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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.



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 ethyly-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-piperidinoisobutyrylthiophen 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, Prⁿ, Prⁱ, $NR''R''' = NMe_2$, $N < C_5H_{10}$). 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, Prⁿ, Pr^j), 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. Α 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 -dimethyl-amino-, β -diethylamino-, β -pyrrolidino-, and β -piperidino-propionates (II; R = Et, R' = H, NR''R''' = NMe₂, NEt₂, N < C₄H₈, N < C₅H₁₀) 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; $R = R' = Me, NR''R''' = N < C_4H_a$)

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, CO₂R•CH₂•CHR'•NR''R'''.

				Yield.			Fo	und, 9	%.	Req	uired,	%.
R.	R'.	NR''R'''.	Method.	%.	B. p. (mm.).	Formula.	C.	H.	N.	с.	н.	N.
Et	Me	NH.	Α	58	63-64° (12) *							
,,	,,	NHMe	в	70	6668 (12) ^{'b}							
,,	,,	NHEt	,,	78	7779 (12) °							
,,	,,	NHBun	,,	80	100 (17)	$C_{10}H_{21}O_{2}N$	63·4	10.7	7.5	64.2	11.2	7.5
,,	,,	,,	С	42			—					
Me	,,	NMe_2	в	79	66 (17)	$C_7H_{15}O_2N$	57.5	10.0	9.4	57.9	10.3	9.7
Et	,,	,,	,,	75	178—180 °							
Me	,,	NEt ₂	,,	57	84 (18)	$C_9H_{19}O_2N$	61.8	11.3	8.5	$62 \cdot 4$	11.0	$8 \cdot 1$
Et	,,	,,	,,	85	91-92 (18) *							
Me	,,	NPr ⁿ 2	,,	40	116-118 (15)	$C_{11}H_{23}O_2N$	66 ·0	11.5	$7 \cdot 1$	65.7	11.4	7.0
,,	,,	NBu ⁿ 2	,,	29	134—136 (15)	$C_{13}H_{27}O_2N$	68.1	11.8	$6 \cdot 4$	68 ·1	11.8	$6 \cdot 1$
Et	,,	NMe•CH ₂ Ph	С	41	156 - 158 (16)	$C_{14}H_{21}O_{2}N$	71.7	8.7	$6 \cdot 4$	71.5	8.9	6.0
Me	,,	$N < C_4 H_8$	D	89	100-102(23)	$C_9H_{17}O_2N$	62.8	9.9	8.6	63.2	9.9	$8 \cdot 2$
Et	,,	$N < C_5 H_{10}$	С	85	$110-114(13)^{\circ}$							
.,,	.,,	$N < [CH_2]_4 > O$	· <u>,,</u>	42	121 - 122(12)	$C_{10}H_{19}O_{3}N$	59.3	9.2	7.3	59.7	9.5	7.0
Me	Et	NMe ₂	E	50	7880 (18)	$C_8H_{17}O_2N$	60.1	10.6	8.9	60·4	10.7	8.8
	,,	.,	F	83				10 7				
Et	,,		ä	85	8890 (20)	$C_9H_{19}O_2N$	61.9	10.5	7.9	62.4	11.0	8.1
ме	,,	$N < C_5 H_{10}$	E	65	122 - 123 (21)	$C_{11}H_{21}O_{2}N$	<u>60.9</u>	10.3	6.9	66.3	10.0	7.0
<i></i>	,,	,,	Г	76	100 100 (01)		<u></u>	10.		0 - 0	10.0	~~~~
Et	ň	,, ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	,,	73	130 - 132(21)	$C_{12}\Pi_{23}U_{2}N^{+}$	607-2	10.4	0.9	01.0	10.9	0.0
Me	Pru	NMe ₂	,,	74	90 (15)	$C_{9}H_{19}O_{2}N$	02.7	10.7	8.2	62·4	11.0	8.1
Et	,,	N".C II	,,	83	110 - 118 (24)	$C_{10}H_{21}O_{2}N +$	04.3	10.7	7.3	04.2	11.2	1.0
Me	,,	$N < C_5 H_{10}$,,	09	140 - 141(22)	$C_{12}H_{23}O_{2}N^{+}$	01.0	10.7	0.9	01.0	10.8	0.0
Et	<u>,,,</u>	NIM.	,,	49	108 - 100 (30)	$C_{13}\Pi_{25}U_{2}N^{+}$	60.6	10.7		60 4	110	0 1
Me	\mathbf{PT}	NMe ₂	,,	09	80	C H O N *	02.0	10.7	1.9	02.4	11.0	9.1
Et Mo	,,	N ["] CH	,,	14	100	C H O N *						
me	,,	$N < C_5 \Pi_{10}$	• •	29	130 - 133 (22)	$C_{12}\Pi_{23}O_{2}N^{+}$						
£ί	,,		.,	40	140141 (17)	$C_{13} C_{25} C_{21} C_{13} $						

Philippi and Spenner, Monatsh., 1915, 36, 97.
Morsch, Monatsh., 1932, 60, 50.
Breckpot, Bull. Soc. chim. Belg., 1923, 32, 412.
Philippi and Galter, Monatsh., 1929, 51, 253.
* Decomposes on storage.

β-Amino-esters.—Higher homologues (II; R' = Et, Prⁿ, Prⁱ). β-Ethyl-, β-n-propyl-, and β-isopropylacrylic 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. C₆H₁₀O₂ requires C, 63·2; H, 8·8%), methyl β-n-propylacrylate, b. p. 62—64°/22 mm. (Found : C, 65·7; H, 9·5. C₇H₁₂O₂ requires C, 65·6; H, 9·4%), methyl β-isopropylacrylate, 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"'' = NMe₂, N<C₅H₁₀) were prepared by mixing methyl β-ethylacrylate with the amine (1 mol.) in an equal volume of the poly of the periodic visual distinct 4 days (method F).

Methyl β -dimethylamino- and β -piperidino-valerates (II; R = Me, R' = Et, NR''R''' = NMe₂, N < C₅H₁₀) were prepared by mixing methyl β -ethylacrylate with the amine (I 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^a, Prⁱ, NR''R''' = NMe₂, N < C₅H₁₀). Preparation of Amino-carbinols by Means of 2-Thienyl-lithium.—The 3-amino- and N-substituted 3-amino-lith-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 excitations of the general method employed being illustrated by the example described below.

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 with shaking, the chloroform layer separated, washed with water, and dried (Na₂SO₄), 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). Recrystal-lisation from ethanol gave 36 g., m. p. 90-91°, unchanged by further crystallisations.

			3 -Amino-1 : 1-di-2'-thie	nylalkan-1-ols, [[:C(0]	H)•CH2	-CHR-1	NR'R".						
				ί Α	5	F_0	und, %	. :			Requ	ired, %		
1		Yield,	4 ·· 14	ц 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	ر	1		0		ار			5	
: =	N N N	.0/	196 197°		78.4 7	1. 1.9	.ч К.О.	03.8		79.7 79.7	.11. 6.4		0. 04.0	
11	2 ATTAT	1	170171 *	CH. ONS, C.H.O.	20.6	12	21			50.4	1 6. 2			
:	:	18,	65	C. H.ONS.	6.09	1.2	4.6	21.3		0.10	1.7	4.7	21.7	
:	:		196-197 *	C15H21ONS2,HCI	l]	-	19-0	10.9		ł		19-3	10.7
	:		193-194 *	C16H24ONS21			.	14.7	28.9].	14.6	20·1
:	$N < C_4 H_8$	7:3	118119	C ₁₆ H ₁₀ ONS ₂	$61 \cdot 5$	5	4.6	21.6		61-4	6.5	÷ ×	21:8 	
				C ₁₅ H ₁₉ ONS ₃ , HCl	1	1		19.3	10.8	1]	1	4.61	8 0 0
	N -C H	บบ	. 00101 T	CIGH23CN32L	1.09	9.9	0.1	0.1.0	÷.0.7	69.5	3.9	9.4	- a.00	7.67
:	01119A / NT	00	(h n 176—180/0:04 mm)	C161121/17/22	1	0	р Н	2.17			0		0	İ
			108 *	C., H., ONS., HCI	1		ļ	1	10.4			1	1	10.3
			188-189 *	C, H, ONS, I	ŀ		۱	14.1	28.1			1	14.3	28·3
Mc	NH.	34	126 - 127	C, H, ONS,	56.9	6·1	5.3	25.0]	56-9	5.9	5.5	25.3	
	•		151152 *	C ₁₂ H ₁₆ ONS ₂ , JC ₃ H ₂ O ₄	52.1	5.3				52.4	5.4			1
=	NHEt	÷.	8081	C ₁₄ H ₁₉ ONS ₂	60.3	6.6	4.9	22.6	ļ	59.8	6·8	5.0	22·8	1
			(b. p. 139—143/0·1 mm.)											
			204-205 *	C ₁₄ H ₁₆ ONS ₂ , ¹ ₄ C ₂ H ₂ O ₄	55.6	6.2 0]]		55-2	6·1		1	
:	NHBu	-10	63 - 64	C ₁₆ H ₂₃ ONS ₂	62.4	7.3	4.7	21·1	1	62·I	7.4	4·5	20.7]
			183-184 *	C ₁₆ H ₂₃ ONS ₂ , JC ₂ H ₂ O ₃	57.5	6.8]]	57·6	6·8]		I
	NMc ₂	12	16-06	C ₁₄ H ₁₉ ONS ₂	60.1	6·9	4·8	22.7]	59·8	8·9	0.0 0	55.8 57.8	1
				C14H10ONS2, HCI	1]		: 	1	İ			11-2 2000
			+ 681	C18H22ONS21			1		29-8	1]]		30-0
:	NEt ₂	79	75-76	C ₁₆ H ₂₃ ONS ₂	62.1		.	21·1		62-1	+ <u>-</u>	£.4	20.7	ļ
		i	117-118	C16H23ONS2, C2H2O4	54·5	9] [ļ	54.1	: : : :	13		1
:	$\rm NPr_{2}^{n}$	70	91—92 100	CIRH TONS	64-0 20 0	Ç x x	4.5	18·9	1	64·1	0.0 X X	7. 1	0.6T	ļ
	NIM DIS	32			2.00 8.7.8	6.9	0.5	17.8		4.DC	0 V.9	0.6	0.71	
:		00	143-144 *	C ₂₀ H ₂₃ CNO ₂ C. H. ONS, C. H. O.	20.3	10	n.e			59.1				
	N < C.H.	77	8889	C. H. ONS.	62.8	-0-L	4.6	20.9	[62.5	9.8 9.9	4.6	20.9	
:		•	172-173 *	C, H, ONS, C, H, O,	54.3	5.9		16-0	[54.4	5.8 2	1	16.1	
:	$N < C_{s}H_{s0}$	55 °	8283	C,H,HONS,	63.6	7.2	4.5	19.6	I	63.6	7.2	4.4	19-9	1
			(b. p. 146—148/0.02 mm.)											
			166-167 *	C ₁ , H ₂₃ ONS ₂ , C ₂ H ₂ O ₄	55.6	57 - 9 -	•		1	55-5 7				ļ
:	N<[CH ₂] ₄ >0	48		C16Ha1OaNSa	59-4 29-1	6.4 4.0	4·3	19.8		59-4 20-8	6-5 7	4.3	8.61	1
ļ		i i	134-135 *	C16H21O2NS2,C2H2O	52.7	0 r 6 -			1	52.3	0.0 1			
Εt	NMc2	. 21	8384	C16H21ONS2	0.10		4.1	21.3	!	0.10	1.2	4.1	1.12	I
. (I			1/1	C16H21CINS2, C2H2C4	1.00	0 E]		I	0.00	2]
rl.r		43	(), 118 147 ().06)	C16H23CN32	7.70	1./	1 . 1	0.07	l	1.70	1 .	6. 1	1.07	ļ
			(0. p. 1±0	C., H., ONS, C. H.O.	54-3	6.3	-	!		54.1	6.3	ļ	1	{
PrI	:	11	5657	C, H, ONS,	62.2	i.	4·5	20.8	1	62.1	7.4	4.5	20.7	[
	:		125 - 126	C1,H2ONS2,C2H2O	54.2	6.1	!	15.9	١	54·1	6.3	1	16.0	1
		a 2-Thie	surl-lithium prepared from u .	-butvl-lithium. ^b Pr	epared	bv th	e Grigi	nard re	action.					
	* M. p. 1	vith decor	nposition. î f The m. p. a	nd formula of the base ar	re giver	ı first,	followe	d by th	ose of i	ts deriv	ratives.			

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TABLE II.

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Adamson: Aminoalkyl Tertiary Carbinols

and Derived Products. Part II.

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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 creamcoloured 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 (Na₂SO₄), and the chloroform evaporated. The residual brown mobile oil was distilled at 0.1 mm. pressure and the following fractions collected : (1) b. p. $<160^{\circ}$, 16.5 g., (ii) b. p. $160-188^{\circ}$, 2.0 g., (iii) b. p. $188-194^{\circ}$, 15.3 g., and (iv) b. p. $>194^{\circ}$, approx. 10 g. (resinous). Fraction (iii) which rapidly crystallised was the amino-carbinol, m. p. $70-72^{\circ}$ after recrystallisation from ethanol (yield 24%). Redistillation of fraction (i) gave, besides some low-boiling material, a mobile liquid, b. p. $102-105^{\circ}/0.03$ mm. (10.1 g., 10.1 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)].

IABLE III.	
3-Amino-1: 1-di-2'-thienylalk-1-enes,	:C:CH·CHR·NR'R"

Hydrochloride.

R.	NR'R".	Base. B. p. (mm.).	М. р.	Formula.	Foun Cl.	d, %. S.	Reqd Cl.	l., %. S.
Н	NMe.	$91 - 94^{\circ} (0.05)$	$144 - 145^{\circ}$	C13H15NS9,HCl	12.5	22.7	12.4	22.4
	NEt.	` ´	116-117	C, H, NS, HCl	11.5	19.8	11.3	20.4
	N<Č.H.		102-103	C.H.NS.HCI	11.3	20.3	11.4	20.5
,,	N <c.h.< td=""><td>$143 (0.05)^{a}$</td><td>171-173 *</td><td>C.H.NS.HCI</td><td>10.9</td><td>19.8</td><td>10.9</td><td>19.7</td></c.h.<>	$143 (0.05)^{a}$	171-173 *	C.H.NS.HCI	10.9	19.8	10.9	19.7
Ŵе	NH.		174—175 *	C ₁ ,H ₁ ,NS,HCl	12.8	$23 \cdot 2$	13.1	$23 \cdot 2$
	NHÉt	112 - 114 (0.03)	134 - 135	C, H, NS, 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.	123	169-170	C,H,NS,HCI	$12 \cdot 1$	$22 \cdot 0$	11.8	21.4
	NEt.	122 - 128 (0.03)	152 - 153	C ₁₆ H ₉ NS ₂ HCl	10.6	19.5	10.8	19.5
	NPr ⁿ ,	119—121 (0·01)	112—115 °	C ₁₈ H ₂₅ NS, HCl	10.0	17.8	10.0	18.0
	NMe•CH ₂ Ph	146—148 (0·01)	160-161 *	C ₂₀ H ₂₁ NS ₂ ,HCl	9.6	16.3	9.5	17.0
	N <c.h.< td=""><td>132 - 135(0.1)</td><td>167 - 169</td><td>C₁₆H₁₉NS, HCl</td><td>10.9</td><td>19.5</td><td>10.9</td><td>19.7</td></c.h.<>	132 - 135(0.1)	167 - 169	C ₁₆ H ₁₉ NS, HCl	10.9	19.5	10.9	19.7
	N <c.h<sub>10</c.h<sub>	132 - 136(0.05)	188 - 189	C, H, NS, HCl	10.5	18.6	10.5	18.9
	$N < [CH_{2}] > O$	130—136 (0.05)	181 - 182	C ₁₆ H ₁₀ ONS, HCl	10.4	18.4	10.4	18.7
Et	NMe,	110 - 112 (0.03)	138139	C ₁₅ H ₁₉ NS ₂ ,HCl	11.5	20.3	11.3	20.4
Prn	- ,,	116-118(0.03)	158 - 159	C ₁₆ H ₂₁ NS ₂ ,HCl	10.8	19.6	10.8	19.5
$\mathbf{Pr^{i}}$,,	$107 - 109 (0.03)^{d}$	(159-160 *)					

^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. $C_{16}H_{21}NS_2$ requires C, 66.0; H, 7.2; N, 4.8; S, 22.0%. ^e 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: C, 66.0; H, 7.2; N, 4.8; S, 22.0%. ^e Found: C, 66.0; H, 7.2; N, 4.8; S, 22.0%. ^e Found, for hydrogen oxalate: S, 16.7. $C_{16}H_{21}NS_2$, $C_{2}H_2O_4$ 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 -diethylaminopropionate (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 aminocarbinols 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 diphenylcarbinols (Part I, loc. cit.) was successfully applied to the aminopropanols (I; R = H), the yields of

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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'' = 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 refuw for 20 minutes. The density application was effective and the accurate the solution boiled under the formation by a dissolved of the carbinol with a presention and the solution boiled under concentrated hydrochloric acid (30 c.c.) and glacial acetic acid (100 c.c.), and the solution boiled under the formation by a dissolved of the presention are the activation and the solution boiled under the presention of the activation and the activation activation activation and the solution boiled under

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 (Na₂SO₄), 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 columns and the of the deele. The product acide the product of the state of the state of the state.

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.

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_3H_{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 solutionbecame pale brown, and drops of water separated. The chloroform solution was dried (Na₄SO₄) andevaporated under reduced pressure to small wolume and ether added gradually until corrections.

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

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'-thienylak-1-enes and their hydrochlorides are recorded in Table III. The hydrochloride pressure is propertied in a cimilar memory to the amino archively was evaporated.

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-Diethyl-amino-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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