SYNTHESIS OF NOVEL HEXAHYDROQUINOLINES AND HEXAHYDROACRIDINES

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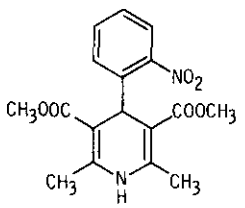
Abstract - Novel hexahydroquinolines and hexahydroacridines were prepared as potential antihypertensive agents.

INTRODUCTION

1,4-Dihydropyridine-3,5-dicarboxylates comprise a class of chemical compounds known as calcium channel blockers or calcium antagonists. Calcium antagonists with suitable pharmacological profiles are of interest in the therapy of coronary heart disease. Recently, various dialkyl 4-aryl-1,4-dihydropyridine-3,5-dicarboxylates were synthesized and several of these compounds inhibited the contractility of vascular smooth muscle and were found to be useful as antihypertensive agents.[1-6] Nifedipine (1)[7-8] is a member of this class and is now being thera- peutically used as an effective antihypertensive agent.



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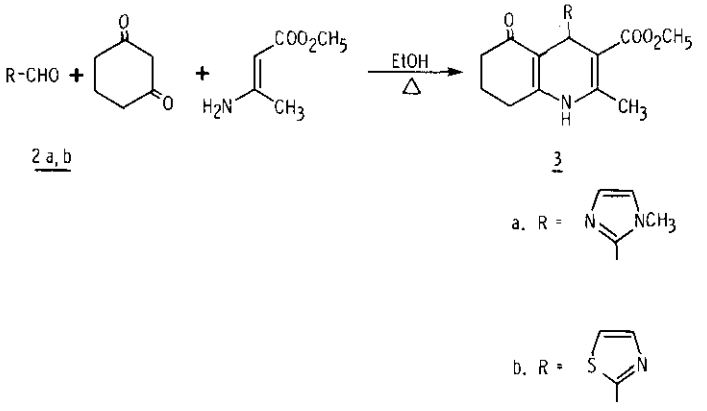
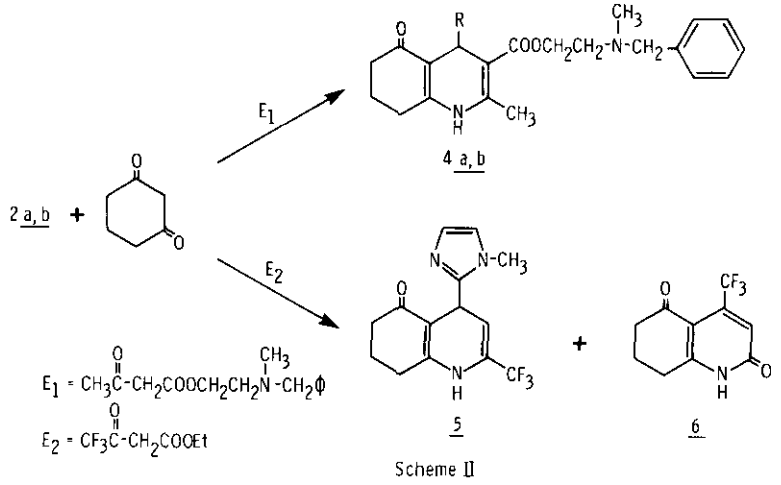
Our interest in developing novel calcium antagonists as antihypertensive agents[9] led to the synthesis of several novel fused 1,4-di-hydropyridines. The present investigation describes the synthesis of two series of compounds, hexahydroquinoline carboxylic esters and hexahydroacridines in which the fused dihydropyridine nucleus is substituted with a heterocyclic moiety. The two heterocyclic aldehyde precursors N-methylimidazole-2-carbox- aldehyde (2a) and thiazole-2-carboxaldehyde (2b) were readily accessible by a two step synthesis following literature procedures.[10,11] When 2a,b were refluxed with equimolar quantities of 1,3-cyclo-hexanedione and ethyl 3-aminocrotonate under conditions employed by Collie[12] in ethanol, it afforded the corresponding hexahydroquinoline-carboxylic esters 3a and 3b in 37% and 72% yields, respectively (Scheme I).



Scheme I

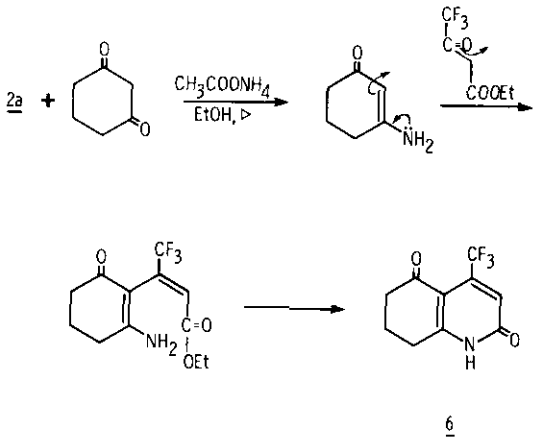
Alternatively, 3a,b were prepared in a 20% yield by refluxing 2a,b with equimolar amounts of acetoacetic esters and 1,3-cyclohexanedione in ethanol in the presence of ammonium acetate. During the course of our structure activity relationship studies, the ester moiety in 3a,b was varied by incorporating a basic functionality or electron withdrawing group in the acetoacetic ester. Accordingly, treatment of the heterocyclic aldehyde with equimolar quantities of 1,3-cyclohexanedione and 2-(N-benzyl-N-methylamino)ethyl acetoacetate in

refluxing ethanol in the presence of ammonium acetate, it afforded the desired hexahydroquinolines 4a and 4b in 22% and 43% yields, respectively (Scheme II).



Scheme II

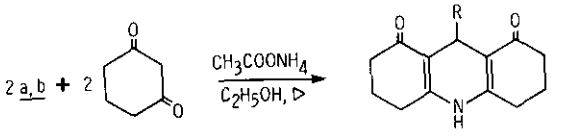
In contrast, when trifluoroacetoacetic ester was used, the desired hexahydroquinoline ester 5 was isolated in low yield (10%) in addition to 7,8-dihydro-4-(trifluoromethyl)-2,5-(1H,6H)quinolinedione 6 in 78% yield (Scheme II). The unexpected formation of 6 could be rationalized through the intermediacy of a ketoenamine 7 which subsequently undergoes Michael addition to the trifluoroacetoacetic ester, followed by ring closure to afford 6 (Scheme III).



Scheme III

Structure of 5 was confirmed via spectral analyses and by formation of its oxime 8 (Table 1).

The reaction of the heterocyclic aldehyde 2a,b with two equivalents of 1,3-cyclohexanedione, afforded a class of tricyclic dihydropyridines 4a,b (hexahydroacridines) in 69% and 30% yields, respectively.



9 a,b

EXPERIMENTAL

General Procedure for the Synthesis of Hexahydroquinolinecarboxylic Esters 3-5

To a stirred mixture of 1,3-cyclohexandione (0.05 mol), appropriately substituted acetoacetic ester (0.05 mol) and ammonium acetate (0.1 mol) in 50 ml of absolute ethanol was added (0.05 mol) of the suitable heterocyclic aldehyde and the reaction mixture was heated at reflux for 12 h. The solution was cooled, evaporated under reduced pressure, and the residue was extracted in 200 ml of methylene chloride. The methylene chloride layer was washed with water, dried and evaporated in vacuo. The brown oil was separated by HPLC using 30% methanol-ethyl acetate mixture as eluent to afford the desired hexahydroquinoline carboxylic ester (Table 1).

In the synthesis of compound 3a,b, ethyl 3-aminocrotonate (0.05 mol) was used in place of the appropriately substituted acetoacetic ester and the desired product was precipitated upon cooling after reflux for 12 h.

It was filtered and recrystallized from hexane-ethylacetate (1:1) mixture (Table 1).

In the synthesis of 5, the unexpected product 6 was also precipitated upon cooling after reflux for 12 h and was recrystallized from absolute ethanol.

General Synthesis of Hexahydroacridines 9

A mixture of 0.045 mol of the appropriate heterocyclic aldehyde, 0.09 mol of 1,3-cyclohexandione and 0.06 mol of ammonium acetate in 50 ml of absolute ethanol were refluxed for 24 h. The reaction mixture was cooled and the separated solid was filtered and recrystallized from absolute ethanol (Table 1).

Table 1 lists the physical and spectral data of the prepared hexahydroquinolines and hexahydroacridines.

Table 1. Hexahydroquinolecarboxylic esters and Hexahydroacridines*

Compound	mp°C	Yield	Spectral Data
3a	271-272	37%	NMR($CDCl_3$) δ1.0(t, 3H, CH_2CH_3), 1.5-2.4 (m, 6H, cyclohexenone), 2.5(s, 3H, $C=CCH_3$), 3.9-4.0 (q, 2H, OCH_2CH_3), 4.0(s, 3H, NCH_3), 5.2(s, 1H, dihydropyridine-H), 6.3(d, 1H, imidazole-H), 6.5(d, 1H, imidazole-H) and 9.5(s, 1H, NH) MS, m/z 315 (M^+)
3b	239-240	72%	NMR($CDCl_3$) δ1.1(t, 3H, CH_2CH_3), 1.9-2.5 (m, 6 H, cyclohexenone), 2.4(s, 3H, $C=CCH_3$), 4.0(q, 2H, OCH_2CH_3), 5.4(s, 1H, dihydropyridine-H), 7.5(d, 1H, thiazole-H), 7.7(d, 1H, thiazole-H) and 8.0(s, 1H, NH) MS, m/z 318 (M^+)
4a	184-186	22%	NMR($CDCl_3$) δ1.5-2.4(m, 6 H, cyclohexenone), 2.20(s, 3H, $C=CCH_3$), 2.5(s, 3H, NCH_3), 3.4(s, 2H, CH_2ph), 4.0(t, 2H, (CH_2CH_2N), 4.1(t, 2H, OCH_2CH_2), 5.1(s, 1H, dihydro-pyridine-H), 6.5(d, 1H, imidazole-H), 6.6 (d, 1H, imidazole-H), 7.25(s, 5H, ph) and 8.5 (s, 1H, NH) MS, m/z 434 (M^+)

Table 1 - cont'd

Compound	mp°C	Yield	Spectral Data
4b	119-120	43%	NMR($CDCl_3$) δ 1.6-2.5(m, 6H, cyclohexenone), 2.2(s, 3H, $C=CCH_3$), 2.3(s, 3H, NCH_3), 3.5(s, 2H, CH_2Ph), 3.6(t, 2H, CH_2CH_2N), 4.1(t, 2H, OCH_2CH_2), 5.5(s, 1H, dihydropyridine-H), 7.1 (d, 1 H, thiazole-H), 7.2(s, 5H, Ph), 7.6(d, 1H, thiazole-H) and 8.6(s, 1H,NH) MS, m/z 437 (M^+)
5	197-198	7%	NMR($CDCl_3$) δ 1.0(t,3H, CH_2CH_3), 1.5-2.4 (m, 6H, cyclohexenone), 3.7(s, 3H, NCH_3), 4.0(q, 2H, OCH_2CH_3), 5.0(s, 1H, dihydropyridine-H), 6.5(d, 1H, imidazole-H), 6.8(d, 1H, imidazole-H) and 9.6(s, 1H, NH) MS, m/z 369 (M^+)
6	264-266	78%	NMR(DMSO-d_6) δ 1.95-3.0(m, 6 H, cyclohexenone), 6.6(s, 1H, $CF_3C=CH$) and 12.5 (broad, 1H, NH) MS, m/z 231 (M^+)
8	258-260	85%	NMR(DMSO-d_6) δ 1.85-2.5(m, 6H, cyclohexenone), 6.65(s, 1H, $CF_3C=CH$), 11.1 (s, 1 H, NOH) and 12.4 (broad, 1H, dihydropyridine-H) MS, m/z 246 (M^+)
9a	285-287	69%	NMR(DMSO-d_6) δ 1.9(m, 4H, cyclohexenone), 2.5-2.7(m, 8H, cyclohexenone), 4.1(s, 3H, NCH_3), 5.0(s, 1H, dihydropyridine-H), 5.4 (s, 1H, NH), 7.4(d, 1H, imidazole-H) and 7.5(d, 1 H, imidazole-H) MS, m/z 297 (M^+)

Table 1 - cont'd

Compound	mp°C	Yield	Spectral Data
9b	278-281	30%	NMR($CDCl_3$) δ1.7-2.1(m, 4H, cyclohexenone), 2.5-2.6(m, 8H, cyclohexenone), 5.4(s, 1H, dihydropyridine-H), 7.8(d, 1H, thiazole-H), 7.9(d, 1H, thiazole-H) and 9.7 (s, 1H, NH)

* All compounds had correct elemental analyses.

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