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SYNTHESIS AND BIOLOGICAL STUDIES OF ISOXAZOLES FROM BENZOSUBERONES

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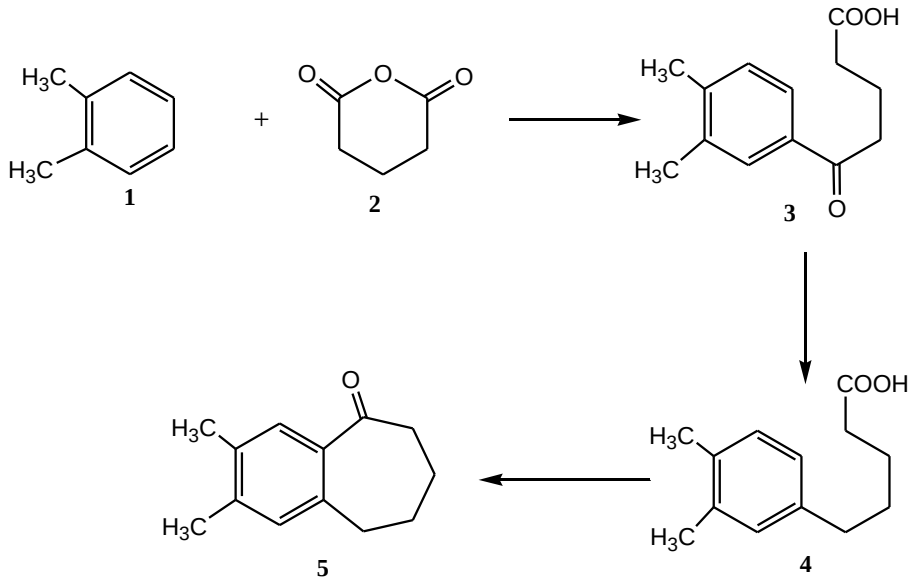
Abstract:
6-Arylidene-3,4-dimethyl-6,7,8,9-tetrahydro-5*H* benzo[a]cyclohepten-5-ones (**6a-g**) were obtained by the condensation of 3,4-dimethyl-6,7,8,9-tetrahydro-5*H*-bezo[a]cyclohepten-5-ones (**5**) with appropriate aromatic aldehydes. Cycloaddition of **6a-g** with hydroxylamine hydrochloride in alkaline medium yielded 8,9-dimethyl-3-phenyl-3a,4,5,6-tetrahydro-3*H*-benzo[6,7] cyclohepta[c]isoxazole derivatives **7a-g**.

Key words: benzosuberone, isoxazole, fungicides, bactericide, type 2 diabetes mellitus.

Introduction:

Isoxazoles display interesting biological properties such as herbicidal, plant growth regulatory, hypoglycemic and anti-tumor activities[I-IV]. 5-Aminoethylisoxazolin-3-ol showed the existence of a powerful agonistic activity at the post-synaptic 4-aminobutyric acid receptor complex, associated with a significant interaction with the 4-aminobutyric acid-uptake system[V]. Number of isoxazoline derivatives[VI-VII] were found to possess anti-convulsant activity. Chalcones are potential biocides as some benzosuberone chalcones owe their biological activity due to the α,β unsaturated carbonyl group. Chalcone are associated with wide range of biological activities[VIII]. Chalcone being a very good synthon, variety of novel heterocycles like isoxazoles can be designed with good pharmacological profile.
Prompted by these observations and in continuation of our work on the synthesis of biologically active nitrogen and sulfur containing heterocycles[IX-XIII], we report in this paper the conversion of 6-arylidene-3,4-dimethyl-6,7,8,9-tetrahydro-5*H*-bezo[a]cyclohepten-5-ones (**6a-g**) into derivatives of a new heterocyclic system containing isoxazoline moiety **(7a-g)** showed with good pharmacological results **table-I.**

The required starting compound 3,4-dimethy-6,7,8,9-tetrahydrobenzo cyclohepten-5-one (**1**) was prepared[XIV] starting from δ-(p-toloyl)valeric acid (**2**). Friedal-Crafts acylation of aromatic hydrocarbons with glutaric anhydride furnished tolylbutyric acid (**3**) which on Wolff-Kishner reduction followed by cyclization of **4** with excess of polyphosphoric acid gave (**5**) (**Scheme-1**). The structures of these compounds were established on the basis of their analytical and spectral data.

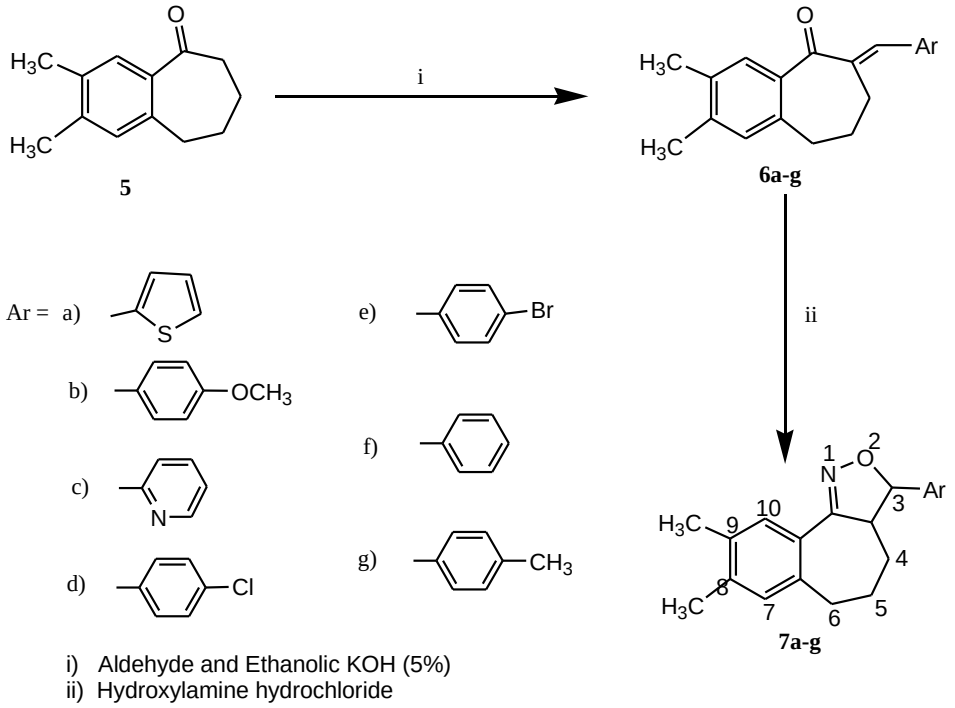


Scheme-1

Results and Discussion:

6-Arylidene-3,4-dimethyl-6,7,8,9-tetrahydro-5*H* benzo[a]cyclohepten-5-ones (**6a-g**) were obtained by the condensation of 3,4-dimethyl-6,7,8,9-tetrahydro-5*H*-bezo[a]cyclohepten-5-ones (**5**) with appropriate aromatic aldehydes. In the enones **6a-g**, the olefinic proton =CH-Ar appeared at δ 7.80 in their ^{1}H NMR spectra.

Cycloaddition of **6a-g** with hydroxylamine hydrochloride in alkaline medium yielded 8,9-dimethyl-3-phenyl-3a,4,5,6-tetrahydro-3*H*-benzo[6,7] cyclohepta[c]isoxazole derivatives **7a-g**. The IR spectra of **7a-g** exhibited a band due to -C-O-N- (1246-1261 cm^{-1}) and C=N (1640-1655 cm^{-1}) respectively, which indicates the presence of isoxazoline ring. Similarly, the absence of C=O band proves the formation of the ring. Further, in their ^{1}H NMR spectrum, disappearance of the olefinic proton (=CH-Ar) at δ 7.80 and appearance of a doublet at δ 3.30-3.40 (1H, d, J=4.32-5.0 Hz, -CH-Ar) and δ 2.85-3.00 (1H, m, isoxazoline bridge proton –CH) confirms the presence of oxazoline ring. The aryl protons resonated as multiples in the range of δ 6.80-7.55. The proton signals of two methyl groups and aliphatic protons appeared at expected region.



Scheme-2

Experimental:

Melting points were determined using Gallankamp apparatus and are uncorrected. IR spectra were recorded on a FT-IR 1605 Perkin-Elmer; 1H NMR in CDCl3 on a Varian FT-80A spectrometer with TMS as an internal standard; and mass spectra on a VG-micro mass 7070H mass spectrometer. TLC was run on Silica gel G coated plates and iodine vapor as visualizing agent.

8,9-dimethyl-3-thiophene-3a,4,5,6-tetrahydro-3*H*-benzo[6,7]cyclohepta [c]isoxazole (30a-g) : General procedure:

A mixture of 6-Arylidene-3,4-dimethyl-6,7,8,9-tetrahydro-5*H*-benzo[a] cyclohepten-5-ones **6a** (0.00068 mole) and hydroxylamine hydrochloride (0.00068 mole) in 2% ethanolic sodium hydroxide solution (5 mL) was heated under reflux for 3 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure and the residue was added to ice water (15 mL). The resulting solution was neutralized with dilute hydrochloric acid and extracted with chloroform (20 mL). Upon evaporations, the organic layer gave the crude product, which was purified by preparative TLC using 10% ethyl acetate-petroleum ether afforded products **7a**: Yield: 75%; m.p. 80-82^{0}C; IR (KBr): 1259 (-C-O-N), 1650 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.80-1.95 (2H, m, 4-CH_2), 2.00-2.15 (2H, m, 5-CH_2), 2.35 (6H, s, 8 & 9-CH_3), 2.55-2.78 (2H, m, 6-CH_2), 2.85-3.10 (1H, m, 2-CH), 3.45-3.55 (1H, d, *J*=4.5Hz 3-CH), and 6.80-7.55 (5H, m, Ar-CH); MS: m/z 297 ($M^{+\cdot}$); Anal. Found: C, 72.69; H, 6.35; N, 4.68. $C_{18}H_{19}NOS$ requires C, 72.72; H, 6.39; N, 4.71%.

Compound 7b: Yield: 75%; m.p. 125-127^{0}C; IR (KBr): 1259 (-C-O-N), 1654 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.60-1.78 (2H, m, 4-CH_2), 2.20-2.30
(2H, m, 5-CH_2), 2.38 (6H, s, 8 & 9-CH_3), 2.65-2.75 (2H, m, 6-CH_2), 2.90-3.05 (1H, m, 3-CH), 3.30-3.38 (1H, d, *J*=4.3Hz 2-CH), 3.80 (3H, s, OCH_3) and 6.80-7.50 (6H, m, Ar-CH); MS: m/z 321 ($M^{+\cdot}$); Anal. Found: C, 78.48; H, 7.14; N, 4.34. $C_{21}H_{23}NO_2$ requires C, 78.50; H, 7.16; N, 4.36%.

Compound 7c: Yield: 68%; m.p. 89-91^{0}C; IR (KBr): 1261 (-C-O-N), 1648 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.62-1.80 (2H, m, 4-CH_2), 1.95-2.10 (2H, m, 5-CH_2), 2.40 (6H, s, 8 & 9-CH_3), 2.60-2.78 (2H, m, 6-CH_2), 2.90-3.05 (1H, m, 3-CH), 3.32-3.40 (1H, d, *J*=4.5Hz 2-CH), 6.80-7.50 (5H, m, Ar-CH) and 8.30 (1H, d, N=CH); Anal. Found: C, 78.05; H, 6.82; N, 9.56. $C_{19}H_{20}N_2O$ requires C, 78.08; H, 6.84; N, 9.58%.

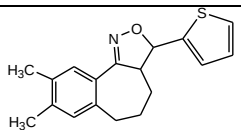
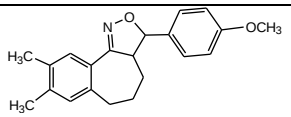
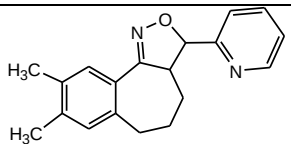
Compound 7d: Yield: 72%; m.p. 93-95^{0}C; IR (KBr): 1250 (-C-O-N), 1647 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.98-2.16 (2H, m, 4-CH_2), 2.28-2.32 (2H, m, 5-CH_2), 2.38 (6H, s, 8 & 9-CH_3), 2.55-2.80 (2H, m, 6-CH_2), 2.85-3.00 (1H, m, 3-CH), 3.30-3.40 (1H, d, *J*=4.5Hz 2-CH), and 6.95-7.55 (6H, m, Ar-CH); Anal. Found: C, 73.71; H, 6.12; N, 4.28. $C_{20}H_{20}NOCl$ requires C, 73.73; H, 6.14; N, 4.30%.

Compound 7e: Yield: 60%; m.p. 115-117^{0}C; IR (KBr): 1252 (-C-O-N), 1643 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.60-1.70 (2H, m, 4-CH_2), 1.90-2.10 (2H, m, 5-CH_2), 2.40 (6H, s, 8 & 9-CH_3), 2.55-2.75 (2H, m, 6-CH_2), 2.82-3.00 (1H, m, 3-CH), 3.30-3.38 (1H, d, *J*=5.0Hz 2-CH), and 6.90-7.55 (6H, m, Ar-CH); Anal. Found: C, 6.84; H, 5.38; N, 3.76. $C_{20}H_{20}NOBr$ requires C, 64.86; H, 5.40; N, 3.78%.

Compound 7f: Yield: 65%; m.p. 75^{0}C; IR (KBr): 1250 (-C-O-N), 1645 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.50-1.60 (2H, m, 4-CH_2), 2.00-2.35 (6H, s, 8 & 9-CH_3) 2.50-2.60 (2H, m, 5-CH_2), 2.60-2.70 (2H, m, 6-CH_2), 2.80-3.90 (1H, m, 3-CH), 3.40-3.50 (1H, d, *J*=5.0Hz 2-CH), and 6.90-7.80 (7H, m, Ar-CH); Anal. Found: C, 82.45; H, 7.19; N, 4.79. $C_{20}H_{21}NO$ requires C, 82.47; H, 7.21; N, 4.81%.

Compound 7g: Yield: 55%; m.p. 72-75^{0}C; IR (KBr): 1248 (-C-O-N), 1647 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.50-1.63 (2H, m, 4-CH_2), 1.72-1.90 (2H, m, 5-CH_2), 2.20-2.40 (9H, s, 8,9-CH_3 & Ar-CH_3), 2.60-2.80 (2H, m, 6-CH_2), 2.90-3.32 (1H, m, 3-CH), 3.40-3.50 (1H, d, *J*=4.5Hz 2-CH), and 6.92-7.40 (6H, m, Ar-CH); Anal. Found: C, 82.60; H, 7.52; N, 4.57. $C_{21}H_{23}NO$ requires C, 82.62; H, 7.54; N, 4.59%.

Pharmacological results:

S.NO.	STRUCTURE	ANALGESIC ACTION (% PROTECTION)		ANTIINFLMMATORY ACTIVITY (% INHIBITION OF EDEMA)	ANTIBACTERIAL ACTIVITY	
		TAIL CLIP	WRITHING		STAPHYLOCOCCUS	E.COLI/KLEBSIELLA
7a		14	13	29	2.3	6
7b		13	12	25	2.5	5.5
7c		117	13	29	2	7

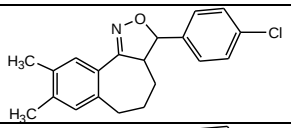
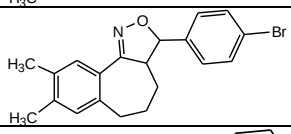
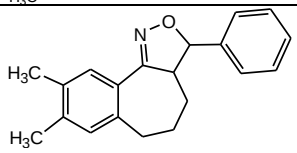
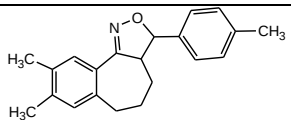
7d		113	15	32	2.5	5
7e		13	14	30	3	4.5
7f		14	15	29	2	3
7g		15	16	31	2	4
	Aspirin	555	46	17		
	Phenylbutazone	30	20	39		
	Rifampicin				8	13

Table-I

Conclusion:

Based on the wide range of various biological activities of benzosuberonee derivatives and emergence of multidrug resistance of the continued use of antibacterial and antifungal of different microorganisms, we synthesized herein a new serious of benzosuberone derivatives and we thought these molecules will give better results. Most of our molecules have been observed the high rate of anti-inflammatory activity than anti-bacterial activity.

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