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SYNTHESIS OF NEW ADAMANTYLATED HETEROCYCLES

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Abstract: A new adamantyl heterocycle has been prepared by condensation between o-phenylenediamine and β-keto ester and also by rearrangement of adamantylated compound. The synthesised products have been characterised by ^{1}H-NMR, IR and mass spectrum.

Over the last few years, studies of adamantane and its derivatives have shown that the introduction of adamantyl group in biologically active molecules increases considerably their pharmacological efficiency. This increase is attributed principally to the good lipophilic character of adamantyl group and its resistance to the metabolic degradation of compounds containing this group[1-10].

Thus we have carried the condensation of o-phenylenediamine with the 3-(1-adamantyl)-3-oxo ethyl propionate for the synthesis of the corresponding benzodiazepine whose pharmacological properties are not unrecognised.

It is of interest to prepare new heterocycles containing an adamantyl group with different links.

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Two approaches can be adopted to synthesize these heterocycles

-Condensation of o-phenylenediamines with one β-keto ester containing an adamantyl group,

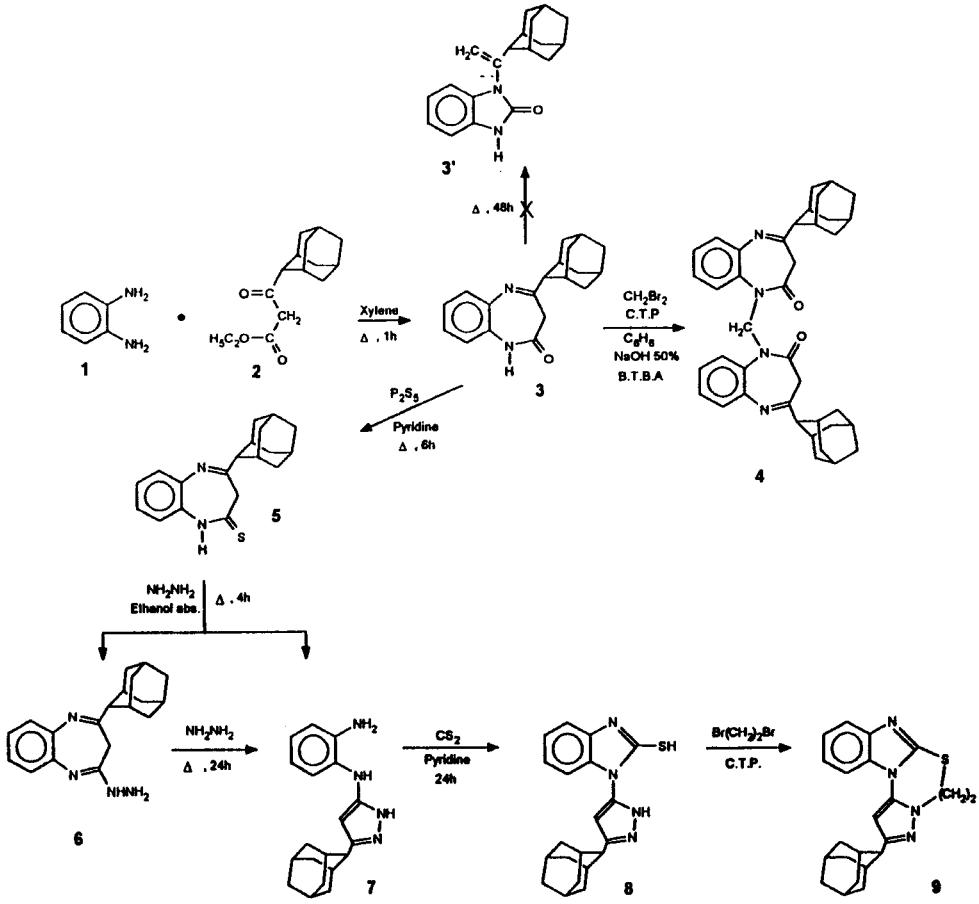
-Rearrangement of an adamantylated compound to a heterocycle of a smaller size and a higher stability.

The action of o-phenylenediamine 1 with 3-(1-adamantyl)-3-oxo ethyl propionate 2, heated in xylene for an hour, leads to 4-adamantyl-1,5-benzodiazepin-2-one 3. The prolongation of the reaction for 48 hours did not permit to obtain the 1-(α-adamantyl vinyl)-benzimidazol-2-one 3' a compound which may be derived from 1,3 sigmatropic transposition of compound 3 (scheme 1), as observed previously for 4-methyl (and 4-cyclopropyl)-1,5-benzodiazepin-2-one[11-12] during the heating in xylene.

The structure of compound 3 was characterised by spectral data (^{1}H-NMR, IR and MS).

The alkylation by phase transfer catalyst(C.T.P) of 4-adamantyl-1,5-benzodiazepin-2-one 3 was performed in 50°C temperature in benzene a together with a concentrated soda solution at 50% by weight. The catalyst used is the tetra n-butylammoniumbromide (T.B.A.B) and dibromomethane as an alkylating agent. Only 1,1'-bis-[4-adamantyl-1,5-benzodiazepin-2-oxo-1-yl] methane 4 was isolated with 65% yield.

In order to prepare other adamantylated heterocycles, we have studied the opening of a seven member ring of benzodiazepines by treatment with hydrazin[13-14] Thus, the hydrazine treatment in ethanol and heating, of 4-adamantyl 1,5-benzodiazepine-2-thione 5, obtained by phosphorus pentasulfide treatment of 1,5-benzo-



diazepin-2-one 3 in pyridine, permitted the isolation of two isomeric products 6 and 7 (scheme 1). The reaction of the prolongation for 24hours gave only the pyrazolic compound 7. This result is the same as the one obtained by Essassi et al[15] during the s-triazolo-triazepine hydrazinolysis. On the contrary, it is different from the one observed by Salem et al[14] during the 4-phenyl-1,5-benzodiazepines hydrazinolysis.

So it turns out that the introduction of adamantyl group on the carbon in position 4 reduces its reactivity because of the steric hindrance created by the group around the imine function,which explains the hydrazinobenzodiazepine 6 formation.

All compound were characterised by ^{1}H-NMR,MS and IR spectral data.

The action of the carbon disulphide on compound 7 in pyridine for 24 hours leads to sulphur product 8. The latter, treated by dibromoethane in the usual conditions of the CTP, has permitted to isolate the tetracyclic product 9.

Thus, we have been able to prepare new heterocycles with seven and five links including an adamantyl group:

- By the action of o-phenylenediamine on one β-keto-ester with an adamantyl group a new molecule of type 4-adamantyl-1,5-benzodiazepin -2-one has been isolated.
- On the other hand, the rearrangement of 1,5-benzodiazepine-2-thione in the presence of hydrazine has permitted the obtention of adamantylated product of pyrazolic type which leads to a tetracyclic compound by the carbon disulphide action, then by 1,2-dibromoethane in CTP conditions.

Typical experimental procedure

4-adamantyl-1,5-benzodiazepin-2-one 3

A 0,012 mole of o-phenylenediamine in 20 ml of xylene was refluxed for 30 min, then a 0,013 mole of 3-(1-adamantyl)-3-oxo ethyl propionate in 2 ml of xylene was added. The mixture was refluxed for one hour with an Deansterk trap. The precipitated product

was filtered and dried. Recrystallisation from acetone gave 3 in 56% yield, mp. 250-252°C.

1,1'-Bis-[4-adamantyl-1,5-benzodiazepin-2-oxo-1-yl] - methane 4

To a suspension of 3 (0.010 mole) in 60 ml of benzene was added 0.010 mole of dibromomethane in 10ml of NaOH 50% and 0.001 mole of T.B.A.B. The mixture was stirred for 6hours. After diluting and decanting, the organic phase was washed with HCl (10%) and dried over sodium sulphate. The solvent was evaporated and the residue was chromatographied on a column (SiO_2; hexane-chloroform: 1-1)to yield 4 which was then recrystallised from chloroform affording the pure material in 65% yield; mp. 160-162°C.

4-adamantyl-1,5-benzodiazepin-2-thione 5

A solution of 3 (0.01 mole) and phosphorus pentasulphide (0.02 mole) in 40 ml of pyridine was refluxed for 6 hours. The solvent was then removed under reduced pressure and the resulting residue was washed with 20ml of boiling water. The precipitate which formed after cooling was then filtered and recrystallised from chloroform/ cyclohexane: 90/10 to give 5 in 45% yield; mp.247-248°C.

Action of hydrazine on 5

To a suspension of 5(0.02mole) in 40ml of absolute ethanol was added hydrated hydrazine 99% (0.04 mole) and the mixture was heated to reflux for 4 hours. The solvent was then removed under reduced pressure and the residue obtained was chromatographied on a column (SiO_2; chloroform)to yield compounds 6 and 7.

Action of hydrazine on 7:8

A solution of 7(0.005 mole) in 40ml of carbon disulphide and 2ml of pyridine was stirred for 24hours The precipitate was filtered, washed with water and dried. Recrystallisation from ethanol afforded 8 in 43% yield; mp. 242-244°C.

Action of dibromoethane on 8:9

A suspension of 8(0.01 mole) in 60ml of benzene was added 0.010 mole of dibromoethane in 10ml of soda (NaOH 50%) and 0.001 mole of T.B.A.B. After diluting and decanting, the organic layer was washed with HCl 10% and died over sodium sulphate. The benzene was evaporated under reduced pressure and the residue was chromatographied on a column (SiO_2; chloroform) to give 9 as an oily product (yield 35%).

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