[1950]

## **212.** Aminoalkyl Tertiary Carbinols and Derived Products. Part III. 3-Tertiary-amino-1-aryl-1-(2-pyridyl)-propan-1-ols and -prop-1-enes.

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3-Tertiary-amino-1-aryl-1-(2-pyridyl)propan-1-ols (VI) were prepared by treating 2-pyridyllithium with the appropriate aryl 2-tertiary-aminoethyl ketone. Dehydration of the aminopropanols gave the corresponding substituted allylamines (VII), several of which were catalytically hydrogenated to the substituted propylamines (VIII); some of these had been previously prepared by other methods. Some of the allylamines, like the known propylamines, had a very powerful antihistamine action.

SEVERAL of the 3-tertiary-amino-1: 1-diphenyl-prop-1-enes (I) and -propanes (II), described in Part I  $(J., 1949, S \ 144)$  exerted a moderate antihistamine action (White, Fawcett, Green, and Hudson, to be published).

#### (I.) $Ph_2C:CH:CH_2:NR^1R^2$ $Ph_2CH:CH_2:CH_2:NR^1R^2$ (II.)

It is known that replacement of the N-phenyl group of the antihistamine "Antergan" (III) by the 2-pyridyl group, as in "Pyribenzamine" (IV;  $\mathbb{R}^3 = \mathbb{P}h$ ) increases the potency. Similarly, many recently developed compounds having high antihistamine activity are ethylenediamine derivatives carrying a 2-pyridyl substituent [e.g., "Neoantergan"; (IV),  $\mathbb{R}^3 = p$ -MeO·C<sub>6</sub>H<sub>4</sub>. "Thenylene";  $\mathbb{R}^3 = 2$ -thienyl] (reviewed by Huttrer, Enzymologia, 1948, 12, 277). Some aminoalkyl ethers [e.g., "Decapryn" (V)], which may be regarded as 2-pyridyl analogues of "Benadryl," have effective antihistamine action (Tilford, Shelton, and Van Campen, J. Amer. Chem. Soc., 1948, 70, 4001; Sperber, Papa, Schwenk, and Sherlock, *ibid.*, 1949, 71, 887).



Accordingly we sought to increase the antihistamine activity of the substituted allylamines (I) and propylamines (II) by replacing one of the phenyl groups by 2-pyridyl to give (VII) and (VIII). While this work was in progress La Belle and Tislow (Fed. Proc., 1948, 7, 236) described the antihistamine properties of 3-dimethylamino-1-phenyl-1-(2-pyridyl)propane ("Trimeton") (VIIIa) and recently it has been reported that "Chlor-Trimeton" (VIIIe) is considerably more active than "Trimeton" or "Pyribenzamine" (Tislow et al., Fed. Proc., 1949, 8, 338). In other series of antihistamines, also, maximum potency is associated with a halogen substituted aryl group, as for example in "Chlorothen" [IV;  $\mathbb{R}^3 = 2$ -(5-chlorothienyl)] (Clapp, Clark, Vaughan, English, and Anderson, J. Amer. Chem. Soc., 1947, 69, 1549) and in 4-(4-chlorobenzhydryl)-1-methylpiperazine (Baltzly, DuBreuil, Ide, and Lorz, J. Org. Chem., 1949, 14, 775; Hamlin, Weston, Fischer, and Michaels, J. Amer. Chem. Soc., 1949, 71, 2731).



The *amino-propanols* (VI) were prepared in satisfactory yield by treating the appropriate aryl 2-tertiary-aminoethyl ketone with 2-pyridyl-lithium, and were converted into watersoluble neutral *oxalates* for pharmacological test. The ketones, some of which are new, were prepared by the Mannich reaction.

Surprisingly few descriptions of the preparation of 2-pyridyl-lithium are to be found in the literature; Berger, Ziering, and Lee (J. Org. Chem., 1947, 12, 904) mention the preparation of

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4-hydroxyl-4-(2-pyridyl)-1-methylpiperidine, and the reagent is discussed by Spatz (*Iowa State Coll. J. Sci.*, 1942, **17**, 129), but in both cases without experimental details. We prepared 2-pyridyl-lithium by the halogen-interconversion method (Gilman and Spatz, *J. Amer. Chem. Soc.*, 1940, **62**, 446) from 2-bromopyridine and *n*-butyl-lithium; the reagent was characterised by conversion into picolinic acid by reaction with carbon dioxide. In an early experiment the ethereal solution of the reagent decomposed spontaneously, probably because of a rise in temperature as no trouble was experienced when the temperature was kept below  $-45^{\circ}$ .

An experiment with 2-pyridylmagnesium bromide, obtained by the entrainment method (Overhoff and Proost, *Rec. Trav. chim.*, 1938, **57**, 179), in place of 2-pyridyl-lithium was not successful. Recently Tilford, Shelton, and Van Campen (*loc. cit.*) described the reaction between 2-pyridyl magnesium bromide and  $\beta$ -dimethylaminopropiophenone; their product, obtained in 4% yield, had b. p. 150—160°/1 mm. (dihydrochloride, m. p. 168—170°). 3-Dimethylamino-1-phenyl-1-(2-pyridyl)propan-1-ol (VIa), now obtained in 83% yield from 2-pyridyl-lithium, is a crystalline solid, m. p. 99—100° [dihydrochloride, m. p. 207—208° (decomp.)].

The reaction discovered by Ashworth, Daffern, and Hammick (J., 1939, 811) by which tertiary pyridylcarbinols are prepared by heating picolinic acid with ketones offered a potentially attractive alternative route to the aminopropanols (VI). However, we failed to isolate any of the desired product when the reaction was applied to  $\beta$ -dimethylaminopropiophenone and to *p*-chloro- $\beta$ -pyrrolidinopropiophenone.

The pyridylcarbinols (VI), in contrast with the analogous diphenylcarbinols, were resistant to moderately severe conditions of dehydration, *e.g.*, they were recovered unchanged from a boiling mixture of acetic and hydrochloric acids (cf. Part I, *loc. cit.*). This relative stability is in accord with the electrophilic nature of the 2-pyridyl group. Dehydration to the 3-tertiary*amino*-1-*aryl*-1-(2-*pyridyl*)*prop*-1-*enes* (VII) was effected by aqueous sulphuric acid (85%; 2 vols.) at temperatures between 100° and 170°. Aminopropanols (VIa and k) were dehydrated by thionyl chloride in boiling benzene or chloroform, but this method was not successful when applied to other carbinols.

A number of the allylamines (VII*a*, *c*, *e*, *f*, *g*) were hydrogenated (palladised charcoal) to give the corresponding propylamines in moderate yield. Sperber, Papa, Schwenk, Sherlock, and Fricano (*Abs.* 1948 *Chicago Meeting, Amer. Chem. Soc.*, p. 4K; B.P. Applns. 25947, 26873, and 27020/48) have prepared an extensive series of these propylamines, including "Trimeton" and "Chlor-Trimeton," by condensation of 2-tertiary-aminoethyl halides with  $\alpha$ -(2-pyridyl)-benzyl cyanide and subsequent removal of the cyano-group, and by related methods. Some of the propylamines now described, namely (VIII *c*, *f*, and *g*) appear to be new.

The compounds have been examined for pharmacological activity by Dr. A. C. White and Mr. A. F. Green of the Biological Division of these Laboratories. The carbinols were not of interest. The allylamines, like the propylamines, were outstanding for their antihistamine activity (assessed in histamine-induced asthma in the guinea-pig and in the isolated ileum of the guinea-pig). The influence of the tertiary-amino-substituent did not appear to run parallel in the two series; in the allylamine series the pyrrolidino-group (as in VIIg), had the most favourable effect, whilst in the propylamine series the highest activity is found in the dimethylamino-compounds (as in VIIIe, "Chlor-Trimeton"). The pharmacology of these compounds will be described elsewhere.

Investigations in this series are being continued.

### EXPERIMENTAL.

### (Micro-analyses by Mr. A. Bennett. M. p.s are uncorrected.)

Aryl 2-Tertiary-aminoethyl Ketones (Table I).—The amino-ketones were readily prepared by the Mannich reaction (Blicke, Organic Reactions, 1942, Vol. I, p. 303). The aryl methyl ketone (1 mol.) and paraformaldehyde (1.5 equivs.) were added to a solution of the secondary amine hydrochloride (1 mol.) in ethanol (250 c.c.) containing a few drops of concentrated hydrochloric acid. (It was convenient to prepare solutions of the hydrochlorides of pyrrolidine, piperidine, and morpholine by adding concentrated hydrochloric acid to an ethanolic solution of the base until the solution was acid to Congo-red.) The mixture was boiled under reflux for 3—4 hours; approximately half of the solvent was then removed by sufficiently pure for subsequent use. Further quantities were obtained from the mother-liquor by basification, extraction with ether, and reconversion into the hydrochloride which was then recrystallised.

The hydrochlorides were converted into the bases shortly before use by suspension in water, basification with aqueous ammonia, and extraction with chloroform. The extract was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated under reduced pressure (bath-temp  $>50^{\circ}$ ). The bases dissolved readily in ether, except p-chloro- $\beta$ -morpholinopropiophenone which was sparingly soluble; in this case benzene was used as solvent in the subsequent reaction with 2-pyridyl-lithium.

R4.	NR <sup>1</sup> R <sup>3</sup> .	Ary. Compound.	l 2-tertiary- M. D.	aminoethyl ketones Solvent for recrystn.	, R4•CO•CH2•CH2•N Formula.	C. RIR.	Found, H.	N. C	لن	Requii H.	ed, %. N.	[ <sup>5</sup>
Ph Ph	NMe <sub>a</sub>	hydrochloride «	152-153°	EtOH-COMe <sup>2</sup>		5	:		5		1	5
Ph L	$N < [CH_a]_3 > CH_a$	hydrochloride		EtOH-EtOAc	C <sub>13</sub> H <sub>1</sub> ,ON,HCl	64.8	7.6	5.7 14	9 65.1	7.5	5.8	14.8
도문	N < [CH <sub>3</sub> ] < >CH <sub>3</sub> N < [CH <sub>3</sub> ] < >0	hydrochloride	189-190 181-182	EtOH aq. EtOH (95%)	1						11	
p-C₀H₄CI	NMe <sub>3</sub>	base hvdrochloride	58-59 174-175	EtOH EtOH	C <sub>11</sub> H <sub>14</sub> ONCI CHONCI.HCI	62.6 53.1	6.5 6.1	6.6 17 5.5 28	·2 62.4	6.6 6.1	6.6 5.6	16.8 28.6
<i>p</i> −C <sub>6</sub> H <sub>4</sub> Cl	NEt <sub>2</sub>	base	oil	1107a		101						08.7
p-C₀H₄Cl	N<[CH <sub>2</sub> ] <sub>3</sub> >CH <sub>2</sub>	nyarochloride base	141 - 142 72 - 73	EtOH	C13H16ONCI, HCI	00:4 65:4	6.1 9	0.0 0.0 10	1 00.0	6.0	0.1 0.0	14.9
₽-C₀H₄Cl	N<[CH <sub>3</sub> ] <sub>4</sub> >CH <sub>3</sub>	hydrochloride base	$187 - 188 \\ 49 - 51$	EtOH light petroleum (40_60)	C <sub>13</sub> H <sub>16</sub> ONCI,HCI C <sub>14</sub> H <sub>16</sub> ONCI	6.99	6.8	5-4 13	-0 9999 9999	7.2	6.6	20-9 14-1
		hydrochloride •	189-191	EtOH	ł	I	I	1	1		]	}
<i>р</i> -С <sub>в</sub> Н₄СІ	N<[CH <sub>2</sub> ] <sub>4</sub> >0	base hydrochloride	(decomp.) 8990 208-209	EtOH MeOH	C13H16O2NCI C13H16O2NCI,HCI	61.3	6.3	5-4 14 24	-1 61-5 -9	6.3	5.5	14-0 24-5
р-MeO·C <sub>6</sub> H <sub>4</sub> 2-C <sub>4</sub> H <sub>3</sub> S	$NMe_2$ $NMe_3$	hydrochloride • hydrochloride <b>f</b>	(decomp.) 187—188 178—179	EtOH EtOH-COMe,	1 1	11						[]
<b>55</b> , 3510. 1949, <b>71</b> , 2	iich and Heilner, <i>Ber</i> <sup>d</sup> Harradence and L 2048. <sup>f</sup> Levvy and ?	., 1922, <b>55</b> , 356. yons, <i>J. Proc. Roy</i> Nisbet, <i>J.</i> , 1938, 10	<sup>b</sup> Blicke and . <i>Soc.</i> , N.S. <b>)53</b> .	I Burckhalter, J. A Wales, 1939, <b>72</b> , 2	mer. Chem. Soc., 194 33. • Denton, Turn	.2, <b>64</b> , 4 er, Neie	451. ° 1, Lawi	Mannich son, and	and La Schedl,	.mmering J. Amen	, Ber., . Chem.	1922, Soc.,
	R4-CH-CH2	CH3. NR1R2		TABLE IV								
	- I	3-	Tertiary-an	nino-1-aryl-1-(2-þy	vidyl)propanes (VII	I).						
c		f	4	1, p. of salt.			-	ound, %	. 0	Requ	iired, %	
com- pound. R VIIIa Ph	4. NR <sup>1</sup> R <sup>2</sup> . NMe <sub>2</sub>	B. p./mm. of base. 104—106°/0·05	Salt. 		ystn. Formu - C <sub>16</sub> H <sub>20</sub> N <sub>2</sub> - C <sub>16</sub> H <sub>20</sub> N <sub>2</sub> ,C	lla. 2H2O4	C. 79-4 85-5	H. N 8-2 11- 6-6 8-4		C. H. 80.0 8.5 65.5 6.7	N. 11.7 8.5	[j
dd <i>J</i> III	N<[CH2]3>CH	1 <sub>a</sub> 120—122/0·01				0.11	1   L					
VIIIe p-C <sub>0</sub>	H₄CI NMe₂	120 - 122 / 0.01				лаQ4	0.10		2 12.7		10.2	12.9
VIIIf p-C	H <sub>4</sub> Ci Net <sub>3</sub>	1			TELOAC CIGHINA CI		09-0			1.18 1.18	1	
VIII <i>g p</i> -C <sub>6</sub> 1	$H_4Cl N < [CH_2]_3 > CH$	<sup>2</sup> 155—160/0·01	oxalate 1			C.H.O.	e-10	-	0.0		1.2	
• B.P.	Appln. No. 27020/48	gives m. p. 152-	152.5°. <sup>b</sup> F	laley and Keenan [	J. Amer. Pharm. Ass	oc. (Sci.	Edn.),	1949 <b>, 3</b> 8	, 381] gi	ve m. p.	203-2	04.5°.

TABLE I.

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			[ರ]	12.9		{	1		13.0 9.8	11-8 9-1	11.9	œ	11.3	20.8	9.6	
		.ed, %	z.	$11.8 \\ 10.2$	10.5	10-6 7-9	1	10.1	10.3 7.7 7.2	9-3	-6   <del>8</del> 4   8	0.1	8.9	10.4	11	
		Requir	H.	6.9	8.3 6.7	7.6 6.2	6·8	7.9 6.5	0.2	7.0			0.0	0.0 0.0	5.4	
			رن	69-9	81·2 67·4	81.8 67.8	68·3	82.0 68.5	70-5 59-6	71-8 61-4	72.4 61.8 63.7	69 6 - 69	68.7	76.1 60.0	57.5	L.
			[ö	 13·1	11		1		13.0	$11.9 \\ 8.9$	1.1	2.7	11.4	21.4	10.0	ulphuı
		1, %.	z.	11-6 10-3	10-5	$10.5 \\ 8.2$	1	10.1	10.0 7.5 7.3	9.1 2.5	-6-1-8-1-8-1-8-1-8-1-8-1-8-1-8-1-8-1-8-1	0.9	8.9	10.7		s for s
		Foun	H.	6.8	7-9 6-6	7.7 6.3	6.5	7.8 6.4	6.3 5.2	6.9 5.0	0.5 7 4 1	2.8	0.1 1.9 1.2	6.5 6.2	5.5	nalysi
			لن	69.7	81.7 67.1	81·3 67·8	6.7.9	82.0 68.5	70.4 60.0	71.2	72-5 62-0 64-0		68.7	22.0 60.0	58.0	۰ Aı
	vop-1-enes (VII).		Formula.	C <sub>16</sub> H <sub>16</sub> N <sub>2</sub> C <sub>16</sub> H <sub>18</sub> N <sub>2</sub> ,HCl	C18H22N2 C18H22N2,C2H2O4	C18H20N2,C2H2O4 C18H20N2,C2H2O4	C1.6H20N2, AC6H10O6	C <sub>19</sub> H <sub>22</sub> N <sub>2</sub> C <sub>19</sub> H <sub>22</sub> N <sub>2</sub> ,C <sub>3</sub> H <sub>3</sub> O <sub>4</sub>	C1 <sub>6</sub> H17N2CI C1 <sub>6</sub> H17N2CI,C2H2O4 C1 <sub>6</sub> H17N2CI,C2H2O4	C18H21N2CI	C18H18N2C1 C18H18N2C1 C18H18N2C1C3H20		Clift NON CI	C17H20ON2 C17H20ON2 C17H20ON2,2HCI	C1,H1,N.S C1,H1,N.S,C2H2O2	eum (b. p. 40-60°).
TABLE III.	o-1-aryl-1-(2-pyridyl)p	M. p. of salt, Solvent	comp. recrystn.	181—182° EtOH-	163—155 (d) EtOH-	165-167 (d) EtOH- EtOAc	151-152 (d) EtOH	170 (d) EtOH- EtOAc	171 (d) EtOH 165166 (d) EtOH- F+OAC		177 (d) EtOH		11017 (b) 601-101	-206-208 (d) EtOH-	161—162 (d) MeOH	allised from light petrol
	3-Tertiary-amin		Salt.	hydro-	oxalate	oxalate	mucate	oxalate	oxalate maleate		oxalate	ovalata	ovalato	dihydro	oxalate	, recryst
		B n /mm	of base.	108°/0.05	119-121/0.01	128-135/0.01		154 - 158 / 0.01	118120/ 0.01 <sup>8</sup>	136-138/0.01	165-169/0.01	182 - 184 / 0.01	186-188/	156-158/0.3	116-122/0.5	p. 60-61°
R1R3		Temp.	shydrn	170°	170	120		170	170	170	100	170	150	1	100	ь М.
R4-C:CH-CH3-NI	z		NR <sup>1</sup> R <sup>2</sup> . de	NMe <sub>3</sub> c	NEt <sub>3</sub>	N<[CH2]3>CH2		N<[CH2]4>CH2	NMe <sub>a</sub>	NEt_	N<[CH <sub>8</sub> ] <sub>8</sub> >CH <sub>2</sub>	N<[CH <sub>2</sub> ] <sub>4</sub> >CH <sub>2</sub>	$N < [CH_2]_4 > O$	A NMes <sup>a</sup>	NMe <sub>2</sub>	by thionyl chloride.
			R4.	Ч	Ph	ЧЧ		ЧЧ	₽-C <sub>6</sub> H <sub>4</sub> Cl	₽-C <sub>6</sub> H <sub>4</sub> Cl	∕¢-C <sub>6</sub> H₄Cl	₽-C₀H₄CI	p-C₅H₄Cl	₽-MeO•C₀H,	2-C <sub>4</sub> H <sub>3</sub> S	Dehydration
		Com-	pound.	VIIa	VIIb	VIIc		VIId	VIIe	VIIf	VIIB	ИIIЛ	VIIi	VIIj	VIIk	8

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3-Tertiary-amino-1-aryl-1-(2-pyridyl)propan-1-ols (VI) (Table II).—The method used for the preparation of all the amino-propanols is illustrated by the following example. 3-Pyrrolidino-1-(p-chlorophenyl)-1-(2-pyridyl)propan-1-ol (VIg). n-Butyl chloride (37 g., 0.4 mol.) in anhydrous ether (200 c.c.) was added dropwise with stirring to freshly sliced lithium (6.9 g., 1 atom) mixed with a few glass beads. The reaction was initiated by warming, and thereafter the rate of addition of the chloride was adjusted to maintain gentle reflux. After the addition (about 30 minutes) the mixture was boiled under reflux with stirring for 1 hour. Excess of lithium was removed by filtration through glass wool (anhydrous conditions), and the filtrate cooled to -45°. 2-Bromopyridine (55 g., 0.35 mol.) in aphydrous ether (75 c.c.) was added during 15 minutes and stirring continued for 6 minutes 0.35 mol.) in anhydrous ether (75 c.c.) was added during 15 minutes and stirring continued for 6 minutes p-Chloro- $\beta$ -pyrrolidinopropiophenone (23.8 g., 0.1 mol.) in anhydrous ether (100 c.c.) was then added dropwise during 20 minutes, after which the temperature was allowed to rise to  $-15^{\circ}$  and stirring continued for 30 minutes. An inert atmosphere was maintained up to this stage by passing a slow stream of dry nitrogen through the apparatus.

The reaction mixture was poured on crushed ice (100 g.), and glacial acetic acid was added until the solution was acid to litmus. The aqueous layer was separated and washed with ether, aqueous ammonia added, and the base extracted with chloroform. The chloroform extract was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. The residual brown syrup (24 g.) was boiled under reflux with light petroleum (b. p. 60-80°; 500 c.c.) and then cooled, and the supernatant liquid was decanted from insoluble tar. Evaporation of the solvent gave an orange-coloured solid, m. p. 128-130° (22 g., 69%). Recrystallisation from ethanol gave clusters of cream-coloured needles, m. p. 130-131°. The amino-propanols prepared by this method are recorded in Table II. Omitting to remove the

excess of unchanged lithium reduced the yields of carbinols from the p-chlorophenyl ketones, but those from the unsubstituted phenyl ketones were not affected. The majority of the carbinols were purified as described in the example, but in some cases the preliminary purification by treatment with light petroleum was unnecessary. In two examples (VIf and k) the crude product was purified by distillation under reduced pressure.

The neutral oxalates were prepared by mixing the base (1 mol.) in ethanol (2 vols.) with a warm solution of anhydrous oxalic acid  $(1 \cdot 1 \text{ mols.})$  in ethanol (2 vols.). The salt crystallised on cooling and was usually pure after one recrystallisation. The *dihydrochlorides* of (VIa and *j*) were prepared by passing dry hydrogen chloride into a cooled solution of the base in chloroform until acid to Congo-red. Ether was then added in small portions with scratching, and the solid precipitate filtered off and recrystallised. The *methiodide* of (VI*a*) was prepared by adding methyl iodide (2 c.c.) to a solution of the carbinol (1.0 g.) in acetone (5 c.c.). After several hours, the crystalline precipitate (1.4 g.) was filtered off and recrystallised from ethanol.

Picolinic Acid from 2-Pyridyl-lithium.-A small sample of the 2-pyridyl-lithium solution prepared as above was treated with solid carbon dioxide. The precipitated solid was filtered off, washed with hot ether, and dissolved in dilute sulphuric acid. The solution was heated to boiling and excess of hot saturated copper sulphate solution added. The salt which separated on cooling was recrystallised from water, redissolved in hot water, and decomposed with hydrogen sulphide. The filtrate was evaporated and the residue recrystallised from ethanol-benzene to give substantially pure picolinic

acid, m. p. 135-136°. Use of 2-Pyridylmagnesium Bromide.-Ethyl bromide (3 g., 0.028 mol.) in anhydrous ether (10 c.c.) was added to magnesium turnings (12.5 g., 0.51 mol.). A solution of 2-bromopyridine (39.5 g., 0.25 mol.) and ethyl bromide (12.5 g., 0.115 mol.) in ether (250 c.c.) was then added with continuous stirring at such a rate as to maintain gentle boiling. After the mixture had boiled for 2 hours, finely powdered  $\beta$ -piperidinopropiophenone hydrochloride (104 g., 0.41 mol.) was added in portions to the cooled and stirred solution, and the mixture boiled under reflux for 3 hours. The product was decomposed by ice and ammonium chloride and worked up in the usual manner to give a brown syrup (88 g.). Distillation gave two main fractions, (a) b. p. 112-128/0.8 mm. (44 g.) and (b) b. p. 100-138/0.03 mm. (20 g.). Some decomposition occurred when fraction (b) was fractionally distilled under reduced pressure and the fractions failed to yield the required solid carbinol (VId).

Reaction of Picolinic Acid with Amino-ketones .- Reaction between picolinic acid and β-dimethylaminopropiophenone or *p*-chloro- $\beta$ -pyrrolidinopropiophenone, either as base or as hydrochloride, failed to yield the desired carbinols. *E.g.*, picolinic acid (0.5 g., 0.004 mol.) and *p*-chloro- $\beta$ -pyrrolidino-propiophenone (2.9 g., 0.012 mol.) were mixed, the temperature slowly raised to 180°, evolution of carbon dioxide then beginning, and kept at 180° until evolution of the gas had ceased (3 hours). The product was dissolved in dilute hydrochloric acid and ether, and the aqueous layer separated and washed with ether. Excess of aqueous ammonia was added, the oil extracted with ether, and the ethereal extract washed with water, dried  $(Na_2SO_4)$ , and evaporated. Extraction of the residual gum (0.5 g)with light petroleum (b. p.  $60-80^\circ$ ) gave a yellow oil (0.1 g.) from which the required crystalline carbinol (VIg) could not be isolated.

3-Tertiary-amino-1-aryl-1-(2-pyridyl)propan-1-enes (VII) (Table III).—(a) The allylamines (VIIa and k) were obtained in 95% yield by dehydration of the corresponding carbinols with thionyl chloride, as below. Repetitions of these experiments did not give uniform results, and the method failed when applied to other carbinols, quantities of non-volatile tars being formed.

Example : Thionyl chloride (7 g.) in benzene (7 c.c.) was slowly added with cooling to 3-dimethyl-amino-1-phenyl-1-(2-pyridyl)propan-1-ol (VIa) ( $7\cdot5$  g.) in benzene (25 c.c.). The solution, from which an oil had separated, was boiled under reflux for 2 hours and then evaporated under reduced pressure. The residue was dissolved in dilute hydrochloric acid, boiled with charcoal, filtered, basified, and extracted with chloroform. The chloroform extract was washed with water, dried  $(Na_2SO_4)$ , and

evaluated with which be bold of the evaluation with water was washed with which which the evaluation of the residual oil was distilled under reduced pressure to give 3-dimethylamino-1-phenyl-1 (2-pyridyl)prop-1-ene (VIIa) as a pale yellow oil, b. p.  $108^{\circ}/0.05 \text{ mm}$ . (6.7 g., 95%). (b) The most satisfactory general method and one which gave reproducible results was to heat the carbinols in aqueous sulphuric acid (85%) for 10-20 minutes at 100-170°, the required temperature varying as shown in Table III. The yields of distilled product were 60-85%.

## The Replacement of the Haiogen Group, etc.

Example: 3-Pyrrolidino-1-(p-chlorophenyl)-1-(2-pyridyl)propan-1-ol (VIg) (25 g.) in aqueous sulphuric acid (85%; 50 c.c.) was heated on the steam-bath for 20 minutes. The product was poured into water, excess of aqueous ammonia added, and the base extracted with chloroform. The chloroform and the base exclusion and the base exclusion in the choice of the control of the control of the choice of the control of the choice of the cho

of the base was treated with hydrogen chloride.

3-Tertiary-amino-1-phenyl-1-(2-pyridyl) propanes (VIII) (Table IV).—The propylamines summarised in Table IV were prepared by catalytic hydrogenation of an ethanolic solution of the corresponding In Table 1, which here by catalytic hydrogeneration of an enhanced solution of the corresponding allylamine hydrochloride or of a solution of the base in glacial acetic acid as below. The yields were 55-70%. The bases were purified by distillation and converted into neutral *oxalates*; the neutral oxalate of (VIIIf) was obtained directly from the crude base. The m. p.s of the oxalate and picrate of (VIIIa) ("Trimeton") were similar to the published figures.

Example: 3-Dimethylamino-1-(p-chlorophenyl)-1-(2-pyridyl)prop-1-ene (VIIe) (3.0 g.) in glacial acetic acid (15 c.c.) was shaken in hydrogen in the presence of 3% palladised charcoal (2.0 g.) (prepared by a method similar to that described in Org. Synth., 1946, 26, 78) until absorption had ceased. The product was diluted with water, filtered to remove the catalyst, made alkaline with aqueous ammonia, and extracted with ether. The ethereal extract was washed with water, dried  $(Na_2SO_4)$ , and evaporated. The residue (2.4 g.) was distilled under reduced pressure to give 3-dimethylamino-1-(p-chlorophenyl)-1-

(2-pyridyl)propane (VIIIe), b. p. 122-124/0.01 mm. (2.1 g. 70%). The base (1.0 g.) was dissolved in ethanol (1 c.c.) and mixed with oxalic acid (0.36 g.) in ethanol (1 c.c.). Ethyl acetate was added dropwise, with scratching, to the point of crystallisation. The crude m. p. 137-139°.

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