SYNTHESIS OF AMIDES CONTAINING 3,4,5-TRIMETHOXYPHENYL GROUPS FROM *Eucalyptus* WOOD TAR

F. Carazza, M.F.C. Alcântara, M.O.S. Pereira

ABSTRACT: 3,4,5-trimethoxybenzoic acid (I) obtained by distillation and oxidation from *Eucalyptus* wood tar was converted to the 3,4,5-trimethoxybenzoyl chloride (II) and subsequently to amides: N-phenyl-3,4,5-trimethoxybenzamide (III), n-butyl-3,4,5-trimethoxybenzamide (IV) , 1-N-3,4,5-trimethoxybenzoyl-adamantanamine (V) and the novel compound N,N-1,3(3,4,5-trimethoxybenzoyl) adamantanediamine(VI).

INTRODUCTION

Reforestation in Brazil involves mainly plants of the genus *Eucalyptus*. Wood from this reforestation is mainly used by paper and cellulose industries, and charcoal siderurgies. Some siderurgies recover *Eucalyptus* tar. Fractionation of the tar furnishes 5 fractions: below 105°C , from 105° to 180°C, from 180° to 240°C, from 240° to 270°C and the pitch. The 240° - 270°C fraction (12%,tar) turned out to be rich in 4-alkyl-2,6-dimethoxyphenol derivatives. This fraction was methylated and subsequently oxidized furnishing 3,4,5-trimethoxybenzoic acid as the main product[1]. In nature there is a large number of biologically actives aromatic substances containing three vicinal methoxyl groups. Some of them are amides and amines[2,3]. Some N-alkylated amides and amines obtained from 1-adamantanamine have already been studied as potential antiviral[4] and dopaminergic[5] agents. Inhibitions of Rous sarcoma[6,7], and Esh sarcoma viruses has also been reported. Amantadine.HCl(1-adamantanamine.HCl) has been demonstraded to benefit patients suffering from Parkinson's disease[8] and the N,N-(3,4,5-trimethoxybenzoyl - 3,4,5-trimethoxyphenylmethyl) adamantanamine is a potential dopaminergic agent[5].

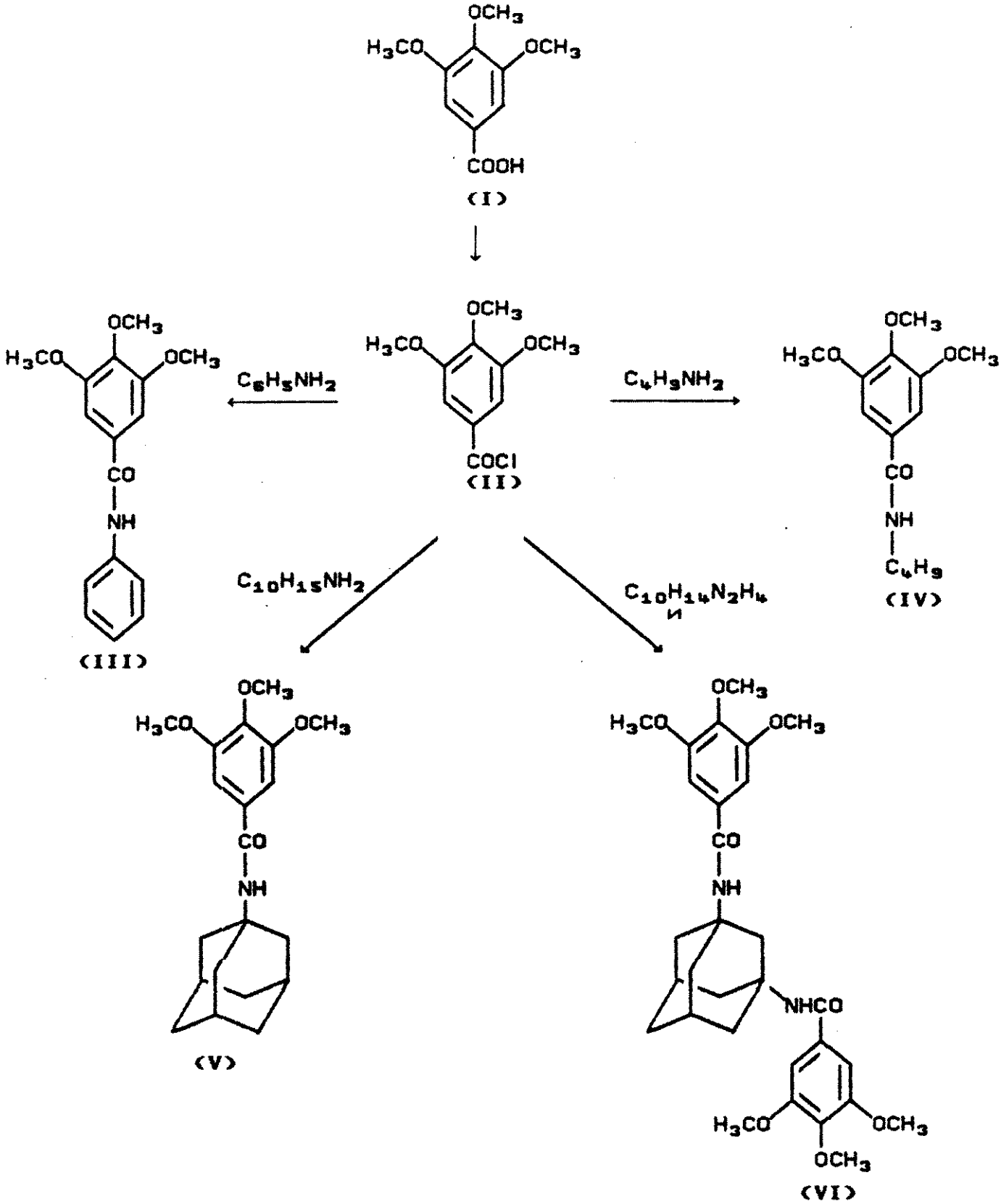
Thus in order to prepare analogous compounds, 3,4,5-trimethoxybenzoic acid was converted to the corresponding acid chloride and subsequently to the amide aiming to prepare potentially useful compounds. (scheme 1)

EXPERIMENTAL

All melting points are uncorrected. Infra-red analyses were performed on a Shimadzu/IR-408 spectometer; nuclear magnetic

resonance spectra were run in a Brucker AC-80, using $Me_4Si_{o_4}$ as a reference and mass spectra were run in a INCOS-50 mass spectrometer (70eV).

SCHEME 1



3,4,5-trimethoxybenzoyl Chloride (II): In 25 ml round bottommed flask, equipped with a reflux condenser, are placed 414 mg (2,0 mmol) of 3,4,5-trimethoxybenzoic acid and 5 mmol (0.3 ml) of thionyl chloride. The flask is warmed until gentil reflux and kept under this conditions for 6 h. Them the thionyl chloride is destilated under reduced pressure. Yield 90%.
IR (KBr): $\nu max/cm^{-1}$: 1750, 1595, 1510, 1465, 1420, 1325, 1245, 1130, 1050, 990, 850, 800, 770, 740, 690, 660.
^{1}H-NMR (80 MHz, $CDCl_3$) δ : 10,1 (1H,s,CO-H) , 7.3 (2H,s,Ar-H), 4,1 (9H,s,O-CH_3).

Preparation of amides (II) (VI) In a 50 ml two necked round bottommed flask equipped with a magnetic stirrer, a thermometer and a dropping funnel are placed 1,0 ml of NaOH 10%, 2,0 ml dry $CHCl_3$ and 2 mmol of phenylamine, n-butilamine, 1-adamantanamine for the production of the respectives amides (III),(IV), and (V); and 2,0 mmol of 1,3-adamantanediamine , 2,0 ml of NaOH 20%, 8,0 ml of dry $CHCl_3$ for the preparation of amide (VI) (scheme I). The flask is imersed in a ice-salt bath and cooled below 0°C. To the flask is added dropwise and with rapid stirring 2,0 mmol of 3,4,5-trimethoxybenzoyl chloride freshly prepared, dissolved in 4 ml of dry $CHCl_3$. When all the acid chloride has been added the ice-bath is removed. The stirring is continued at room temperature for 12 hours. It is then extrated with 3 x 20 ml portions of $CHCl_3$. The $CHCl_3$ is evaporated The solid formed is then recristallized in ethanol furnishing the amides:

N-phenyl-3,4,5-trimethoxybenzamide (III) yield-30%, m.p.137-139°C
IR (KBr): $\nu max/cm^{-1}$: 3300, 1645, 1600, 1580, 1510, 1440, 1320, 1270, 1240, 1220, 1170, 1150, 1110, 1030, 1020, 870, 710, 750, 690.
^{1}H-NMR (80 MHz, $CDCl_3$):δ - 8.05 (1H, broad, N-H); 7.68 -7.06 (7H, m, Ar-H), 3.88 (3H, s,-OCH_3), 3.86 (6H, s,-OCH_3)
EIMS: m/z / rel. int.: 287 [M^+] (28,8), 195 (100)
Elemental Analysis: ($C_{16}H_{17}O_4N$): Found C=66.98%; H=5.87%; N=4.88%. Calc C=66.89%; H=5.92%; N=4.88%.

N-butyl-3,4,5-trimethoxybenzamide (IV) yield-78%, m.p. 124-127°C
IR (KBr): $\nu max/cm^{-1}$: 3250, 2900, 1630, 1580, 1540, 1505, 1415, 1340, 1240, 1130, 1000, 850.
^{1}H-NMR (80Mhz, $CDCl_3$):δ - 7.02 (2H, s, Ar-H); 3.85 (9H, s,-OCH_3); 3.40 (2H, m, CO-CH_2); 1.50 (4H, m , -CH_2-); 0.92 (3H, m, C-CH_3)
EIMS: m/z / rel. int.: 267 [M^+] (66,6) ,225 (26,3), 211 (32,7) 195 (100).
Elemental Analysis ($C_{14}H_{21}O_4N$) : Found C=62.41%; H=7.88%; N=4.99%. Calc. C=62.92%; H=7.86%; N=5.24%

N-adamantyl-3,4,5-trimethoxybenzamide (V) yield-82%, m.p. 221-223°C.
IR (KBr) $\nu max/cm^{-1}$: 3250, 2850, 1630, 1580, 1530, 1500, 1410, 1345, 1334, 1230, 1220, 1130, 1090, 1020, 850, 760.
^{1}H NMR (80 MHz, $CDCl_3$) δ : 7.26 (2H, s, Ar-H); 5.7 (1H, broad, N-H); 3.89 (6H, s, OCH_3); 3.86 (3H, s, -OCH_3); 2.13 (9H, m, -CH-CH_2-); 1.73 (6H, m, -CH_2-)
EIMS: m/z / rel. int.: 345 [M^+] (85.3); 330 (23.0); 288 (23.0); 195 (100).
Elemental Analysis: ($C_{20}H_{27}O_4N$) Found: C=69.07%, H=7.88%, N=3.97%. Cal. C=69.5%, H=7.83%, N=4.05%.

N,N-1,3-(3,4,5-trimethoxybenzoyl)adamantanediamine (VI) yield: 50% m.p. 225-227°C
IR (KBr) $\nu max/cm^{-1}$: 3450-3250, 2900, 1630, 1580, 1535, 1500, 1415, 1335, 1225, 1125, 1050.
^{1}HMNR (60 MHz, $CDCl_3$) δ: 7.0 (4H, s, Ar-H); 6.0(2H, broad, N-H); 3.90 (18H, s,-OCH_3); 2.60 (2H, m,-CH); 2.0 (8H, m, -CH_2); 1.75 (4H, m,-CH_2)
EIMS: m/z / rel.int.: 554 [$M.^+$](10.8); 359(13.1); 195(100).
Elemental Analysis: ($C_{30}H_{38}O_8N_2$): Found: C=62.44%, H=6.81%, N=4.74. Calc. C=64.98%, H=6.85%, N=5.05%.

RESULTS AND DISCUSSION

The 3,4,5-trimethoxybenzoic acid was obtained via oxidation of the previously methylated[4] 240-270°C fraction from *Eucalyptus* tar. We obtained 3,4,5-trimethoxybenzoyl chloride from the acid which is the basic intermediate in the preparation of the amides. The method employed in the preparation of the amide was Schotten-Baumann, in wich an aqueous solution of NaOH below 0°C[9,10] is utilized. Aliphatic amines gave the best yields. These preparations although simple demanded the use of model compounds in order to get the ideal reaction conditions. So amides containing the 3,4,5-trimethoxyphenyl groups were prepared from primary aliphatic and aromatic amines. N,N-1,3(3,4,5-trimethoxybenzoyl)adamantanediamine was prepared using 1,3-adamantanediamine hydrochloride and it was necessary to increase the amount of NaOH solution to achieve a quantitative nucleophilic attack. The utilization of the conditions referred to in the experimental part furnished a solid (50%) .Elemental analysis results agree with the molecular formula $C_{30}H_{38}O_8N_2$. The EIMS analysis showded a [$M.^+$] peak at m/z 554 (10.8) followed by the characteristic peaks at 359 (13.1%) and 195 (100%). These data associated with those obtained through the ^{1}H-NMR and IV analysis confirm the identity of this inedit diamide obtained.

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