A Convenient Route to Diazepines by Intramolecular Cyclisation of Carbonylazides

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The appropriate substituted carbonylazides **I** treated with warm acetic acid give the corresponding acetamide **IV** or the cyclic lactam **VI**. This is a convenient route to 10,11-Dihydro-5*H*-pyrrolo[1,2-*a*][1,4]-benzodiazepin-11-one and 10,11-Dihydro-4*H*-thieno[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-10-one.

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Since Butler [1] described the formation of phenanthridone by the intermolecular Friedel and Crafts cyclisation of the corresponding isocyanate, a number of investigators have used the method to form cyclic lactams fused to an heterocycle [2,3]. During our investigations for the synthesis and evaluation of the biological properties of tricyclic compounds containing both thiophene ring and 7 or 8 membered cyclic lactam we wished to report herein a convenient intramolecular cyclisation of isocyanate in acidic medium.

We previously reported [4] that in the Friedel and Crafts conditions isocyanate **2** did not react to form the cyclic lactam **4** but a new thienoisothiazolinone **3** namely 4H-thieno[2,3-*b*]isothiazolin-5-one due to the fragility of the -CH_2-S- linkage (Scheme I). On the other hand, Robba [5,6] reported that the cyclisation of the isocyanate derivatives of 2(3)-(1-pyrrolyl)-3(2)-thienylcarboxylic acid resulted in the formation of the 4,5-dihydropyrrolo[1,2-*a*]thieno[3,2-*e*]-pyrazin-5-one and 4,5-dihydropyrrolo[1,2-*a*]thieno[2,3-*e*]-pyrazin-5-one. The reaction was carried out in a hydrochloric acid solution and it was also mentioned that

Scheme I

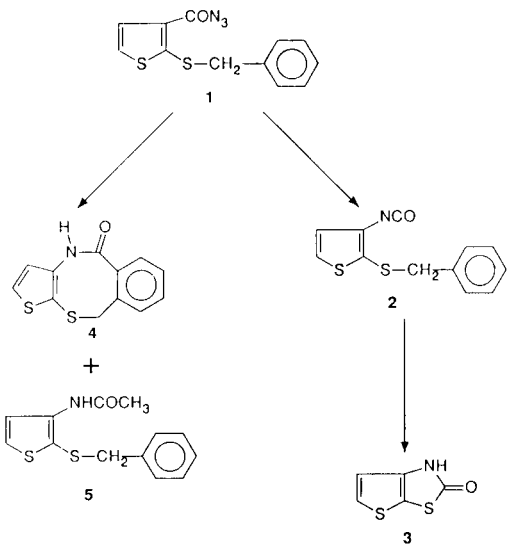
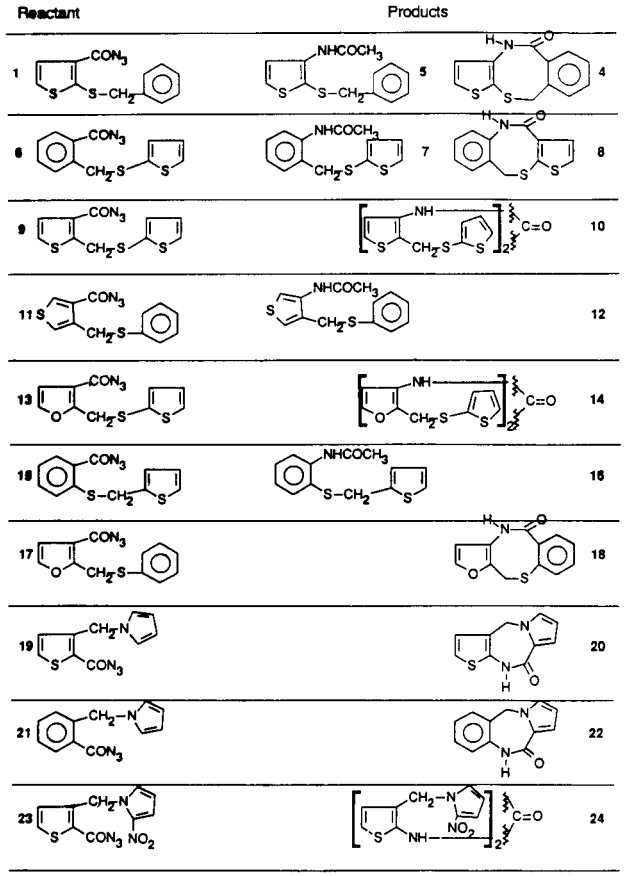


Table I



the same cyclisation occurred in the presence of formic acid or acetic acid but with no further explanation.

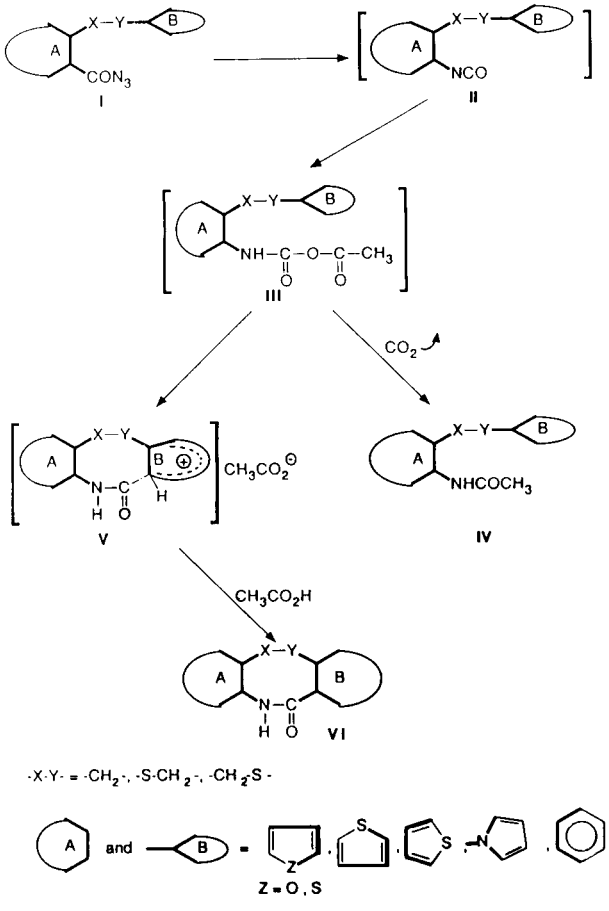
Because of the difficulty encountered in the cyclisation of the azide **1** we have submitted this compound to boiling acetic acid. Reaction begins by the thermal Curtius rearrangement and the resulting isocyanate reacts with the carboxylic acid to give two products (52% yield). The normal acetylated product **5** (25%) is formed and a cyclic product (75%) namely 5,10-dihydro-4*H*-thieno[3,2-*b*]benzo[*f*]-[1,4]thiazocin-5-one (**4**).

The same reaction with the azide **15** (Table I) furnished

only the acetylated product **16**. So it was interesting to understand the selectivity of this reaction.

Acetylating of an isocyanate is a well known reaction in the literature [7,8]. Reaction of carboxylic acid with the isocyanate **II** (Scheme II) gives an intermediate which is almost certainly the mixed carboxylic carbamic acid anhydride **III**. Generally, this spontaneously decomposes with loss of carbon dioxide to an amide, in our case the acetylated amide **IV**. The cyclic amide **VI** seems to be due to the reactivity of the benzene ring toward an electrophilic substrate like the anhydride intermediate. Cyclisation would occur with elimination of an acetate anion and formation of the adduct **V**. The loss of a proton would give the aromatic compound **VI**.

Scheme II



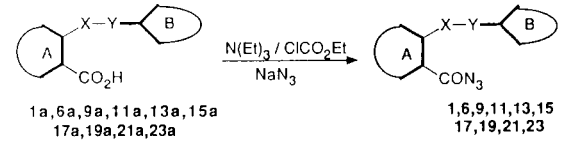
In order to confirm the selective cyclic lactam formation, several attempts have been necessary. The results are summarized in Table I. Then, with the structure **I** if B is a pyrrole ring, compounds **19**, **21**, much more reactive toward electrophilic substitution than benzene, only the cyclisation occurs and no acetylated product is isolated. Nevertheless, substituted with an electron withdrawing group such as a nitro group compound **23** gave, the corresponding urea **24**.

Moreover, with structure **I**, if B is a thiophene ring, compounds **9**, **13**, **15**, we have never obtained the cyclic lactam but always the corresponding acetylated product or ureas **10**, **14**, **16**. Urea would result from a condensation of the acetylated product with the intermediate isocyanate. Thiophene toward electrophilic substitution is less reactive than a pyrrole ring, as we have already noticed in a preceding paper [9]. Nevertheless, with an activated thiophene, compound **6**, cyclisation occurs and the cyclic lactam **8** (75%) was formed with a part (25%) of the acetylated product **7**. The reactivity of the isocyanate intermediate is also a factor of the selectivity, for example compound **11** gave only the acetamide **12** although the benzene ring is activated with a thioether group, while the furan azide **17** gave the cyclic lactam **18**.

On the other hand, attempts to use an other carboxylic acid (formic acid, benzoïc acid) failed. The corresponding amide was founded but more often a tar due to the instability of the intermediate isocyanate under these conditions.

All the required carbonylazides were prepared from the corresponding carboxylic acid using the method of Weinstock [10] (Scheme III).

Scheme III



Acids **1a**, **6a**, **9a**, **11a** and **15a** have been described before by ourselves [4,11]. The pathway used to obtain acids **19a** and **23a** will be described in a next paper [12]. The known 2-[1-pyrrolyl]methylbenzoic acid (**21a**) [14] was synthesized by a new way from methyl 2-bromomethylbenzoate in a similar manner to the analogous thiophene [9]. The unknown acids **13a** and **17a** were prepared in the same fashion as described in the thiophene series [9] from methyl 2-methyl-3-furancarboxylate [14] (Scheme IV).

Scheme IV

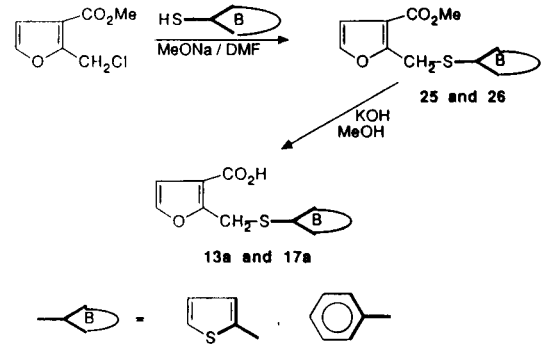


Table II

Yields and Physical Data of Carbonylazides

Compound Number	Formula	Mp °C	Yield	Analyses % (Calcd./Found) C		H		N	
1	$C_{12}H_9N_3OS_2$	120	80	52.34	52.21	3.29	3.51	15.26	15.40
6	$C_{12}H_9N_3OS_2$	78	85	52.34	52.75	3.29	3.26	15.26	15.71
9 [a]	$C_{10}H_7N_3OS_3$	liq	65	42.69	42.20	2.51	2.70	14.93	14.66
11	$C_{12}H_9N_3OS_2$	101	82	52.34	52.53	3.29	3.41	15.26	15.12
13 [a]	$C_{10}H_7N_3O_2S_2$	liq	67	44.93	45.29	3.39	3.56	15.72	15.33
15	$C_{12}H_9N_3OS_2$	88	88	52.34	52.66	3.29	3.56	15.26	15.32
17 [a]	$C_{12}H_9N_3O_2S$	liq	71	55.59	55.30	3.50	3.39	16.21	16.42
19	$C_{10}H_8N_4OS$	76	62	51.71	51.39	3.47	3.53	24.12	24.02
21 [a]	$C_{12}H_{10}N_4O$	liq	58	63.71	63.88	4.45	4.83	24.76	24.21
23	$C_{10}H_7N_5O_3S$	114	78	43.32	42.91	2.55	2.37	25.26	25.86

[a] These compounds were used for the next step without further purification.

Table III

Yields and Physical Data of the Cyclic Lactams

Compound Number	Formula	Mp °C	Yield	Analyses % (Calcd./Found) C		H		N	
4	$C_{12}H_9NOS_2$	221	40	58.29	58.73	3.65	4.18	5.67	6.71
8	$C_{12}H_9NOS_2$	201	40	58.29	58.69	3.67	4.04	5.67	5.92
18	$C_{12}H_9NOS$	183	35	62.32	62.02	3.92	4.17	6.06	6.36
20	$C_{10}H_8N_2OS$	232	53	58.80	58.38	3.95	4.11	13.71	13.42
22	$C_{12}H_{10}N_2O$	223	62	lit [15] mp = 223-224°					

Table IV

Yields and Physical Data of the Acetamides

Compound Number	Formula	Mp °C	Yield	Analyses % (Calcd./Found) C		H		N	
5	$C_{13}H_{13}NOS_2$	liq	15	59.28	59.66	4.97	5.15	5.32	5.17
7	$C_{13}H_{13}NOS_2$	68	15	59.28	59.39	4.97	4.87	5.32	5.16
10	$C_{19}H_{16}N_2S_6O$	106	72	44.97	44.63	3.35	2.99	5.83	5.55
12	$C_{13}H_{13}NOS_2$	liq	75	59.28	59.61	4.97	4.60	5.32	5.02
14	$C_{19}H_{16}N_2O_3S_4$	115	41	50.87	50.84	3.59	3.58	6.24	6.14
16	$C_{13}H_{13}NOS_2$	76	58	lit [16] mp = 78°					
24	$C_{19}H_{16}N_6O_5S_2$	197	19	48.30	48.04	3.41	3.07	17.78	17.33

In conclusion, cyclisation of a carbonylazide in warm acetic acid seems to be a convenient route to cyclic lactam. This is a new method to the thienobenzothiazocinone ring system. Furthermore this method is particularly interesting to obtain pyrrolo[1,2-*a*][1,4]diazepinones. Thus from the readily available *o*-toluic acid and pyrrole in few we can obtain the pyrrolo[1,2-*a*][1,4]benzodiazepin-11-one (**22**) in a few steps compared to the less convenient preparation described earlier [15]. In a similar manner thieno[2,3-*e*]-pyrrolo[1,2-*a*][1,4]diazepin-10-one is prepared. Further studies concerning these new types of diazepinones and biological screening are under investigations. A paper in the furan series will be published soon in this journal.

Table V

^{1}H NMR Parameter of the Cyclic Lactams **4**, **8**, **18**, **20**, and Ureas **10**, **14**, **24**

Compound Number	Solvent	^{1}H NMR δ ppm
4	DMSO-d_6	3.80 (s, 2H, CH_2-S), 6.40 (s, 1H, -NH-), 7.00-7.50 (m, 5H, aromatic-4H, thiophene-H_β), 7.70 (d, 1H, thiophene-H_α)
8	DMSO-d_6	4.30 (s, 2H, CH_2-S), 7.40-7.80 (m, 4H, aromatic-3H, thiophene-H_β), 8.00-8.30 (m, 1H, aromatic-1H), 8.45 (d, 1H, thiophene-H_α), 8.95 (s, 1H, -HN-)
18	DMSO-d_6	4.30 (s, 2H, CH_2-S), 6.70 (d, 1H, furan-H_β), 7.15-7.42 (m, 4H, aromatic-4H). 7.45 (d, 1H, furan-H_α), 8.20 (s, 1H, -NH-)
20	DMSO-d_6	5.15 (s, 2H, CH_2-N), 6.15 (m, 2H, pyrrole-2H), 6.80-7.05 (m, 3H, thiophene-2H, pyrrole-H_α), 10.50 (s, 1H, -NH-)
10	DMSO-d_6	3.27 (s, 2H, CH_2-S), 6.05 (m, 3H, thiophene- 2H, thiophene-H_β), 6.55 (dd, 1H, thiophene-H), 6.65 (d, 1H, thiophene-H_α), 7.20 (s, 1H, -NH-)
14	DMSO-d_6	4.20 (s, 2H, CH_2-S), 6.75 (d, 1H, furan-H_β), 7.05 (dd, 1H, thiophene-H), 7.15 (dd, 1H, thiophene-H), 7.45 (d, 1H, furan-H_α), 7.65 (dd, 1H, thiophene-H), 8.00 (s, 1H, -NH-)
24	DMSO-d_6	5.55 (s, 2H, CH_2-N), 6.35 (dd, 1H, pyrrole-H), 6.50 (d, 1H, thiophene-H_β), 7.03 (d, 1H, thiophene-H_α), 7.30-7.45 (m, 2H, pyrrole-2H), 9.65 (s, 1H, -NH-)

EXPERIMENTAL

The ir spectra were recorded on a Beckmann IR-20 spectrometer. The ^{1}H nmr spectra were obtained on a Varian EM 360 spectrometer and a Bruker AC 200 (200 MHz) spectrometer in the solvents indicated. Chemical shifts are reported in ppm from TMS as an internal reference and are given in δ units. Elemental analyses were performed by Laboratoire de microanalyse de l'Insa de Rouen, place Emile Blondel, 76130 Mont-Saint-Aignan France. Melting points were determined on a Kofler-banc and are uncorrected.

General Procedure for the Synthesis of Carbonylazides **1**, **6**, **9**, **11**, **13**, **15**, **17**, **19**, **21** and **23**.

A solution of 0.01 mole of carboxylic acid, 75 ml of anhydrous acetone and 0.027 mole of triethylamine was cooled in a ice-salt bath. To the well stirred and cooled solution, in an atmosphere of nitrogen, a solution of 0.035 mole of ethyl chloroformiate in 7.5 ml of acetone was added over a period of 30 minutes. When the addition was stopped the reaction mixture was allowed to stir at 0° for 15 minutes and a solution of 0.045 mole of sodium azide in 10 ml of water was added dropwise over 20 minutes. The mixture was allowed to stir at 0° for 30 minutes then poured on to crushed ice. The solid azide was separated from the aqueous solution by filtration. It was used for the next reaction without further purification. If the azide did not crystallize, it was extracted several times with carbon tetrachloride. The combined organic layers were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the solid residue was crystallized from anhydrous diethyl ether.

The physical constants are summarized in Table II.

General Procedure for the Synthesis of Cyclic Lactams and Acetamides.

A solution of 0.005 mole of carbonylazide and 50 ml of acetic acid was refluxed for 30 minutes. After cooling and evaporation of the solvent *in vacuo* the solid residue was filtered, washed with ethyl acetate and air dried. A crystallization from the appropriate solvent give an analytical sample of the cyclic lactams **4**, **8**, **18**, **20**, **22**, the acetamides **5**, **7**, **12**, **16** or the ureas **10**, **14**, **24**. Compounds **4** and **5**, **7** and **8** were separated by chromatography on a fluorisil column and eluting with petroleum ether-benzene (80-20). Physical constants are summarized in Tables III, IV, V and VI.

Synthesis of the Acid **17a**. Methyl 2-(Phenylthiomethyl)-3-furancarboxylate (**25**).

To a well stirred suspension of thiophenol (2.2g, 0.02 mole) and dimethyl sulfoxide (20 ml), a solution of sodium methoxide (prepared from methanol (10 ml) and sodium metal (0.46, 0.02 mole) et 10°) was added slowly dropwise at 0-5°. After 30 minutes of reaction, methyl 2-chloromethylfuran-3-carboxylate (3.50 g, 0.02 mole) in 10 ml of dimethyl sulfoxide was added slowly dropwise to the reaction mixture at the same temperature and was allowed to react 4 hours at room temperature. The reaction solution was poured onto crushed ice and extracted several times with diethyl ether. The combined organic layers were washed

Table VI

^{1}H NMR Chemical Shifts of the Acetamides **5**, **7** and **12**

Compound Number	Solvent	^{1}H NMR δ ppm
5	deuteriochloroform	1.65 (s, 3H, CH_3-CO-), 3.75 (s, 2H, CH_2-S), 6.90-7.50 (m, 7H, aromatic-5H, thiophene-H_β, -NH-), 7.90 (d, 1H, thiophene-H_α)
7	deuteriochloroform	1.85 (s, 3H, CH_3-CO-), 3.75 (s, 2H, CH_2-S), 6.85-7.45 (m, 7H, aromatic-4H, thiophene-2H, -NH-), 7.90 (dd, 1H, thiophene-H)
12	deuteriochloroform	1.85 (s, 3H, CH_3-CO-), 3.60 (s, 2H, CH_2-S), 6.50-7.30 (m, 6H, aromatic-5H, thiophene-H), 7.45 (s, 1H, -NH-), 7.70 (d, 1H, thiophene-H)

with water, dried over anhydrous magnesium sulphate. Diethyl ether was removed under reduced pressure and the oily residue was purified by distillation (bp 0.04, 117-120°) to give 4.4 g (89%) of the desired product; ir (neat): ν cm^{-1} 1710 (carboxylate C=O); ^1H nmr (deuteriochloroform): δ ppm 3.78 (s, 3H, $COOCH_3$), 4.50 (s, 2H, CH_2-S), 6.65 (d, 1H, furan-H_β), 7.17-7.47 (m, 6H, benzene-5H, furan-H_α).

Anal. Calcd. for $C_{13}H_{12}O_3S$: C, 62.83; H, 4.87. Found: C, 62.77; H, 4.75.

2-(Phenylthiomethyl)-3-furancarboxylic Acid (**17a**).

A mixture of 2.1 g (0.0084 mole) of methyl 2-benzothiomethylfuran-3-carboxylate, 3.0 g (0.06 mole) of potassium hydroxide pellets in a mixture of 25 ml of methanol and 20 ml of water was refluxed for 4 hours. After cooling, the reaction mixture was extracted twice times with 25 ml diethyl ether. The water layer was treated with charcoal, filtered and acidified cautiously with hydrochloric acid. The precipitate was collected by filtration, washed with water and air dried. The desired carboxylic acid (1.7 g, 87%) obtained after crystallization from a mixture of ethanol-water (50/50) melted at 117-119°; ir (potassium bromide): ν cm^{-1} 3300-2250 (OH), 1670 (carboxylic C=O); ^1H nmr (deuteriochloroform): δ ppm 4.45 (s, 2H, CH_2-S), 6.66 (d, 1H, furan-H_β), 7.17-7.47 (m, 6H, benzene-5H, furan-H_α).

Anal. Calcd. for $C_{12}H_{10}O_3S$: C, 61.52; H, 4.30. Found: C, 61.35; H, 4.15.

Synthesis of Acid **21a**. Methyl 2-(1-Pyrrolylmethyl)benzoate.

To a well stirred suspension of potassium pyrrole (prepared from pyrrole (4.5 g, 0.065 mole) and potassium metal (2.5 g, 0.064 g-atom) in anhydrous tetrahydrofuran (80 ml), kept under nitrogen, a solution of methyl 3-bromomethylbenzene-2-carboxylate (11.4 g, 0.05 mole) in the same solvent (100 ml) was added slowly dropwise at room temperature. The mixture was refluxed for 4 hours. After cooling to room temperature, cyclohexane or hexane (100 ml) was added to the reaction mixture and was allowed to stand at room temperature 2 hours. The mixture was filtered. Evaporation of the solvents afforded 9.5 g of crude methyl 2-(1-pyrrolylmethyl)benzoate as an oily material. The oily was purified by distillation (bp 0.05, 85-90°) to give 8.6 g (80%) of desired compound which solidified on cooling. An analytical sample of mp = 51° was obtained as colourless prisms by crystallization from petroleum ether/hexane (75/25); ir (potassium bromide): ν cm^{-1} 1720 (carboxylic C=O); ^1H nmr (deuteriochloroform): δ ppm 3.94 (s, 3H, CH_3), 5.52 (s, 2H, CH_2-N<), 6.20 (t, 2H, pyrrole -H_β,$H_{\beta'}$), 6.70 (t, 2H, pyrrole-H_α,$H_{\alpha'}$), 7.20-7.60 (m, 3H, benzene-3H), 7.9-8.10 (m, 1H, benzene-1H).

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.19; H, 6.03; N, 6.08.

2-(1-Pyrrolylmethyl)benzoïc Acid (**21a**).

A mixture of 4.4 g (0.02 mole) of methyl 3-(1-pyrrolylmethyl)-benzene-2-carboxylate, 1.3 g (0.03 mole) of potassium hydroxide pellets in a mixture of 10 ml of methanol and 10 ml of water was refluxed for 2 hours. After cooling, the reaction mixture was acidified (*p*H = 1.5-2) with a cooled solution of 2*N* hydrochloric acid (25 ml). The precipitate formed was collected by filtration, washed with water and air dried. The carboxylic acid (3.2 g, 79%) after crystallization from benzene melted at 157°; ir (potassium bromide): ν cm^{-1} 3500-2300 (O-H), 1670 (caboxylic C=O); ^1H nmr (DMSO-d_6): δ ppm 5.55 (s, 2H, CH_2-N), 6.10 (t, 2H, H_3 and H_4 pyrrole), 6.67 (s, 1H, OH), 6.82 (t, 2H, H_2 and H_5 pyrrole), 7.30-7.60 (m, 3H, benzene-3H), 7.80-8.05 (m, 1H, benzene-1H).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.52; N, 6.96. Found: C, 71.97; H, 5.55; N, 6.87.

Synthesis of the Acid **13a**. Methyl 2-(2-Thienylthiomethyl)-3-furancarboxylate (**26**).

This compound was prepared from 2-mercaptothiophene (2.3 g, 0.02 mole) and methyl 2-chloromethyl furan-3-carboxylate (3.50 g, 0.02 mole) in the same manner as above. The crude oil was purified by distillation (bp 0.07, 90°) and afforded 4.5 g (91%) of the desired compound; ir (neat): ν cm^{-1} 1695 (C=O); ^1H nmr (deuteriochloroform): δ ppm 3.77 (1, 3H, CH_3 ($COOCH_3$)), 4.34 (s, 2H, CH_2-S), 6.7 (d, 1H, furan-H_β), 6.96-7.1 (m, 2H, thiophene-2H), 7.35-7.45 (m, 2H, furan-H_α and thiophene-1H).

Anal. Calcd. for $C_{11}H_{10}O_3S_2$: C, 51.94; H, 3.96. Found: C, 51.88; H, 3.87.

2-(2-Thienylthiomethyl)-3-furancarboxylic Acid (**13a**).

In a similar manner as described for the synthesis of **17a**, the preceding ester (2.28 g, 0.009 mole) with 3 g (0.05 mole) of potassium hydroxide pellets was converted to the corresponding acid, which was recrystallized from a mixture of ethanol-water (3/2) to give 1.7 g (88%) of **13a**, mp 117-120°; ir (potassium bromide): ν cm^{-1} 3250-2300 (O-H), 1705 (-COOH); ^1H nmr (deuteriochloroform): δ ppm 4.31 (S, 2H, CH_2-S), 6.67 (d, 1H, furan-H_β), 6.9-7.1 (m, 2H, thiophene-2H), 7.25-7.45 (m, 2H, furan-H_α and thiophene-1H), 9.8 (s, 1H, O-H).

Anal. Calcd. for $C_{10}H_8O_3S_2$: C, 49.98; H, 3.35. Found: C, 49.70; H, 3.20.

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