1.0-ml. portions of absolute ethanol, after which the filtrate and washings were evaporated in an air stream. Crystallization of the residue from 0.8 ml. of nitromethane yielded 0.5 g., m.p. 111–112°. The yield is 80% of theory on the basis of III to IV. Three crystallizations from nitromethane raised the melting point to 113–113.2°.

Anal. Calcd. for $C_3H_5N_3O_3$: C, 27.45; H, 3.82; N, 32.1. Found: C, 27.30; H, 3.69; N, 31.7.

This compound is easily converted to the starting material (1-β-chloroethyl-3-nitrourea). A mixture of 0.5 g. (0.004 mole) of IV in 2.0 ml. of 18% hydrochloric acid was warmed on a steam-bath for 6 minutes during which time the solid dissolved. Upon chilling, 0.55 g., m.p. 113–116°, was obtained, which constitutes an 86% yield. Admixture of this compound with 1-β-chloroethyl-3-nitrourea did not lower the melting point.

Similarly, when IV is treated with boiling acetyl chloride, 1-β-chloroethyl-3-nitrourea is obtained. A solution of 0.20 g. (0.0015 mole) of IV in 5.0 ml. of acetyl chloride was refluxed under dry nitrogen for 3 hours. The solvent was distilled off and 0.75 ml. of absolute ethanol added to the residue. A precipitate of 0.1 g., m.p. 98–104° (39% of theory), was obtained. Crystallization from 0.5 ml. of ethanol raised the melting point to 111–113.5°. The melting point was not lowered when this sample was mixed with a sample of 1-β-chloroethyl-3-nitrourea.

2-Nitraminoöxazoline (IV) with Nitric Acid.—To 10 ml. of 100% nitric acid stirred by a stream of dry nitrogen, was added over a 6-minute period 1.0 g. (0.0076 mole) of IV. The temperature was maintained at 3° during the addition of the compound, after which the solution was warmed to 22° for 25 minutes. The solution was poured over 100 g. of ice, but no precipitate appeared. The clear aqueous solution was evaporated to dryness *in vacuo* leaving a trace of an oil which resisted attempts to crystallize. An identical procedure as described above resulted in an 88% yield of N,N'-dinitroethyleneurea from ethyleneurea.

2-Nitriminoöxazolidine (IV) with Diazomethane.—To a solution of 0.5 g. (0.0037 mole) of IV in 5.0 ml. of absolute ethanol was added 15 ml. of an ethereal solution of diazomethane. The mixture was stirred at 4° for 90 minutes during which time the solid slowly dissolved. The solvent was removed by distillation and the residue dissolved in 1.5 ml. of 5% sodium hydroxide. This solution was extracted five times with a total of 15 ml. of ether. The ether extract was dried over sodium sulfate and evaporated, leaving 0.1 g. of an oil which is water soluble but forms a cloudy solution in acid. The acidified aqueous layer was extracted four times with a total of 12 ml. of chloroform. Evaporation of this extract *in vacuo* left only a trace of an oil.

Potentiometric Titrations.—The potentiometric titrations were performed with a Coleman Electrometer. In each case 0.00063 mole of the compound was dissolved in an excess of 15 ml. of 0.0867 *N* NaOH and titrated with 0.1140 *N* HCl, except in the titration of β-aminoethylnitramine (VI). A solution of 55×10^{-5} mole of this compound was dissolved in 10.2 ml. of 0.1140 *N* alkali and titrated immediately with 0.1140 *N* HCl. Three inflections were observed in the titrimetric curve: with 5 ml. acid at *p*H 10.7; 10.2 ml. acid at *p*H 7.4; and 15.5 ml. acid at *p*H 3.0. The substance is thus a typical amino-acid with the expected formula weight.

Ethyl β-Aminoethylnitrocarbamate Nitrate (IX).—To a solution of 30 ml. (0.73 mole) of 99% nitric acid and 15 ml. (0.15 mole) of acetic anhydride in a Dry Ice-bath was added 5 ml. (0.043 mole) of ethyl β-aminoethylcarbamate over 1 hour. The reaction mixture was warmed to 0° over 1 hour and then poured on 300 g. of ice. The aqueous solution was evaporated to dryness *in vacuo* and the residue dissolved in 50 ml. of ethanol. Addition of 50 ml. of ether caused precipitation of 7.9 g., m.p. 79–80° (87% yield). Three crystallizations from ethanol (2.2 ml. per g.) raised the melting point to 82.5–83.5°. The product is very water soluble and it gives a precipitate with nitron. It does not decolorize Karl Fischer reagent.

Anal. Calcd. for $C_5H_{12}N_4O_7$: C, 25.0; H, 5.00; N, 23.3. Found: C, 25.1; H, 5.19; N, 23.4.

Ethyl β-Nitraminoethylcarbamate (XII).—A solution of 2.4 g. (0.01 mole) of IX in 5 ml. of water was made slightly alkaline with 2.5 *N* aqueous NaOH and then acidified with 6 *N* HCl. The water-washed precipitate weighed 1.75 g. (99% yield) and melted at 87–90°. Three crystallizations from ethanol (2 ml. per g.) raised this melting point to 88.5–90.5°. The molecular weight was determined by potentiometric titration of the sodium salt with hydrochloric acid: calcd. 177; found 175.

Anal. Calcd. for $C_5H_{11}N_3O_4$: C, 33.9; H, 6.21; N, 23.7. Found: C, 33.9; H, 6.35; N, 23.9.

β-Aminoethylnitramine (VI).—A solution of 0.37 g. (0.0021 mole) of XII in 2.5 ml. of 2.5 *N* aqueous sodium hydroxide was boiled for 1 hour under reflux. Neutralization with concd. hydrochloric acid precipitated 40% of unchanged XII. The filtrate was evaporated to dryness at 20–30° and the residue crystallized from 1 ml. of water. The yield of β-aminoethylnitramine (m.p. 240°) was 0.021 g. or 12% of theoretical. A mixed melting point with the substance obtained from propyl β-chloroethyliminonitrocarbamate (II) was not depressed.

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[CONTRIBUTION FROM THE WARNER INSTITUTE FOR THERAPEUTIC RESEARCH]

α-Thienyl Substituted Aminoesters with Analgetic and Spasmolytic Properties

BY FREDERICK LEONARD AND IRVING EHRENTHAL[1]

A series of ethyl 4-dialkylamino-2-phenyl-2-α-thienyl)- and 2,2-di-(α-thienyl) alkanoates was synthesized for pharmacological study and for conversion to "α-thienyl-methadone" and its homologs. The aminoacid esters were prepared by alkylating the appropriately disubstituted ethyl acetate with basic-alkyl chlorides. Compounds of the methadone series could not be obtained by the action of Grignard reagents on either the intermediate disubstituted acetates or the 4-dialkylaminoalkanoates. None of the esters demonstrated appreciable antispasmodic or analgetic activity and are apparently less effective than their benzene isosteres.

Esters of aminodiarylalkanoic acids (I) which are useful as antispasmodics and analgetics have been described[2] in the patent literature. In view of the lack of quantitative data on esters of this type, their marked structural similarity to, and the theoretical possibility of their conversion to congeners of 6-dimethylamino-4,4-diphenyl-3-heptanone (methadone, II), a number of ethyl 4-dialkylamino-2-phenyl-2-(α-thienyl)- and 2,2-di-(α-thienyl)-alkanoates (VI) were prepared for pharmacological evaluation and use in the synthesis of "thienyl-methadone" and its homologs.

$ROOCC(Ar)_2C_nH_{2n}Am$

I

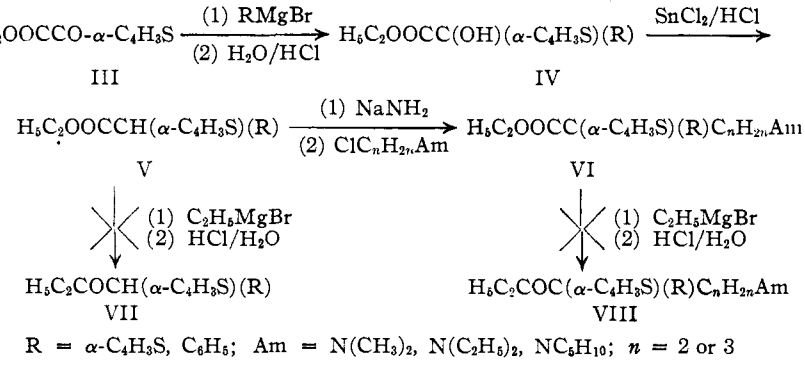
$H_5C_2COC(C_6H_5)_2CH_2CH(CH_3)N(CH_3)_2$

II

The Grignard reaction between ethyl α-thienylglyoxylate (III) and α-thienylmagnesium bromide or phenylmagnesium bromide gave the glycolic

(1) Department of Agricultural Biochemistry, University of Minnesota, St. Paul, Minnesota.

(2) M. Bockmühl and G. Erhart, U. S. Patent 2,230,771 [*C. A.*, **35**, 3391 (1941)].



esters (IV) which were reduced to the acetic esters (V). The acetates (V) were alkylated in the presence of sodamide with several basic-alkyl chlorides to yield the desired aminoesters (VI).

All attempts, using the Grignard reaction, failed to convert the esters (V and VI, R = C_6H_5) to the corresponding ethyl ketones. Both compounds yielded precipitates when treated with ethylmagnesium bromide but the only identifiable products which could be obtained from the reaction mixtures were the starting materials.

The failure in the attempted conversion of ethyl phenyl-(α-thienyl)-acetate (V, R = C_6H_5) to ethyl phenyl-(α-thienyl)-methyl ketone (VII) R = C_6H_5) may be due to a rapid removal of the ester α-hydrogen with the formation of a bromomagnesium derivative. The magnesium bromide derivative would be expected to condense with unreacted ester to yield a β-keto ester. In this instance, as in the case of the reaction of ethyl diphenylacetate with isopropylmagnesium bromide described by Hauser, Saperstein and Shivers,[3] it would seem that steric factors prevented an acetoacetic ester condensation, for decomposition of the Grignard complex regenerated the starting material.

The negative results obtained in the reaction between ethyl 4-dimethylamino-2-phenyl-2-(α-thienyl)-butyrate (VI, R = C_6H_5) and ethylmagnesium bromide, even when working at elevated temperatures (refluxing benzene and toluene) may have been caused by coupling of the reagent with the dimethylamino group to form an ether insoluble and heat stable (up to 110°) coördination complex. From a consideration of the analytical data found for the products isolated from this reaction, it would seem that the ester was partially reduced to the corresponding alcohol.

The aminoacid esters were converted to hydrochlorides or hydrobromides for evaluation in the Pharmacology Department of this Institute. Screening tests indicated the substances lacked sufficient analgetic or spasmolytic activity to warrant extensive investigation.

After the completion of this work two articles were published on related compounds. Speeter, Byrd, Cheney and Binkley[4] found that the minimal analgetic doses of ethyl 2,2-diphenyl 4-(4′-morpholinyl)-butyrate and the homologous 4-dimethylaminovalerate were, respectively, equal to and one and one-half times that of methadone. Brown, Cook and Heilbron[5] prepared ethyl 4-diethylamino-2-phenyl-2-(α-thienyl)-butyrate and ethyl 4-(4′-morpholinyl)-2-phenyl-2-(α-thienyl)-butyrate and found that the latter was four times as effective as ethyl 1-methyl-4-phenyl-4-piperidinecarboxylate (meperidine). They also synthesized several of the corresponding ketones by the alkylation of 1-phenyl-1-(α-thienyl)-2-butanone (obtained in low yield by the condensation of the potassium derivative of α-benzylthiophene with ethyl propionate with basic-alkyl chlorides. One of their ketones, 6-diethylamino-4-phenyl-4-(α-thienyl)-3-hexanone proved to be only one-third as active as meperidine. It should be noted that Blicke and Channin[6] found that isosteric replacement of the phenyl by the α-thienyl group in the ethyl 4-piperidinecarboxylate series, likewise resulted in a decrease in the activity.

Experimental[7]

Ethyl Phenyl-(α-thienyl)-glycolate.—A filtered solution of phenylmagnesium bromide prepared from 66.0 g. (0.42 mole) of bromobenzene, 11.3 g. (0.46 g.-atom) of magnesium and 200 cc. of absolute ether was added dropwise with stirring and cooling (ice–salt-bath) to 55.2 g. (0.30 mole) of ethyl α-thienylglyoxylate,[8] dissolved in 450 cc. of absolute ether. The addition product started to precipitate at once. The reaction mixture was stirred for one hour in the ice-bath, for two hours at room temperature and finally refluxed for three hours. The Grignard complex was decomposed with dilute hydrochloric acid, the ethereal solution washed neutral and dried over anhydrous sodium sulfate. The ether was removed and the residual oil fractionated *in vacuo*. Ethyl phenyl-(α-thienyl)-glycolate was obtained in 70% yield (53.6 g.), b.p. 139–141° (2 mm.); $n^{20}D$ 1.5712. A redistilled sample had b.p. 138–140° (2 mm.), $n^{20}D$ 1.5725, and solidified to a yellow solid melting at 58–61°.

Anal. Calcd. for $C_{14}H_{14}O_3S$: C, 64.10; H, 5.38. Found: C, 64.30; H, 5.61.

Ethyl Di-α-thienylglycolate.—Prepared in the same manner as ethyl phenyl-(α-thienyl)-glycolate, the di-α-thienylglycolate was obtained in 55% yield from the interaction of α-thienylmagnesium iodide and ethyl α-thienylglyoxylate. The product boiled at 134–139° (1 mm.), $n^{20}D$ 1.5860, and crystallized on standing to a yellow solid, m.p. 52–55°. On refractionation the ester boiled at 127–129° (0.5 mm.), had $n^{20}D$ 1.5848, and crystallized to a yellow solid which melted at 53–56°.

Anal. Calcd. for $C_{12}H_{12}O_3S_2$: C, 53.71; H, 4.51. Found: C, 53.94; H, 4.63.

Ethyl Phenyl-(α-thienyl)-acetate.—A well-stirred solution of 34.1 g. (0.125 mole) of ethyl phenyl-(α-thienyl)-glycolate and 61.0 g. (0.27 mole) of stannous chloride dihydrate in 500 cc. of glacial acetic acid was treated with a stream of dry hydrogen chloride at 15° for three hours. Complete reduction was indicated when a drop of the reaction mixture added to sulfuric acid did not turn red. The mixture was poured into ice-water, extracted with ether, the ether extract washed neutral and dried over sodium sulfate.

(3) C. R. Hauser, P. O. Saperstein and J. C. Shivers, THIS JOURNAL, **70**, 606 (1948).

(4) M. E. Speeter, W. M. Byrd, L. C. Cheney and S. B. Binkley, *ibid.*, **71**, 57 (1949).

(5) D. J. Brown, A. H. Cook and I. Heilbron, *J. Chem. Soc.*, Suppl. No. 1, 1949, S113.

(6) F. F. Blicke and M. Channin, Abstracts Am. Chem. Soc. Meeting No. 109, 54K (April, 1946).

(7) Microanalyses by Mr. L. Dorfman and Miss B. Baumgarten of this Institute. Melting points are uncorrected.

(8) F. F. Blicke and M. U. Tsao, THIS JOURNAL, **66**, 1645 (1944).

TABLE I

DIALKYLAMINOACID ESTERS AND SALTS, $H_2C_3OOC(\alpha\text{-}C_4H_3S)(R)C_nH_{2n}Am$

Compound 1 was recrystallized from an absolute isopropyl alcohol–ether mixture. All of the other crystalline compounds were recrystallized from a mixture of absolute ethyl alcohol and ether.

			Bases			Salts					
			B.p.,			M.p.,		Analyses, % Nitrogen		Halogen	
No.	R	$C_nH_{2n}Am$	°C.	Mm.	n_D	°C.	Empirical formula	Calcd.	Found	Calcd.	Found
1	C_6H_5	$CH_2CH_2N(CH_3)_2$	173–176	2	1.5500^{30}	178–179	$C_{18}H_{24}O_2SNCl$	3.96	4.16	10.02	10.08
2	C_6H_5	$CH_2CH_2N(C_2H_5)_2$	171–181	2		[a]					
3	C_6H_5	$CH_2CH_2NC_5H_{10}$	204–210	2	1.5549^{29}	162–163	$C_{21}H_{28}O_2SNCl$	3.56	3.64	9.00	9.29
4	C_6H_5	$CH_2CH(CH_3)N(CH_3)_2$ [b]	179–184	4		89–90 [c]	$C_{19}H_{26}O_2SNBr$	3.40	3.56	19.38	19.41
5	α-C_4H_3S	$CH_2CH_2N(CH_3)_2$	165–176	2	1.5589^{30}	195–196	$C_{16}H_{22}O_2S_2NCl$	3.89	4.00	9.85	9.95
6	α-C_4H_3S	$CH_2CH_2N(C_2H_5)_2$	176–181	2	1.5469^{29}	125–126	$C_{18}H_{26}O_2S_2NCl$	3.61	3.78	9.14	9.30
7	α-C_4H_3S	$CH_2CH_2NC_5H_{10}$	208–214	3	1.5571^{31}	163–164	$C_{19}H_{26}O_2S_2NCl$	3.50	3.24	8.86	9.13
8	α-C_4H_3S	$CH_2CH(CH_3)N(CH_3)_2$ [b]	175–181	2	1.5539^{29}	[a]					

[a] Salt did not crystallize. [b] And/or $CH(CH_3)CH_2N(CH_3)_2$. [c] Very hygroscopic compound; melting point taken in sealed tube.

The residue after removal of the solvent was collected at 142–143° (2 mm.); $n^{20}D$ 1.5664; yield 25.9 g. (84.0%). A sample, redistilled at 1 mm., boiled at 120–121° and had $n^{20}D$ 1.5676.

Anal. Calcd. for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73. Found: C, 68.03; H, 5.64.

Ethyl Di-α-thienylacetate.—Obtained in 85.5% yield by reduction of ethyl di-α-thienylglycolate in glacial acetic acid with stannous chloride dihydrate and gaseous hydrogen chloride; b.p. 152–154° (3 mm.); $n^{20}D$ 1.5686. The ester on redistillation boiled at 146–146.5° (2 mm.) and had $n^{20}D$ 1.5738.

Anal. Calcd. for $C_{12}H_{12}O_2S_2$: C, 57.11; H, 4.80. Found: C, 57.29; H, 4.78.

Ethyl 4-Dimethylamino-2-phenyl-2-(α-thienyl)-butyrate Hydrochloride.—Ethyl phenyl-(α-thienyl)-acetate, 12.3 g. (0.05 mole), dissolved in 50 cc. of dry benzene was added to a stirred suspension of 1.95 g. (0.05 mole) of sodamide in 50 cc. of benzene. The mixture was refluxed for 2.5 hours and a solution of 5.9 g. (0.055 mole) of 2-dimethylaminoethyl chloride dissolved in 15 cc. of dry benzene added dropwise with stirring and heating. The mixture was refluxed for eight hours, cooled, water added, the benzene layer separated, washed with water and saturated sodium chloride solution and concentrated *in vacuo*. The residue was fractionated at 2.5 mm. and the product distilling from 173–176° collected; yield 10.9 g. (69.0%), $n^{30}D$ 1.5500.

The aminoester, 8.48 g., dissolved in 55 cc. of ether, gave upon neutralization with 8.53 cc. of 3.29 *N* alcoholic hydrochloric acid, 7 g. (m.p. 175–178°) of a crystalline hydrochloride, which after recrystallization from an ethanol–ether mixture melted at 178–179°.

The alkylation procedure described above was employed in the preparation of all of the compounds in the table.

Attempted Preparation of 6-Dimethylamino-4-phenyl-4-(α-thienyl)-3-hexanone.—A solution of 11.0 g. (0.0348 mole) of ethyl 4-dimethylamino-2-phenyl-2-(α-thienyl)-butyrate in 50 cc. of dry ether was treated dropwise at 0° with a Grignard reagent prepared from 3.8 g. (0.0348 mole) of ethyl bromide, 0.81 g. (0.0348 g. atom) of magnesium and 30 cc. of ether. A white granular precipitate formed at once. The mixture was stirred for one-half hour at 0° after all of the reagent had been added, then at room temperature for one-half hour. The precipitate became gummy at room temperature. The mixture was acidified with dilute hydrochloric acid, the aqueous layer removed, extracted with ether and basified with concentrated ammonia water. The liberated oil was taken up in ether and the ethereal solution washed and dried over anhydrous potassium carbonate. After removal of the ether and fractionation of the residue, there was obtained 6.0 g. of a base, b.p. 183–186° (4 mm.) and $n^{30}D$ 1.5488, which was converted to a hydrochloride. The salt melted at 179–180° after recrystallization from an ethanol–ether mixture.

Anal. Calcd. for $C_{18}H_{24}OSNCl$ (ketone): C, 63.98; H, 7.16; N, 4.15; Cl, 10.49. Calcd. for $C_{18}H_{24}OSNCl$ (ester): C, 61.09; H, 6.48; N, 3.96; Cl, 10.02. Calcd. for $C_{18}H_{22}OSNCl$ (alcohol): C, 61.61; H, 7.11; N, 4.49; Cl, 11.37. Found: C, 60.83; H, 6.71; N, 4.43; Cl, 11.09.

When the reagent was added to the ethereal solution at 0°, the mixture refluxed for two hours, the ether replaced by 60 cc. of dry benzene and refluxing continued for eight hours, 5.0 g. of a yellow oil, b.p. 175–184° (3 mm.), $n^{27}D$ 1.5527, were recovered from 8.0 g. of starting material. The corresponding hydrochloride melted at 173–174°.

Anal. Found: C, 61.41, 61.51; H, 6.95, 7.05; N, 4.44; Cl, 10.26.

Use of toluene instead of benzene to replace the ether resulted in a poor recovery (36.3%) of starting material and no ketone; b.p. base 189–193° (3 mm.), $n^{29}D$ 1.5539; m.p. hydrochloride 166–167°.

Anal. Found: C, 61.21, 61.48; H, 6.94, 6.93; N, 4.06; Cl, 10.36.

Attempted Preparation of 1-Phenyl-1-(α-thienyl)-2-butanone.—A Grignard reagent prepared from 6.05 g. (0.055 mole) of ethyl bromide, 1.34 g. (0.055 g.-atom) of magnesium and 30 cc. of ether was added at −70° with stirring to a solution of 12.6 g. (0.05 mole) of ethyl phenyl-(α-thienyl)-acetate dissolved in 60 cc. of absolute ether. A precipitate formed on addition of the reagent. The mixture was stirred and let warm to room temperature and finally refluxed for one hour. The addition product was decomposed with dilute hydrochloric acid, the ether layer removed, washed with water and dried over anhydrous potassium carbonate. Fractionation at 3 mm. gave 10.5 g. of unchanged ester, b.p. 157–164°, $n^{30}D$ 1.5618.

When the reaction was repeated, adding the reagent at 0°, with subsequent stirring of the mixture at 0° for 1 hour, warming to room temperature and finally refluxing for 2 hours, there was obtained from 12.6 g. of acetate, 9.2 g. of unchanged ester, b.p. 167–171° (4 mm.), $n^{24}D$ 1.5578.

Brown, *et al.*,[5] obtained this ketone in low yield by refluxing the potassium derivative of α-benzylthiophene with ethyl propionate in dry ether. They found b.p. 125–127° (0.5 mm.) and $n^{18}D$ 1.5800.

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