2-DIETHYLAMINOETHYL ESTERS OF 1,3-DISUBSTITUTED PROPANE-2-CARBOXYLIC ACIDS

Vladimír VALENTA, Jiří HOLUBEK, Emil SVÁTEK, Vladimír MILLER, Marie VLKOVÁ and Miroslav PROTIVA

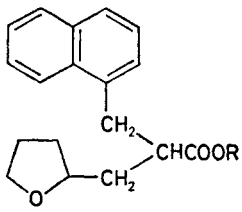
Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

Received February 6th, 1987

Alkaline hydrolysis of diethyl 1-(tetrahydro-2-furyl)-3-(1-naphthyl)propane-2,2-dicarboxylate (*IV*) gave the crude acid *V* which was purified *via* the dipotassium salt and was obtained as the homogeneous higher melting crystal form. Its thermic decarboxylation yielded the acid *II* as a mixture of two racemates (38 : 62); crystallization led to the almost homogeneous racemate B (10 : 90). Reaction of the sodium salt of *II* with dimethyl sulfate in methanol gave the methyl ester *III* which afforded by ester exchange with 2-diethylaminoethanol the ester *I* (mixture of two racemates 34 : 66). 2-Diethylaminoethyl 1,3-bis(1-naphthyl)propane-2-carboxylate (*VII*) was synthesized in three steps from diethyl (1-naphthylmethyl)malonate. Ester *X* was obtained from 1,3-bis(tetrahydro-2-furyl)propane-2-carboxylic acid by treatment with 2-diethylaminoethyl chloride in boiling 2-propanol in the presence of potassium carbonate. The acid *V* gave similarly the diester *VI*. 2-Diethylaminoethyl esters *I*, *VI*, *VII*, and *X* were transformed to the hydrogen oxalates. Pharmacological screening showed for the diester *VI* hypotensive, spasmolytic, antiarrhythmic, and antitussic activity.

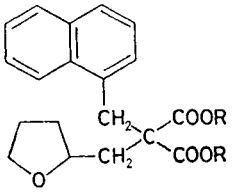
Dialkylaminoalkyl (especially 2-diethylaminoethyl) esters of 1,3-disubstituted propane-2-carboxylic acids with bulky substituents in positions 1 and 3 (naphthyl, methoxynaphthyl, tetrahydronaphthyl, furyl, tetrahydrofuryl *etc.*) were prepared and found to have antispasmodic and vasodilating activity[1-6]. The best known representative of this group of compounds is 2-diethylaminoethyl 1-(tetrahydro-2-furyl)-3-(1-naphthyl)propane-2-carboxylate (*I*) (refs[2-4]), bearing the generic name naftidrofuryl, which is used as the hydrogen oxalate of the stereoisomeric mixture. It has spasmolytic, local anaesthetic, cerebral vasodilating, and antiserotonin activities, improves the oxygen and glucose utilization in the brain tissues, and increases the energetic potential and formation of adenosine triphosphate in the brain. In geriatric and arteriosclerotic patients it improved the general clinical condition and the intelectual performance; it was recommended for routine clinical use in gerontopsychiatry[7-11]. The present paper discloses new or improved procedures of synthesis of *I* and the corresponding intermediates, and describes the synthesis of three analogues.

The synthesis of *I* may start either from tetrahydrofurfuryl alcohol or from furfural. Tetrahydrofurfuryl alcohol was transformed to tetrahydrofurfuryl bromide[12]



I, R = $CH_2CH_2N(C_2H_5)_2$
II, R = H
III, R = CH_3

by treatment with phosphorus tribromide in toluene in the presence of pyridine with a yield of 50%. From the distillation residue there were obtained 6% of 1,2,5--tribromopentane. This by-product, which was not described[12] in the mentioned reaction, resulted by substitution of the hydroxy group and by the cleavage of the ether ring; it seems unlikely that its formation was caused by substituting benzene[12] with toluene as the reaction medium. The literature[13] described the synthesis of diethyl furfurylidenemalonate by refluxing a mixture of furfural, diethyl malonate, and acetic anhydride. In this paper a different method is described consisting in the reaction of furfural with diethyl malonate in toluene in the presence of piperidine acetate (analogy[14]); the yield was 85% (purity 99·7% according to gas chromatography). The alkylation of diethyl malonate with tetrahydrofurfuryl bromide was carried out according to the literature[15] and gave 61% diethyl tetrahydrofurfurylmalonate. Attempts to alkylate diethyl malonate with tetrahydrofurfuryl chloride[16,17] under similar conditions showed the very slow reaction: After refluxing for 14 h the yield was only 11%. A more advantageous method proved the catalytic hydrogenation of diethyl furfurylidenemalonate in ethanol (*cf.*[13,18]). Using the hydrogen pressure of 7·5 MPa enabled to work at 80°C and to obtain a very pure product in high yield (at higher temperatures, ref.[13] described the isolation of two by-products). Further alkylation of diethyl tetrahydrofurfurylmalonate with 1-(chloromethyl)naphthalene[19] in ethanol (*cf.*[1,5,20]) yielded 76% of the homogeneous ester *IV*.



IV, R = C_2H_5
V, R = H
VI, R = $CH_2CH_2N(C_2H_5)_2$

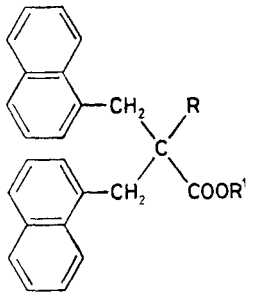
The malonate *IV* was hydrolyzed with potassium hydroxide in aqueous ethanol (*cf.*[5]) to the acid *V*. In our hands it crystallized from benzene as the 2 : 1 benzene solvate (m.p. 42°C), from aqueous ethanol as the nonsolvated less stable crystal modification A melting at 81–84°C, and from a mixture of acetone and hexane as the more stable modification B melting at 142–143°C. For preparing further intermediates and the final product I in pure form without the need of distillations, it proved advisable to purify the acid *V*. The dipotassium salt of *V* crystallized in good yield as the trihydrate from the strongly alkaline solution. Its decomposition with hydrochloric acid afforded the pure form B of the acid *V*. This was decarboxylated by heating to 140–160°C (*cf.*[5]) to the acid *II* (by high-pressure liquid chromatography the ratio of the racemates A and B was 38 : 62). The literature[1,21] described a different procedure. This mixture could further be purified either *via* an aqueous solution of its potassium salt or *via* its solid calcium salt. Long standing of the purified mixture led to partial crystallization and gave a product melting at 84–87°C (according to HPLC *II*-A : *II*-B = 10 : 90). This product is probably identical with the racemate *II*-B, described in a patent[22]. Reaction of the crystalline acid *V* (form B) with 2-diethylaminoethyl chloride hydrochloride in boiling 2-propanol in the presence of potassium carbonate gave the diester *VI* which was isolated and characterized in the form of the bis(hydrogen oxalate). A different procedure for preparing this ester has recently been described[23].

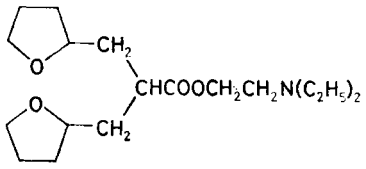
The acid *II* (38% A, 62% B) was transformed by treatment with sodium methoxide in methanol to a solution of the sodium salt which was refluxed with dimethyl sulfate giving the methyl ester *III*. After distillation, the ratio of racemates A and B was found to be 35 : 65 (HPLC). The same product was obtained by esterification of *II* with methanol in boiling benzene in the presence of sulfuric acid (this method was mentioned in the literature[21]).

Preparation of the ester *I* was described by reaction of the acid *II* with 2-diethylaminoethyl chloride or its hydrochloride in boiling 2-propanol in the presence of potassium carbonate[2–4], by azeotropic esterification of the acid *II* with 2-diethylaminoethanol[3], and by further, less convenient methods[18,23]. Now, it has been obtained in a high yield and in a very good quality by the ester exchange reaction from *III* and 2-diethylaminoethanol in boiling toluene and in the presence of a catalytic amount of sodium 2-diethylaminoethoxide. The undistilled ester *I* was transformed to the hydrogen oxalate, and the distilled ester was used for recording the spectra. According to HPLC, the crude product consisted of 33·6% racemate A and 66·4% racemate B. Recrystallization of the hydrogen oxalate from acetone shifted this ratio in favour of the racemate B. After a single recrystallization the ratio of A : B is 28·4 : 71·6. Literature[22] described the preparation of homogeneous racemate B by repeated crystallization of hydrogen oxalate from acetone.

The esters *VII* and *X* were prepared for pharmacological screening. The known diethyl (1-naphthylmethyl)malonate[24] was treated with sodium ethoxide in ethanol

and alkylated with 1-(chloromethyl)naphthalene[19] to give diethyl 1,3-bis(1-naphthyl)-propane-2,2-dicarboxylate (*VIII*). This was hydrolyzed with potassium hydroxide in boiling aqueous ethanol and the primarily formed disubstituted malonic acid was decarboxylated by heating in acid solution (pH 2–3) to 45°C. The obtained acid *IX* was characterized by spectra and transformed by refluxing with 2-diethylaminoethyl chloride hydrochloride in 2-propanol in the presence of potassium carbonate to the ester *VII* (transformed for characterization and for pharmacological testing to the hydrogen oxalate). The ester *X* was obtained similarly from the known 1,3-bis-(tetrahydro-2-furyl)propane-2-carboxylic acid[15]; it was also transformed to the hydrogen oxalate.





X

VII, R = H ; R' = $CH_2CH_2N(C_2H_5)_2$
VIII, R = $COOC_2H_5$; R' = C_2H_5
IX, R = R' = H

The esters *VI*, *VII*, and *X* in the form of hydrogen oxalates were subjected to pharmacological screening. Acute toxicity in mice (LD_{50} in mg/kg) and doses used in the screening (D in mg/kg): *VI*, 15 *i.v.*, 3 *i.v.*; *VII*, >2 500 *p.o.*, 300 *p.o.*; *X*, 85 *i.v.*, 17 *i.v.* *VI* and *X* in doses D elicited in anaesthetized normotensive rats deep and brief drops of the blood pressure. In concentrations of 1–10 μg/ml, *VI* and *X* inhibited the acetylcholine-induced contractions of the isolated rat duodenum (approximately to 50% of the control which means a mild spasmolytic effect of the parasympatholytic type); in the same concentrations, compound *VI* inhibited also the barium chloride-induced contractions (strong spasmolytic effect of the papaverine type). Compound *VI* in doses of 1–3 mg/kg *i.v.* had antiarrhythmic activity in rats towards aconitine-induced arrhythmia (quinidine-like effect). In the dose D, compound *VI* had significant antitussic effect in guinea-pigs (reduced the frequency of the cough attacks, elicited by the aerosol of an aqueous citric acid solution, by 35%). Compound *VII* in the oral dose of 100 mg/kg showed hyperglycaemic effect in rats (increased the blood sugar level by 20%). Antimicrobial activity *in vitro* (microorganisms and the minimum inhibitory concentrations in μg/ml given):

Streptococcus β-haemolyticus, VII 6·2; *Staphylococcus pyogenes aureus, VII* 12·5; *Saccharomyces pasterianus, VII* 50; *Trichophyton mentagrophytes, VI* 50, *VII* 50.

EXPERIMENTAL

The melting points of analytical preparations were determined in the Kofler block and were not corrected. The samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra were recorded with a Unicam SP 8000 spectrophotometer, IR spectra with a Perkin–Elmer 298 spectrophotometer, ^{1}H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487 C (80 MHz) spectrometer, and the mass spectra with MCH 1320 and Varian MAT 44 S spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). Gas chromatographic analyses were made on Perkin–Elmer F 7, Chrom 4, and Chrom 66 instruments. High-pressure liquid chromatography was carried out on a Micro-Bondapak CN column (Waters 30 × 0·39 cm).

Tetrahydrofurfuryl Bromide

Tetrahydrofurfuryl alcohol (204 g) was treated with 230 g PBr_3 in 10 0 ml toluene and 40 g pyridine according to Smith[12] who used benzene instead of toluene. Similar processing gave 164 g (50%) product, b.p. 71—74°C/4 kPa (purity of 97·7% according to GC). Ref.[12], b.p. 69—70°C/2·0 kPa. Distillation of the residue afforded 36 g (6%) 1,2,5-tribromopentane, b.p. 129—131°C/2·3 kPa. ^{1}H NMR spectrum: 1·70—2·50 m, 4 H (Br—C—CH_2CH_2); 3·40 and 3·80 2 m, 4 H (2 CH_2Br); 4·20 m, 1 H (CH—Br). The analysis was in agreement with the elemental composition $C_5H_9Br_3$. Ref.[25], b.p. 128—132°C/1·5 kPa (different way of formation).

Diethyl Furfurylidenemalonate

A stirred solution of 288 g furfural in 300 ml toluene was treated with 480 g diethyl malonate, 10·2 g piperidine, and 36 g acetic acid, the mixture was heated to 100—104°C and the azeotropic mixture of toluene and water (b.p. 84°C) was distilled off for 1·5 h. The temperature of the mixture was then increased to 110—120°C over 4 h and the boiling point approached 110°C. After cooling the mixture was filtered through a column of 600 g neutral Al_2O_3 (activity II) and the column was washed with 200 ml toluene, the filtrate was evaporated *in vacuo*, and the residue was distilled. The crude product (665 g) boiling at 118—122°C/53 Pa was redistilled using a 35 cm column; 605 g (85%), b.p. 116—118°C/40 Pa (99·7% according to GC). On standing at 10°C for 2 days, the product crystallized, m.p. 40—40·5°C. UV spectrum (ethanol): λ_{max} 310 nm (log ε 4·38). IR spectrum (KBr): 1 250 (C—O of ester), 1 630 (C=C), 1 720 (C=C—COOR), 2 990 cm^{-1} (C—H in CH_3, CH_2). ^{1}H NMR spectrum: 1·30 and 1·35 2 t, 6 H (2 CH_3, J = 6·0 Hz); 4·24 and 4·35 2 q, 4 H (2 OCH_2, J = 7·0 Hz); 6·44 dd, 1 H (4-H, J = 3·3; 1·7 Hz); 6·71 bd, 1 H (3-H, J = 3·3 Hz); 7·40 s, 1 H (C=CH); 7·49 bd, 1 H (5-H, J = 1·7 Hz). For $C_{12}H_{14}O_5$ (238·2) calculated: 60·49% C, 5·92% H; found: 60·77% C, 5·86% H. Ref.[13], b.p. 172—175°C/1·2 kPa.

Diethyl Tetrahydrofufurylmalonate

A) Diethyl malonate (272 g) was treated with sodium ethoxide (from 39·1 g Na) in 500 ml ethanol and then refluxed with 280 g tetrahydrofurfuryl bromide to give 252 g (61%) title product, b.p. 102—105°C/0·027 kPa), in agreement with ref.[15] (b.p. 123°C/0·133 kPa).

B) Raney Ni (100 g) was added to a solution of 351 g diethyl furfurylidenemalonate in 1·4 l ethanol and the mixture was hydrogenated in an autoclave at 80°C and 7·5 MPa H_2 under stirring. After 6 h the reaction was finished, after cooling the catalyst was filtered off and washed with ethanol. The filtrate was evaporated under reduced pressure at 50°C, and the residue was distilled; 314 g (88%), b.p. 103–104°C/40 Pa (purity 99·12% by GC). UV spectrum (ethanol): λ_{max} 221 nm (log ε 2·31). IR spectrum (KBr): 1 725 cm^{-1} (RCOOR'). ^{1}H NMR spectrum: 1·21 t, 6 H (2 CH_3, J = 7·0 Hz); 1·20–1·50 m, 6 H ($CH_2CH_2C(=O)CH_2$); 3·40–4·00 m, 4 H (CH_2OCH—C—CH); 4·18 q, 4 H (2 CH_2O in the ester groups, J = 7·0 Hz). Ref.[13] described a similar hydrogenation at 100–130°C, b.p. 150–151°C/1·33 kPa.

Diethyl 1-(Tetrahydro-2-furyl)-3-(1-naphthyl)propane-2,2-dicarboxylate (*IV*)

Diethyl tetrahydrofurfurylmalonate (270 g) was treated with 196 g 1-(chloromethyl)naphthalene[19] in 670 ml ethanol in the presence of sodium ethoxide from 25·5 g Na according to refs[1,5,20]; 319 g (76%) *IV*, b.p. 190–192°C/40 Pa (purity 100% by GC). UV spectrum (ethanol): λ_{max} 228 nm (log ε 4·85), 276 nm (3·81), 286 nm (3·88), 316 nm (2·62). IR spectrum ($CHCl_3$): 1 180 (C—O of ester), 1 595 (Ar), 1 720 cm^{-1} (RCOOR'). ^{1}H NMR spectrum: 1·10 t, 6 H (2 CH_3, J = 7·0 Hz); 1·20–2·10 m, 6 H ($CH_2CH_2C(=O)—CH_2$); 3·60–4·10 m, 3 H (CH_2OCH in tetrahydrofuryl); 3·85 s, 2 H (CH_2Ar); 3·98 q, 4 H (2 OCH_2 in the malonate fragment, J = = 7·0 Hz); 7·20–8·20 m, 7 H (Ar—H of naphthyl). Refs[1,5,20], b.p. 211°C/127 Pa, 225–226°C/ /0·4 kPa, and 200°C/133 Pa, respectively.

Diethyl 1,3-Bis(1-naphthyl)propane-2,2-dicarboxylate (*VIII*)

Na (3·22 g) was dissolved in 100 ml ethanol, the stirred solution was treated at 40–50°C with 42·0 g diethyl (1-naphthylmethyl)malonate[24], the mixture was stirred for 20 min and treated over 15 min with 24·7 g 1-(chloromethyl)naphthalene[19]. After the exothermic reaction (spontaneous rise of temperature to 65°C) was over, the mixture was refluxed for 6 h. Ethanol was distilled off at normal pressure, the residue was diluted with 50 ml water and extracted with ether. The extract was washed with water, dried with $MgSO_4$ and evaporated. The residue (60·4 g) was dissolved in 50 ml hexane and the solution was allowed to stand for 12 h. There crystallized 38·6 g (63%) crude product, m.p. 60–75°C. Analytical sample, m.p. 76–80°C (hexane). IR spectrum (KBr): 770, 780, 800 (4 and 3 adjacent Ar—H of 1-naphthyl); 1 190, 1 240 (C—O of ester); 1 485, 1 510, 1 600, 3 050 (Ar); 1 720, 1 745 cm^{-1} (RCOOR'). ^{1}H NMR spectrum: 0·80 t, 6 H (2 C—CH_3, J = 7·0 Hz); 3·70 q, 4 H (2 $COOCH_2$, J = 7·0 Hz); 3·82 s, 4 H (2 $ArCH_2$); 7·00–8·10 m, 14 H (14 Ar—H of 2 naphthyl residues). For $C_{29}H_{28}O_4$ (440·5) calculated: 79·06% C, 6·41% H; found: 79·11% C, 6·36% H.

1-(Tetrahydro-2-furyl)-3-(1-naphthyl)propane-2,2-dicarboxylic Acid (*V*)

A) A mixture of 22·0 g *IV*, 80 ml ethanol, 40 g 85% KOH, and 40 ml water was stirred and refluxed for 3 h. Ethanol was distilled off, the residue was diluted with 120 ml water. and the solution was washed with ether. It was then neutralized with 5M-HCl, filtered with charcoal, and the filtrate was acidified with 5M-HCl to pH 1. The semi-solid product was extracted with 50 ml benzene which was evaporated under reduced pressure; 11·7 g (60%) 2 : 1 solvate with benzene, m.p. 42°C. IR spectrum (Nujol): 775, 789 (Ar—H of 1-substituted naphthalene); 1 195, 1 215, 1 235 (C—O of COOH); 1 637, 1 703, 1 725, infl. 1 750, 2 595, 2 720, infl. 3 160 cm^{-1} (COOH); in $CHCl_3$: 1 655, 1 685, 1 705, 1 750 cm^{-1} (COOH). ^{1}H NMR spectrum ($C^2H_3SOC.^2H_3$) is practically identical with that of the modification A. For $C_{19}H_{20}O_5$ + 0·5 C_6H_6 (341·4) calculated: 70·36% C, 6·20% H; found: 70·09% C, 6·32% H.

Crystallization of the crude product from 50% aqueous methanol gave the nonsolvated less stable modification A, m.p. 81–84°C. IR spectrum (Nujol): 788 (Ar—H of 1-substituted naphthalene); 1 168 (C—O—C), 1 196, 1 219 (C—O in COOH); 1 640, 1 655, 1 733, 2 675, 3 150 cm^{-1} (COOH); in $CHCl_3$: 1 653, 1 674, 1 750 cm^{-1} (COOH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): 1·20–2·20 m, 6 H ($CH_2CH_2C(=O)—CH_2$); 3·20–4·10 m, 5 H (CH_2OCH and $ArCH_2$); 7·40–8·40 m, 7 H (Ar—H of naphthyl). For $C_{19}H_{20}O_5$ (328·4) calculated: 69·50% C, 6·14% H; found: 68·96% C, 6·27% H.

Crystallization of the crude product from a 1 : 2 mixture of acetone and hexane gave the nonsolvated more stable modification B, m.p. 142–143°C. UV spectrum (ethanol): λ_{max} 228 nm (log ε 4·84), 276 nm (3·81), 286 nm (3·89), 318 nm (2·56). IR spectrum (Nujol): 722, 790 (Ar—H of 1-substituted naphthalene); 900 (O—H in COOH); 1 170 (C—O—C of tetrahydrofuran); 1 200, 1 220 (C—O of COOH); 1 640, 1 653, 1 733, 2 670, 3 150 cm^{-1} (COOH); in $CHCl_3$ the spectrum is identical with that of modification A. ^1H NMR spectrum ($C^2H_3SOC^2H_3$) is also identical with that of modification A. For $C_{19}H_{20}O_5$ (328·4) calculated: 69·50% C, 6·14% H; found: 69·19% C, 6·30% H.

B) The crude *IV* (332 g) (prepared like described above but not distilled; such a product was obtained in the yield of 98%, purity by GC at least 94%) was dissolved at 60–70°C in 660 ml ethanol, the solution was treated with a solution of 483 g 85% KOH in 483 ml water, and the mixture was refluxed under stirring for 2·5 h. A part of the solvents (660 ml) was distilled of at normal pressure and the residue was treated at 60°C with 500 ml 15% aqueous solution of KCl (120 g KCl). The solution obtained was washed with toluene at 50–60°C. Under 40°C the dipotassium salt of the product started to crystallize; the crystallization was finished by standing at 5°C overnight. After cooling to −4°C the salt was filtered, washed with 20% aqueous KCl, and dried at 60°C; 244 g. This crude salt was dissolved in 560 ml boiling 80% aqueous ethanol, the undissolved part was filtered off, and the filtrate was allowed to crystallize first at room temperature and finally for 16 h at 5°C; 173 g (46%) trihydrate, decomposition above 230°C. For $C_{19}H_{18}.K_2O_5 + 3\ H_2O$ (458·6) calculated: 11·78% H_2O; found: 12·50% H_2O.

A solution of 80·8 g trihydrate of the dipotassium salt in 150 ml water was stirred and slowly acidified at max. 25°C with 45 ml hydrochloric acid (final pH 1). The free acid *V* was extracted with 300 ml dichloromethane, the extract was washed with water at 25–30°C, and allowed to crystallize for 16 h at 0–5°C; 60·4 g crude *V*-B, m.p. 135–140°C. A single crystallization from a mixture of acetone and hexane gave the completely pure product melting at 142–143°C which was found identical with crystal modification B (described under *A*).

1-(Tetrahydro-2-furyl)-3-(1-naphthyl)propane-2-carboxylic Acid (*II*)

Crystalline *V* (60·4 g crystal modification B) was decarboxylated by heating to 140°C for 1 h and to 160°C for 1 h (*cf.*[5]). The waxy residue (50·2 g; 96%) is the mixture of two racemates of the title acid (38% racemate A and 62% racemate B by HPLC). In this form it can be used for further work. Refs[1,21], b.p. 212–214°C/133 Pa.

For further purification, 12·0 g of this mixture was dissolved in 450 ml toluene, from this solution the acid *II* was extracted with 300 ml 10% K_2CO_3, the aqeous solution was acidified with 60 ml 6M-HCl (final pH 1), and the product was extracted with chloroform. The solvent was evaporated and the residue was allowed to stand at −10°C. After 2 months standing it crystallized partly; it was diluted with a mixture of benzene and hexane and the solid was filtered; 4·1 g. Repeated crystallization from a mixture of benzene and hexane gave the product melting at 84–87°C (10% racemate A and 90% racemate B by HPLC). UV spectrum (ethanol): λ_{max} 228 nm (log ε 4·79), 275 nm (3·72), 317 nm (2·49). IR spectrum ($CHCl_3$): 1 710, 2 600 cm^{-1}

(COOH). ^{1}H NMR spectrum: 1·00—2·20 m, 6 H ($CH_2CH_2C(=O)—CH_2$); 2·80—4·00 m, 6 H (CH_2OCH and $ArCH_2CHCO$); 7·00—8·20 m, 7 H (Ar—H of naphthyl); 11·30 bs, 1 H (COOH). For $C_{18}H_{20}O_3$ (284·4) calculated: 76·02% C, 7·10% H; found: 75·64% C, 7·11% H. Ref.[22], m.p. 90°C for the homogeneous racemate B.

Neutralization of the stereoisomeric mixture *II* with a suspension of $Ca(OH)_2$ in hot water gave the solid Ca salt (m.p. 190—220°C with decomposition) which is too insoluble in water making the recrystallization impossible; the acid *II* was regenerated from the Ca salt by decomposing a suspension of this salt in water with 2·5M-HCl and by extraction with chloroform.

1,3-Bis(1-naphthyl)propane-2-carboxylic Acid (*IX*)

A suspension of 36·0 g *VIII* in 70 ml ethanol was treated with a solution of 16·8 g 85% KOH in 35 ml water, and the mixture was refluxed for 7 h. Ethanol was distilled off, the residue was diluted with 150 ml water and the mixture was heated to 75°C in order to obtain a solution. This was acidified under stirring at 60—70°C with hydrochloric acid to the final pH 2—3. The mixture was stirred for 1·5 h at 45°C. The primarily formed substituted malonic acid was decarboxylated during this procedure. After cooling to 15°C, the crystalline product was filtered, washed with water, and dried; 17·2 g crude *IX* giving by a single crystallization from a mixture of 200 ml benzene (undissolved part was removed by filtration) and 250 ml light petroleum 22·1 g (72%) product melting at 169—174°C. Analytical sample, m.p. 174—176°C (benzene–light petroleum). IR spectrum (Nujol): 770, 795 (4 and 3 adjacent Ar—H of 1-naphthyl); 955 (O—H of COOH); 1 250 (C—O of COOH); 1 508, 1 595, 3 000, 3 050, 3 060 (Ar); 1 700 (COOH); 2 560, 2 660, infl. 3 050 cm^{-1} (OH in COOH). ^{1}H NMR spectrum: 3·00—3·70 m, 5 H ($ArCH_2CH(COO)—CH_2Ar$); 7·00—8·00 m, 14 H (14 Ar—H of two naphthyls); 11·00 bs, 1 H (COOH). For $C_{24}H_{20}O_2$ (340·4) calculated: 84·68% C, 5·92% H; found: 84·94% C, 5·92% H.

Methyl 1-(Tetrahydro-2-furyl)-3-(1-naphthyl)propane-2-carboxylate (*III*)

A) Na (1·8 g) was dissolved in 20 ml methanol and the stirred sodium methoxide solution was slowly treated at 25°C with a solution of 19·6 g *II* (stereoisomeric mixture) in 20 ml methanol. At 40°C a solution of 9·7 g dimethyl sulfate in 10 ml methanol was added dropwise over 1 h, the mixture was stirred for 2 h at 50°C, 2·7 g dimethyl sulfate were added, and the mixture was refluxed for 2 h. Methanol was distilled off at normal pressure, the residue was diluted with chloroform, the solution was washed with 10% $NaHCO_3$, with water, and dried with Na_2SO_4. Chloroform was evaporated under reduced pressure and the crude *III* (stereoisomeric mixture) was distilled; 16·5 g (79%), b.p. 176—180°C/67 Pa, purity 95% (GC). HPLC separated the two racemates A and B and estimated their ratio 35 : 65. ^{1}H NMR spectrum: 1·20—2·20 m, 6 H ($CH_2CH_2C(=O)—CH_2$); 3·52 s, 3 H ($COOCH_3$); 2·80—4·00 m, 6 H ($CH_2OCH—C—CH.(—COO)—CH_2Ar$); 7·10—8·15 m, 7 H (Ar—H of naphthyl). Ref.[21] gave for the product, prepared differently, the b.p. 170°C/53 Pa.

B) *II* (66·5 g of stereoisomeric mixture) was dissolved in 75 ml warm benzene, the solution was added with stirring to a solution of 55 g H_2SO_4 in 400 ml methanol, and the mixture was refluxed for 5 h. A part of the solvents (400 ml) was distilled off and was substituted with 400 ml toluene. After cooling, the bottom layer (H_2SO_4) was separated, the toluene layer was washed with water, 10% $NaHCO_3$ and water, was dried with Na_2SO_4, and evaporated under reduced pressure. The residue gave by distillation 40·2 g (58%) *III*, b.p. 172—175°C/80 Pa, purity 95% (GC). The product (stereoisomeric mixture) was identical with that obtained under *A*) and the procedure was probably similar to that mentioned in ref.[21] (without experimental details).

2-Diethylaminoethyl 1-(Tetrahydro-2-furyl)-3-(1-naphthyl)propane-2-carboxylate (*I*)

Na (0·23 g) was dissolved in 25·8 g 2-diethylaminoethanol, 50 ml toluene and 31·7 g *III* were added and the mixture was slowly distilled through a column. The distilling mixture of toluene and methanol was continuously substituted with dry toluene. Over 20 h 165 ml toluene–methanol mixture were distilled off and 165 ml toluene were added. The mixture was then diluted with 150 ml toluene, washed with water (35°C), dried with Na_2SO_4, and evaporated under reduced pressure; 37·3 g (92%) crude oily base (mixture of two racemates). This product could directly be transformed to the hydrogen oxalate of good quality but for recording the spectra, samples were distilled; b.p. 204°C/53 Pa or 189–193°C/3–4 Pa (diffusion pump). Mass spectrum, *m/z* (%): 383 (M^+, $C_{24}H_{33}NO_3$, 0·2), 141 ($C_{11}H_9$, 5·5), 100 (10), 99 (37), 87 (3), 86 ($CH_2{=}\overset{+}{N}(C_2H_5)_2$, 100), 71 (7), 58 (5). UV spectrum (ethanol): λ_{max} 228 nm (log ε 4·87), 276 nm (3·80), 286 nm (3·87), 316 nm (2·59). IR spectrum (film): 775, 795, 800 (3 and 4 adjacent Ar—H in 1-naphthyl); 1 070, 1 170 (C—O—C); 1 508, 1 595, 3 045 (Ar); 1 728 (RCOOR'); 2 800 cm^{-1} (CH_2—N). ^{1}H NMR spectrum: 0·90 t, 6 H (2 C—CH_3, J = 7·0 Hz); 1·20–2·20 m, 6 H (CH_2CH_2—C.(—O)—CH_2); 2·40 m, 6 H ($N(CH_2)_3$); 2·70–4·10 m, 6 H (CH_2OCH—C—CH(—COO)——CH_2Ar); 3·98 t, 2 H ($COOCH_2$, J = 7·0 Hz); 7·20–8·20 m, 7 H (7 Ar—H of 1-naphthyl). Ref.[3], b.p. 190°C/67 Pa.

Hydrogen oxalate, m.p. 109–111°C (acetone), ratio of racemates A and B 33·6 : 66·4. Recrystallization from acetone shifts this ratio in favour of the racemate B, A : B = 28·4 : 71·6 (HPLC), m.p. 108–110°C. Refs[3,22], m.p. 110–111°C (mixture of racemates), 110°C (racemate B).

Bis(2-diethylaminoethyl) 1-(Tetrahydro-2-furyl)-3-(1-naphthyl)propane-2,2-dicarboxylate (*VI*)

A mixture of 10·0 g *V*, 120 ml 2-propanol, 6·1 g 2-diethylaminoethyl chloride hydrochloride, and 5·8 g K_2CO_3 was stirred and refluxed for 12 h. After cooling, the solid was filtered off, washed with ethanol, and the filtrate was evaporated under reduced pressure. The residue was dissolved in 80 ml benzene, the solution was washed with 10% $NaHCO_3$ and water, dried with K_2CO_3, and evaporated *in vacuo*; 9·3 g (81%) crude oily base. Neutralization with 3·0 g oxalic acid dihydrate in 25 ml boiling acetone gave 5·6 g bis(hydrogen oxalate), m.p. 112–122°C. Analytical sample, m.p. 132–135°C (ethanol–ether). Ref.[23], m.p. 130°C (the base was prepared differently). The analysis confirmed the elemental composition $C_{35}H_{50}N_2O_{13}$.

2-Diethylaminoethyl 1,3-Bis(1-naphthyl)propane-2-carboxylate (*VII*)

A mixture of 7·0 g *IX*, 50 ml 2-propanol, 3·9 g 2-diethylaminoethyl chloride hydrochloride, and 6·1 g K_2CO_3 was stirred and refluxed for 22 h. After cooling to 20°C, the solid was filtered off, the filtrate was evaporated under reduced pressure, the residue was dissolved in 100 ml benzene, the solution was washed with 10% $NaHCO_3$ and water, dried with K_2CO_3, and evaporated *in vacuo*; 9·0 g (83%) crude oily base. This was dissolved in 25 ml acetone and neutralized with a solution of 2·5 g oxalic acid dihydrate in 10 ml acetone. Addition of 45 ml ether induced crystallization of 8·9 g (82%) hydrogen oxalate, m.p. 135–136°C (acetone–ether). Mass spectrum, *m/z* (%): 439 (M^+, $C_{30}H_{33}NO_2$, 0·3), 298 ($C_{19}H_{24}NO_2$, 3), 225 ($C_{15}H_{13}O_2$, 0·5), 153 ($C_{12}H_9$, 3), 141 ($C_{11}H_8$, 13), 99 ($C_6H_{13}N$, 27), 86 ($C_5H_{12}N$, 100). For $C_{32}H_{35}NO_6$ (529·6) calculated: 72·57% C, 6·65% H, 2·65% N; found: 72·69% C, 6·72% H, 2·50% N.

A sample of the hydrogen oxalate was decomposed by an aqueous K_2CO_3 solution and the released base was isolated by extraction with ether. It was used for recording the ^{1}H NMR spectrum: 0·82 t, 6 H (2 C—CH_3, J = 7·0 Hz); 2·22 t, 2 H (COO—C—CH_2N, J = 7·0 Hz); 2·28 q, 4 H (CH_2NCH_2, J = 7·0 Hz); 3·30 m, 5 H ($ArCH_2$—CH(—COO)—CH_2Ar); 3·88 t, 2 H ($COOCH_2$, J = 7·0 Hz); 7·00–7·90 m, 14 H (14 Ar—H of two naphthyls).

2-Diethylaminoethyl 1,3-Bis(tetrahydro-2-furyl)propane-2-carboxylate (*X*)

A stirred mixture of 5·1 g 1,3-bis(tetrahydro-2-furyl)propane-2-carboxylic acid[15], 45 ml 2-propanol, 4·1 g 2-diethylaminoethyl chloride hydrochloride, and 6·9 g K_2CO_3 was refluxed for 20 h. After cooling the solid was filtered off and the filtrate was evaporated under reduced pressure. The residue was dissolved in 60 ml benzene, the solution was washed with 1M-NaOH and water, dried with $MgSO_4$, and evaporated *in vacuo*; 7·2 g (99%) crude oily base. A sample for analysis was distilled; b.p. 155°C/40 Pa. Mass spectrum, *m/z* (%): 327 (M^+, $C_{18}H_{33}NO_4$, very weak), 172 ($C_9H_{18}NO_2$, 3), 100 (26), 99 (27), 86 (100), 71 (18), 58 (5), 44 (9), 43 (9), IR spectrum (film): 1 070, 1 165 (C—O—C), 1 730 (RCOOR') cm^{-1}. For $C_{18}H_{33}NO_4$ (327·5) calculated: 66·33% C, 10·16% H, 4·28% N; found: 66·38% C, 10·13% H, 4·46% N.

Hydrogen oxalate, 7·1 g (76% calculated *per* the starting carboxylic acid) obtained from 7·2 g crude base, m.p. 80—82°C (acetone). For $C_{20}H_{35}NO_8$ (417·5) calculated: 57·53% C, 8·45% H, 3·36% N; found: 57·72% C, 8·48% H, 3·38% N.

The authors wish to thank their colleagues at this Institute for their contributions to the work described: Drs M. Ryska and I. Koruna (mass spectra), Mrs J. Komancová and Mrs V. Šmídová (elemental analyses), Mrs D. Sluková, Mr S. Vaněček, and Mr V. Zoula (gas chromatography), Dr S. Wildt (pharmacological screening), and Dr V. Holá (microbiological screening).

REFERENCES

1. Szarvasi E., Neuvy L., Fontaine L. (Lipha, Lyonnaise Industrielle Pharmaceutique): Belg. 613,547 (Fr. Appl. 23. 02. 61—23. 01. 62); Chem. Abstr. *58*, 1435 (1963).
2. Szarvasi E., Bayssat M. (Lipha, Lyonnaise Industrielle Pharmaceutique): Fr. 1,363,948 (Appl. 28. 03. 63); Chem. Abstr. *61*, 14640 (1964).
3. Szarvasi E., Bayssat M., Fontaine L., Grand M., Letourneur C., Auger B.: Bull. Soc. Chim. Fr. *1966*, 1838.
4. Szarvasi E., Bayssat M., Fontaine L. (Lipha, Lyonnaise Industrielle Pharmaceutique): Fr. M 3843 (Appl. 17. 03. 64); Chem. Abstr. *68*, 78145 (1968).
5. Mndzhoyan A. L., Badalyan V. E.: Arm. Khim. Zh. *22*, 671 (1969); Chem. Abstr. *72*, 21590 (1970).
6. Szarvasi E. (Lipha, Lyonnaise Industrielle Pharmaceutique): Ger. Offen. 2,237,078; U.S. 3,872,112 (Fr. Appl. 29. 07. 71); Chem. Abstr. *79*, 31842 (1973).
7. Judge T. G., Urquhart A.: Curr. Med. Res. Opin. *1*, 166 (1972).
8. Bouvier J. B., Passeron O., Chupin M. P.: J. Int. Med. Res. *2*, 59 (1974).
9. Lehmann H. E.: Psychopharmacol. Bull. *12* (*2*), 49 (1976).
10. Hronek J., Laciga Z., Vaňková H., Vencovský E.: Cesk. Psychiat. *73*, 239 (1977).
11. Litomerický Š., Smoleňová L., Traubner P., Šimoni M., Sluková J., Belan P., Gašparíková N.: Farm. Obzor *51*, 309 (1982).
12. Smith L. H.: Org. Synth., Coll. Vol. *3*, 793 (1955).
13. Hinz A., Meyer G., Schücking G.: Ber. Dtsch. Chem. Ges. *76*, 676 (1943).
14. Cope A. C., Hofmann C. M., Wyckoff C., Hardenbergh E.: J. Am. Chem. Soc. *63*, 3452 (1941); Chem. Abstr. *36*, 1011 (1942).
15. Barger G., Robinson R., Smith L. H.: J. Chem. Soc. *1937*, 718; Chem. Zentralbl. *1937*, II, 787.
16. Brooks L. A., Snyder H. R.: Org. Synth., Coll. Vol. *3*, 698 (1955).
17. Ansell M. F., Brown S. S.: J. Chem. Soc. *1957*, 1788.

18. Blasioli C., Heymes A. (Parcor): Fr. 2,444,034 (Appl. 11. 12. 78); Chem. Abstr. *94*, 174854 (1981).
19. Grummitt O., Buck A.: Org. Synth., Coll. Vol. *3*, 195 (1955).
20. Szarvasi E., Neuvy L.: Bull. Soc. Chim. Fr. *1962*, 1343.
21. Szarvasi E., Neuvy L., Fontaine L.: Bull. Soc. Chim. Fr. *1963*, 1181.
22. Blasioli C., Heymes A. (Sanofi): Eur. Pat. Appl. 69,013 (Fr. Appl. 30. 06. 81); Chem. Abstr. *99*, 22297 (1983).
23. Blasioli C., Heymes A. (Parcor): Fr. 2,444,033 (Appl. 11. 12. 78); Chem. Abstr. *95*, 7031 (1981).
24. Fieser L. F., Gates M. D. jr: J. Am. Chem. Soc. *62*, 2335 (1940); Chem. Zentralbl. *1941* I, 889.
25. Braun J. v., Köhler Z.: Ber. Dtsch. Chem. Ges. *51*, 79 (1918).

Translated by the author (M.P.).