Synthesis of Quinazolinophanes Containing Bridgehead Nitrogen Atoms from Quinazoline-2,4(1*H*, 3*H*)-dione

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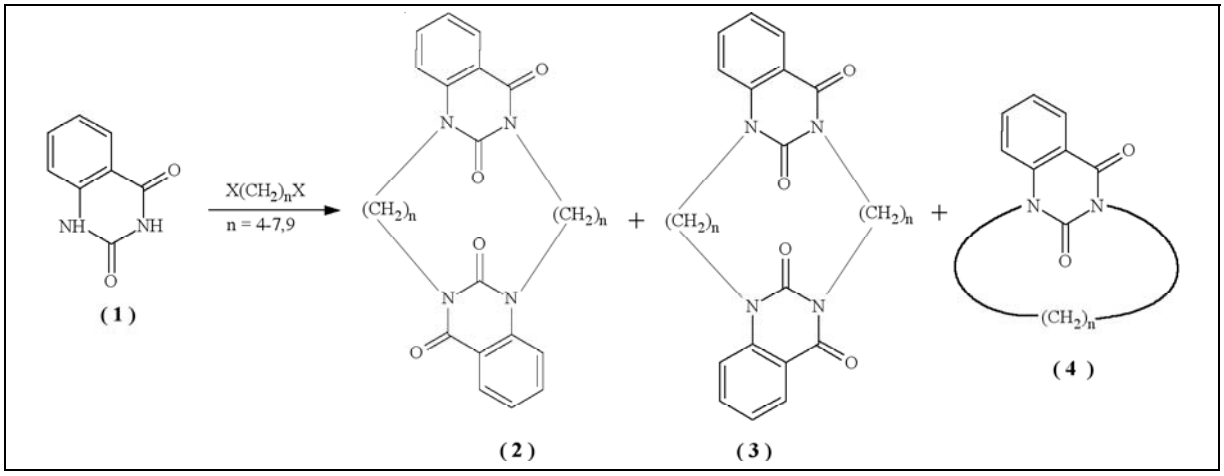

Quinazoline-2,4(1*H*,3*H*)-dione (1) reacts with α,ω-dihaloalkanes to generate three types of quinazolinophanes. When the number of carbon atoms in the dihaloalkanes is **9**, a mixture of all the three types of quinazolinophanes (**2**), (**3**) and (**4**) was produced; and when the number of carbon atoms in the dihaloalkane used is from **4** to **7**, a mixture of only two types of quinazolinophanes (**2**) and (**3**) were produced. When the number of carbon atoms of the dihaloalkane used is odd (**5, 7** and **9**), the different structural types of quinazolinophanes produced were easily identifiable and distinguishable on the basis of ^{13}C NMR and mass spectral data.

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INTRODUCTION

The term "Cyclophanes" applies to cyclic systems consisting of a ring(s) or ring system(s) having the maximum number of non-cummulative double bonds connected by saturated or unsaturated chains. These are of intrest in connection with supermolecular chemistry and in connection with synthetic receptors in molecular recognition [1]. Purinophanes and pyrimidinophanes are the cyclophanes containing nucleic acid bases, purinophanes have been extensively studied in connection with the stacking structures in DNA by Sakata and Misumi *et al* [2], pyrimidinophanes have not adequately been investigated except for a few compounds and are regarded as a sort of meta-cyclophanes containing pyrimidine bases. The pyrimidinophanes may also be of interest in connection with the formation of pyrimidine photodimers in DNA by ultraviolet light [3] and the mechanistic studies on DNA photolyse [4]. Htay and Meth-Cohn reported [5] the formation of pyrimidinophanes by the treatment of thymine with $Br(CH_2)_6Br$ but the structure was equivocal. Renizk *et al.* [6] prepared a pyrimidinophane whose structure was not confused with that of the isomer by the treatment of 1-(4-bromobutyl) uracil with *p*-toluenesulphonamide. They also studied the reaction of uracil and 6-methyluracil sodium salts with $Br(CH_2)_nBr$, but the isolation of pyrimidinophanes was not reported [7]. Golankiewicz *et al* reported [8] that the treatment of 1,1-trimethylene bis[thymine] with $Br(CH_2)_3Br$ gave pyrimidinophane and cyclic tetramer of thymine. Toshio Itahara described [9] the direct preparation of three types of pyrimidinophanes from uracil, thymine and 5-fluorouracil which are of importance as anticancer agents [10].

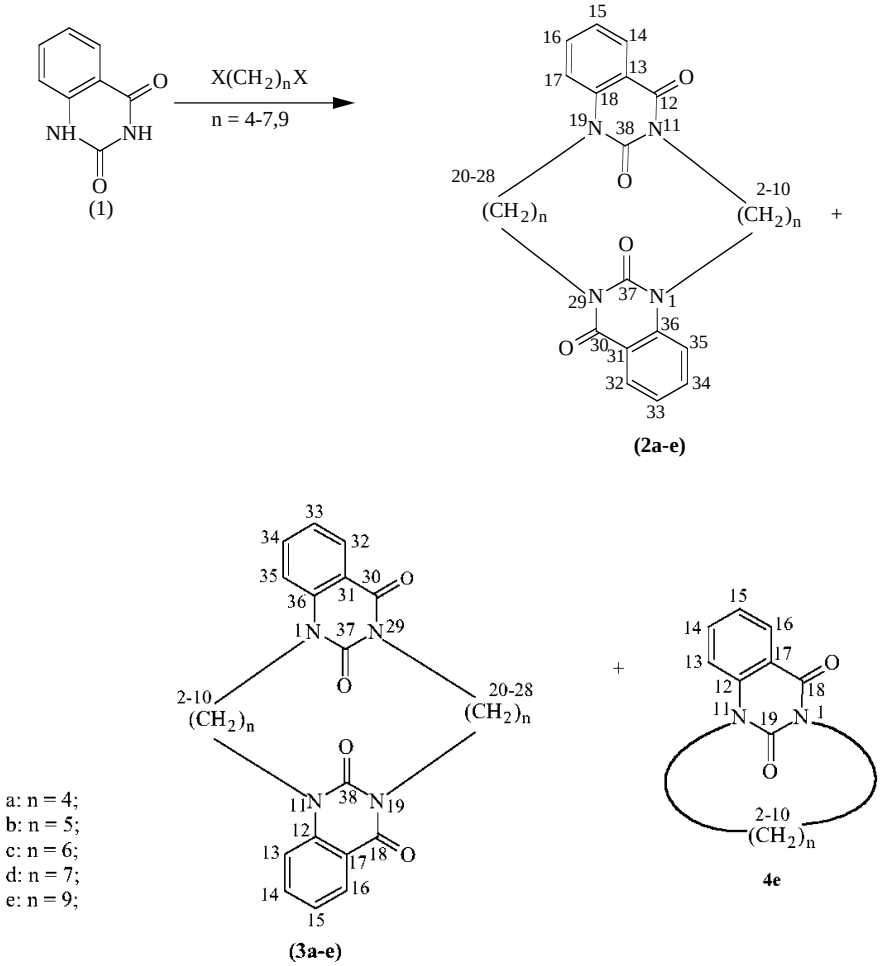
Thorough studies of literature revealed that quinazolinophanes are either not available or invisible in literature as regard their synthesis, application in general, spectral studies and pharmacological utility. It was worthwhile and logically appropriate to design the synthesis of possibly expected quinazolinophanes on somewhat similar grounds to those of pyrimidinophanes. Hence we report herein the generation of three types of quinazolinophanes (2), (3) and (4) which have been investigated as a sort of metacyclophanes. 1,2,3,4-Tetrahydro-2,4-quinazolinedione (1) commonly called as benzoylene urea was

taken as the basic quinazoline based synthon which was reacted at the outset with α,ω–dihaloalkanes. The structures of three kinds of quinazolinophanes were identifiable and distinguishable by means of ^{13}C NMR and mass spectral data. These quinazolinophanes are important and interesting compounds with novel heterocyclic bridged systems whose applications in general and particular are under active study. The preliminary investigation, regarding pharmacology is highly promising. The α,ω-dihaloalkanes used in the present study have X=Br and I and n = 4-7, 9.

RESULTS AND DISCUSSION

Treatment of 1,2,3,4-tetrahydro-2,4-quinazolinedione (**1**) with X-$(CH_2)_n$-X(X = Br or I, n = 4-7) in *N,N*-dimethylformamide containing sodium hydride gave a mixture of (**2**) and (**3**) (in 1:1 ratio) as main products. Selective formation of either (**2**) or (**3**) was not observed in any of the experiments. With n = 9 in X–$(CH_2)_n$ – X, the compound (**4**) was also obtained along with a mixture of (**2**) and (**3**). The ^1H NMR and mass spectra of the quinazolinophanes (**2**) and (**3**) were almost similar. However, when the number of methylene groups in X-$(CH_2)_n$-X is odd (n = 5, 7 and 9), the structures of (**2**) and (3) were differentiated on the basis of number of peaks of the ^{13}C NMR spectra, *e.g*. the number of peaks of the pentamethylene chain of ^{13}C NMR spectrum of (**2b**) was five whereas that of (**3b**) was six. On the other hand, ^{13}C NMR spectra data did not give any evidence to distinguish the structures of (**2**) and (**3**), with even number of methylene groups (n = 4 and 6) such as (**2a**) and (**3a**); and (**2c**) and (**3c**). The structure of (**4**) was distinguishable from those of (**2**) and (**3**) on the basis of mass spectral data; *e.g*., both M^+ of both (**2e**) and (**3e**) is 572, while that of (**4e**) is 286. Attempted isolation of quinazolinophanes from the treatment of benzoylene urea with $I(CH_2)_3I$ was not successful. The yields of (**2**), (**3**) and (**4**) are shown in the experimental part. In an effort to determine the relationship between the formation of quinazolinophanes and the base used, treatment of 1,2,3,4-tetrahydro-2,4-quinazolinedione with X-$(CH_2)_n$-X in presence of some other bases such as K_2CO_3, Na_2CO_3, t-BuOK and KOH con-

Scheme I



Note : The numbering has been indicated for **(2)**, **(3)** and **(4)** only with n = 9

taining small amounts of H_2O and CH_3COOK instead of NaH in DMF was studied but the quinazolinophanes were not obtained as the main products, although the reaction with K_2CO_3 and Na_2CO_3 gave a mixture of various products containing quinazolinophanes.

EXPERIMENTAL

The melting points were determined in open capillary and are uncorrected. The ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were obtained with JEOL GSX400 spectrometer. Chemical shifts were reported as ppm (δ) downfield from tetramethylsilane. Mass spectra were obtained with a JEOL JMS-D 300 spectrometer. The elemental analysis were performed by the simple CHN-analyser.

Quinazolinophanes (2,3 and 4) from 1,2,3,4-tetrahydro-2,4-quinazolinedione (1). Into a solution of 1,2,3,4-tetrahydro-2,4-quinazolinedione (1) (20 mmol) and sodium hydride (30 mmol) in DMF (200 ml), $X(CH_2)_nX$ (X = Br or I, n=4-7,9) (20 mmol) was added. The resulting mixture was stirred at room temperature for 12 hours and then heated at 80 °C for 4 hours. The reaction mixture was evaporated to give a residue which was submitted to chromatography over silica gel. Elution of a mixture of hexane and ethyl acetate (1:1) gave (4). Further elution of this mixture (1:3) gave (2) and (3) in that order. Some intermediate fractions contained mixture of (2) and (3). Final elution of the ethyl acetate only gave (3)

1,6,14,19-Tetraazapentacyclo[17.7.1.^{16,14}.0^{8,13}.0^{21,26}]octacosa-8(13),9,11,21(26),22,24-hexaene-7, 20,27,28-tetrone (2a). Mp>300 °C. ^{1}H NMR ($CDCl_3$); δ 1.55-1.82 (8H, br); 3.9 – 4.5 (8H, br); 6.72-7.52 (6H, m, Ar-H); 8.25 (2H, d, J = 8.2 Hz, Ar-H); ^{13}C NMR (DMSO-d_6); δ 21.12; 22.70; 39.15; 48.53; 122.12; 126.22; 129.46; 135.25; 140.33; 145.54; 150.55; 169.55; MS m/z: 433(M^++1; 25), 432 (M^+;100). *Anal* calcd for $C_{24}H_{24}N_4O_4$: C, 66.66; H, 5.55; N,12.96; Found C, 66.64; H, 5.55; N, 12.94.

1,7,15,21-Tetraazapentacyclo[19.7.1.1^{7,15}.0^{9,14}.0^{23,28}]triaconta-9(14),10,12,23(28),24,26-hexaene-8,22,29,20-tetrone (2b). Mp> 210-212 °C. ^{1}H NMR ($CDCl_3$); δ 1.15-1.30 (4H, m); 1.66-1.86 (8H, m); 3.9 (4H, br); 4.1 (4H, t, J = 6Hz); 6.92 – 7.79 (6H, m, Ar-H); 8.15 (2H, d, J = 8.2 Hz, Ar-H); ^{13}C NMR ($CDCl_3$) δ 21.13;24.21; 26.22; 42.12; 48.53; 123.12; 124.11; 127.12; 129.42; 139.12; 142.13; 151.52; 169.12; MS m/z: 461 (M^++1;22), 460 (M^+;100). *Anal* calcd for $C_{26}H_{28}N_4O_4$: C,67.82; H,6.12; N,12.17; Found C, 67.84; H, 6.06; N, 12.15.

1,8,16,23-Tetraazapentacyclo[21.7.1.1^{18,16}.0^{10,15}.0^{25,30}]dotriaconta-10(15),11,13,25(30),26,28-hexaene-9,24,31,32-tetrone (2c). Mp. 190-192 °C. ^{1}H NMR ($CDCl_3$): δ 1.31-1.51 (8H, m); 1.65-1.80 (8H,m); 3.75 (4H, t, J = 6Hz); 3.95 (4H, t, J = 6Hz); 6.95-7.82 (6H, m, Ar-H); 8.12 (2H, d, J = 8.2 Hz, Ar-H), ^{13}C NMR ($CDCl_3$): δ 22.35; 28.46; 32.14; 36.72; 41.36; 47.16; 125.32; 126.41; 128.34; 131.75; 138.21; 143.26; 152.12; 169.26; MS m/z: 489 (M^++1; 24), 488 (M^+; 98). *Anal* calcd for $C_{28}H_{32}N_4O_4$: C, 66.85; H, 6.55; N, 11.47; Found C, 68.86; H, 6.54; N, 11.47.

1,9,17,25-Tetraazapentacyclo[23.7.1.1^{9,17}.0^{11,16}.0^{27,32}]tetratriaconta-11(16),12,14,27(32),28,30-hexaene-10,26,33,34-tetrone (2d). Mp. 178-180 °C. ^{1}H NMR ($CDCl_3$): δ1.23-1.32 (12H, m); 1.58-1.80 (8H,m); 3.80 (4H, t, J = 6Hz); 3.93 (4H, t, J = 6.5 Hz); 6.93-7.86 (6H, m, Ar-H); 8.1 (2H, d, J = 8.2 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 22.31; 25.16; 28.13; 30.43; 36.36; 42.12; 48.34; 122.11; 125.12; 129.21; 134.57; 138.12; 146.26; 159.12; 167.32; MS m/z: 517 (M^++1; 22), 516 (M^+; 100). *Anal*. Calcd. For $C_{30}H_{30}N_4O_4$: C, 62.5; H, 6.97; N, 10.85; Found C, 62.47; H, 6.95; N, 10.83.

1,11,19,29-Tetraazapentacyclo[27.7.1.1^{11,19}.0^{13,18}.0^{31,36}]octatriaconta-13(18),14,16,31(36),32,34-hexaene-12,30,37,38-tetrone (2e). Mp. 175-177 °C. ^{1}H NMR ($CDCl_3$): δ 1.2-1.39 (20H, m); 1.57-1.72 (8H, m); 3.75 (4H, t, J = 6.5 Hz), 3.95 (4H, t, J = 6.5 Hz); 6.95-7.9 (6H, m, Ar-H); 8.1 (2H, d, J = 8.2 Hz, Ar-H); ^{13}C NMR ($CDCl_3$) : δ 21.31; 24.54; 26.44; 29.21; 32.24; 36.31; 39.12; 46.44; 49.21; 123.41; 125.32; 127.21; 132.12; 137.21; 147.31; 158.26; 168.41; MS m/z : 573 (M^++1;24), 572 (M^+;99). *Anal*. Calcd. For $C_{34}H_{34}N_4O_4$: C, 72.02; H, 7.69; N, 9.79; Found C, 72.0; H, 7.69; N, 9.8.

1, 6, 14, 19-Tetraazapentacyclo [17.7.1^{16,14}.0^{7,12}.0^{21,26}]octacosa-7(12),8,10,21(26),22,24-hexaene-13,20,27,28-tetrone (3a). Mp> 300 °C. ^{1}H NMR ($CDCl_3$); δ 1.30-1.43 (4H, br); 1.54-1.62 (4H, br); 3.5 – 4.0 (4H, br); 4.0 – 4.5 (4H, br); 6.72-7.5 (6H, m, Ar-H); 8.45 (2H, d, J = 8.2 Hz, Ar-H); ^{13}C NMR (DMSO-d_6): δ 21.13; 22.12; 38.52; 47.12; 121.12; 122.12; 128.52; 136.21; 140.22; 145.42; 151.55; 173.55; MS m/z: 433 (M^++1;12), 432 (M^+;92). *Anal*. Calcd for $C_{24}H_{24}N_4O_4$: C, 66.66; H, 5.55; N, 12.96; Found C, 66.64; H, 5.55; N, 12.94.

1,7,15,21-Tetraazapentacyclo[19.7.1.1^{7,15}.0^{8,13}.0^{23,28}]triaconta-8(13),9,11,23(28),24,26-hexaene-14,22,29,30-tetrone (3b). Mp. 268-270 °C. ^{1}H NMR ($CDCl_3$): δ 1.12-1.32 (2H, m); 1.25-1.34 (2H, m); 1.66-1.86 (8H, m); 3.95 (4H, br); 4.2 (4H, t, J = 6Hz), 6.92 – 7.79 (6H, m, Ar-H); 8.05 (2H, d, J = 8.2 Hz, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 22.13; 24.12; 26.12; 28.13; 41.12; 49.53; 120.12; 123.12; 127.12; 135.12; 141.32; 144.12; 150.53; 171.13; MS m/z: 461 (M^++1;17), 460 (M^+;99). *Anal* calcd. For $C_{26}H_{28}N_4O_4$: C, 67.82; H, 6.08; N, 12.17; Found C, 67.84; H, 6.06; N, 12.17.

1,8,16,23-Tetraazapentacyclo[22.7.1.1^{8,16}.0^{9,14}.0^{25,30}]dotriaconta-9(14), 10,12,25(30),26,28-hexaene-15,24,31,32-tetrone (3c). Mp. 220-222 °C. ^{1}H NMR ($CDCl_3$): δ 1.21-1.42 (8H, m); 1.58-1.80 (8H, m); 3.75 (4H, t, J = 6Hz); 3.95 (4H, t, J = 6Hz); 6.96-7.84 (6H, m, Ar-H); 8.2 (2H, d, J = 8.2 Hz, Ar-H); ^{13}C NMR($CDCl_3$): δ 22.12; 24.31; 26.12; 29.12, 45.31; 48.12; 122.21; 128.32; 131.21; 135.52; 141.22; 145.71; 149.23; 170.26; MS m/z: 489 (M^++1; 14), 488 (M^+;92). *Anal*. Calcd for $C_{28}H_{32}N_4O_4$: C, 66.85; H, 6.55; N, 11.47; Found C, 68.86; H, 6.54; N, 11.47.

1,9,17,25-Tetraazapentacyclo[23.7.1.1^{9,17}.0^{10,15}.0^{27,32}]tetratriaconta-10(15),11,13,27(32),28,30-hexaene-16,26,33,34-tetrone (3d). Mp. 182-183 °C. ^{1}H NMR ($CDCl_3$): δ1.2-1.34 (12H, m); 1.57-1.8 (8H, m); 3.81 (4H, t, J = 6Hz); 3.93 (4H, t, J = 6.5 Hz); 6.94-7.86 (6H, m, Ar-H); 8.2 (2H, d, J = 8.2 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 22.32; 23.62; 27.31; 29.21; 35.41; 38.33; 45.12; 49.64; 120.42; 123.32; 127.12; 131.12; 138.46; 144.12; 148.21; 169.31; MS m/z: 517 (M^++1;14), 516 (M^+;94). *Anal*. Calcd for $C_{30}H_{36}N_4O_4$: C, 62.5; H, 6.97; N, 10.85; Found C, 62.47; H, 6.95; N, 10.83.

1,11,19,29-Tetraazapentacyclo[27.7.1.^{11,19}.0^{12,17}.0^{31,36}]octatriaconta-12(17),13,15,31(36),32,34-hexaene-18,30,37,38-tetrone (3e). Mp. 190-192 °C. ^{1}H NMR ($CDCl_3$): δ 1.2-1.39 (20 H, m); 1.57-1.72 (8H, m); 3.74 (4H, t, J = 6.5 Hz), 6.95-7.92 (6H, m, Ar-H); 8.0 (2H, d, J = 8.2 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 21.12; 24.12; 26.12; 29.12; 32.21; 35.21; 39.31; 42.41; 45.31; 48.44; 122.31; 125.32; 128.21; 130.22; 135.41; 145.12; 147.34; 168.36; MS m/z: 573 (M^++1; 12), 572 (M^+;100). *Anal*. Calcd. for $C_{34}H_{44}N_4O_4$: C, 72.02; H, 7.69; N, 9.79; Found C, 72.0; H, 7.69; N, 9.8.

1,11-Diazatricyclo[9.7.1.0^{12,17}]nonadeca-12(17),13,15-triene-18,19-dione (4e). Mp. 94-95°C. ^{1}H NMR ($CDCl_3$): δ 1.65-3.12 (14H, m); 4.08-4.25 (2H, m); 4.64 (2H, dd, J = 14.9 and 4.5 Hz); 6.8-7.5 (3H, m, Ar-H); 8.3 (1H, d, J = 8.2 Hz, Ar-H). ^{13}C NMR ($CDCl_3$): δ 22.52; 22.88; 23.05; 24.12; 25.95; 26.10; 26.12; 40.15; 49.12; 122.12; 126.02; 128.34; 135.26; 138.22; 142.33; 154.22; 167.73; MS m/z :347 (M^++1; 16), 346 (M^+; 100). *Anal*. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.32; H, 7.69; N, 9.79; Found C, 71.30; H, 7.69; N, 9.81.

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