Synthesis of some novel 5, 6-dihydro-6-[4'-substituted phenyl]-12H-indeno[2, 1-c]-1, 5-benzodiazepin-7-ones

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Although a number of [1, 5] diazepines fused to a variety of carbocyclic 1,2 and heterocyclic 3,5 ring systems have been synthesized in the past and screened for their various biological properties such as anticonvulsants 6, antivasopressin 7, sedative 8, anticholecytokinin 9 and anti-HIV activity 10, but the literature does not record any attempts made towards the synthesis of indenobenzodiazepines. In view of these biological properties and in continuation of our interest in utilizing 2-benzylideneindane-1, 3-diones for the synthesis of novel multicyclic heterocyclic ring systems, we report in this paper one pot synthesis of some hitherto unknown 5, 6-dihydro-6-phenyl-12H-indeno[2, 1-c]-1, 5-benzodiazepin-7-ones 2 through Michael type addition of o-phenylenediamine to 2-benzylideneindane-1, 3-diones 1, 3-diones is reported.

Keywords: Benzodiazepin-7-ones, Michael type addition of o-phenylenediamine

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Although a number of [1, 5] diazepines fused to a variety of carbocyclic 1,2 and heterocyclic 3,5 ring systems have been synthesized in the past and screened for their various biological properties such as anticonvulsants 6, antivasopressin 7, sedative 8, anticholecytokinin 9 and anti-HIV activity 10, but the literature does not record any attempts made towards the synthesis of indenobenzodiazepines. In view of these biological properties and in continuation of our interest in utilizing 2-benzylideneindane-1, 3-diones for the synthesis of novel multicyclic heterocyclic ring systems, we report in this paper one pot synthesis of some hitherto unknown 5, 6-dihydro-6-[4'-substituted phenyl]-12H-indeno[2, 1-c]-1, 5-benzodiazepin-7-ones 2 through Michael type addition of o-phenylenediamine to 2-benzylideneindane-1, 3-diones 1.

Synthesis of hitherto unknown 5, 6-dihydro-6-phenyl-12H-indeno[2, 1-c]-1, 5-benzodiazepin-7-ones 2 through Michael type addition of o-phenylenediamine to 2-benzylideneindane-1, 3-diones 1 in refluxing ethanol afforded the corresponding 5, 6-dihydro-6-phenyl-12H-indeno[2, 1-c]-1, 5-benzodiazepin-7-ones 2 (Scheme I) in excellent yields.

The structures of all the indenobenzodiazepinones 2 have been corroborated through their IR, 1H NMR and mass spectral analysis. The IR spectra of 2 showed a broad band of medium intensity in the region 3228-3306 cm⁻¹ due to N-H stretching along with a strong band in the region 1663-1690 cm⁻¹ due to C=O (stretching) in an α, β-unsaturated five-membered ketone. A shift of about 30-60 cm⁻¹ of this peak to lower wavenumber as compared to C=O (1720 cm⁻¹) in the starting 2-benzylideneindane-1, 3-diones 1 is probably partly due to endocyclic double bond and partly due to further increase in conjugation of the C=O group with the n-electrons of the β-imino group.

The 1H NMR spectra of 2 in the aliphatic region exhibited a one-proton singlet at δ 5.60 assignable to the benzylic C6-H. A noteworthy feature of the aromatic region of 1H NMR spectra of compounds 2 was the appearance of two one proton doublet of doublet (J=7.3 and 1.15 Hz) in the region δ 7.35-7.40 and 6.50-6.60 due to C8-H and C4-H, respectively. The deshielding of the former proton is due to anisotropic effect of the adjacent C7-keto group while the shielding of the later proton (i.e. C4-H) is due to +R effect of C5-NH group.

The structure of these indenobenzodiazepinones 2 have been further supported by their mass spectra which besides their respective molecular peaks showed two common prominent ion peaks i.e. m/z 247 and 219 whereas the former peak must have arisen due to the elimination of 6-phenyl or substituted phenyl group from their respective molecular ions, the later peak is derived from the peak at m/z 247 by loss of 28 mass units i.e. CH=NH moiety.

Biological activity

All the indenodiazepinones 2 prepared in the present investigation were screened for their antibacterial activity against S. aureus (gram-positive) and P. aeruginosa (gram-negative) species by the Filter Paper Disk method with Muller-Hinton agar as medium using 100μg / mL of the compound. Against these bacteria, the zone of inhibition of the various controls were ampicillin (14-22 mm), chloramphenicol (15-18 mm), penicillin G (14-22 mm) while the indenobenzodiazepinones 2 showed an inhibition zone of only (2-5 mm) thereby suggesting that these compounds do not have any significant antibacterial activity.

Experimental Section

Melting points reported are uncorrected. IR spectra were recorded in KBr on a Buck scientific M500 IR
spectrophotometer and $^1$H NMR spectra in DMSO + CDCl$_3$ on a 300 MHz Bruker spectrometer, the chemical shifts are recorded on a $\delta$ scale using TMS as the internal standard.

5, 6-Dihydro-6-[4'-substituted phenyl]-12H-indeno[2, 1-c][1, 5] benzodiazepin-7-one: General procedure. A solution of a suitable 2-benzylidene-indane-1, 3-dione (5 mmoles) and o-phenylenediamine (7.5 mmoles) in ethanol (50 mL) containing HCl (6-7 drops) was refluxed for 4 hr, progress of reaction being monitored by TLC. Thereafter the reaction mixture was cooled to room temperature and poured into aqueous NaHCO$_3$ and extracted with CHCl$_3$ (2 × 50 mL). The organic layer was washed with water (2 × 50 mL), dried over anhydrous MgSO$_4$ and distilled. The crude mass so obtained was passed through a column of silica gel using benzene-ethyl acetate (9:1) mixture as eluent to obtain a shining orange crystals of 5, 6-dihydro-6-substituted phenyl-12H-indeno[2, 1-c][1, 5] benzodiazepin-7-one 2.

5, 6-Dihydro-6-(4'-methylphenyl)-12H-indeno[2, 1-c][1, 5] benzodiazepin-7-one 2a. m.p. 197-99°; Yield (80.2%); IR (KBr, cm$^{-1}$): 3306 (m, N-H stretch), 1690 (s, C=O stretch); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.56 (s, 1H, C$_6$-H), 6.50-6.60 (dd, 1H, C$_4$-H, J = 7.30 and 1.26 Hz), 6.85-6.88 (m, 2H, C$_2$-H and C$_3$-H), 6.90 (d, 2H, C$_2$'-H, C$_6$'-H, J = 8.10 Hz), 7.05-7.10 (md, 3H, C$_9$-H, C$_10$-H, C$_11$-H), 7.32-7.38 (m, 4H, C$_9$-H, C$_10$-H, C$_11$-H, N-H), 7.42-7.48 (dd, 1H, C$_8$-H, J = 8.26 and 1.56 Hz); MS: (m/z, % relative intensity), M$^+$ (338, 62.6), (309, 34.4), (247, 59.4), (219, 100), (91, 21.4), (77, 26.3).

5, 6-Dihydro-6-(4'-methoxyphenyl)-12H-indeno[2, 1-c][1, 5] benzodiazepin-7-one 2c. m.p. 210-11°; Yield (71%); IR (KBr, cm$^{-1}$): 3293 (s, N-H stretch), 1670 (s, C=O stretch), 1520 (s, asymmetric NO$_2$ stretch), 1320 (s, symmetric NO$_2$ stretch); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.68 (s, 3H, C$_4$-OCH$_3$), 5.51 (s, 1H, C$_6$-H), 6.50-6.60 (dd, 1H, C$_4$-H, J = 7.30 and 1.26 Hz), 6.66-6.70 (d, 2H, C$_3$-H and C$_5$-H, J = 6.73 Hz), 6.84-6.88 (m, 2H, C$_2$-H & C$_3$-H), 6.98-7.00 (d, 2H, C$_2$'-H and C$_6$'-H, J = 8.7 Hz), 7.05-7.10 (dd, 1H, C$_1$-H, J = 7.72 and 1.36 Hz), 7.32-7.38 (m, 4H, C$_9$-H, C$_10$-H, C$_11$-H, N-H), 7.45-7.50 (dd, 1H, C$_8$-H, J = 8.25 and 1.56 Hz); MS: (m/z, % relative intensity), M$^+$ (354, 64.8), (339, 7.6), (325, 27.5), (247, 38.5).

5, 6-Dihydro-6-(4'-nitrophenyl)-12H-indeno[2, 1-c][1, 5] benzodiazepin-7-one 2d. m.p. 259-60°; Yield (69%); IR (KBr, cm$^{-1}$): 3282 (s, N-H stretch), 1664 (s, C=O stretch), 1520 (s, asymmetric NO$_2$ stretch), 1320 (s, symmetric NO$_2$ stretch); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.56 (s, 1H, C$_6$-H), 6.55-6.58 (dd, 1H, C$_4$-H, J = 7.75 and 1.47 Hz), 6.88-6.98 (m, 2H, C$_2$-H & C$_3$-H), 7.08 (dd, 1H, C$_1$-H, J = 7.72 and 1.38 Hz), 7.32-7.34 (d, 2H, C$_2$-H & C$_6$-H, J = 8.1 Hz), 7.34-7.46 (m, 4H, C$_9$-H, C$_10$-H, C$_11$-H, N-H), 7.48 (dd, 1H, C$_8$-H, J = 8.26 and 1.26 Hz), 6.50-6.60 (dd, 1H, C$_4$-H, J = 7.30 and 1.26 Hz), 6.85-6.88 (m, 2H, C$_2$-H and C$_3$-H), 6.90 (d, 2H, C$_2$'-H, C$_6$'-H, J = 8.10 Hz), 7.05-7.10 (dd, 1H, C$_1$-H, J = 7.72 and 1.36 Hz), 7.32-7.38 (m, 4H, C$_9$-H, C$_10$-H, C$_11$-H, N-H), 7.45-7.50 (dd, 1H, C$_8$-H, J = 8.25 and 1.56 Hz); MS: (m/z, % relative intensity), M$^+$ (338, 62.6), (309, 34.4), (247, 59.4), (219, 100), (91, 21.4), (77, 26.3).
1.36 Hz), 8.05 (d, 2H, C3- and C5-H, J= 6.73 Hz); MS: (m/z, % relative intensity), M+ (369, 99.8), (341, 109), (247, 66.1), (221, 100), (219, 88.6), (194, 62), (102, 24.5), (77, 29.9).

5, 6-Dihydro-6-(4′-chlorophenyl)-12H-indeno[2, 1-c][1, 5] benzodiazepin-7-one 2e. m.p. 237-38°; Yield (82%); IR (KBr, cm−1): 3306 (s, N-H stretch), 1668 (s, C=O stretch); 1H NMR (300 MHz, CDCl3): δ 5.56 (s, 1H, C6-H), 6.54-6.60 (dd, IH, C4-H, J=7.10 and 1.85 Hz), 6.60-6.80 (m, 2H, C2-H and C3-H), 7.02 (dd, IH, C1-H, J=7.28 and 1.29 Hz), 7.12-7.15 (m, 4H, C2′-H, C3′-H, C5′-H, C6′-H), 7.30-7.40 (m, 4H, C9-H, C10-H, C11-H, N-H), 7.45-7.50 (dd, IH, C8-H, J= 8.15 and 1.42 Hz); MS: (m/z, % relative intensity), M+1(358, 89.5), (329, 39.5), (247, 60), (219, 100) (193, 14.6), (102, 11.6).

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