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NEW FACILE PREPARATION OF DIHYDRO SPIRO-1,5-BENZODIAZEPINES [+]

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Abstract: 2,3-Cycloalkano-3,4-dihydro(5H)-7-benzoyl-1,5-benzodiazepine-4-spirocycloalkanes have been prepared from 4-benzoyl-o-phenylenediamine and cycloalkanones in presence of acetic acid. Only in the case of cyclohexanones, dihydrospiro benzimidazoles are formed as coproducts which are absent in others.

Following the earliest synthesis of 2,3-cyclopentano-3,4-dihydro(5H)-1,5-benzodiazepine-4-spiro cyclopentane, we desired to prepare dihydro spiro benzodiazepines derived from other cyclic ketones under the same procedure[1]. The expected products were not obtained even after a reaction time of 24 h. Addition of glacial acetic acid to provide a mild acidic medium did not improve the reaction. This experience induced us to differentiate the relative reactivity of the amino groups in o-phenylenediamine, in order to make the reaction to be of any significant preparative value. This was achieved by introducing a benzoyl group in the 4-position of o-phenylenediamine, as in (**1**) and carrying out the reaction in acetic acid medium. Yields of dihydro spiro benzodiazepines (**2**, **3** & **4**) were more than 70%. The function of the 4-benzoyl group is to facilitate the stepwise formation of the

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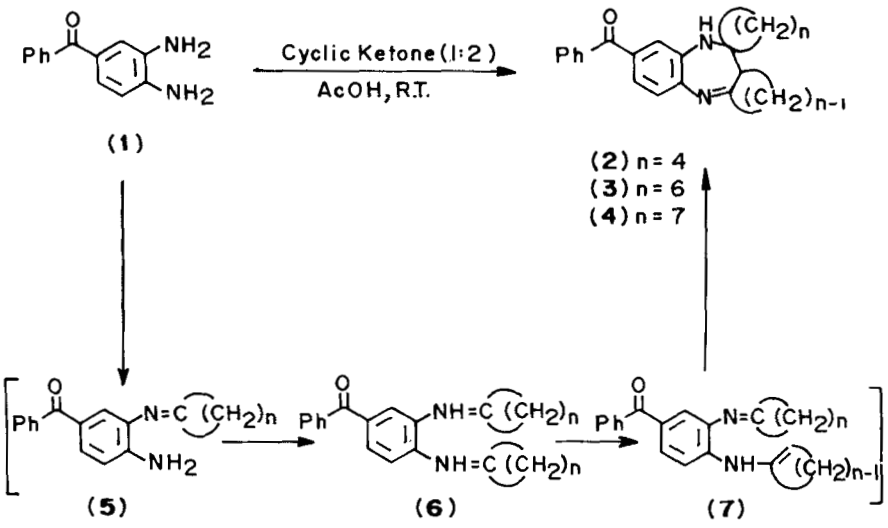


SCHEME - I

intermediates (5 & 6) and to selectively drive (6) into the enamine form (7) in presence of acetic acid for facile cyclisation. Dihydro spiro benzimidazoles arising out of (5) are not formed in this reaction. Absence of acetic acid inhibits the formation of diazepine products, thus establishing its requirement for the conversion of (6) to (7). Synthesis of similar spiro diazepines have been reported by the reductive condensation of o-phenylenediamine and ketones in the presence of sodium borohydride[2], but the products are preferentially tetrahydro diazepines in admixture with dihydrodiazepines. The present procedure affords dihydrodizepines exclusively, even with different mole ratios of reactants.

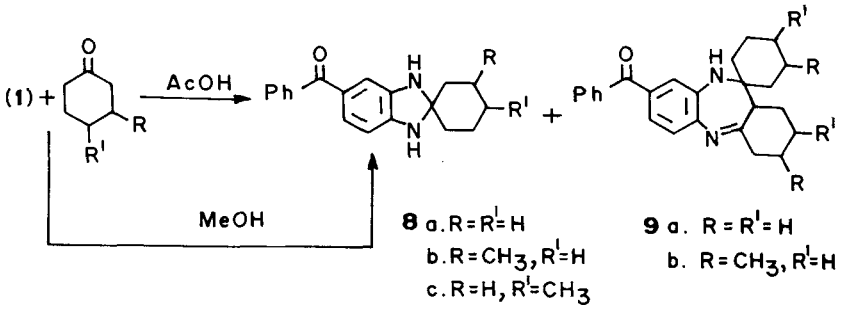
Table 1

Comp. No.	m.p. °C	Yield* %	IR(KBr) ν cm^{-1}	^{1}HNMR	MS
2	85	70	3320, 1650, 1620	0.88-2.88, m(15H) 4.44-4.93, b(1H)$^+$ 6.44-8.20 m (8H)	344,236 105,77
3	173	75	3250,1640 1620	1.10-2.88, m(23H) 4.00-4.66, b(1H)$^+$ 6.44-8.00, m(8H)	400,249 236,105 77
4	165	77	3250, 1645 1635	0.62-3.00, m(27H) 4.30-4.75, b(1H)$^+$ 6.37-7.90, m (8H)	428, 357 249, 236 105, 77

* yields based on isolated and crystallised product.

$^+$ Exchangeable with D_2O

The structures of the dihydro benzo diazepines follow from the mode of formation from the most probable intermediate (7). The spectral data given in the Table-1 conform to the structures assigned. The isomeric structures to the dihydro benzo diazepines have been ruled out because of the improbability of the relevant enamine intermediate isomeric to (7). The influence of benzoyl group on the para imino group provides the driving force for the facile formation of (7) in acetic acid medium and brings about the cyclisation to the diazepines. The mass spectra of the products besides the moelcular ion, are characteristic in that they show three common fragment ions viz., m/z 236, 105 and 77. While m/z 105 and 77 are well known, the



SCHEME-2

structure of m/z 236 as dihydroquinoxaline rather than 2-methylene-benzimidazoline is under investigation.

The same reaction with cyclohexanone and its substituted derivatives show variations with respect to the degree of ring flexibility. Trans-4-tert-butyl cyclohexanone with rigid conformation produces no product. The 4-methylcyclohexanone with a slight degree of conformational freedom produces only the dihydro spiro benzimidazole (**8c**). Cyclohexanone and 3-methylcyclohexanone produce mixtures of dihydro spiro benzimidazoles (**8a,b**) and dihydro spiro benzodiazepines (**9a,b**) in which the spiro benzimidazoles are predominating. The results and spectral data are summarised in Table 2. The spiro benzimidazoles (**8a-c**) have also been independently synthesised from (1) and the corresponding cyclohexanone in methanol medium. It is evident that the best configurational requirements for the formation of dihydro benzo diazepines are attained in the case of cyclopentanone, cycloheptanone and cyclooctanone.

Table 2

Comp. No.	m.p. °C	Yield* %	IR(KBr) cm^{-1}	^1H NMR	MS
8a	210	64	3250-3350 1620	1.11-2.44, m (10H) 3.50-4.33, b (2H)+ 6.22-7.78, m (8H)	292, 249 236, 105 77
9a	87	16	3350, 1650 1625	1.12-2.66, m (19H) 3.88-4.55, b (1H)+ 6.44-8.00, m (8H)	372, 249 236, 105 77
8b	152	66	3200-3400 1620	0.62-2.35, m (12H) 3.10-4.00, b (2H)+ 6.22-7.80, m (8H)	306, 263 236, 105 77
9b	98	21	3350, 1650 1630	0.62-2.44, m (22H) 3.55-4.20, b (1H)+ 6.44-7.90, m (8H)	400, 357 236, 105 77
8c	208	77	3350, 1640 1620	0.80-2.22, m (12H) 3.77-4.44, b (2H)+ 6.22-7.78, m (8H)	306, 249 236, 105 77

* Yield based on isolated and crystallised product.

+ Exchangeable with D_2O.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Perkin Elmer 810 model, ^1H NMR and ^{13}C NMR spectra were recorded on Jeol FX90Q, FT NMR and Varian Gemini-200 spectrometers respectively using tetramethylsilane as internal standard and the chemical shifts are reported in ppm (δ values). Mass spectra were recorded onVG Micromass 7070H instrument. The spectral data (IR, ^1H NMR) of the compounds are summarised in Tables 1 and 2.

2,3-Cycloalkano-3,4-dihydro(5H)-7-Benzoyl-1,5-benzodiazepine-4-spirocyclo alkane(2-4) General Procedure:

To a solution of **1** (0.5 g; 0.0023 mole) in acetic acid (10 g) appropriate cycloalkanone (0.0046 mole) was added with constant stirring and kept at room temperature for 8 h. The mixture was poured into ice water, neutralised with amonia solution (20%) and the resultant solids were recrystallised from benzene to give the respective dihydro benzodiazepines.

Compound (2): 2,3-Cyclopentano-3,4-dihydro (5H)-7-benzoyl-1,5-benzodiazepine-4-spiro cyclopentane.

Compound (3): 2,3-Cycloheptano-3,4-dihydro (5H)-7-benzoyl-1,5-benzodiazepine-4-spiro cycloheptane. ^{13}C NMR ($CDCl_3$) : 175.2 (C=N), 194.8 (CO), 54.0 (C_{tert}), 65.5 (C_{quart}), 42.3, 38.7, 38.4, 26.0, 22.0, 21.7, 21.2, 29.8, 29.6, 28.4, 26.8 (C_{aliph}), 142.6, 138.4, 135.5, 132.0, 130.9, 129.1, 128.2, 127.7, 127.4, 127.2, 127.0, 118.6 (C_{arom}).

Compound (4): 2,3-Cyclooctano-3,4-dihydro (5H)-7-benzoyl-1,5-benzodiazepine-4-spirocyclooctane.

Condensation of (1) with cyclohexanones : Products 8a-c and 9a,b:

The diamine **1** (0.5 g; 0.0023 mole) and appropriate cyclohexanone (0.0046 mole) dissolved in acetic acid (10 g) and the mixture was kept at room temperature with constant stirring for 8 h. It was diluted with water, neutralised with ammonia solution (20%) and the resultant gummy material was subjected to column chromatography to give compounds dihydro spiro benzodiazepines and dihydro spiro benzimidazoles respectively. When 4-methylcyclohexanone was reacted with (**1**) exclusively **8c** was obtained.

Compound (8a): 2,3-Dihydro-5(or 6) benzoyl benzimidazole-2-spiro cyclohexane.

Compound (8b): 2,3-Dihydro-5(or 6) benzoyl benzimidazole-2-spiro-3'-methyl cyclohexane.

Compound (8c): 2,3-Dihydro-5(or 6) benzoyl benzimidazole-2-spiro-4'-methyl cyclohexane.

Compound (9a): 2,3-Cyclohexano-3,4-dihydro (5H)-7-benzoyl-1,5-benzodiazepine-4-spiro cyclohexane. ^{13}C NMR ($CDCl_3$) : 175.6 (C=N), 195.0 (CO), 54.2 (C_{tert}), 67.0 (C_{quart}), 42.0, 34.3, 21.7, 21.6, 21.2, 29.0, 28.0, 25.0, 25.4 (C_{aliph}), 144.0, 139.0, 135.8, 135.4, 134.0, 131.4, 129.6, 129.1, 128.7, 128.1, 127.0, 119.6 (C_{arom}).

Compound (9b): 2,3-(3'-Methylcyclohexano)-3,4-dihydro (5H)-7-benzoyl-1,5-benzodiazepine-4-spiro-3'-methylcyclohexane.

Reaction of (1) with cyclohexanones in methanol : General Procedure: To a solution of **1** (0.5 g; 0.0023 mole) in methanol (25 ml) appropriate cyclohexanone (0.0023 mole) was added and the mixture was stirred at room temperature for 5 h. The solvent was concentrated to half of its volume and the resultant solid was filtered, dried and characterised as dihydro spiro benzimidazole **(8a-c).**

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