180. *Aminoalkyl Tertiary Carbinols and Derived Products. Part II. 3-Amino-1 : 1-di-2′-thienyl-alkan-1-ols and -alk-1-enes.*

By D. W. Adamson.

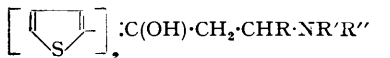
3-*Amino*- and *N*-substituted 3-*amino*-1 : 1-*di*-2′-*thienylalkan*-1-*ols* (I) were prepared from 2-thienyl-lithium and 2-aminoalkanecarboxylates (II), obtained by addition of the appropriate amine to substituted acrylic esters. Substantial quantities of 2-β-piperidinopropionylthiophen (III), as well as the carbinol, were isolated in the Grignard reaction between 2-thienylmagnesium bromide and ethyl β-piperidinopropionate. The amino-carbinols were dehydrated to the 3-*amino*- and *N*-substituted 3-*amino*-1 : 1-*di*-2′-*thienylalk*-1-*enes* (IV).

Several amino-carbinols had high antispasmodic activity and a number of *NN*-disubstituted 3-*amino*-1 : 1-*di*-2′-*thienylbut*-1-*enes* were potent analgesics.

A number of the *N*-substituted 3-amino-1 : 1-diphenyl-propan-1-ols and -prop-1-enes described in Part I (*J.*, 1949, S 144) had interesting pharmacological properties (White, Fawcett, Green, and Hudson, to be published). The investigation of related compounds in which both phenyl groups of the parent compound are replaced by 2-thienyl groups, the synthesis of which is now described, forms part of our programme in this series.

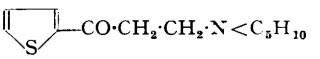
Several *NN*-disubstituted 3-*amino*-1 : 1-*di*-2′-*thienylpropan*-1-*ols* (I; R = H) were prepared by reaction of 2-thienyl-lithium with ethyl *NN*-disubstituted β-aminopropionates (II; R′ = H). 3-*Amino*-1 : 1-*di*-2′-*thienylbutan*-1-*ol* (I; R = Me; R′ = R″ = H) and an extensive series of *N*-substituted derivatives were obtained similarly from the appropriate β-aminobutyrates (II; R′ = Me), and the method was extended to the preparation of 3-*dimethylamino*-1 : 1-*di*-2′-*thienyl-pentan*-1-*ol*, -*hexan*-1-*ol*, and -4-*methylpentan*-1-*ol* (I; R = Et, Pr^n, or Pr^i; R′ = R″ = Me) from the corresponding *methyl* 2-*dimethylaminoalkanecarboxylates*. The yields of tertiary amino-carbinols were good, but those of the primary and secondary amino-butanols were less satisfactory (cf. Part I, *loc. cit.*) (Table II). The tertiary amino-carbinols were converted into water-soluble *hydrochlorides* or *hydrogen oxalates* and some into *methiodides*; the primary and secondary amino-carbinols gave neutral *oxalates*.

The yields of amino-carbinol were poor in the two examples in which the Grignard reaction was employed. Ethyl β-piperidinopropionate on reaction with 2-thienylmagnesium bromide (3 mols.) gave 2-β-piperidinopropionylthiophen (III) in 23% yield in addition to the expected 3-*piperidino*-1 : 1-*di*-2′-*thienylpropan*-1-*ol* (I; R = H; NR′R″ = N<C_5H_{10}) in similar yield.

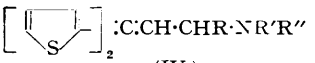


(I.)

(II.)



(III.)



(IV.)

The formation of substantial amounts of ketone by the action of a Grignard reagent on an ester is usual but it has been recorded in a few instances in which the ester bears a tertiary amino-substituent, *e.g.*, the isolation of a small quantity of ketone from the reaction between ethyl β-piperidinopropionate and phenylmagnesium bromide was described in Part I (*loc. cit.*); Prelog and Hanonsek (*Chem. Abs.*, 1931, **25**, 4525) obtained 1-dimethylaminohexan-4-one as

well as 6-dimethylamino-3-ethylhexan-3-ol from ethylmagnesium bromide and ethyl γ-dimethylaminobutyrate; recently it has been claimed that ketones are formed exclusively from Grignard reagents and 4-carbalkoxy-4-phenyl-1-methylpiperidines (B.P. 614,567).

2-β-Piperidinopropionylthiophen (III) (also preparable by the Mannich reaction; Blicke and Burckhalter, *J. Amer. Chem. Soc.*, 1942, **64**, 451) on further reaction with 2-thienylmagnesium bromide (3 mols.) gave the amino-carbinol in 31% yield. A similar reaction between 2-β-piperidino*iso*butyrylthiophen and phenylmagnesium bromide to give 3-piperidino-1-phenyl-1-2′-thienyl-2-methylpropan-1-ol is described in B.P. Appl. 2255/47; Berger, Ziering, and Lee (*J. Org. Chem.*, 1946, **12**, 904) describe the preparation of 4-hydroxy-4-2′-thienyl-1-butylpiperidine from 2-thienyl-lithium and 1-butyl-4-piperidone.

The 2-aminoalkane-carboxylic esters (II) (Table I) required as starting materials were conveniently prepared by addition of an amine to the appropriate substituted acrylic ester. This method has already been used for the preparation of a series of ethyl β-aminopropionates (Part I, *loc. cit.*) and of some ethyl β-aminobutyrates (Philippi and Spenner, *Monatsh.*, 1915, **36**, 97; Philippi and Galter, *ibid.*, 1929, **51**, 253; Morsch, *ibid.*, 1932, **60**, 50). The method has now been successfully applied to a series of methyl and ethyl β-aminobutyrates (II; R = Me, Et; R′ = Me) many of which are new, and to *methyl* and *ethyl* β-*dimethylamino*- and β-*piperidino-valerate* and -δ-*methylvalerate* and the corresponding *hexoates* (II; R = Me, Et, R′ = Et, Pr^n, Pr^i, NR″R‴ = NMe_2, $N<C_5H_{10}$). Some of the higher homologues were unstable and decomposed when kept at room temperature for short periods.

Dehydration of the amino-carbinols furnished the corresponding 3-*amino*- and *N*-substituted 3-*amino*-1 : 1-*di*-2′-*thienylalk*-1-*enes* (IV). The method of dehydration employed for the related diphenyl compounds (Part I, *loc. cit.*), namely, boiling under reflux in a mixture of acetic and hydrochloric acids, was successfully applied to the amino-propanols (I; R = H). The homologues (I; R = Me, Et, Pr^n, Pr^i), however, suffered considerable degradation with tar formation under these conditions, but warming with the mixed acids for a limited time on the steam-bath was usually satisfactory. In one example, dehydration was effected by warming in hydrochloric acid alone. 3-Amino-1 : 1-di-2′-thienylbut-1-ene, like the analogous diphenylallylamine (Part I, *loc. cit.*), was unstable, and it was necessary to employ milder conditions in its preparation from the amino-carbinol. The alkenylamines (Table III), which were purified by distillation under reduced pressure, were mobile liquids which became highly coloured on exposure to air; they were converted into water-soluble crystalline *hydrochlorides*, and some into *methiodides*.

The pharmacological properties of these compounds, which have been studied by Dr. A. C. White and Mr. A. F. Green of the Biological Division of these Laboratories, were of considerable interest. High antispasmodic activity was shown by several amino-carbinols, *e.g.*, the activity of (I; R = H, NR′R″ = $N<C_5H_{10}$) was favourable in relation to synthetic spasmolytics now in clinical use. The majority of the amino-carbinols were powerful local anæsthetics. A number of tertiary amino-butenes, in particular (IV; R = Me, NR′R″ = NMe_2, NEt_2, $N<C_4H_8$, $N<C_5H_{10}$), were potent analgesics, as active as morphine in the rat, with undesirable side-effects (in the dog) at a minimum; the alkenylamines (IV) in general also exhibited spasmolytic, antihistamine, and local anæsthetic activity. The detailed pharmacology will be reported elsewhere; a preliminary communication has been published (Adamson and Green, *Nature*, 1950, **165**, 122).

Our investigations in this series are being extended.

Experimental.

(M. p.s are uncorrected.)

2-Aminoalkanecarboxylic Esters (see Table I).—*β-Aminopropionates* (II; R′ = H). Ethyl β-dimethylamino-, β-diethylamino-, β-pyrrolidino-, and β-piperidino-propionates (II; R = Et, R′ = H, NR″R‴ = NMe_2, NEt_2, $N<C_4H_8$, $N<C_5H_{10}$) were prepared as described in Part I (*loc. cit.*).

β-Aminobutyrates (II; R′ = Me). Methyl or ethyl crotonate was added to the amine (1 mol.) under the various conditions described below, and the esters were isolated from the product by fractional distillation under reduced pressure. The results, and references to earlier syntheses, are summarised in Table I.

Method A. The primary amino-ester (II; R = Et, R′ = Me, R″ = R‴ = H) was prepared by mixing ethyl crotonate (100 g.) with ethanolic ammonia (400 c.c.; saturated at 15°) and heating in an autoclave for 7 hours at 105—110°.

Method B. The amine, dissolved in an equal volume of ethanol, was mixed with methyl or ethyl crotonate, and the product distilled after being kept for 14 days.

Method C. A mixture of the amine and ethyl crotonate was boiled under reflux for 3 hours.

Method D. In the preparation of *methyl β-pyrrolidinobutyrate* (II; R = R′ = Me, NR″R‴ = $N<C_4H_8$)

sufficient heat to cause boiling of the mixture was generated when pyrrolidine was mixed with methyl crotonate. The mixture was allowed to cool and was distilled after being kept overnight.

TABLE I.

2-Aminoalkane carboxylic esters, $CO_2R{\cdot}CH_2{\cdot}CHR'{\cdot}NR''R'''$.

R.	R'.	NR''R'''.	Method.	Yield, %.	B. p. (mm.).	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
Et	Me	NH_2	A	58	63—64° (12) [a]	—	—	—	—	—	—	—
,,	,,	NHMe	B	70	66—68 (12) [b]	—	—	—	—	—	—	—
,,	,,	NHEt	,,	78	77—79 (12) [c]	—	—	—	—	—	—	—
,,	,,	$NHBu^n$	,,	80	100 (17)	$C_{10}H_{21}O_2N$	63·4	10·7	7·5	64·2	11·2	7·5
,,	,,	,,	C	42	—	—	—	—	—	—	—	—
Me	,,	NMe_2	B	79	66 (17)	$C_7H_{15}O_2N$	57·5	10·0	9·4	57·9	10·3	9·7
Et	,,	,,	,,	75	178—180 [c]	—	—	—	—	—	—	—
Me	,,	NEt_2	,,	57	84 (18)	$C_9H_{19}O_2N$	61·8	11·3	8·5	62·4	11·0	8·1
Et	,,	,,	,,	85	91—92 (18) [b]	—	—	—	—	—	—	—
Me	,,	NPr^n_2	,,	40	116—118 (15)	$C_{11}H_{23}O_2N$	66·0	11·5	7·1	65·7	11·4	7·0
,,	,,	NBu^n_2	,,	29	134—136 (15)	$C_{13}H_{27}O_2N$	68·1	11·8	6·4	68·1	11·8	6·1
Et	,,	$NMe{\cdot}CH_2Ph$	C	41	156—158 (16)	$C_{14}H_{21}O_2N$	71·7	8·7	6·4	71·5	8·9	6·0
Me	,,	$N<C_4H_8$	D	89	100—102 (23)	$C_9H_{17}O_2N$	62·8	9·9	8·6	63·2	9·9	8·2
Et	,,	$N<C_5H_{10}$	C	85	110—114 (13) [d]	—	—	—	—	—	—	—
,,	,,	$N<[CH_2]_4>O$	,,	42	121—122 (12)	$C_{10}H_{19}O_3N$	59·3	9·2	7·3	59·7	9·5	7·0
Me	Et	NMe_2	E	50	78—80 (18)	$C_8H_{17}O_2N$	60·1	10·6	8·9	60·4	10·7	8·8
,,	,,	,,	F	83	—	—	—	—	—	—	—	—
Et	,,	,,	,,	85	88—90 (20)	$C_9H_{19}O_2N$	61·9	10·5	7·9	62·4	11·0	8·1
Me	,,	$N<C_5H_{10}$	E	65	122—123 (21)	$C_{11}H_{21}O_2N$	66·5	10·3	6·9	66·3	10·6	7·0
,,	,,	,,	F	76	—	—	—	—	—	—	—	—
Et	,,	,,	,,	73	130—132 (21)	$C_{12}H_{23}O_2N$ *	67·2	10·4	6·8	67·6	10·8	6·6
Me	Pr^n	NMe_2	,,	74	90 (15)	$C_9H_{19}O_2N$	62·7	10·7	8·2	62·4	11·0	8·1
Et	,,	,,	,,	83	116—118 (24)	$C_{10}H_{21}O_2N$ *	64·3	10·7	7·3	64·2	11·2	7·5
Me	,,	$N<C_5H_{10}$	,,	69	140—141 (22)	$C_{12}H_{23}O_2N$ *	67·6	10·7	6·8	67·6	10·8	6·6
Et	,,	,,	,,	49	158—160 (30)	$C_{13}H_{25}O_2N$ *	—	—	—	—	—	—
Me	Pr^i	NMe_2	,,	69	86—88 (24)	$C_9H_{19}O_2N$	62·6	10·7	7·8	62·4	11·0	8·1
Et	,,	,,	,,	72	108—110 (25)	$C_{10}H_{21}O_2N$ *	—	—	—	—	—	—
Me	,,	$N<C_5H_{10}$	,,	29	130—133 (22)	$C_{12}H_{23}O_2N$ *	—	—	—	—	—	—
Et	,,	,,	,,	26	140—141 (17)	$C_{13}H_{25}O_2N$ *	—	—	—	—	—	—

[a] Philippi and Spenner, *Monatsh.*, 1915, **36**, 97. [b] Morsch, *Monatsh.*, 1932, **60**, 50. [c] Breckpot, *Bull. Soc. chim. Belg.*, 1923, **32**, 412. [d] Philippi and Galter, *Monatsh.*, 1929, **51**, 253.

* Decomposes on storage.

β-Amino-esters.—Higher homologues (II; R' = Et, Pr^n, Pr^i). β-Ethyl-, β-*n*-propyl-, and β-*iso*propyl-acrylic acids were prepared by known methods (von Auwers, *Annalen*, 1923, **432**, 74) and were esterified with boiling methanol or ethanol and concentrated sulphuric acid. The methyl esters appear to be new: *methyl β-ethylacrylate*, b. p. 144—145° (Found: C, 63·1; H, 8·9. $C_6H_{10}O_2$ requires C, 63·2; H, 8·8%), *methyl* β-n-*propylacrylate*, b. p. 62—64°/22 mm. (Found: C, 65·7; H, 9·5. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%), *methyl* β-iso*propylacrylate*, b. p. 60—62°/22 mm. (Found: C, 65·4; H, 9·6%).

Methyl β-dimethylamino- and *β-piperidino-valerates* (II; R = Me, R' = Et, $NR''R''' = NMe_2$, $N<C_5H_{10}$) were prepared by mixing methyl β-ethylacrylate with the amine (1 mol.) in an equal volume of ethanol, and the product was distilled after 4 days (method E). Higher yields were obtained when 1·5 mols. of the amine were used (method F), and accordingly these conditions were employed in the preparation of *methyl* and *ethyl β-dimethylamino-* and *β-piperidino-valerates*, and -δ-methylvalerates and the corresponding *hexoates* (II; R = Me, Et, R' = Et, Pr^n, Pr^i, $NR''R''' = NMe_2$, $N<C_5H_{10}$).

Preparation of Amino-carbinols by Means of 2-Thienyl-lithium.—The 3-*amino-* and *N*-substituted 3-*amino*-1 : 1-*di*-2'-*thienylalkan*-1-*ols* (I) (Table II) were prepared from 2-thienyl-lithium and the appropriate β-amino-ester, the general method employed being illustrated by the example described below. As indicated in Table II, the preparation of three carbinols was repeated, with the difference that the 2-thienyl-lithium was prepared from *n*-butyl-lithium (Gilman and Shirley, *J. Amer. Chem. Soc.*, 1949, **71**, 1870); the yields were very similar to, and the products identical with, those obtained by the general method as given in the example.

3-*Dimethylamino*-1 : 1-*di*-2'-*thienylbutan*-1-*ol* (I; R = R' = R'' = Me). A slow stream of dry nitrogen was led into the apparatus throughout the reaction in order to maintain an inert atmosphere. Thiophen (50 g., 0·6 mol.) in ether (50 c.c.) was added to an ethereal solution of phenyl-lithium prepared from bromobenzene (94 g., 0·6 mol.), lithium (8·5 g., 1·2 atoms), and ether (400 c.c.), and the mixture boiled under reflux for 2 hours. Ethyl β-dimethylaminobutyrate (32·0 g., 0·2 mol.) in ether (50 c.c.) was then added gradually to the mixture, stirred and cooled at −20°. Stirring was continued for 1 hour at room temperature and the mixture, from which a fawn-coloured solid had separated, was kept overnight. Ice (100 g.) was added with stirring, followed by glacial acetic acid until the solution was acidic to litmus. The crude amino-carbinol hydrobromide which separated as a brown crystalline solid was filtered off and washed with ether. The salt was suspended in chloroform, excess of ammonia added with shaking, the chloroform layer separated, washed with water, and dried (Na_2SO_4), and the chloroform evaporated. The residual dark brown oil (46 g.) rapidly crystallised; it was dissolved in boiling light petroleum (500 c.c.; b. p. 40—60°), and the solution filtered from black amorphous material and evaporated to *ca.* 120 c.c. The amino-carbinol crystallised on cooling and had m. p. 85—88° (40 g., 71% yield). Recrystallisation from ethanol gave 36 g., m. p. 90—91°, unchanged by further crystallisations.

TABLE II.

3-*Amino*-1 : 1-*di*-2′-*thienylalkan*-1-*ols*, :C(OH)·CH$_2$·CHR·NR′R″.

					Found, %.					Required, %.				
R.	NR′R″.	Yield, %.	M. p.†	Formula.†	C.	H.	N.	S.	Cl or I.	C.	H.	N.	S.	Cl or I.
H	NMe_2	72[a]	136—137°	$C_{13}H_{17}ONS_2$	58·4	6·4	5·0	23·8	—	58·5	6·4	5·2	24·0	—
			170—171 *	$C_{13}H_{17}ONS_2,C_2H_2O_4$	50·6	5·5	—	—	—	50·4	5·3	—	—	—
,,	,,	18[b]	65	$C_{15}H_{21}ONS_2$	60·9	7·2	4·6	21·3	—	61·0	7·1	4·7	21·7	—
			196—197 *	$C_{15}H_{21}ONS_2,HCl$	—	—	—	19·0	10·9	—	—	—	19·3	10·7
			193—194 *	$C_{16}H_{24}ONS_2I$	—	—	—	14·7	28·9	—	—	—	14·6	29·1
,,	N<C_4H_8	73	118—119	$C_{15}H_{19}ONS_2$	61·5	6·2	4·6	21·6	—	61·4	6·5	4·8	21·8	—
			196—197 *	$C_{15}H_{19}ONS_2,HCl$	—	—	—	19·3	10·8	—	—	—	19·4	10·8
			179—180 *	$C_{16}H_{22}ONS_2I$	—	—	—	14·3	29·4	—	—	—	14·7	29·2
,,	N<C_5H_{10}	66	70—72	$C_{16}H_{21}ONS_2$	62·7	6·8	4·8	21·0	—	62·5	6·8	4·6	20·8	—
			(b. p. 176—180/0·04 mm.)											
			198 *	$C_{16}H_{21}ONS_2,HCl$	—	—	—	—	10·4	—	—	—	—	10·3
			188—189 *	$C_{17}H_{24}ONS_2I$	—	—	—	14·1	28·1	—	—	—	14·3	28·3
Me	NH_2	34	126—127	$C_{12}H_{15}ONS_2$	56·9	6·1	5·3	25·0	—	56·9	5·9	5·5	25·3	—
			151—152 *	$C_{12}H_{15}ONS_2,\frac{1}{2}C_2H_2O_4$	52·1	5·3	—	—	—	52·4	5·4	—	—	—
,,	NHEt	24	80—81	$C_{14}H_{19}ONS_2$	60·3	6·6	4·9	22·6	—	59·8	6·8	5·0	22·8	—
			(b. p. 139—143/0·1 mm.)											
			204—205 *	$C_{14}H_{19}ONS_2,\frac{1}{2}C_2H_2O_4$	55·6	6·2	—	—	—	55·2	6·1	—	—	—
,,	NHBu	40	63—64	$C_{16}H_{23}ONS_2$	62·4	7·3	4·7	21·1	—	62·1	7·4	4·5	20·7	—
			183—184 *	$C_{16}H_{23}ONS_2,\frac{1}{2}C_2H_2O_4$	57·5	6·8	—	—	—	57·6	6·8	—	—	—
,,	NMe_2	71	90—91	$C_{14}H_{19}ONS_2$	60·1	6·9	4·8	22·7	—	59·8	6·8	5·0	22·8	—
			198—199 *	$C_{14}H_{19}ONS_2,HCl$	—	—	—	—	11·3	—	—	—	—	11·2
			189 *	$C_{15}H_{22}ONS_2I$	—	—	—	—	29·8	—	—	—	—	30·0
,,	NEt_2	79	75—76	$C_{16}H_{23}ONS_2$	62·1	7·3	4·4	21·1	—	62·1	7·4	4·5	20·7	—
			117—118	$C_{16}H_{23}ONS_2,C_2H_2O_4$	54·5	6·3	—	—	—	54·1	6·3	—	—	—
,,	NPr^n_2	70	91—92	$C_{18}H_{27}ONS_2$	64·0	8·0	4·2	18·9	—	64·1	8·0	4·2	19·0	—
			100	$C_{18}H_{27}ONS_2,C_2H_2O_4$	56·2	6·7	—	—	—	56·2	6·8	—	—	—
,,	NMe·CH_2Ph	56	73—74	$C_{20}H_{23}ONS_2$	67·6	6·2	3·9	17·6	—	67·2	6·4	3·9	17·9	—
			143—144 *	$C_{20}H_{23}ONS_2,C_2H_2O_4$	59·3	5·7	—	—	—	59·1	5·6	—	—	—
,,	N<C_4H_8	77	88—89	$C_{16}H_{21}ONS_2$	62·8	7·0	4·6	20·9	—	62·5	6·8	4·6	20·9	—
			172—173 *	$C_{16}H_{21}ONS_2,C_2H_2O_4$	54·3	5·9	—	16·0	—	54·4	5·8	—	16·1	—
,,	N<C_5H_{10}	55[a]	82—83	$C_{17}H_{23}ONS_2$	63·6	7·2	4·5	19·6	—	63·6	7·2	4·4	19·9	—
			(b. p. 146—148/0·02 mm.)											
			166—167 *	$C_{17}H_{23}ONS_2,C_2H_2O_4$	55·6	6·2	—	—	—	55·5	6·1	—	—	—
,,	N<$[CH_2]_4$>O	48	105—106	$C_{16}H_{21}O_2NS_2$	59·4	6·4	4·3	19·8	—	59·4	6·5	4·3	19·8	—
			134—135 *	$C_{16}H_{21}O_2NS_2,C_2H_2O_4$	52·7	5·9	—	—	—	52·3	5·6	—	—	—
Et	NMe_2	73[a]	83—84	$C_{15}H_{21}ONS_2$	61·0	7·1	4·7	21·3	—	61·0	7·1	4·7	21·7	—
			170—171 *	$C_{15}H_{21}ONS_2,C_2H_2O_4$	53·1	5·9	—	—	—	53·0	6·0	—	—	—
Pr^n	,,	43	—	$C_{16}H_{23}ONS_2$	62·4	7·1	4·4	20·8	—	62·1	7·4	4·5	20·7	—
			(b. p. 145—147/0·05 mm.)											
			138—139 *	$C_{16}H_{23}ONS_2,C_2H_2O_4$	54·3	6·3	—	—	—	54·1	6·3	—	—	—
Pr^i	,,	71	56—57	$C_{16}H_{23}ONS_2$	62·2	7·1	4·5	20·8	—	62·1	7·4	4·5	20·7	—
			125—126	$C_{16}H_{23}ONS_2,C_2H_2O_4$	54·2	6·1	—	15·9	—	54·1	6·3	—	16·0	—

[a] 2-Thienyl-lithium prepared from *n*-butyl-lithium. [b] Prepared by the Grignard reaction.
* M. p. with decomposition. † The m. p. and formula of the base are given first, followed by those of its derivatives.

Preparation of Amino-carbinols by the Grignard Reaction.—**3-*Piperidino*-1 : 1-*di*-2′-*thienylpropan*-1-*ol*** (I; R = H, NR′R″ = N<C_5H_{10}). Ethyl β-piperidinopropionate (37 g., 0·2 mol.) in ether (50 c.c.) was added gradually to an ethereal solution of the Grignard reagent made from 2-bromothiophen (98 g., 0·6 mol.) and magnesium (14·6 g., 0·6 atom) in ether (50 c.c.), stirred and cooled in a bath at 0°. The mixture, from which a heavy oil had separated, was boiled under reflux for 5 hours and kept overnight at room temperature. Crushed ice (100 g.) was added, followed by aqueous ammonium chloride (25%; 100 c.c.). Acetic acid was then added gradually with stirring until the solution was acid to litmus, and the cream-coloured solid which separated was filtered off and washed with ether. The solid was dissolved in chloroform and shaken with excess of ammonia; the chloroform layer was washed with water and dried (Na_2SO_4), and the chloroform evaporated. The residual brown mobile oil was distilled at 0·1 mm. pressure and the following fractions collected: (i) b. p. <160°, 16·5 g., (ii) b. p. 160—188°, 2·0 g., (iii) b. p. 188—194°, 15·3 g., and (iv) b. p. >194°, approx. 10 g. (resinous). Fraction (iii) which rapidly crystallised was the amino-carbinol, m. p. 70—72° after recrystallisation from ethanol (yield 24%). Redistillation of fraction (i) gave, besides some low-boiling material, a mobile liquid, b. p. 102—105°/0·03 mm. (10·1 g., 23%), which was identified as 2-β-piperidinopropionylthiophen (III) [hydrochloride (recrystallised from methanol), m. p. 203—205°, not depressed by a specimen prepared by the Mannich reaction (Blicke and Burckhalter, *J. Amer. Chem. Soc.*, 1942, **64**, 451)].

TABLE III.

3-*Amino*-1 : 1-*di*-2′-*thienylalk*-1-*enes*, []$_2$:C:CH·CHR·NR′R″

		Base.	Hydrochloride.					
						Found, %.		Reqd., %.
R.	NR′R″.	B. p. (mm.).	M. p.	Formula.	Cl.	S.	Cl.	S.
H	NMe_2	91—94° (0·05)	144—145°	$C_{13}H_{15}NS_2$,HCl	12·5	22·7	12·4	22·4
,,	NEt_2	—	116—117	$C_{15}H_{19}NS_2$,HCl	11·5	19·8	11·3	20·4
,,	N<C_4H_8	—	102—103	$C_{15}H_{17}NS_2$,HCl	11·3	20·3	11·4	20·5
,,	N<C_5H_{10}	143 (0·05) [a]	171—173 *	$C_{16}H_{19}NS_2$,HCl	10·9	19·8	10·9	19·7
Me	NH_2	—	174—175 *	$C_{12}H_{13}NS_2$,HCl	12·8	23·2	13·1	23·2
,,	NHEt	112—114 (0·03)	134—135	$C_{14}H_{17}NS_2$,HCl	11·9	21·3	11·8	21·4
,,	NHBu	122—124 (0·04) [b]	123—124	$C_{16}H_{21}NS_2$,HCl	11·2	19·8	10·8	19·5
,,	NMe_2	123—125 (0·05)	169—170	$C_{14}H_{17}NS_2$,HCl	12·1	22·0	11·8	21·4
,,	NEt_2	122—128 (0·03)	152—153	$C_{16}H_{21}NS_2$,HCl	10·6	19·5	10·8	19·5
,,	NPr^n_2	119—121 (0·01)	112—115 [c]	$C_{18}H_{25}NS_2$,HCl	10·0	17·8	10·0	18·0
,,	NMe·CH_2Ph	146—148 (0·01)	160—161 *	$C_{20}H_{21}NS_2$,HCl	9·6	16·3	9·5	17·0
,,	N<C_4H_8	132—135 (0·1)	167—169	$C_{16}H_{19}NS_2$,HCl	10·9	19·5	10·9	19·7
,,	N<C_5H_{10}	132—136 (0·05)	188—189	$C_{17}H_{21}NS_2$,HCl	10·5	18·6	10·5	18·9
,,	N<[CH_2]$_{4}$>O	130—136 (0·05)	181—182	$C_{16}H_{19}ONS_2$,HCl	10·4	18·4	10·4	18·7
Et	NMe_2	110—112 (0·03)	138—139	$C_{15}H_{19}NS_2$,HCl	11·5	20·3	11·3	20·4
Pr^n	,,	116—118 (0·03)	158—159	$C_{16}H_{21}NS_2$,HCl	10·8	19·6	10·8	19·5
Pr^i	,,	107—109 (0·03) [d]	(159—160 *) [e]	—	—	—	—	—

[a] Found: C, 66·7; H, 6·4; N, 4·7; S, 22·4. $C_{16}H_{19}NS_2$ requires C, 66·4; H, 6·6; N, 4·8; S, 22·2%. [b] Found: C, 66·0; H, 7·2; N, 4·8; S, 22·0. $C_{16}H_{21}NS_2$ requires C, 66·0; H, 7·2; N, 4·8; S, 22·0%. [c] Found, for hydrate: H_2O, 2·3. $C_{18}H_{25}NS_2$,HCl,$\frac{1}{2}H_2O$ requires H_2O, 2·5%. [d] Found: C, 66·0; H, 7·3; N, 4·8; S, 22·0. $C_{16}H_{21}NS_2$ requires C, 66·0; H, 7·2; N, 4·8; S, 22·0%. [e] Found, for hydrogen oxalate: S, 16·7. $C_{16}H_{21}NS_2$,$C_2H_2O_4$ requires S, 16·8%.

* M. p. with decomposition.

The amino-carbinol was also prepared from 2-β-piperidinopropionylthiophen hydrochloride (0·1 mol.) and 2-thienylmagnesium bromide (0·3 mol.) under conditions similar to those described above, a yield of 31% being obtained.

3-*Diethylamino*-1 : 1-*di*-2′-*thienylpropan*-1-*ol* (I; R = H, R′ = R″ = Et). The amino-carbinol was obtained in 18% yield from the reaction between 2-thienyl-lithium (0·3 mol.) and ethyl β-diethylamino-propionate (0·1 mol.) under conditions similar to those described above for the piperidino-analogue. In this example also a considerable quantity of a low-boiling fraction was obtained when the crude product was distilled under reduced pressure, but on redistillation it boiled over a wide range with some decomposition.

The amino-carbinols were purified by recrystallisation from ethanol; in those examples for which a b. p. is recorded in Table II, the crude products were given a preliminary purification by fractional distillation under reduced pressure.

The *hydrochlorides* were prepared by passing dry hydrogen chloride into a solution of the base in chloroform at 0° until neutrality was reached. The salts crystallised on the addition of ether and were recrystallised from ethanol.

The oxalates were prepared by mixing the base (1 mol.) in ethanol with anhydrous oxalic acid (1 mol.) in ethanol at room temperature. The salts which rapidly separated were recrystallised from ethanol. Under these conditions the primary and secondary amino-carbinols gave neutral *oxalates*, and the tertiary amines *hydrogen oxalates*.

The *methiodides* were prepared by adding methyl iodide (2 mols.) to a solution of the tertiary amino-carbinols in a small volume of acetone After several hours, the salts which had separated were recrystallised from methanol.

Dehydration of Amino-carbinols.—The method described for the dehydration of the related diphenyl-carbinols (Part I, *loc. cit.*) was successfully applied to the aminopropanols (I; R = H), the yields of

distilled allylamine being approx. 70% (example 1). When this method was applied to some aminobutanols (I; R = Me), however, extensive degradation occurred and black amorphous solids were formed (example 2). The amino-butanols and higher homologues were therefore dehydrated under milder conditions, whereby the unsaturated amines were obtained usually in yields of 70—90% (example 3). In the preparation of 3-*benzylmethylamino*-1 : 1-*di*-2′-*thienylbut*-1-*ene* (IV; R = R′ = Me, R″ = CH_2Ph) by this method considerable quantities of tar were produced, and the yield was 40%. 3-Amino-1 : 1-di-2′-thienylbutan-1-ol (I; R = Me, R′ = R″ = H) was completely decomposed to tarry products by this method, and therefore dehydration was effected under milder conditions as described in example 4. Dehydration by warming of the carbinol with hydrochloric acid alone was successful in the preparation of 3-*diethylamino*-1 : 1-*di*-2′-*thienylbut*-1-*ene* (IV; R = Me, R′ = R″ = Et) (example 5).

Example 1. 3-Dimethylamino-1 : 1-di-2′-thienylpropan-1-ol (15 g.) was dissolved in a mixture of concentrated hydrochloric acid (30 c.c.) and glacial acetic acid (100 c.c.), and the solution boiled under reflux for 20 minutes. The deeply coloured solution was then concentrated under reduced pressure, the residue treated with excess of ammonia, and the base extracted with ether. The ethereal solution was dried (Na_2SO_4), the ether evaporated, and the residue distilled under reduced pressure. The product, 3-*dimethylamino*-1 : 1-*di*-2′-*thienylprop*-1-*ene* (IV; R = H, R′ = R″ = Me), was a colourless mobile liquid which became purple on exposure to air and had b. p. 91—94°/0·05 mm. (yield 9·9 g., 71%).

Example 2. 3-Dimethylamino-1 : 1-di-2′-thienylbutan-1-ol (15 g.) was boiled under reflux in acidic solution as described in example 1. A black solid was deposited on the walls of the flask. The mixture was concentrated under reduced pressure and filtered. The residue was a black intractable solid (melting between 135° and 180°), insoluble in boiling water or aqueous mineral acids; the dark filtrate gave a small amount of tarry material when basified.

Example 3. 3-Piperidino-1 : 1-di-2′-thienylbutan-1-ol (20 g.) was warmed on the steam-bath for 15 minutes with concentrated hydrochloric acid (40 c.c.) and glacial acetic acid (130 c.c.). The solution was worked up as described in example 1 (care being taken to keep the temperature low during the concentration of the solution), and the product, 3-*piperidino*-1 : 1-*di*-2′-*thienylbut*-1-*ene* (IV; R = Me, NR′R″ = N<C_5H_{10}), was distilled under reduced pressure, having b. p. 132—136°/0·05 mm. (yield 14·5 g., 78%).

Example 4. Dry hydrogen chloride was led into a cooled solution of 3-amino-1 : 1-di-2′-thienylbutan-1-ol (1·6 g.) in chloroform (8 c.c.). The white solid which separated quickly dissolved, the solution became pale brown, and drops of water separated. The chloroform solution was dried (Na_2SO_4) and evaporated under reduced pressure to small volume, and ether added gradually until crystallisation commenced. 3-*Amino*-1 : 1-*di*-2′-*thienylbut*-1-*ene hydrochloride* (IV; R = Me, R′ = R″ = H) was obtained as fawn-coloured crystals, m. p. 174—175° (decomp.).

Example 5. 3-Diethylamino-1 : 1-di-2′-thienylbutan-1-ol (15 g.) was added to hydrochloric acid (6N.; 75 c.c.), and the mixture heated on the steam-bath for 15 minutes. The resulting deeply coloured solution was cooled, excess of ammonia added, and the base extracted with chloroform. The chloroform was evaporated, and the residual oil distilled under reduced pressure to give 3-*diethylamino*-1 : 1-*di*-2′-*thienylbut*-1-*ene* (IV; R = Me, R′ = R″ = Et), b. p. 122—128°/0·03 mm. (10·5 g., 74%).

The 3-*amino*-1 : 1-*di*-2′-*thienylalk*-1-*enes* and their *hydrochlorides* are recorded in Table III. The hydrochlorides, prepared in a similar manner to those of the amino-carbinols, were recrystallised from ethanol–ethyl acetate. In some cases the hydrochlorides were also isolated directly from the dehydration mixture by evaporation to dryness and recrystallisation of the solid residue.

The following methiodides were prepared by mixing the base with excess of methyl iodide in acetone solution. After several hours, the product was filtered off and recrystallised from methanol. 3-*Diethylamino*-1 : 1-*di*-2′-*thienylprop*-1-*ene methiodide*, m. p. 174—175° (decomp.) (Found: I, 31·0. $C_{16}H_{22}NIS_2$ requires I, 30·3%); 3-*pyrrolidino*-1 : 1-*di*-2′-*thienylprop*-1-*ene methiodide*, m. p. 186° (decomp.) (Found: I, 30·0. $C_{16}H_{20}NIS_2$ requires I, 30·5%); 3-*piperidino*-1 : 1-*di*-2′-*thienylprop*-1-*ene methiodide*, m. p. 193—194° (decomp.) (Found: I, 29·3. $C_{17}H_{22}NIS_2$ requires I, 29·5%); 3-*dimethylamino*-1 : 1-*di*-2′-*thienylbut*-1-*ene methiodide*, decomposes from 130° (Found: I, 32·3. $C_{15}H_{20}NIS_2$ requires I, 31·4%).

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CHEMICAL DIVISION, WELLCOME RESEARCH LABORATORIES,
BECKENHAM, KENT.

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