Notes

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Synthesis of 3-Amino-2-cyanocarbazole and 3,4-Dihydro-4-oxo-6*H*-pyrimidino[5,4-*b*]carbazoles

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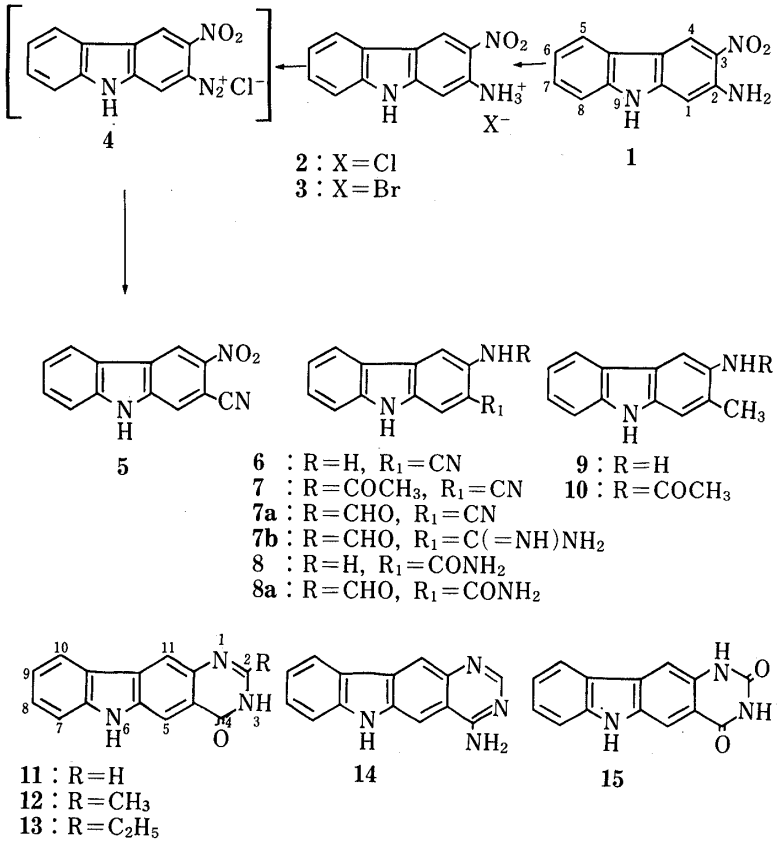
The application of the Sandmeyer reaction to 2-amino-3-nitrocarbazole (**1**) gave 2-cyano-3-nitrocarbazole (**5**), which could be reduced to 3-amino-2 cyanocarbazole (**6**), 3-amino-2-carbamoylcarbazole (**8**) or 3-amino-2-methylcarbazole (**9**) according to the reaction conditions used. Intramolecular cyclization of the carbazoles (**6**), (**7**) and (**8**) afforded 3,4-dihydro-4-oxo-6*H*-pyrimidino[5,4-*b*]carbazoles (**11**), (**12**) and (**13**). 4-Amino-6*H*-pyrimidino[5,4-*b*]carbazole (**14**) was obtained by cyclization of 3-amino-2-cyano-carbazole (**6**) with formamide. Treatment of 3-amino-2-carbamoylcarbazole (**8**) with carbonyl chloride gave 1,2,3,4-tetrahydro-2,4-dioxo-6*H*-pyrimidino-[5,4-*b*]carbazole (**15**). The proton nuclear magnetic resonance spectra of the products were studied.

Keywords——2-cyano-3-nitrocarbazole; 3-amino-2-cyanocarbazole; 3,4-dihydro-4-oxo-6*H*-pyrimidino[5,4-*b*]carbazole; Sandmeyer reaction; ^{1}H-NMR spectra

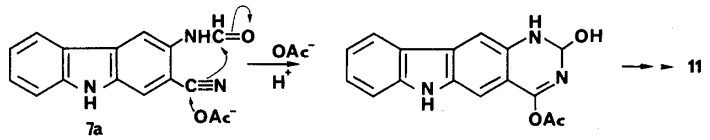
As a part of our program directed at the synthesis of new polyheterocyclic systems, including the evaluation of their antineoplastic activity, we have reported the synthesis of 7*H*-pyrimidino[5,4-*c*]carbazoles.[1-3] As a continuation of this work, we wish to report herein a synthetic study leading to new isomers, namely 6*H*-pyrimidino[5,4-*b*]carbazoles.

The title compounds could be synthesized from 2-amino-3-nitrocarbazole (**1**)[4,5] as a starting material. Thus, bubbling hydrogen chloride or hydrogen bromide gas through an ethanolic solution of **1** gave the corresponding salts **2** and **3**, respectively. The hydrochloride **2** was converted into its diazonium salt and then reacted with cuprous cyanide *via* the Sandmeyer reaction to give 2-cyano-3-nitrocarbazole (**5**). When the latter compound was reduced with stannous chloride, 3-amino-2-cyanocarbazole (**6**) was obtained; it was then treated with acetic anhydride to give the acetamido nitrile (**7**). On the other hand, the reduction of **5** using Raney nickel in the presence of hydrazine hydrate followed by hydrolysis gave 3-amino-2-carbamoylcarbazole (**8**). Alternatively, catalytic hydrogenation of **5** over Raney nickel under 100 kg pressure yielded the 3-amino-2-methylcarbazole (**9**), which in turn gave the acetamido derivative **10**.

Following a procedure similar to that of Bogert and Hand,[7,8] the aminocyanocarbazole (**6**) was treated with formic acid and fused sodium acetate at 100 °C to cyclize it directly into 3,4-dihydro-4-oxo-6*H*-pyrimidino[5,4-*b*]carbazole (**11**). It is probable that 3-formamido-2-carbamoylcarbazole (**8a**) was formed as an intermediate product in this reaction, since the 3-amino-2-carbamoylcarbazole (**8**) was cyclized to **11** under similar reaction conditions. Nevertheless, 2-cyano-3-formamidocarbazole (**7a**) seems to be another possible intermediate giving **11** after attack on the cyano group by acetate ion. Furthermore, when **8** was treated with propionic anhydride at 70 °C followed by treatment of the product with aqueous sodium



hydroxide at 100 °C, the homologous 2-ethylpyrimidinocarbazolone (**13**) was obtained.



Similarly, treatment of 3-acetamido-2-cyanocarbazole (**7**) with aqueous sodium hydroxide at 100 °C for 2 h yielded 2-methyl pyrimidinocarbazolone (**12**).

The infrared (IR) spectra (in KBr) of the pyrimidino[5,4-*b*]carbazol-4-ones **11**, **12** and **13** showed a carbonyl absorption at 1630—1660 cm^{-1} with an NH absorption at 3160—3400 cm^{-1}, indicating the preponderance of lactam tautomers in the solid state.

The Niementowski cyclization reaction[9] was found to be easily carried out with 3-amino-2-cyanocarbazole (**6**) (**6** was refluxed for 4 h with formamide), giving 4-amino-6*H*-pyrimidino[5,4-*b*]carbazole (**14**) possibly *via* the formamidonitrile (**7a**) and the formamidoamidine (**7b**) as intermediates.

Treatment of 3-amino-2-carbamoylcarbazole (**8**) with carbonyl chloride in refluxing toluene resulted in the formation of 2,4-dioxo-1,2,3,4-tetrahydro-6*H*-pyrimidino[5,4-*b*]-carbazole (**15**). In the IR spectrum (KBr tablet), two strong absorption bands appear at 1685—1625 cm^{-1}, corresponding to the CO stretching vibration, and strong NH bands appear at 3180 cm^{-1}. This can be well interpreted in terms of the bislactam structure **15**.

The proton nuclear magnetic resonance (^{1}H-NMR) were recorded in DMSO-d_6 (Tables I and II) and were consistent with the proposed structures. The assignment of all signals was based on the chemical shifts using previously calculated increments.[5,10]

The distinction between the H5 and H11 protons of pyrimidinocarbazoles (**11**), (**12**), (**13**) and (**14**) could be achieved by consideration of the known substituent effects in the aromatic

Table I. ^{1}H-NMR Chemical Shifts of Carbazoles

No.	δ H of carbazolic protons						δ of other protons
	H-1	H-4	H-5	H-6	H-7	H-8	
2	6.90	8.76	8.03	7.16	7.16	7.16	NH=11.49; NH_3^+=6.48
3	7.00	8.83	8.05	7.21	7.21	7.21	NH=11.61; NH_3^+=6.30
5	8.13	9.26	8.40	7.43	7.43	7.43	NH=12.34
6	7.48	7.40	7.91	7.16	7.16	7.16	NH_2=5.30; NH=11.40
7	8.16	7.88	8.16	7.28	7.28	7.28	NH=11.76, 9.96; CH_3=2.10
8	7.58	7.26	7.83	7.15	7.15	7.15	NH=10.68; NH_2=5.81
9	7.25	7.25	7.76	7.06	7.06	7.06	NH=10.47; CH_3=2.21; NH_2=4.36
10	7.91	7.33	7.91	7.19	7.10	7.10	NH=9.25, 11.00; CH_3=2.26, 2.03

Table II. ^{1}H-NMR Chemical Shifts of Pyrimidinocarbazoles

No.	δ H of CH protons							δ of other protons
	H-2	H-5	H-7	H-8	H-9	H-10	H-11	
11	8.45	8.13	7.35	7.35	7.35	8.26	7.93	NH=7.35, 11.57
12	—	8.33	7.31	7.31	7.31	8.25	8.13	NH=7.31, 11.43; CH_3=2.38
13	—	7.95	6.76	6.76	6.76	7.90	7.78	NH=9.91, 9.78 CH_2=2.33; CH_3=1.11
14	8.41	7.33	7.33	7.33	7.33	8.18	8.30	NH=11.34; NH_2=5.08
15	—	7.96	7.30	7.30	7.30	8.06	7.75	NH=11.04, 11.27

ring. In the case of pyrimidinocarbazol-4-ones (**11**), (**12**) and (**13**), the proximity of the lactam group at the 4 position causes deshielding of the H5 proton due to carbonyl anisotropy. In contrast, in the case of the 4-aminopyrimidinocarbazole (**14**), the presence of an amino group at the 4 position causes an upfield shift of the H5 proton resonance. Such an effect due to an amino group has already been observed in the case of 4-amino-[1]benzofuro[3,2-*g*]-cinnolines.[11]

Experimental

All melting points were measured on a Maquenne or Kofler apparatus. IR spectra were recorded on a Perkin–Elmer 257 spectrometer (in KBr), and ^{1}H-NMR spectra were recorded on a Varian EM 390 spectrometer at 90 MHz in hexadeuteriodimethylsulfoxide with tetramethylsilane as an internal reference. Chemical shifts are expressed as δ (ppm) downfield from tetramethylsilane (TMS).

2-Amino-3-nitrocarbazole Hydrochloride (2)——A solution of the 2-amino-3-nitrocarbazole (**1**) (21 g) in abs. EtOH (180 ml) was bubbled through for 15 min at 50 °C with gaseous hydrochloric acid, then concentrated. The precipitate was collected by filtration, washed with Et_2O and recrystallized from acetonitrile (17 g), mp 267 °C. *Anal.* Calcd for $C_{12}H_{10}ClN_3O_2$: C, 54.64; H, 3.79; Cl, 13.47. Found: C, 54.72; H, 3.82; Cl, 13.42. IR ν_{max}^{KBr} cm^{-1}: 3420 and 1620 (NH), 2800 and 2680 ($-NH_3^+$), 1300 (NO_2).

2-Amino-3-nitrocarbazole Hydrobromide (3)——The same method was applied to 2-amino-3-nitrocarbazole (**1**) (12 g) in abs. EtOH (150 ml) with gaseous hydrobromic acid to give red needles (8 g), mp 220 °C (EtOH). *Anal.* Calcd for $C_{12}H_{10}BrN_3O_2$: C, 52.21; H, 3.65; Br, 28.93. Found: C, 52.36; H, 3.57; Br, 28.84. IR ν_{max}^{KBr} cm^{-1}: 3340 and 1625 (NH), 2840 and 2600 (NH_3^+), 1320 (NO_2).

2-Cyano-3-nitrocarbazole (5)——A solution of $NaNO_2$ (6.06 g) in water (30 ml) was added to a suspension of 2-amino-3-nitrocarbazole hydrochloride (**2**) (16 g) in 10% HCl aq. (80 ml) at 5 °C with stirring, and the mixture was stirred at the same temperature for 1 h. The orange precipitate of the diazonium salt **4** was collected by filtration,

washed with ice-cold water (30 ml), then added to a suspension of cuprous cyanide (40 g) in water (250 ml). The mixture was heated with stirring at 70 °C for 2 h. The grey precipitate was collected by filtration, washed with cold water (1 l) and dried. Recrystallization from EtOH gave white crystals (10 g), mp 276 °C, sublimable at 280 °C under 0.05 mmHg. *Anal.* Calcd for $C_{13}H_7N_3O_2$: C, 65.82; H, 2.97; N, 17.11. Found: C, 65.52; H, 2.85; N, 17.31. IR ν_{max}^{KBr} cm^{-1}: 3360 (NH), 2200 (CN), 1320 (NO_2).

3-Amino-2-cyanocarbazole (6)——A mixture of conc. HCl aq. (90 ml) and a solution of stannous chloride dihydrate (37.8 g) in AcOH (60 ml) was stirred at 10 °C for 20 min, then a warm solution of 2-cyano-3-nitro-carbazole (**5**) (17 g) in *N*, *N*-dimethylformamide (DMF) (60 ml) was added in one portion. The reaction mixture was cooled at 0 °C and stirred for 5 min, then poured with stirring into 40% NaOH aq. (1 l). The white precipitate was collected by filtration, washed twice with water (500 ml), dried and recrystallized from EtOH to give white crystals (8.5 g), mp 272 °C, sublimable at 280 °C under 0.05 mmHg. *Anal.* Calcd for $C_{13}H_9N_3$: C, 75.34; H, 4.38; N, 20.28. Found: C, 75.55; H, 4.29; N, 19.99. IR ν_{max}^{KBr} cm^{-1}: 3420, 3340, 3240 and 1620 (NH), 2230 (CN).

3-Acetamido-2-cyanocarbazole (7)——A solution of 3-amino-2-cyanocarbazole (**6**) (5 g) in Ac_2O (20 ml) was stirred at 20 °C for 10 min. The precipitate was collected by filtration, washed with Et_2O and recrystallized from acetonitrile to give white crystals (4.2 g), mp 278 °C. *Anal.* Calcd for $C_{15}H_{11}N_3O$: C, 72.27; H, 4.45; N, 16.96. Found: C, 72.17; H, 4.31; N, 16.83. IR ν_{max}^{KBr} cm^{-1}: 3330 and 3260 (NH), 2240 (CN), 1660 (CO).

3-Amino-2-carbamoylcarbazole (8)——Hydrazine hydrate (40 ml) was added portionwise to a stirred and refluxed mixture of 2-cyano-3-nitrocarbazole (**5**) (7 g) and Raney Ni (*ca.* 5 g) in EtOH (1 l). The mixture was refluxed for 5 h, cooled and filtered to remove the catalyst. The filtrate was concentrated *in vacuo* and after addition of Et_2O, the precipitate was collected by filtration, dried and recrystallized from EtOH to give green needles (5 g), mp 302 °C. *Anal.* Calcd for $C_{13}H_{11}N_3O$: C, 69.34; H, 4.92; N, 18.66. Found: C, 69.65; H, 4.84; N, 18.63. IR ν_{max}^{KBr} cm^{-1}: 3410, 3300, 3160, 1595 (NH), 1675 (CO).

3-Amino-2-methylcarbazole (9)——A suspension of 2-cyano-3-nitrocarbazole (**5**) (4 g) and Raney Ni (*ca.* 3 g) in abs. EtOH (700 ml) was hydrogenated at 100 °C under 100 kg pressure for 1 h. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure. Purification of the residue by recrystallization from EtOH gave green needles (2.1 g), mp 236 °C. *Anal.* Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.28. Found: C, 79.57; H, 6.10; N, 14.24. IR ν_{max}^{KBr} cm^{-1}: 3380, 3340, 3200 and 1605 (NH). Compound **9** (1 g), was acetylated with Ac_2O in the same way as **6** to give 3-acetamido-2-methylcarbazole (**10**), yellow crystals (1 g), mp 240 °C (acetonitrile). *Anal.* Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.70; H, 5.96; N, 11.81. IR ν_{max}^{KBr} cm^{-1}: 3400, 3260 (NH), 1665 (CO).

3,4-Dihydro-4-oxo-6*H*-pyrimidino[5,4-*b*]carbazole (11)——Method A: A solution of 3-amino-2-cyanocarbazole (**6**) (2 g) and NaOAc (1.5 g) in HCOOH (30 ml) was refluxed for 6 h. After cooling, the mixture was evaporated under reduced pressure and the residue was dissolved in 20% NaOH aq. (50 ml). The solution was decolorized with charcoal, filtered and made acidic by adding 10% HCl aq. The precipitate was collected by filtration, washed with water, dried and sublimed at 320 °C under 0.05 mmHg to give white crystals (1.2 g), mp 292 °C (DMSO). *Anal.* Calcd for $C_{14}H_9N_3O$: C, 71.48; H, 3.86; N, 17.86. Found: C, 71.52; H, 3.89; N, 17.72. IR ν_{max}^{KBr} cm^{-1}: 3380, 3240 (NH), 1630 (CO), 1585, 1500, 1415, 1335, 1240, 1125, 1050, 935, 810 and 760 (main bands).

Method B: A solution of 3-amino-2-carbamoylcarbazole (**8**) (1.7 g) in HCOOH (35 ml) was refluxed for 8 h. The mixture was evaporated under reduced pressure and the residue was dissolved in 20% NaOH aq. (40 ml). The solution was treated with charcoal, filtered and made acidic with 10% HCl aq. The precipitate was collected, washed with water, dried and recrystallized from DMSO to give **11** (1.3 g). This material was identical (mp, IR spectrum) with a sample obtained by method A.

3,4-Dihydro-2-methyl-4-oxo-6*H*-pyrimidino[5,4-*b*]carbazole (12)——A solution of 3-acetamido-2-cyano-carbazole (**7**) (1.4 g) in 40% NaOH aq. (30 ml) was heated at 100 °C for 2 h. After cooling, the mixture was made acidic with 20% HCl aq. The precipitate was collected by filtration, washed with water, dried and recrystallized from DMSO to give yellow crystals (0.7 g), mp 350 °C. *Anal.* Calcd for $C_{15}H_{11}N_3O$: C, 72.27; H, 4.45; N, 16.86. Found: C, 72.09; H, 4.27; N, 16.79. IR ν_{max}^{KBr} cm^{-1}: 3160 (NH), 1660 (CO), 1520, 1450, 1330, 1300, 1250, 1155, 1025, 875, 745 and 730 (main bands).

3,4-Dihydro-2-ethyl-4-oxo-6*H*-pyrimidino[5,4-*b*]carbazole (13)——A solution of 3-amino-2-carbamoylcarbazole (**8**) (1 g) in propionic anhydride (15 ml) was heated at 70 °C for 15 min, then cooled. The precipitate was collected by filtration, and dissolved in 20% NaOH aq. (20 ml), and the solution was heated at 100 °C for 20 min. After cooling, the solution was made acidic with 20% HCl aq. The precipitate was collected by filtration, dried and sublimed at 320 °C under 0.05 mmHg to give white crystals (0.3 g), mp 350 °C. *Anal.* Calcd for $C_{16}H_{13}N_3O$: C, 72.98; H, 4.98; N, 15.96. Found: C, 72.84; H, 4.67; N, 15.82. IR ν_{max}^{KBr} cm^{-1}: 3400, 3370 (NH), 1645 (CO), 1585, 1520, 1425, 1320, 1230, 1075, 1000, 920, 825, 785 and 735 (main bands).

4-Amino-6*H*-pyrimidino[5,4-*b*]carbazole (14)——A solution of 3-amino-cyanocarbazole (**6**) (2 g) in $HCONH_2$ (5 ml) was refluxed for 4 h. The mixture was evaporated and the residue was dissolved in cold water (5 ml). The solution was kept for 12 h at 5 °C, and the precipitate was collected by filtration, dried and recrystallized from acetonitrile to give yellow crystals (0.7 g), mp 302 °C, sublimable at 300 °C under 0.05 mmHg. *Anal.* Calcd for $C_{14}H_{10}N_4$: C, 71.78; H, 4.30; N, 23.92. Found: C, 71.62; H, 4.40; N, 23.87. IR ν_{max}^{KBr} cm^{-1}: 3400, 3190, 1655 (NH),

1570, 1495, 1445, 1305, 1040, 920, 875, 790 and 745 (main bands).

2,4-Dioxo-1,2,3,4-tetrahydro-6*H*-pyrimidino[5,4-*b*]carbazole (15)——A mixture of 3-amino-2-carbamoylcarbazole (**8**) (2.6 g) in toluene (200 ml) and 20% $COCl_2$ in toluene (15 ml) was refluxed for 2 h. After bubbling a stream of nitrogen through the mixture to eliminate the excess $COCl_2$, the precipitate was collected by filtration, washed with Et_2O, dried and recrystallized from DMSO to give orange crystals (1.3 g), mp 300 °C. *Anal.* Calcd for $C_{14}H_9N_3O_2$: C, 66.92; H, 3.61; N, 16.73. Found: C, 66.74; H, 3.66; N, 16.68. IR ν_{max}^{KBr} cm^{-1}: 3310, 3180 (NH), 1685, 1625 (CO), 1525, 1435, 1325, 1245, 1035, 865 and 750 (main bands).

References

1) M. Robba and N. Boutamine, *C. R. Acad. Sci. Ser. C*, **282**, 671 (1976).
2) M. Robba, J. M. Lecomte and M. Cugnon de Sévricourt, *Tetrahedron*, **27**, 487 (1971).
3) J. C. Lancelot, J. M. Gazengel and M. Robba, *Chem. Pharm. Bull.*, **31**, 2652 (1983).
4) J. C. Lancelot, J. M. Gazengel, S. Rault and M. Robba, *Chem. Pharm. Bull.*, **31**, 45 (1983).
5) J. C. Lancelot, J. M. Gazengel and M. Robba, *J. Heterocycl. Chem.*, **18**, 1281 (1981).
6) E. Sawicki, *J. Am. Chem. Soc.*, **76**, 664 (1954).
7) M. T. Bogert and W. F. Hand, *J. Am. Chem. Soc.*, **24**, 1031 (1902).
8) M. T. Bogert and W. F. Hand, *J. Am. Chem. Soc.*, **25**, 935 (1903).
9) V. Niementowski, *J. Prakt. Chem.*, **51**, 564 (1895).
10) J. C. Lancelot, J. M. Gazengel, S. Rault and M. Robba, *Chem. Pharm. Bull.*, **30**, 1674 (1982).
11) D. Ladurée, D. Florentin and M. Robba, *J. Heterocycl. Chem.*, **17**, 1189 (1980).