, with methanol as a solvent in both cases.

1,3-Dimethyl-5-(2,5-dihydroxyphenyl)-6-aminouracil (2): mp 270 °C; CI mass spectrum (CH_4), *m/e* (relative intensity); 292 (M^+ + 29, 11.9), 264 (M^+ + 1, 100), 263 (M^+, 59), 245 (6.9); EI mass spectrum, *m/e* (relative intensity): 263 (52.1), 246 (55.5), 245 (18.8), 189 (47.8), 57 (100); 100-MHz ^1H NMR (Me_2SO-d_6) δ 3.20 (s, 3 H, NCH_3), 3.35 (s, 3 H, NCH_3), 5.90 (s, 2 H, NH_2), 8.00 and 8.55 (s, 1 H, OH), 6.45 (d, 1 H, H-1, $J_{H_1-H_2}$ = 1 Hz), 6.55 (dd, 1 H, H-2, $J_{H_1-H_2}$ = 1 Hz, $J_{H_2-H_3}$ = 8 Hz), 6.65 (d, 1 H, H-3, $J_{H_2-H_3}$ = 8 Hz); IR (KBr) 3440, 3350, 3250, 1700 cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.97; N, 15.96. Found: C, 54.81; H, 5.04; N, 15.76.

1,3-Dimethyl-6-hydroxy-9*H*-pyrimido[4,5-*b*]indole-2,4-dione (3): mp >300 °C; EI mass spectrum, *m/e* (relative intensity) 245 (M^+, 100), 188 (60), 173 (21.8), 160 (51.2); 100-MHz ^1H NMR (Me_2SO-d_6) δ 3.30 (s, 3 H, NCH_3), 3.50 (s, 3 H, NCH_3), 12.10 (s, 1 H, OH), 7.35 (d, 1 H, H-1, $J_{H_1-H_2}$ = 1 Hz), 6.75 (dd, 1 H, H_2, $J_{H_1-H_2}$ = 1 Hz, $J_{H_2-H_3}$ = 8 Hz), 7.30 (d, 1 H, H-3, $J_{H_2-H_3}$ = 8 Hz); IR (KBr) 3270, 1680 cm^{-1}. Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.65; H, 4.47; N, 17.20.

1,4-Dihydroxy-2,5-bis(1,3-dimethyl-6-aminouracil-5-yl)-benzene (4): mp >300 °C; EI mass spectrum, *m/e* (relative intensity) 416 (M^+, 19.1), 399 (39.9), 382 (9.1), 325 (9.6), 286 (9.0), 263 (2.0), 246 (3.9), 57 (100); 100-MHz ^1H NMR (Me_2SO-d_6) δ 3.20 (s, 6 H, NCH_3), 3.30 (s, 6 H, NCH_3), 5.80 (s, 4 H, NH_2), 7.90 (s, 2 H, OH), 6.75 (s, 2 H, CH). Anal. Calcd for $C_{18}H_{20}N_6O_6$: C, 51.92; H, 4.84; N, 20.18. Found: C, 52.05; H, 4.89; N, 20.11.

Fischer-Type Cyclization. 1,3-Dimethyl-5-(2-amino-5-methoxyphenyl)-6-aminouracil (6). A solution of (*p*-methoxyphenyl)hydrazine hydrochloride (1.75 g, 0.01 mol) and of 1,3-dimethyl-6-chlorouracil (1.74 g, 0.01 mol) in absolute ethanol (50 cm^3) was refluxed in the presence of 5.8 g of sodium carbonate for 12 h. The hot solution was filtered. The filtrate was collected and the solvent removed under reduced pressure. The obtained residue was taken up with ether, giving a white precipitate of **6**; 63%; mp 242 °C; EI mass spectrum, *m/e* (relative intensity) 277 (M^+, 21.1), 276 (97.0), 260 (30.0), 259 (100), 244 (16.9), 202 (18.1); 100-MHz ^1H NMR (Me_2SO-d_6) δ 3.10 (s, 3 H, NCH_3), 3.30 (s, 3 H, NCH_3), 3.60 (s, 3 H, OCH_3), 4.20 (s, 2 H, NH_2 phenyl), 5.75 (s, 2 H, NH_2 uracil), 6.70 (d, 1 H, H-1, $J_{H_1-H_2}$ = 1 Hz), 6.60 (dd, 1 H, H-2, $J_{H_1-H_2}$ = 1 Hz, $J_{H_2-H_3}$ = 8 Hz), 6.65 (d, 1 H, H-3, $J_{H_2-H_3}$ = 8 Hz); IR (KBr) 3350, 3220, 1685 cm^{-1}. Anal. Calcd for $C_{13}H_{16}H_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.62; H, 5.76; N, 20.26.

1,3-Dimethyl-6-methoxy-9*H*-pyrimido[4,5-*b*]indole-2,4-dione (7). A solution of **6** (2.8 g) in formic acid (50 cm^3) was heated at reflux for 1 h, yielding after cooling the pyrimido[4,5-*b*]indole **7** as a white precipitate; 71%; mp 300 °C; EI mass spectrum, *m/e* (relative intensity) 260 (M^+ + 1, 13.1), 259 (M^+, 72), 202 (100), 187 (69.9); 100-MHz ^1H NMR (Me_2SO-d_6) δ 3.25 (s, 3 H, NCH_3), 3.45 (s, 3 H, NCH_3), 3.75 (s, 3 H, OCH_3), 7.35 (d, 1 H, H-1, $J_{H_1-H_2}$ = 1 Hz), 6.75 (dd, 1 H, H-2, $J_{H_1-H_2}$ = 1 Hz, $J_{H_2-H_3}$ = 8 Hz), 7.30 (d, 1 H, H-3, $J_{H_2-H_3}$ = 8 Hz); IR (KBr) 3420, 1690 cm^{-1}. Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 59.98; H, 5.01; N, 16.27.

1,3-Dimethyl-6-hydroxy-9*H*-pyrimido[4,5-*b*]indole-2,4-dione (3). A mixture of **7** (1 g) and pyridinium chloride (4 g) was heated at 210 °C for 20 min. The residue was taken up with 50 cm^3 of 1 N HCl to give a precipitate of **3** (65%). The analytical data of compounds **3** obtained in this way were identical with those of the sample prepared by the above-described procedure.

Acknowledgment. We gratefully acknowledge the "Institut de la Santé et de la Recherche Médicale" for financial support (Grant No. CRL 79.5.163.3).

Registry No. **1**, 6642-31-5; **2**, 78790-67-7; **3**, 78790-68-8; **4**, 78790-69-9; **5**, 6972-27-6; **6**, 78790-70-2; **7**, 78790-71-3; *p*-benzoquinone, 106-51-4; (*p*-methoxyphenyl)hydrazine hydrochloride, 19501-58-7.

(6) Allen, G. R., Jr. *Org. React.* **1973**, *20*, 337 and references cited therein.
(7) Sakuma, Y.; Yoneda, F. *Heterocycles* **1977**, *6*, 1911.
(8) (a) Duffy, T. D.; Wibberley, D. G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1921. (b) Senda, S.; Hirota, K.; Takahashi, M. *Ibid.* **1975**, 503. (c) Wright, G. E. *J. Heterocycl. Chem.* **1976**, *13*, 539. (d) Wright, G. E.; Gambino, J. *Ibid.* **1979**, *16*, 401.
(9) Robinson, B. *Chem. Rev.* **1963**, *63*, 373.