Available online at www.sciencedirect.com
SCIENCE DIRECT
European Journal of Medicinal Chemistry 41 (2006) 970–977
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://france.elsevier.com/direct/ejmech

Original article

Synthesis of new esters and oximes with 4-aminobicyclo[2.2.2]octane structure and evaluation of their antitrypanosomal and antiplasmodial activities

W. Seebacher [a,*], C. Schlapper [a], R. Brun [b], M. Kaiser [b], R. Saf [c], R. Weis [a]

[a] *Institute of Pharmaceutical Sciences, Pharmaceutical Chemistry, Karl-Franzens-University, Universitätsplatz 1, A-8010 Graz, Austria*
[b] *Swiss Tropical Institute, Socinstrasse 57, CH-4002 Basel, Switzerland*
[c] *Institute of Chemical Technology of Organic Materials, Erzherzog-Johann University, Stremayrgasse 26/1, A-8010 Graz, Austria*

Received in revised form 4 April 2006; accepted 6 April 2006
Available online 26 May 2006

Abstract

New 4-amino-6,7-diphenylbicyclo[2.2.2]octane derivatives, esters of bicyclo[2.2.2]octan-2-ols and *O*-methyl oximes of bicyclo[2.2.2]octan-2-ones were synthesised. Their activities against *Trypanosoma brucei rhodesiense* (STIB 900) and their activity against the K1 strain of *Plasmodium falciparum* (resistant to chloroquine and pyrimethamine) were determined by use of microplate assays. The cytotoxicity was assessed using L6 cells. The antiprotozoal activities of the new compounds are compared with those of former prepared derivatives and drugs in use. Structure–activity relationships are discussed.

Keywords: 4-Aminobicyclo[2.2.2]octane derivatives; *Trypanosoma b. rhodesiense*; *Plasmodium falciparum*; In vitro assays; *O*-methyloximes; Aromatic esters

1. Introduction

Sleeping sickness has re-emerged as a serious problem in sub-Saharan Africa with an estimated 100,000 deaths each year [1]. The two protozoan parasites *Trypanosoma brucei gambiense* and *T. b. rhodesiense* are the causative organisms of this disease which is invariably fatal, if untreated [2]. The current drugs available for treatment suffer from a number of disadvantages, including toxic side effects, poor clinical efficacy, parenteral administration and increasing problems with resistance [3]. The latest introduced drug is eflornithine but it is unfortunately ineffective against *T. b. rhodesiense* [4]. Therefore, there is an urgent need for new drugs with less side effects and activity against the causative agent of East African Human Trypanosomiasis.

At present malaria is considered to be the world's most important tropical parasitic disease, afflicting 300–500 million people and killing 1–2 million annually [5]. It is estimated that nearly 40% of the world's population lives in malaria endemic regions. Of the four species of the disease-causing parasites, *Plasmodium falciparum* is the most dangerous form, accounting for up to 95% of malaria related deaths [6]. A main problem is drug resistance in this species [7]. Drugs in use such as chloroquine and the combination sulphadoxine–pyrimethamine which were once highly effective are almost useless in many parts of the world [8,9]. Loss of sensitivity has been observed even for the most recently introduced artemisinine derivatives [10–14]. Therefore, there is great demand for potent new antimalarial drugs.

Recently we reported the antiprotozoal activities of some methyl thiosemicarbazones of dialkylaminobicyclo[2.2.2]octan-2-ones **1** and esters of dialkylaminobicyclo[2.2.2]octan-2-ols **2** [15]. Especially the esters seemed to be worthy of further investigations because they feature in addition to their enhanced antiplasmodial activity rather low cytotoxicity. In the mean time, we prepared oximes **3** of dialkylaminobicyclo [2.2.2]octan-2-ones which possess remarkable antimalarial potency and moderate toxicity [16]. Starting from these results we

Abbreviations: CC, column chromatography; CH_2Cl_2, dichloromethane; DCC, dicyclohexylcarbodiimide; 4-DMAP, 4-dimethylaminopyridine; ether, diethylether; HCl, hydrochloric acid; MeOH, methyl alcohol; NaOH, sodium hydroxide.

* Corresponding author.
E-mail address: we.seebacher@uni-graz.at (W. Seebacher).

0223-5234/$ - see front matter © 2006 Elsevier SAS. All rights reserved.
doi:10.1016/j.ejmech.2006.04.002

prepared a number of bicyclo[2.2.2]oct-2-yl esters of aromatic acids and *O*-methyl oximes of bicyclic ketones and investigated the new compounds **4–9** for their antitrypanosomal and antiplasmodial activity and their cytotoxicity using in vitro microplate assays (Fig. 1).

2. Chemistry

We described the synthesis of compounds **1** from acyclic starting material via a one-pot procedure and determined their structures with the aid of a single crystal structure analysis [17]. The reaction of ketones **1a–d** with *O*-methyl hydroxylamine was carried out in alkaline medium giving *O*-methyloximes **4**. Their structures were established using NMR spectroscopy. Typically, the signal for C-2 was shifted from 213 ppm to 160 ppm in their ^{13}C NMR spectra due to the formation of oximes **4**. Prior to chromatographic purification, at least traces of different isomers **4a**, **c**, **d** and **4a′**, **c′**, **d′** in the mixtures were detected. In the case of the piperidino compounds, we were able to separate the *E*-isomer **4d′** from its *Z*-isomer **4d**. Their distinction succeeded via the greater upfield shift of the signal for the α-syn carbons in their ^{13}C NMR spectra [18].

The alcohols **2a–d** which served as starting material for esterification were yielded stereospecifically by the reduction of **1a–d** with lithium aluminium hydride. The configuration in position 2 of compounds **2a–d** was determined by measurement of through space couplings (NOEs) from their 2-Hs to their 6-Hs [19].

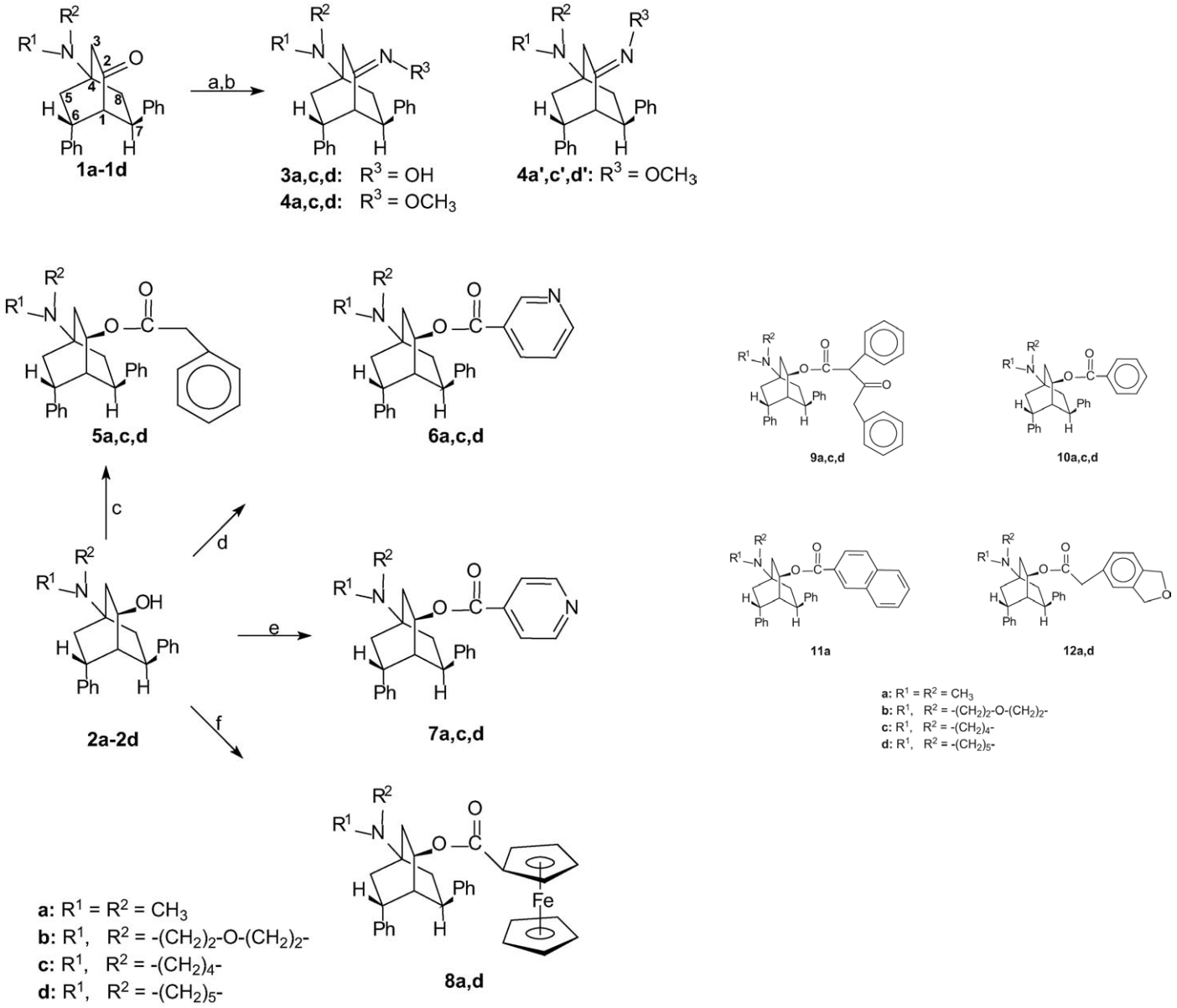

Fig. 1. (a) Hydroxylamine hydrochloride/NaOEt in refluxing EtOH (**3a–d**); (b) *O*-methyl hydroxylamine hydrochloride/NaOEt in refluxing EtOH (**4a–d**); (c) phenyl acetyl chloride/DMAP in CH_2Cl_2; (d) nicotinic acid/DCC/DMAP in CH_2Cl_2; (e) isonicotinic acid chloride/DMAP in CH_2Cl_2; (f) ferrocene carboxylic acid/DCC/DMAP in CH_2Cl_2.