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SYNTHESIS OF NOVEL STEROIDAL N-SUBSTITUTED PYRIMIDINE-2, 4-DIONES: A NEW ENTRY TO STEROIDAL AZAHETEROCYCLES.

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ABSTRACT

Imidates derived from 2, 4-dichloropyrimidine derivatives with cholesterol, underwent Chapman rearrangement under conventional as well as microwave irradiation to afford corresponding steroidal N-substituted heterocyclic compounds.

KEYWORDS: Cholesterol, steroidal, pyrimidine-2, 4-diones, imidates, microwave irradiation, Chapman rearrangement.

INTRODUCTION

Pyrimidine ring represent molecular frameworks that serve as a platform for developing pharmaceutical agents for various applications.[1]

Many steroidal heterocyclic compounds have been reported to possess various therapeutic activities.[2,3]

Condensed pyrimidine derivatives have been reported as anti-tumour[4], anti-neoplastic[5], anti-malarial[6], diuretic.[7]

As it should be expected, the fusion of heterocycles to steroids often led to a change in their physiological activities and the appearance of new interesting biological behavior.

Thus, several steroidal heterocycles have been obtained exhibiting activity as potential inhibitors of cytochrome P450 enzyme aromatase with their subsequent clinical application in the treatment of estrogen-dependent breast cancers.[8,9] Steroidal heterocycles containing anellated rings in the steroidal moiety have prompted a great interest in the biological study

of many heterocyclic compounds. New compounds were synthesized in which the androstane ring-A was condensed with a great variety of heterocyclic rings.[10, 11, 12]

The synthesis of steroidal heterocycles containing the pyrimidine ring fused to the steroid nucleus is reported.[13] Androstenolone acetate when reacted with carbon disulfide, iodomethane and sodium hydride furnishes 3-β-acetoxy-16-[bis(methylthio)methylene]-5-androst-5-en-17-one. Its reaction with amidinium, guanidinium, and isothiuronium salts in the presence of sodium methoxide yielded the 6'-methoxy- pyrimido[5', 4':16, 17]androst-5-en-3-β-ols.

The reaction of 17-β-hydroxy-2-ethoxymethylene-4-androstene-3-one (prepared by reacting testosterone with ethyl orthoformate) with guanidine nitrate and sodium ethoxide in presence of ethanol and DMF gave 17-β-hydroxy-4-androsteno[3, 2-d]-2'-aminopyrimidine. When 17-β-hydroxy-2-bis-(methylthio) methylene-4-androstene-3-one (prepared by reacting testosterone with carbon disulfide in presence of sodium tert. butoxide followed by alkylation with methyl iodide) when refluxed with guanidine nitrate and sodium ethoxide in presence of ethanol and dimethyl formamide afforded 17-β-hydroxy-4-androsteno-[3, 2-d]-2'-amino-6'-ethoxy pyrimidine.[13]

Attempts at direct N-substitution of 2, 4-(1H, 3H)-pyrimidinedione derivatives are tedious and involve substrates that are not easily accessible.[14, 15, 16]

Although most of the above methodologies have their own synthetic values, some limitations mainly due to the long reaction times, harsh reaction conditions, tedious preparation procedures, use of solvents etc.; which could represent significant drawbacks for preparative purposes. Thus, there is scope for the synthesis of them by simple and eco-friendly method.

The present communication describes the synthesis of 1, 3-dicholesteryl-(1H, 3H)-pyrimidine-2, 4-diones in two steps through *Chapman rearrangement* under conventional heating as well as microwave irradiation in absence of solvent in second step.

MATERIALS AND METHODS

The melting points were determined using capillary tube and are uncorrected. The 1H-NMR spectra were recorded on a Bruker AVANCE (300MHz) spectrometer (with TMS as internal references). 13C-NMR spectra were recorded on Bruker AVANCE (75 MHZ) spectrometer. The FTIR spectra were recorded on Spectrum One Perkin Elmer (US). Mass spectra were

recorded on API-3000MD-series (US). UV spectra were recorded on Shimaduz 2401 PC and Shimaduz 2450, Japan, Spectrophotometer. Elemental analyses were carried out in EA 3000, Euro Vector, Italy. The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (200mesh). Modified LG microwave laboratory oven was used for microwave irradiation. The solvents were purified by distillation before use.

RESULTS AND DISCUSSION

The present paper reports the synthesis of 1, 3-dicholesteryl-(1H, 3H)-pyrimidine-2, 4-diones via *Chapman rearrangement* of corresponding 2, 4- dicholesteroxypyrimidines.

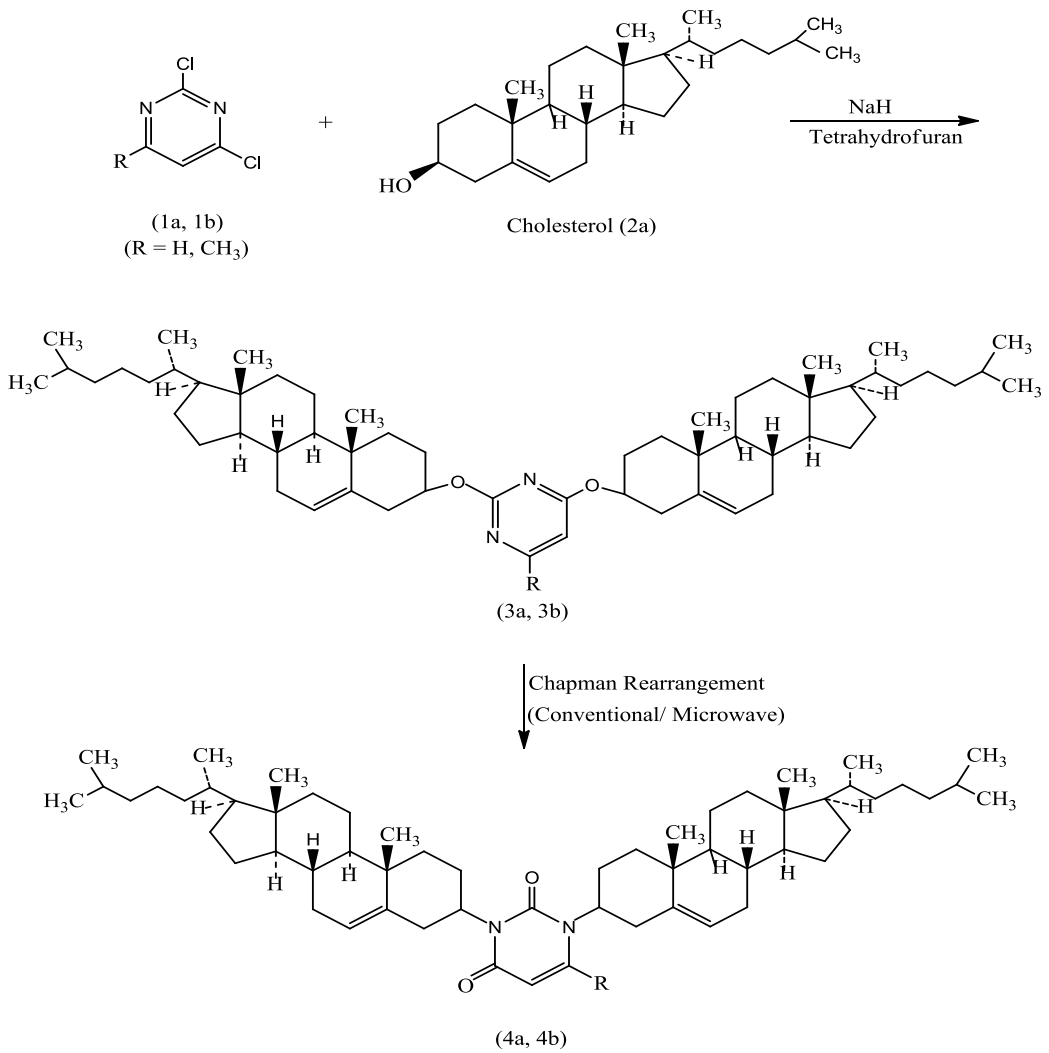
The thermal conversion of aryl N-arylbenzimidates to N-aroyldiphenylamines is known as the *Chapman rearrangement.*[17] Though imidates of different classes of compounds have been subjected to *Chapman rearrangement*, 3, 6-dicholesteroxypyrimidines have not been investigated.

In light of the observations from literature survey as well as our interest in evolving new, simpler, ecofriendly, convenient methodologies in organic synthesis and absence of reports on the *Chapman rearrangement* of 3, 6- dicholesteroxypyrimidines led us to undertake the present work in continuation with earlier work.[18, 19, 20, 21, 22, 23]

For this purpose 2, 4-dichloropyrimidine **(1a)** and 2, 4-dichloro-6-methylpyrimidine **(1b)** were visualized as starting substrates. These when condensed with cholesterol **(2a)** yielded the respective 2, 4-dicholesteroxypyrimidine derivatives **(3a, 3b)**. These were then subjected to *Chapman rearrangement* in absence of solvent to afford the corresponding 1, 3-dicholesteryl-(1H, 3H)-pyrimidine-2, 4-dione derivatives **(4a, 4b)**. **(Scheme).**

2, 4-dichloropyrimidine **(1a)** and 2, 4-dichloro-6-methylpyrimidine **(1b)** has been synthesized as per literature procedure.[24]

Scheme: Synthesis of 1, 3-dicholesteryl-(1H, 3H)-pyrimidine-2, 4-dione derivatives (4a, 4b)



General Procedure for preparation of 2, 4-cholesteroxypyrimidine derivatives. (3a, 3b)

To a solution of cholesterol **(2a)** (0.024 M) in dry tetrahydrofuran (100 ml), Sodium hydride (0.029 M, 60% dispersion in oil) was added in portions to the flask under nitrogen atmosphere. The mixture was gently refluxed for 30 minutes followed by cooling to room temperature. A solution of 2, 4-dichloropyrimidine derivative (0.024 M) **(1a/ 1b)** in tetrahydrofuran was added drop-wise under stirring in 10–15 minutes. Tetrabutylammonium iodide (0.0026 M) was added in one portion and the solution was stirred at 50°C-60°C for 8-10 hours. After completion of the reaction (TLC), the solvent was removed under reduced pressure and the residue was treated with of saturated NaCl solution (50 ml). The mixture was extracted with dichloromethane (3 × 50 ml) and the combined extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure the residue was

flash chromatographed (diethyl ether: petroleum ether, 1:1) to give 2, 4-dicholesteroxypyrimidines **(3a/ 3b)** as viscous oil.

2, 4-dicholesteroxy-pyrimidine (3a).

Yield: 66%. Viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.68 (m, 6H), 0.85 (m, 6H), 0.87 (m, 6H), 0.91 (m, 6H), 0.97 (m, 6H), 1.01 (m, 6H), 1.11 (m, 8H), 1.30 (m, 10H), 1.52 (m, 8H), 1.82 (m, 12H), 1.98 (m, 8H), 2.27 (m, 4H), 3.52 (m, 2H), 5.35 (m, 2H), 6.21, 6.82 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.88, 18.75, 19.50, 21.18, 22.62, 22.83, 23.89, 24.32, 27.09, 28.05, 28.31, 31.69, 32. 01, 35.85, 36.25, 36.54, 37.51, 39.60, 40.01, 42.52, 50.19, 56.30, 57.11, 74.03, 102.34, 121.54, 141.21, 157.67, 165.11, 171.32. Molecular formula: $C_{58}H_{92}N_2O_2$. Elemental analysis: Calculated: C (82.08%), H (10.85%), N (3.30%). Found: C (82.13%), H (10.91%), N (3.19%). HRMS: *m/z* cal. mass for $C_{58}H_{92}N_2O_2$ $[M+H]^+$ =849.3632, obs. mass $[M+H]^+$ = 849.3643. IR (KBr, cm^{-1}): 644, 782 (-CH bend. Ar), 843, 917, 1023 (=C-H bend. Alkene), 1056, 1080 (C-H cycloalkane), 1083, 1191 (C-O-C stretch.), 1212, 1255 (C-N stretch.), 1343, 1366, 1382, 1467 (C-H bend. Alkane), 1611(C=C stretch. Ar), 1635, 1642 (C=C stretch. Alkene), 2868-2933 (-CH stretch. Aliphatic). $[\alpha]^{20}_D$= -18.68 (Methanol, 1%). UV spectrum:λ_{max} 232 Abs. 0.312.

2, 4-dicholesteroxy-6-methylpyrimidine (3b).

Yield: 57%.Viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.62 (m, 6H), 0.79 (m, 6H), 0.81 (m, 6H), 0.93 (6H, m), 0.95 (m, 6H), 1.06 (m, 6H), 1.19 (m, 6H), 1.28 (m, 10H), 1.49 (m, 8H), 1.88 (m, 12H), 1.95 (m, 8H), 2.11 (s, 3H), 2.30 (m, 4H), 3.57 (m, 2H), 5.42 (m, 2H), 6.42, 6.91 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.88, 14.02, 18.81, 19.62, 20.95, 22.44, 22.76, 24.01, 24.41, 26.97, 28.02, 28.44, 31.51, 31. 92, 35.90, 36.07, 36.32, 37.62, 39.74, 39.88, 42.34, 49.90, 55.88, 57.27, 73.83, 101.87, 121.62, 140.92, 158.05, 164.86, 170.88. Molecular formula: $C_{59}H_{94}N_2O_2$. Elemental analysis: Calculated: C (82.13%), H (10.90%), N (3.25%). Found: C (82.05%), H (10.96%), N (3.13%). HRMS: *m/z* cal. mass for $C_{59}H_{94}N_2O_2$ $[M+H]^+$ = 863.3898, obs. mass $[M+H]^+$ = 863.3887. IR (KBr, cm^{-1}): 641, 787 (-CH bend. Ar), 841, 922, 1027 (=C-H bend. Alkene), 1050, 1108 (C-H cycloalkane), 1189 (C-O-C stretch.), 1259, 1338 (C-N stretch.), 1371, 1379, 1470 (C-H bend. Alkane), 1618 (C=C stretch. Ar), 1630, 1648 (C=C stretch. Alkene), 2871-2952 (-CH stretch. Aliphatic). $[\alpha]^{20}_D$ - 19.17^{o}(Methanol, 1%).UV spectrum: λ_{max} 249.8 Abs. 0.337.

General procedure for preparation of 1, 3-dicholesteryl-(1H, 3H)-pyrimidine-2, 4-dione derivatives (4a, 4b) by *Chapman rearrangement* of 2, 4-dicholesteroxypyrimidine derivatives (3a, 3b) under conventional heating.

In a flask, equipped with water condenser 2, 4-dicholesteroxypyrimidine derivative **(3a/ 3b)** (0.005 M) was heated in nitrogen atmosphere at 190^0C for 90 minutes. After completion, (TLC) the reaction mass was cooled to room temperature and petroleum ether (25 ml) was added. It was purified to afford viscous oil.

Thus, 2, 4-dicholesteroxypyrimidines **(3a, 3b)** smoothly underwent *Chapman rearrangement* but the reaction times were larger and percentage yields were moderate. It was therefore thought worthwhile to carryout the *Chapman rearrangement* of these compounds under microwave irradiation.

Reduced reaction times, less effect on the environment and better reaction yields are some of the common advantages of using microwave irradiation for chemical reactions.[25]

General procedure for preparation of 1, 3-dicholesteryl-(1H, 3H)-pyrimidine-2, 4-dione derivatives (4a, 4b) by *Chapman rearrangement* of 2, 4-dicholesteroxypyrimidine derivatives (3a, 3b) under microwave irradiation.

In a flask, equipped with water condenser 2, 4-dicholesteroxypyrimidine derivative **(3a/ 3b)** (0.01M) was irradiated (900W) in a microwave oven for 20 minutes. After completion (TLC), the reaction mass was cooled to room temperature and petroleum ether (25 ml) was added under stirring. It was purified to afford viscous oil.

Percentage Yield and reaction time under conventional heating and microwave irradiation are presented in the **Table**.

1, 3-dicholesteryl-(1H, 3H)-pyrimidine-2, 4-dione (4a).

Viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.61 (m, 6H), 0.83 (m, 6H), 0.88 (m, 6H), 0.93 (m, 6H), 0.98 (m, 6H), 1.03 (m, 6H), 1.12 (m, 6H), 1.32 (m, 10H), 1.53 (m, 8H), 1.85 (m, 12H), 1.96 (m, 8H), 2.31 (m, 4H), 3.58 (m, 2H), 5.39 (m, 2H), 6.41, 6.75 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.72, 19.25, 19.93, 20.78, 22.41, 22.90, 23.66, 24.78, 26.89, 27.86, 28.71, 30.78, 32.23, 35.34, 36.11, 36.71, 37.49, 38.97, 39.89, 42.24, 50.34, 55.67, 57.43, 73.82, 101.32, 120.95, 142.02, 144.10, 150.92, 164.02. Molecular formula: $C_{58}H_{92}N_2O_2$.Elemental analysis: Calculated: C (82.08%), H (10.85%), N (3.30%). Found: C

(82.17%), H (10.93%), N (3.39%). HRMS: *m/z* cal. mass for $C_{58}H_{92}N_2O_2$ $[M+H]^+$ =849.3632, obs. mass $[M+H]^+$ = 849.3624. IR (KBr, cm^{-1}): 670, 782 (-CH bend. Ar), 843, 927, 1023, 1056 (=C-H bend. Alkene), 1110, 1192 (C-H cycloalkane), 1255, 1338 (C-N stretch.), 1382, 1467 (C-H bend. Alkane), 1607 (C=C stretch. Ar), 1613, 1622 (C=C stretch. Alkene), 1687, 1699 (N-C=O stretch.), 2873-2930 (-CH stretch. Aliphatic). $[\alpha]^{20}_D$- 22.06 (Methanol, 1%). UV spectrum: λ_{max} 241 Abs. 0.329.

1, 3-dicholesteryl-(1H, 3H)-6-methylpyrimidine-2, 4-dione (4b)

Viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.68 (m, 6H), 0.77 (m, 6H), 0.83 (m, 6H), 0.94 (m, 6H), 1.02 (m, 6H), 1.07 (m, 6H), 1.16 (m, 6H), 1.43 (m, 10H), 1.56 (m, 8H), 1.82 (m, 12H), 1.94 (m, 8H), 2.19 (s, 3H), 2.37 (m, 4H), 3.61 (m, 2H), 5.41 (m, 2H), 6.52, 6.81 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.79, 12.13, 19.38, 19.83, 20.60, 22.39, 22.83, 23.71, 24.69, 26.78, 27.79, 28.76, 30.81, 32.42, 35.39, 36.21, 36.77, 37.52, 38.82, 39.78, 42.32, 50.53, 55.34, 57.31, 73.75, 102.02, 121.11, 142.08, 143.91, 151.03, 163.94. Molecular formula: $C_{59}H_{94}N_2O_2$. Elemental analysis: Calculated: C (82.13%), H (10.90%), N (3.25%). Found: C (82.21%), H (10.98%), N (3.36%).HRMS: *m/z* cal. mass for $C_{59}H_{94}N_2O_2$ $[M+H]^+$ = 863.3898, obs. mass $[M+H]^+$ = 863.3885. IR (KBr, cm^{-1}): 659, 785 (-CH bend. Ar), 853, 930, 1030 (=C-H bend. Alkene), 1054, 1114 (C-H cycloalkane), 1342, 1371(C-N stretch.), 1379(C-H rock. Alkane), 1472 (C-H bend. Alkane), 1610 (C=C stretch. Ar), 1614, 1621(C=C stretch. Alkene), 1694, 1696 (N-C=O stretch.), 2877-2922 (-CH stretch. Aliphatic). $[\alpha]^{20}_D$ -20.74^o(Methanol, 1%). UV spectrum: λ_{max} 252.8 Abs. 0.341.

Table: Time and yield of the synthesized compounds 4a-4b

	Conventional heating		Microwave irradiation	
	Time (minutes)	**% Yield**	**Time (minutes)**	**% Yield**
4a	90	39	20	51
4b	90	41	20	48

CONCLUSION

For the first time 3, 6-dicholesteroxypyrimidines underwent facile *Chapman rearrangement* to afford the corresponding 1, 2-dicholesterylpyrimidine-2, 4-diones under conventional heating as well as microwave irradiation.

Microwave assisted method of synthesis provides a simpler and environmental-friendly alternative for the conventional procedures. Thus it is a convenient way towards the goal of green, sustainable chemistry, and is strongly recommended to use in organic preparations.

The synthesis of novel heterocycles reported in this paper has the potential of exhibiting pharmacological activities.

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