[Contribution No. 411 From the Research Laboratories of Hoffmann-La Roche, Inc.]

Synthetic Tuberculostats. X. The Structure of the Disubstituted Isonicotinylhydrazines

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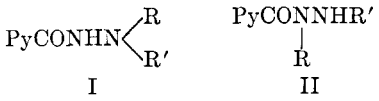
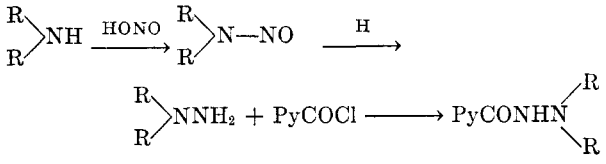
In a previous paper,[1] the study of the tuberculostatic activity of isonicotinylhydrazine derivatives was extended to compounds with two substituent groups—principally alkyl groups—on the hydrazino moiety. Two types of structures were possible: those with both substituents on the same nitrogen as in 1-isonicotinyl-2,2-dialkylhydrazine (I) and those with a substituent on each nitrogen as in 1-isonicotinyl-1,2-dialkylhydrazine (II).

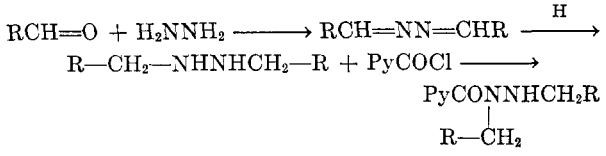


I II

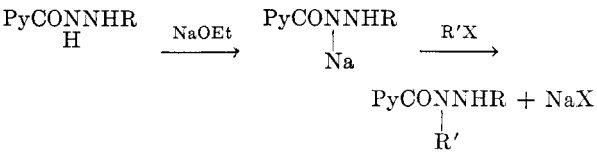
The first two members of Type I to be prepared were 1-isonicotinyl-2,2-dimethylhydrazine (III) and 1-isonicotinyl-2,2-diethylhydrazine (IV). Both compounds were prepared by reacting isonicotinyl chloride with the corresponding asymmetrical dialkylhydrazine which, in turn, was prepared by nitrosating and reducing the corresponding secondary amines according to established methods.[2,3] By virtue of their mode of synthesis, both compounds were confidently assigned Type I structures.



Compounds of Type II were synthesized by preparing symmetrical disubstituted hydrazines and reacting them with isonicotinyl chloride.

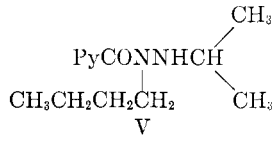


Unfortunately, this method permitted the ready preparation of only those compounds in which the two substituent groups were the same. In order to prepare Type II compounds with different substituents on N^1 and N^2, it was decided to start with a monosubstituted isonicotinylhydrazine with the substituent in the N^2 position and attempt to place the second substituent group on N^1. Since the hydrogen on N^1 was in close proximity to the acyl



group and was therefore more acidic than the hydrogen on N^2, it seemed likely that it could be preferentially replaced with sodium and the resulting metallo-organic intermediate readily converted to the N^1, N^2 disubstituted derivative with the appropriate alkyl halide.

Whether a metallo-organic intermediate would actually form was open to question, but it was felt that the desired structures could be synthesized in the presence of an alkaline catalyst. When, therefore, 1-isonicotinyl-2-isopropylhydrazine was treated with butyl chloride in the presence of sodium ethoxide and a disubstituted isonicotinylhydrazine was isolated, it was tacitly assumed that the new compound was 1-isonicotinyl-1-butyl-2-isopropylhydrazine (V).



V

Subsequently, and in a similar manner, the methyl-isopropyl (VI), allyl-isopropyl (VII), benzyl-ethyl (VIII), and allyl-ethyl (IX) derivatives were prepared.

The authenticity of the structures assigned to the 1, 2- and 2,2-dialkyl derivatives was first brought to question practically simultaneously from two different directions. When an attempt was made to prepare 1-isonicotinyl-1,2-dimethylhydrazine by reacting 1-isonicotinyl-2-methylhydrazine with methyl iodide in the presence of sodium ethoxide, a product was obtained which was identical with 1-isonicotinyl-2,2-dimethylhydrazine (III) previously obtained from asymmetrical dimethylhydrazine and isonicotinyl chloride. The identity of the two compounds was established by means of analysis, melting points, and mixture melting points of the

(1) Fox and Gibas, *J. Org. Chem.*, **20**, 60 (1955).
(2) Fischer, *Ann.*, **199**, 308 (1879).
(3) *Org. Syntheses*, Coll. Vol. II, 211 (1943).

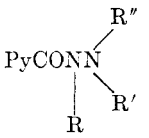
free bases and dihydrochlorides. At about the same time, one of us (A.M.) in studying the ultraviolet absorption spectra of various derivatives of isonicotinylhydrazine, observed in a preliminary investigation that the compounds appeared to fall into two principal categories:

1. those with an absorption band at 300 μ in alkaline solution.
2. those without an absorption band at 300 μ in alkaline solution.

Analysis of the data listed in Table I suggested that the absorption band at or near 300 μ was related to the presence of a free hydrogen atom on N^1 and might indeed be due to an alkali-induced enolization with a consequent transfer of this hydrogen to the carbonyl oxygen.

TABLE I

ULTRAVIOLET ABSORPTION OF ISONICOTINYLHYDRAZINE DERIVATIVES AT 300 μ IN ALKALINE SOLUTION



No.	R	R′	R″	Absorption at 300 μ
1	H	H	H	+
2	H	$CH_3C(=CH_2)$—		+
3	H	$(CH_3)_2CH$—	H	+
4	H	—$CH_2CH_2OCH_2CH_2$—		+
5	H	CH_3CO—	H	+
6	H	C_6H_5CH=		+
7	H	CH_3CH_2CO—	H	+
8	H	C_6H_5CO—	H	+
9	H	C_5H_4NCO—	H	+
10[a]	H	CH_2—	CH_2—	+
11	CH_2=$CHCH_2$—	C_2H_5—	C_2H_5—	−
12	$(CH_3)_2CH$—	$(CH_3)_2CH$—	H	−
13	CH_3CO—	CH_3CO—	H	−

[a] The CH_2— groups are part of a triazine nucleus.

Up to this point, the picture presented by the physical data was quite consistent. The anomaly appeared when it was discovered that the 2,2-dimethyl compound III and 2,2-diethyl compound IV both showed no absorption bands at or near 300 μ though both should have possessed free hydrogens on N^1. There were two obvious interpretations possible in explanation of the apparent anomaly—either the structures assigned to these compounds were wrong despite the previously discussed chemical evidence or a band at about 300 μ was not necessarily correlated with the presence of an N^1 hydrogen. In fact, further investigation—as yet uncompleted—has shown that other bands as well as acid base equilibria must be considered in assessing the structure of these compounds by physical-chemical means.

To resolve this difficulty and to establish unequivocally the structure of the dialkyl compounds made by alkylating isonicotinylhydrazine, the present study was initiated.

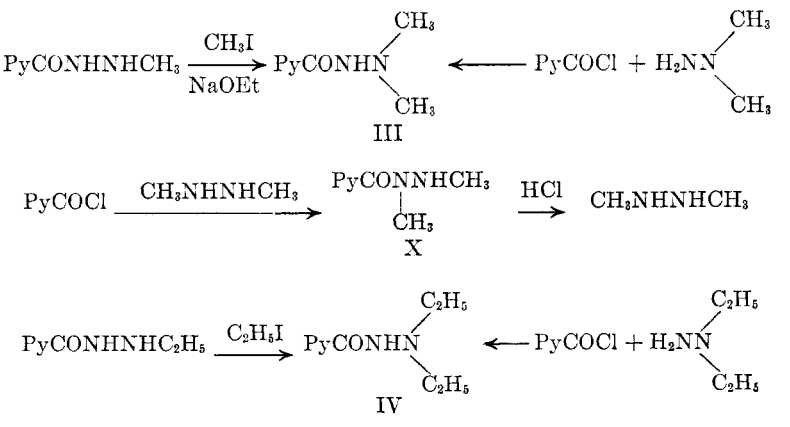
As was indicated previously, the compound obtained by treating 1-isonicotinyl-2-methylhydrazine with methyl iodide in the presence of sodium ethoxide was identical with that obtained by treating asymmetrical dimethylhydrazine with isonicotinyl chloride. The compound was therefore regarded as 1-isonicotinyl-2,2-dimethylhydrazine (III), since its method of synthesis could normally lead only to such a formulation.

To prove the point, symmetrical dimethylhydrazine prepared according to the method of Thiele[4] was treated with isonicotinyl chloride to give a dimethyl derivative which differed from compound III and was undoubtedly 1-isonicotinyl-1,2-dimethylhydrazine (X) particularly since X on hydrolysis gave a compound identical with symmetrical dimethylhydrazine as determined by melting and mixture melting points.

In Table II are listed the physical data establishing the similarities and differences discussed above.

Similarly, treatment of 1-isonicotinyl-2-ethylhydrazine with ethyl iodide in the presence of sodium ethoxide gave 1-isonicotinyl-2,2-diethylhydrazine (IV), identical in all respects with that obtained

(4) Thiele, *Ber.*, **42**, 2576 (1909).



from isonicotinyl chloride and asymmetrical diethylhydrazine.

The data for the diethyl compounds are given in Table III.

When symmetrical dibenzylhydrazine was treated with isonicotinyl chloride, 1-isonicotinyl-1,2-dibenzylhydrazine (XI) was obtained. This differed from the dibenzyl derivative (XII) obtained by benzylation of isonicotinylhydrazine with benzyl chloride in the presence of either sodium ethoxide or pyridine. This latter compound (XII) was undoubtedly 1-isonicotinyl-2,2-dibenzylhydrazine (X-II), especially since upon acid hydrolysis it gave

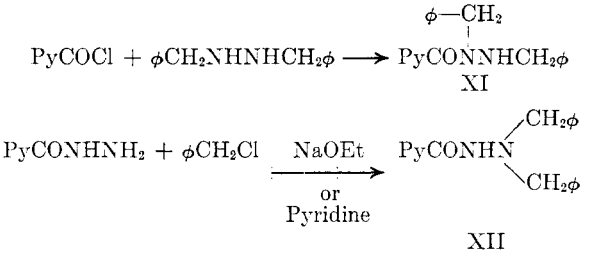


TABLE II

DATA FOR STRUCTURE PROOF OF COMPOUNDS III AND X

Reactants	Compound	Salt	Products M.P., °C.	Analyses C (Calc'd)	C (Fd.)	H (Calc'd)	H (Fd.)
PyCOCl + $H_2NN(CH_3)_2$	$PyCONHN(CH_3)_2$ III	—	120–121	58.2	58.5	6.7	6.4
		2 HCl	210–211	40.3	40.8	5.5	5.1
$PyCONHNHCH_3$ + CH_3I + NaOEt	$PyCONHN(CH_3)_2$	—	120–121.5	58.2	58.3	6.7	6.3
		2 HCl	205–206	Mixture melt with hydrochloride above 207°			
PyCOCl + $CH_3NHNHCH_3$	$PyCONNHCH_3$ | CH_3 X	—	oil, b.p. 130–140°/5				
		$H_2C_2O_4$	142–143	47.1	47.4	5.1	5.4
		HCl	Could not be crystallized				
$PyCONNHCH_3$ + HCl | CH_3	$CH_3NHNHCH_3$	2 HCl	166–167 (froths)	Mixture melt with authentic sample prepared by method of Thiele, m.p. 166–167° (froths)			

TABLE III

DATA FOR STRUCTURE PROOF OF 1-ISONICOTINYL-2,2-DIETHYLHYDRAZINE (IV)

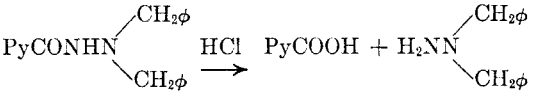
Reactants	Compound	Salt	Products M.P., °C.	Analyses C (Calc'd)	C (Fd.)	H (Calc'd)	H (Fd.)
PyCOCl + $H_2NN(C_2H_5)_2$	$PyCONHN(C_2H_5)_2$	—	89.5–90.5	62.1	62.4	7.8	7.6
		2 HCl	205–208	45.1	44.6	6.4	6.6
$PyCONHNHC_2H_5$ + C_2H_5I + NaOEt	$PyCONHN(C_2H_5)_2$	—	87.5–88.5	Mixture melts with base above unchanged			
		2 HCl	206–207	Mixture melt with hydrochloride above unchanged			

TABLE IV

DATA FOR STRUCTURE PROOF OF COMPOUNDS XI AND XII

Reactants	Compound	Salt	Products M.P., °C.	Analyses C (Calc'd)	C (Fd.)	H (Calc'd)	H (Fd.)
PyCOCl + $\phi CH_2NHNHCH_2\phi$	$PyCONNHCH_2\phi$ | $\phi—CH_2$ XI	—	102–103	75.7	75.9	6.0	6.3
$PyCONHNH_2$ + ϕCH_2Cl + NaOEt or pyridine	$PyCONHN(CH_2\phi)_2$ XII	—	161–162	75.7	75.9	6.0	5.9
$PyCONHN(CH_2\phi)_2$ + HCl	$H_2NN(CH_2\phi)_2$	—	54–56	79.2	79.1	7.5	7.8
		HCl	199–201	67.5	67.8	6.8	7.1

asymmetrical dibenzylhydrazine.



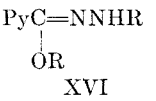
The data for the dibenzyl derivatives are listed in Table IV.

Treatment of symmetrical isopropylhydrazine with isonicotinyl chloride gave 1-isonicotinyl-1,2-diisopropylhydrazine (XIII) which differed from the compound (XIV) obtained by alkylating either isonicotinylhydrazine or 1-isonicotinyl-2-isopropylhydrazine with isopropyl iodide in the presence of sodium ethoxide. The latter, in turn, proved to be identical with 1-isonicotinyl-2,2-diisopropylhydrazine (XIV) obtained by treating asymmetrical diisopropylhydrazine with isonicotinyl chloride.

This was further confirmed by acid hydrolysis of XIV to produce asymmetrical diisopylhydrazine. The data for the diisopropyl derivatives are listed in Table V.

In a particularly cogent experiment, 1-isonicotinyl-2-ethylhydrazine was alkylated with methyl iodide in the presence of sodium ethoxide to give a dialkyl derivative which was identical with that produced by the alkylation of 1-isonicotinyl-2-methylhydrazine with ethyl iodide in the presence of sodium ethoxide. This could only be true if the resulting compound were the 2,2-dialkyl derivative, namely, 1-isonicotinyl-2-ethyl-2-methylhydrazine (XV).

Some time after the completion of the work described above, Libermann, Grumbach, and Rist[5] reported on the synthesis of dialkyl derivatives of isonicotinylhydrazine by condensing isonicotinylhydrazine with the appropriate alkyl halides in the presence of sodium alkoxide. In the compounds so prepared, the alkyl groups were allegedly located on the O and the N^2 atoms to give a structure (XVI) of the following type:



XVI

The factors which motivated the French workers to this choice of structure appeared to be:

(5) Libermann, Grumbach, and Rist, *Compt. rend.*, **237**, 338 (1953).

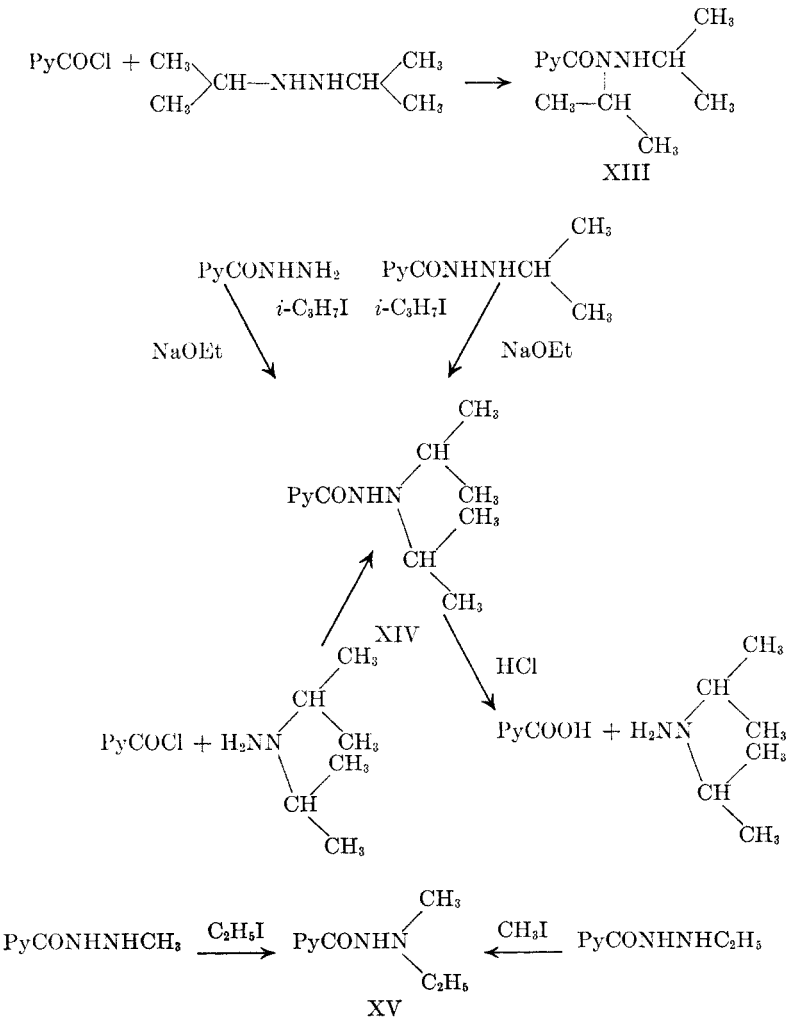
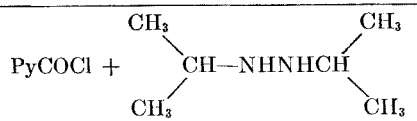
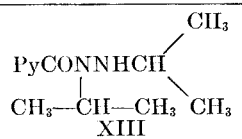
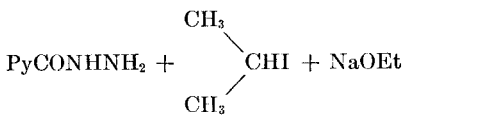
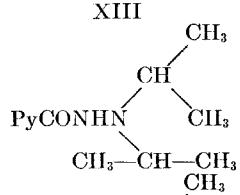
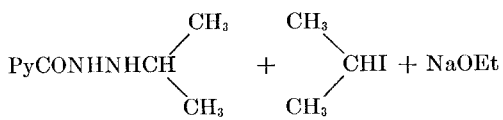
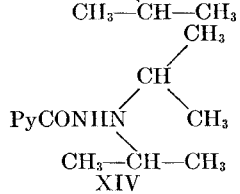
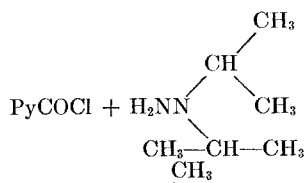
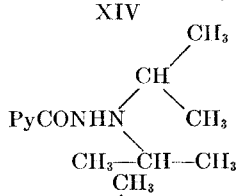
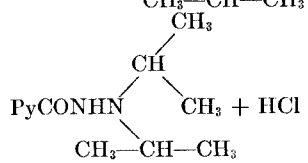
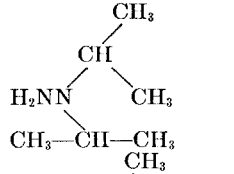
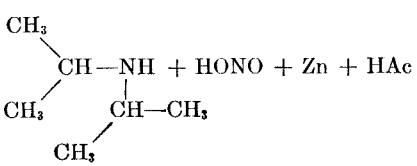
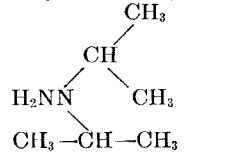


TABLE V

DATA FOR STRUCTURE PROOF FOR COMPOUNDS XIII AND XIV

Reactants	Compound	Salt	Products M.P., °C.	Analyses C (Calc'd)	C (Fd.)	H (Calc'd)	H (Fd.)
	 XIII	—	oil				
		HCl	155–156.5	55.9	55.8	7.8	7.6
		—	111–112				
		2 HCl	201–202				
	 XIV	—	111–112	65.2	65.1	8.6	8.5
		2 HCl	202–203	49.0	49.2	7.1	7.3
		—	109–111	Mixture melt with base above 110–111°			
		$H_2C_2O_4$	129–130	Mixture melt with oxalate below 129–130°			
		$H_2C_2O_4$	129–130	46.6	47.0	8.7	8.4

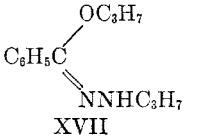
1. Hydrazides readily form sodium salts with either sodium in boiling xylene or sodium alkoxide in alcohol.

2. Curtius in 1894[6] envisaged the possibility of a tautomeric equilibrium with an enolic form for the hydrazides

$$RC(=O)-NHNH_2 \rightleftarrows RC(-OH)=NNH_2$$

3. Fallab and Erlenmeyer[7] recently, demonstrated that isonicotinylhydrazine acts as a pseudo-acid and liberates hydrogen in forming a copper complex.

4. Only one other monosubstituted hydrazino-ether is known to date, namely the *n*-propylhydrazino, *n*-propyl ether derivative of benzoic acid (XVII) prepared by Stolle and Benrath.[8]



XVII

Arguments 1 to 3 are tenuous, to say the least, and argument 4 would, if anything, militate against the choice of the ether-type structure.

Amongst the compounds reported by Libermann and his co-workers is a dibenzyl derivative which melted at 160–161°. This corresponds very well to the melting point of 161–162° (corr.) found for the compound XII which we prepared by the same method and which we conclusively proved to be 1-isonicotinyl-2,2-dibenzylhydrazine by the fact that on hydrolysis asymmetric dibenzylhydrazine was obtained.

To settle the issue, isonicotinylhydrazine and *n*-butyl bromide were interacted in the presence of sodium ethoxide in accordance with Libermann's procedure. A compound (XVIII) was obtained which melted at 115–117° (corr.) (L., G. &. R. m.p. 122°) and analyzed correctly for a dibutyl derivative.

Anal. Calc'd for $C_{14}H_{23}N_3O$: C, 67.5; H, 9.2. Found: C, 67.4; H, 9.0.

Hydrolysis of the dibutyl derivative with concentrated hydrochloric acid gave a compound whose analysis corresponded to dibutylhydrazine hydrochloride (XIX), m.p. 65–67°.

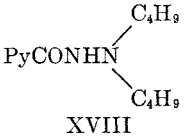
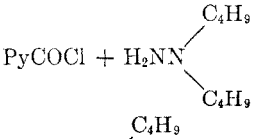
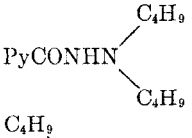
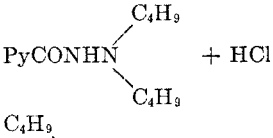
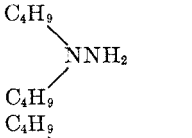
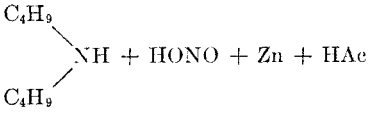
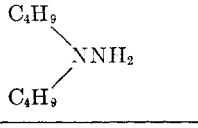
Anal. Calc'd for $C_8H_{20}N_2 \cdot HCl$: C, 53.2; H, 11.6. Found: C, 53.3; H, 11.4.

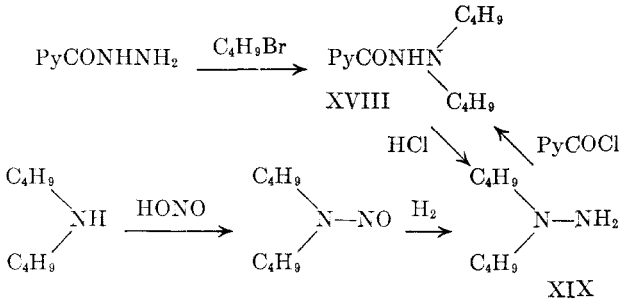
Because of the hygroscopic character of the hydrochloride, it was converted to the oxalate which melted at 171–172° (corr.) and which proved to be identical with an authentic sample of asymmetric dibutylhydrazine oxalate (XIX) prepared from dibutylamine by nitrosation and reduction. It is apparent therefore that the compound prepared according to the method of Libermann and his co-workers cannot have the ether-type structure and indeed must be 1-isonicotinyl-2,2-dibutylhydrazine (XVIII). Moreover, treatment of authentic asymmetric dibutylhydrazine with isonicotinyl chloride gave a dibutyl derivative of isonicotinol hydrazine which was identical with compound XVIII. These data are listed in Table VI.

(6) Curtius, *J. prakt. Chem.*, **50**, 275 (1894).
(7) Fallab and Erlenmeyer, *Experientia*, **8**, 298 (1952).
(8) Stolle and Benrath, *J. prakt. Chem.*, **70**, 263 (1904).

TABLE VI

DATA FOR STRUCTURE PROOF OF XVIII

Reactants	Products: Compound	Salt	M.P., °C.	Analyses: C (Calc'd)	C (Fd.)	H (Calc'd)	H (Fd.)
$PyCONHNH_2 + C_4H_9Br$	 XVIII	—	115–117	67.5	67.4	9.2	9.0
		—	115–116	Mixture melt with above, 115–116°			
		HCl $H_2C_2O_4$	65–67 170–171	53.2	53.3	11.6	11.4
		Mixture melt with oxalate below, 170–171°					
		$H_2C_2O_4$ HCl	171–172 66–68	51.3	51.6	9.4	9.2
		Mixture melt with hydrochloride above, 66–68°					



XIX

CONCLUSION

The compounds produced by the alkylation of isonicotinylhydrazine or 1-isonicotinyl-2-alkylhydrazine in the presence of sodium ethoxide or pyridine have been shown conclusively to have the Type I structure and to be 1-isonicotinyl-2,2-dialkylhydrazines. It is apparent therefore that the ether-type structure proposed by Libermann, Grumbach, and Rist[5] for these compounds is invalid. It is also evident that in addition to the presence or absence of an ultraviolet absorption band in the approximate region of 300 μ when the compounds are in alkaline solution other criteria are needed for the correlation of structure and physical properties.

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