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SYNTHESIS OF NOVEL BENZOCARBOCYCLIC-PYRAZOLO [1,5-A]PYRIMIDINES

N. M. Fathy

Photochemistry Department. National Research Centre, Dokki, Cairo, Egypt

ABSTRACT

A novel synthesis of condensed benzocarbocyclic purine analogues via reaction of amino-diazoles with sodium salt of 2-(hydroxymethylene)-1-tetralone is reported and the synthetic potential of the method is demonstrated.

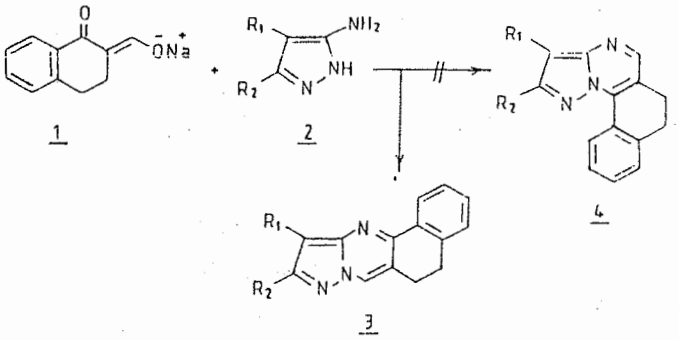
INTRODUCTION

Synthetic analogues of purines are widely used in the medical sciences and clinical medicine. Their effects include one of two processes, the first includes inhibition by the drug of specific enzymes essential for nucleic acid synthesis and the second includes incorporation of metabolites of the drug into nucleic acids, where they affect the base pairing essential to accurate transfer of information.

This investigation is a part of our program directed for development of new,simple and efficient procedures for the synthesis of antimetabolites.[1-4]

The present paper deals with a novel synthesis of condensed benzocarbocyclic-pyrazolo [1,5a] pyrimidines, benzimidazo [1,2-c] pyrimidines, and benzimidazo-[1,2-a]pyridines. Moreover, the results of our work aim to define the scope and limitation of our procedures for the synthesis of purine analogues and antimetabolites are also reported.

Thus, it has been found that sodium salts of 2-(hydroxymethylene)-1- tetralone **1** reacted with 5-aminopyrazoles **2** to give the linear condensed benzocarbocyclicpyrazolo[1,5-a]pyrimidine derivatives **3**. The structures of compounds **3** were established on the basis of their elemental analysis and spectral data .Thus, structure **3a** is supported by its mass spectrum which showed a molecular formula $C_{20}H_{16}N_6$ (M^+ 340). The ^1H NMR revealed a singlet at δ 8.55 ppm assigned for pyrimidine-proton and a broad band at δ 7.36 ppm assigned to the NH_2 group. Although one may argue that the reaction of **1** with **2** may lead to the isomeric angular benzocycloalkane condensed pyrazolo[1,5-a]pyrimidines **4**. Assignment of linear structures to these compounds was assumed based on analogy to previous literature. It has been established that ketoaldehydes when condensed with substituted 6-aminopyrimidines regiospecifically afforded linear isomers,[5] this regiospecificity was confirmed with ^1H NMR, ^{13}C NMR and X-ray crystal studies of the products.[6,7]The behavior of 2-aminobenzimidazole **5** towards salt 1 was investigated, the condensed benzo[g]imidazo[1,2-c]pyrimidine ring system **8** was anticipated via the cyclocondensation of sodium salt of 2-(hydroxymethylene)-1-tetralone **1** with **5**. The structure of the reaction product **8** was established and confirmed by the elemental analysis and spectral data (MS, IR and ^1H NMR) . Thus , the MS spectrum of **8a**



3	R_1	R_2
a,	$N=N-C_6H_5$	NH_2
b,	$N=N-C_6H_4-4-Br$	NH_2
c,	$N=N-C_6H_4-4-Cl$	NH_2
d,	$N=N-C_6H_4-4-CH_3$	NH_2
e,	$N=N-C_6H_4-4-OCH_3$	NH_2
f,	$N=N-C_6H_4-4-NO_2$	NH_2

Chart (1)

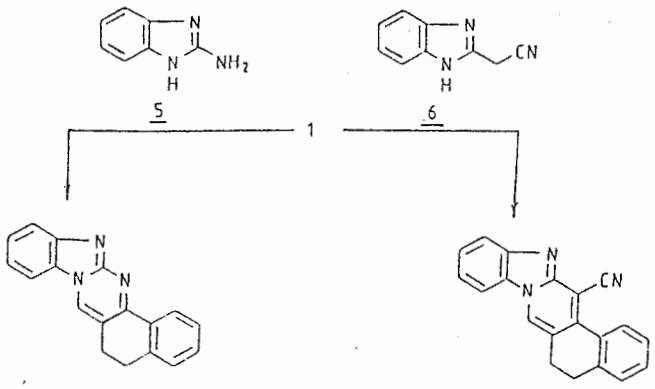


Chart (2)

revealed a molecular formula $C_{18}H_{13}N_3$ (M^+ 271) .The ^1H NMR spectrum showed a signal for a pyrimidine CH proton at δ 8.58 ppm. Similar to the behavior of 2-aminobenzimidazole **5**, 2-cyanomethylbenzimidazole **6** reacted with salt **1** under the same experimental conditions to yield the benzo[g]imidazo[1,2-a]- pyridine derivalive **9** . The structure of **9** was established and confirmed on the basis of its elemental analysis and spectral data (MS, IR, and ^1H NMR) . The MS spectrum of **9** revealed the molecular formula $C_{20}H_{13}N_3$ (M^+ 295). ^1H NMR revealed a multiplet at δ 7.21-7.77 assignable to the aromatic protons and the pyridine CH proton.

EXPERIMENTAL

All melting points are uncorrected. IR were obtained (KBr disc) on a Pye Unicom spectra-1000 or on a Shimadzu IR 200 instrument. ^1H NMR spectra were measured on a Wilmad 270 MHz Spectrometer for solutions in $(CD_3)_2SO$ using $SiMe_4$ as internal standard. Mass spectra were recorded on a Varian MAT 112 Spectrometer. Analytical data were obtained from the Microanalytical Centre at Cairo University.

Benzocycloalkane ring-fused pyrazolo[1,5-a] pyrimidines 3a-f :

General method: A solution of 2-(hydroxymethylene)-1-tetralone sodium salt **1** (0.01 mol),5-aminopyrazole **2** (0.01 mol), and piperidine acetate (9.5 ml) in water (50 ml) and ethanol (30 ml) was refluxed for 10 minutes. Acetic acid (15ml) was added to the hot solution. The precipitated solid was collected by filtration and crystallized from the appropriate solvent.

3a: Yield (25%); m.p. 272 °C (Benzene); IR (KBr) 3500,3520 cm^{-1} (ν NH_2); ^1H NMR (DMSO) δ 2.96 (m, 4H, $2CH_2$), 7.36 (s, br, 2H,

NH_2), 7.51-7.65 (m, 8H, aromatic), 8.55 (s, 1H, pyrimidine), 9.36 (m, 1H, aromatic CH); MS, m/e 340(M^+); (Calcd for $C_{20}H_{16}N_6$: C, 70.6; H, 4.7; N, 24.7. Found: C, 70.7; H, 4.7; N, 24.5 %).

3b: Yield (43%); m.p. 308 °C (Dioxane); IR (KBr) 3560, 3500, 3450-3000 cm^{-1} (νNH_2); ^1H NMR (DMSO) δ 2.98 (m, 4H, $2CH_2$), 7.37 (s, br, 2H, NH_2), 7.45-7.81 (m, 7H, aromatic), 8.57 (s, 1H, pyrimidine), 9.34 (m, 1H, aromatic); MS, m/e 419(M^+); (Calcd for $C_{20}H_{15}BrN_6$: C, 57.3; H, 3.6; N, 20.0. Found: C, 57.1; H, 3.5; N, 20.2 %).

3c:Yield (30%); m.p. 312 °C (Benzene); IR (KBr) 3460-3380 cm^{-1} (ν NH_2); ^1H NMR (DMSO) δ 2.97 (m, 4H, $2CH_2$), 7.37 (s, br,2H, NH_2), 7.46-7.87 (m, 7H, aromatic), 8.56 (s, 1H, pyrimidine), 9.32 (m, 1H, aromatic); MS, m/e 374(M^+); (Calcd for $C_{20}H_{15}ClN_6$: C, 64.1; H, 4.0; N, 22.4. Found: C, 64.2; H, 4.2; N, 22.4 %)

3d: Yield (30%); m.p. 299 °C (Benzene); IR (KBr) 3580, 3490-3400 cm^{-1} (νNH_2); ^1H NMR (DMSO) δ 2.37 (s, 3H, CH_3), 2.96 (m, 4H, $2CH_2$), 7.29 (s, br, 2H, NH_2), 7.30-7.76 (m, 7H, aromatic), 8.55 (s, 1H, pyrimidine), 9.33 (m, 1H, aromatic); MS, m/e 354(M^+); (Calcd for $C_{21}H_{18}N_6$: C, 71.2; H, 5.1; N, 23.7. Found: C, 71.2; H, 5.2; N, 23.6 %).

3e:Yield (35%); m.p. 263 °C (Benzene); IR (KBr) 3380, 3350 cm^{-1} (ν NH_2); ^1H NMR (DMSO) δ 2.96 (m, 4H, $2CH_2$), 3.84 (s, 3H, OCH_3), 7.04-7.09 (m, 2H, aromatic), 7.24 (s, br, 2H, NH_2), 7.49-7.55 (m, 3H, aromatic), 7.79-7.84 (m, 2H, aromatic), 8.53 (s, 1H, pyrimidine), 9.34-9.38 (m, 1H, aromatic); MS, m/e 370(M^+); (Calcd for $C_{21}H_{18}N_6O$: C, 68.1; H, 4.9; N, 22.7 Found: C, 68.2; H, 5.0; N, 22.4 %).

3f:Yield (43%); m.p. 348 °C (DMF); MS, m/e 385(M^+); (Calcd for $C_{20}H_{15}N_7O_2$:C, 62.3; H, 3.9; N, 25.4. Found: C, 62.2; H, 3.8; N, 25.6 %).

Benzocycloalkane ring-fused benzo[g]imidazo[1,2-c]pyrimidines 8:

A mixture of 2-(hydroxymethylene)-1-tetralone sodium salt **1** (0.01 mol), 2-aminobenzimidazole **5** (0.01 mol), and piperidine acetate (9.5 ml) in water (50 ml) and ethanol (30 ml) was refluxed for 10 minutes. Acetic acid (15ml) was added to the hot solution. The precipitated solid was collected by filtration and crystallized from the appropriate solvent.

Yield (25%); m.p.174 °C (Benzene / pet. ether); ^{1}H NMR (DMSO) δ 2.91 (m, 4H, $2CH_2$), 7.08-7.92 (m, 8H, aromatic), 8.58 (s, 1H, pyrimidine); MS, m/e 271(M^+); (Calcd for $C_{18}H_{13}N_3$: C, 79.7; H, 4.8; N, 15.5. Found: C, 79.5; H, 4.7; N, 15.7 %).

Benzocycloalkane ring-fused benzo[g]imidazo[1,2-a]pyridines 9 :

The above procedure was followed using 2-benzimidazolylacetonitrile **6** instead of **5** .

Yield (60%); m.p. 328 °C (Dioxane); IR (KBr) 2218 cm^{-1} (νCN); ^{1}H NMR (DMSO) δ 3.91 (m, 2H, CH_2), 7.21-7.77 (m, 9H, aromatic and pyridine); MS, m/e 295(M^+); Calcd for $C_{20}H_{13}N_3$: C, 81.3; H, 4.4; N, 14.2. Found: C, 81.2; H, 4.3; N, 14.4 %).

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تخليق بنزوكربوسيكلك بيرازولو [٥,١ - أ] بيريميدينات جديدة

ناهد منصور فتحى

قسم الكيمياء الضوئية – المركز القومى للبحوث – الدقى – القاهرة

قد تم أثبات طريقة جديدة لتحضير أشباه البيورين عن طريق تفاعل أمينات ثنائى الأزول مع الملح الصوديومى لمشتق (٢- هيدروكسى ميثيلين) -١- نترالون .