SHORT PAPER

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Nitrogen heterocyclic systems: synthesis of 3,3a-*trans* and *cis*-2-acetyl/phenyl-3-arylhexahydrobenzo[6,7] cyclohepta[1,2-c]pyrazoles†

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Novel pyrazole derivatives (**3a-g**, **3a′–g′**, **4a–g**, **4a′–g′**) have been synthesised by condensation of 3-methylbenzocyclohepten-5-one (**1**) with aryl aldehydes in the presence of a base, followed by treatment with various hydrazines. Biological testing of these compounds for their antimicrobial activity has been carried out.

Keywords: benzosuberone, fused cycloheptanones, fused pyrazolines, enones

As part of our program on the synthesis of heterocyclic systems to study their structure-activity relationships, a new series of pyrazole-annelated benzocycloheptenes (**3**, **4**) has been synthesised. Structure elucidation of **3** and **4** was based on their spectral data.

In continuation of our earlier work on the synthesis of novel bridgehead nitrogen and sulphur heterocyclic systems[1–3] and in view of reported antiimplantation agents[4] and potential intercalators,[5] together with the antimicrobial activity of alkylpyrazoles,[6,7] we undertook and here report the synthesis and antimicrobial activities of **3**, **3a**, **4** and **4a**, *trans*/*cis*-2-acetyl/phenyl-3-aryl-hexahydrobenzo[6,7]cyclohepta[1,2-c]-pyrazoles, members of a novel, hitherto unknown, heterocyclic system.

Results and discussion

6-Arylmethylene-3-methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones (**2a–g**, Scheme 1) were obtained by condensation of **1** with appropriate aldehydes.[8] In the enones **2a–g**, the olefinic proton =CH-Ar appeared at δ = 7.80 in the ^{1}H NMR spectra. On reaction with hydrazine hydrate in glacial acetic acid compounds **2** gave the expected *trans*/*cis* mixtures of hexahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazole derivatives (**3a–g**, **3a′–g′**).

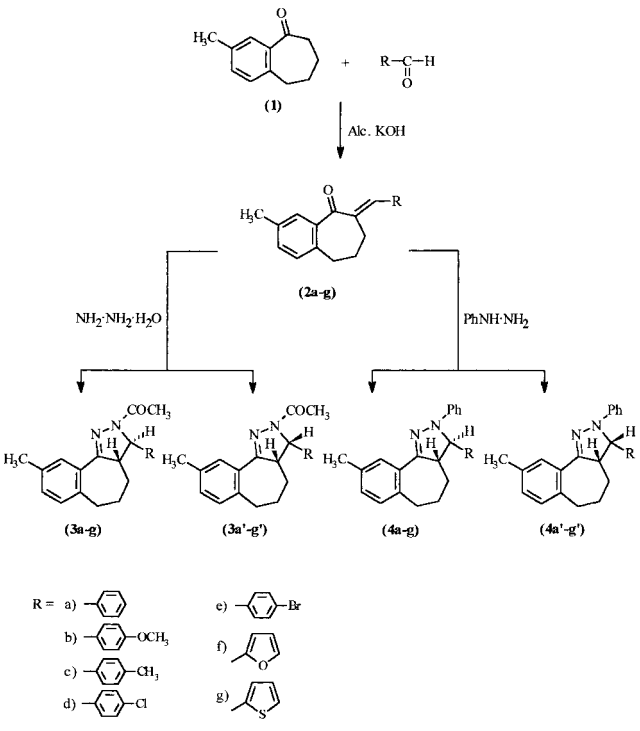
The *trans*/*cis* mixtures were separated on a silica gel column using 20% ethyl acetate – petroleum ether as eluant to give the *trans* isomers in 36-42% and the *cis* isomers in 15–20% yield. In *trans* and *cis* isomers, C_{3a}–H appeared as a multiplet at δ 2.98–3.45 and δ 3.60–3.80 respectively, and C_3–H as a doublet at δ 5.00–5.15 (J = 4.3–5.0 Hz) and δ 5.59–5.65 (J = 10.8–11.3 Hz), respectively.

It has been reported[9] that condensation of compound **2** with phenylhydrazine gave the *cis* isomer, whereas Rastogi *et al.*[10] have observed the formation of only the *trans* isomer. We have repeated the reaction with phenylhydrazine on our benzylidene derivatives (**2a–g**) to see whether we get the *cis* or *trans* isomer or both. This confirmatory work was necessary since there are reports of phenylhydrazine reactions giving a single product without mentioning its geometry.[11]

Condensation of 6-arylmethylene derivatives (**2a–g**) with phenylhydrazine resulted in both *cis* and *trans* isomers. These structures were confirmed by the presence of C_3–H as a doublet at δ 4.05–5.00 (J = 5–7 Hz), C_{3a}–H as a multiplet at δ 2.70–2.90 in the case of the *trans* isomer and C_3–H as a doublet at δ 5.00–5.50 (J = 10–12 Hz), C_{3a}–H as a multiplet at δ 3.00–3.20 in the *cis* isomer. The best purified *cis* isomers were found to contain *ca* 5% of the *trans* isomer which could not be removed by repeated chromatography. Hence we could not record the melting points of the pure *cis* isomers. The structures of all the compounds are confirmed by elemental and spectral analysis. We then proceeded to the evaluation of the biological properties of these compounds.

Biological evaluation

All the compounds were screened for their antimicrobial activity at concentration 20 μg/disc in agar media using ampicillin in antibacterial and clotrimazole in antifungal activity as reference compounds. Some of the compounds showed activity against the gram-positive bacterium *Staphylococcus aureus* and gram-negative bacterium *Pseudomonas*. Compounds **3b, 3b′, 3c, 3e, 3e′** showed moderate activity against *S. aureus*. Compound **4e** showed a greater zone of inhibition (17 mm) as compared with ampicillin (14 mm) against *Pseudomonas*, while compounds **3b′** (14 mm), **3e′**



Scheme 1

* To receive any correspondence.

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Spectral and analytical data

Compd	M.p./°C	Yield/%	^{1}H NMR ($CDCl_3$) δ ppm	CHN analysis found (calc.) (Molecular formula)		
				C	H	N
3a	132–133	38	1.80–2.00 (4H, m, 4 & 5-CH_2), 2.32 (3H, s, N-$COCH_3$), 2.38 (3H, s, -CH_3), 2.70–2.85 (2H, t, 6-CH_2), 3.00–3.15 (1H, m, C_{3a}-H), 5.00 (1H, d, *J* = 4.5 Hz, C_3-H), 6.90–7.50 (8H, m, aromatic)	79.20 (79.24)	6.91 (6.92) ($C_{21}H_{22}N_2O$)	8.75 (8.81)
3a′	195–198	19	2.89–3.10 (1H, m, C_{3a}-H), 5.60 (1H, d, *J* = 11 Hz, C_3-H)	79.22 (79.24)	6.89 (6.92)	8.77 (8.81)
3b	102–103	40	1.60–2.10 (4H, m, 4 & 5-CH_2), 2.37 (3H, s, N-$COCH_3$), 2.40 (3H, s, -CH_3), 2.72–2.98 (2H, t, 6-CH_2), 3.00–3.25 (1H, m, C_{3a}-H), 3.75 (3H, s, -OCH_3), 5.08 (1H, d, *J* = 4.5 Hz, C_3-H), 6.80-7.58 (7H, m, aromatic)	75.81 (75.86)	6.87 (6.90) ($C_{22}H_{24}N_2O_2$)	8.01 (8.05)
3b′	171–173	18	3.00–3.05 (1H, m, C_{3a}-H), 5.60 (1H, d, *J* = 11 Hz, C_3-H)	75.83 (75.86)	6.86 (6.90)	7.97 (8.05)
3c	110–112	39	1.70-2.05 (4H, m, 4 & 5-CH_2), 2.80-3.05 (3H, s, N-$COCH_3$), 2.35 (6H, 2 × CH_3), 2.70–3.00 (2H, t, 6-CH_2), 3.02–3.20 (1H, m, C_{3a}-H), 5.05 (1H, d, *J* = 4.3 Hz, C_3-H), 6.95–7.65 (7H, m, aromatic)	79.48 (79.52)	7.20 (7.23) ($C_{22}H_{24}N_2O$)	8.42 (8.43)
3c′	178–180	19	3.60–3.80 (1H, m, C_{3a}-H), 5.60 (1H, d, *J* = 10.8 Hz, C_3-H)	79.50 (79.52)	7.28 (7.23)	8.40 (8.43)
3d	162–164	40	1.65–2.00 (4H, m, 4 & 5-CH_2), 2.35 (3H, s, N-$COCH_3$), 2.40 (3H, s, -CH_3), 2.70–2.95 (2H, t, 6-CH_2), 2.98–3.20 (1H, m, C_{3a}-H), 5.05 (1H, d, *J* = 4.30 Hz, C_3-H), 7.00-7.70 (7H, m, aromatic)	71.56 (71.59)	5.98 (5.97) $C_{21}H_{21}Cl\,N_2O$	7.92 (7.95)
3d′	192–194	20	3.67–3.85 (1H, m, C_{3a}-H), 5.59 (1H, d, *J* = 11.3 Hz, C_3-H)	71.49 (71.59)	5.92 (5.97)	7.90 (7.95)
3e	197–198	42	1.65–1.87 (4H, m, 4 & 5-CH_2), 2.38 (3H, s, N-$COCH_3$), 2.40 (3H, s, -CH_3), 2.78–2.94 (2H, t, 6-CH_2), 3.00–3.15 (1H, m, C_{3a}-H), 5.05 (1H, d, *J* = 4.5 Hz, C_3-H), 6.95–7.60 (7H, m, aromatic)	63.79 (63.64)	5.22 (5.30) ($C_{21}H_{21}BrN_2O$)	7.05 (7.07)
3e′	140–141	20	3.60–3.80 (1H, m, C_{3a}-H), 5.55 (1H, d, *J* = 11.3 Hz, C_3-H)	63.77 (63.64)	5.25 (5.30)	7.05 (7.07)
3f	112–113	36	1.78–2.05 (4H, m, 4 & 5-CH_2), 2.38 (6H, s, N-$COCH_3$ & -CH_3), 2.77–3.30 (3H, t, 6-CH_2), 3.30-3.45 (1H, m, C_{3a}-H), 5.15 (1H, d, *J* = 5.0 Hz, C_3-H), 6.25 (2H, s, furyl protons), 7.00–7.50 (4H, m, furyl & aromatic)	73.95 (74.03)	6.41 (6.49) ($C_{19}H_{20}N_2O_2$)	9.03 (9.09)
3f′	100–101	16	3.60–3.80 (1H, m, C_{3a}-H), 5.65 (1H, d, *J* = 10.8 Hz, C_3-H)	74.00 (74.03)	6.39 (6.49)	9.01 (9.09)
3g	200–201	38	1.75–2.00 (4H, m, 4 & 5-CH_2), 2.35 (6H, s, N-$COCH_3$ & CH_3), 2.75-3.20 (3H, t, 6-CH_2), 3.30-3.45 (1H, m, C_{3a}-H), 5.12 (1H, d, *J* = 5.0 Hz, C_3-H), 6.26 (2H, s, thienyl protons), 7.00–7.50 (4H, m, thienyl & aromatic)	70.31 (70.37)	6.12 (6.17) ($C_{19}H_{20}N_2OS$)	8.61 (8.64)
3g′	158–159	18	3.65–3.82 (1H, m, C_{3a}-H), 5.64 (1H, d, *J* = 10.8 Hz, C_3-H)	70.30 (70.37)	6.11 (6.17)	8.60 (8.64)
4a	122–125	14	1.97–2.20 (4H, m, 4 & 5-CH_2), 2.39 (3H, s, -CH_3), 2.65 (2H, t, 6-CH_2), 2.75–2.90 (1H, m, C_{3a}-H), 4.05 (1H, d, *J* = 4.5 Hz, C_3-H), 7.00–7.90 (13H, m, aromatic)	85.18 (85.22)	6.78 (6.82) ($C_{25}H_{24}N_2$)	7.91 (7.95)
4a′			3.00–3.15 (1H, m, C_{3a}-H), 5.10 (1H, d, *J* = 10 Hz, C_3-H)		—	
4b	92–94	10	1.95–2.10 (4H, m, 4 & 5-CH_2), 2.32 (3H, s, -CH_3), 2.55 (2H, s, 6-CH_2), 2.65–2.73 (1H, m, -CH_3), 2.70–2.80 (1H, m, C_{3a}-H), 3.75 (3H, s, -OCH_3), 4.50 (1H, d, J = 9.5 Hz, C_3-H), 6.75–7.50 (12H, m, aromatic)	81.64 (81.67)	6.77 (6.81) ($C_{26}H_{26}N_2O$)	7.31 (7.33)
4b′			3.10–3.15 (1H, m, C_{3a}-H), 5.40 (1H, d, *J* = 8 Hz, C_3-H))		—	
4c	100–102	16	2.05–2.20 (4H, m, 4 & 5-CH_2), 2.40 (6H, s, 2 × -CH_3), 2.70 (2H, t, -CH_2), 2.80–2.95 (1H, m, C_{3a}-H), 4.52 (1H, d, *J* = 10 Hz, C_3-H), 6.70–7.52 (12H, m, aromatic)	85.23 (85.25)	7.07 (7.10) ($C_{26}H_{26}N_2$)	7.60 (7.65)
4c′			3.12–3.17 (1H, m, C_{3a}-H), 5.47 (1H, d, *J* = 6 Hz, C_3-H)		—	
4d	147–149	12	2.05–2.20 (4H, m, 4 & 5-CH_2), 2.40 (3H, s, -CH_3), 2.65 (2H, t, -CH_2), 2.72–2.90 (1H, m, C_{3a}-H), 4.60 (1H, d, *J* = 10 Hz, C_3-H),), 6.70–7.90 (12H, m, aromatic)	77.68 (77.72)	5.93 (5.96) ($C_{25}H_{23}ClN_2$)	7.21 (7.25)
4d′			3.05–3.20 (1H, m, C_{3a}-H), 5.35 (1H, d, *J* = 5.2 Hz, C_3-H)		—	

Table 1 *continued*

Compd	M.p./°C	Yield/%	^{1}H NMR ($CDCl_3$) δ ppm	CHN analysis found (calc.) (Molecular formula)		
				C	H	N
4e	154–155	12	1.90–2.20 (4H, m, 4 & 5-CH_2), 2.40 (6H, s, 2 × -CH_3), 2.60 (2H, t, 6-CH_2), 2.75-3.00 (1H, m, C_{3a}-H), 4.90 (1H, d, *J* = 10 Hz, C_3-H), 6.92–7.80 (12H, m, aromatic)	69.75 (69.77)	5.30 (5.35) ($C_{25}H_{23}BrN_2$)	6.49 (6.51)
4e′			3.10–3.22 (1H, m, C_{3a}-H), 5.38 (1H, d, *J* = 5.5 Hz, C_3-H)		—	
4f	85–86	10	2.00–2.20 (4H, m, 4 & 5-CH_2), 2.40 (3H, s, -CH_3), 2.75 (2H, t, 6-CH_2), 2.80–3.10 (1H, m, C_{3a}-H), 4.80 (1H, d, *J* = 5 Hz, C_3-H), 6.20-8.00 (11H, m, aromatic)	80.68 (80.70)	6.39 (6.43) ($C_{23}H_{22}N_2O$)	8.16 (8.19)
4f′			2.90–3.05 (1H, m, C_{3a}-H), 5.35 (1H, d, *J* = 7 Hz, C_3-H)		—	
4g	196–198	11	1.95–2.20 (4H, m, 4 & 5-CH_2), 2.35 (3H, s, -CH_3), 2.75 (2H, t, -CH_2), 2.80–2.95 (1H, m, C_{3a}-H), 4.90 (1H, d, *J* = 5 Hz, C_3-H), 6.72-7.90 (11H, m, aromatic)	77.05 (77.09)	6.12 (6.14) ($C_{23}H_{22}N_2S$)	7.79 (7.82)
4g′			2.85–3.00 (1H, m, C_{3a}-H), 5.60 (1H, d, *J* = 10 Hz, C_3-H)		—	

(12 mm), **3g'** (11 mm) showed almost equal zone of inhibition. All compounds are ineffective against the fungus *Trichoderma*.

Experimental

Melting points were determined using a Gallenkamp apparatus. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian FT 80A spectrometer with TMS as an internal standard, IR spectra on a Shimadzu 470 spectrometer, and mass spectra on VG high resolution 7070H and Finnigan Mat 1020B mass spectrometers. TLC was run on silica gel G coated plates and iodine vapour as visualising agent.

3,3a-trans/cis-*2-acetyl-3-aryl-2,3,3a,4,5,6-hexahydrobenzo[6,7] cyclohepta[1,2-c]pyrazoles* (**3**): *General procedure*: A mixture of **2a** (1 mmole) and hydrazine hydrate (0.4 ml) in glacial acetic acid (3 ml) was heated under reflux for 10–12 h. The solvent was removed under reduced pressure and the residue treated with ice-cold water to give a solid which was filtered, washed with water and dried. Purification of the crude sample by preparative TLC using 16% ethyl acetate in 1:1 petroleum ether-benzene as eluant gave the *trans* isomer **3a** and the *cis* isomer **3a′**.

3,3a-trans/cis-*3-aryl-2,3,3a,4,5,6-hexahydro-2-phenylbenzo[6,7] cyclohepta[1,2-c]pyrazoles* (**4**): *General procedure*: A solution of **2a** (1 mmole) and phenylhydrazine (0.4 ml) in ethanol (4 ml) containing a few drops of glacial acetic acid was heated under reflux for 24 h. After completion of the reaction the solvent was removed under reduced pressure, and the residue was added to water. After the usual work-up the compound was obtained as a gummy mixture which was purified by preparative tlc using 20% ethyl acetate in petroleum ether.

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