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SYNTHETIC TUBERCULOSTATS. IX. DIALKYL DERIVATIVES OF ISONICOTINYLHYDRAZINE[1]

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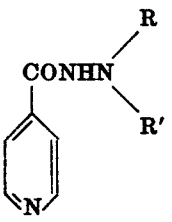
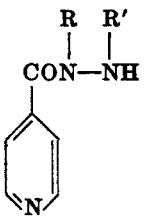
Past experience has shown that the anti-tuberculous activity of isonicotinylhydrazine is maintained through a wide range of structural variation (1–5). Extension of this experience to dialkyl derivatives of isonicotinylhydrazine leads to two types of structures, namely, Type A, in which both hydrogens of the terminal nitrogen atom (N^2) are replaced by alkyl groups or by a ring structure and, Type B, in which one hydrogen on each of the hydrazine nitrogens is replaced by an alkyl or equivalent group.



Type A



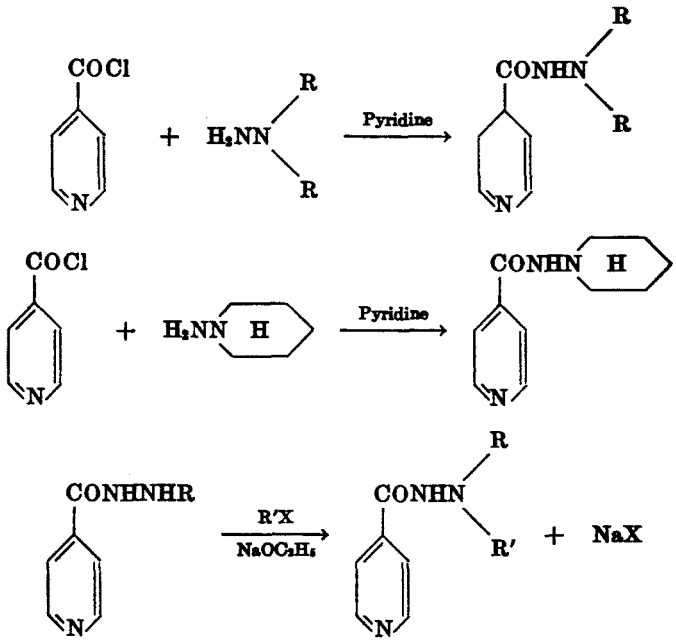
Type B

It was anticipated but, of course, by no means certain, that compounds of Type A might show some anti-tuberculous activity by analogy to the alkylidene (2), the phthaloyl (5) and possibly the diacetyl (5) derivatives of isonicotinylhydrazine since these latter compounds are generally active and are also distinguished by the fact that they, too, have both hydrogen atoms on the terminal nitrogen (N^2) replaced by substituent groupings. This judgment was indeed borne out by the observation that most of the Type A compounds reported on in this study are anti-tuberculous in mice infected with *M. tuberculosis*, human strain H37Rv.

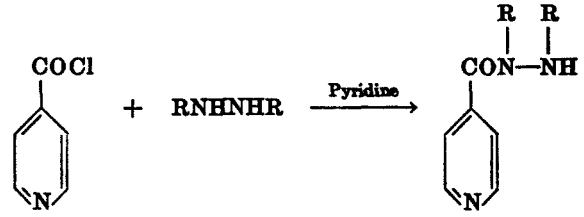
For compounds of Type B, there was no prior experience to encourage the hazard of guessing since N^1 substituted derivatives of isonicotinylhydrazine had not previously been made and tested. It is interesting to note, therefore, that the Type B compounds herein reported are of a much lower order of activity.

The synthesis of Type A compounds was effected by two general methods. In one of these, isonicotinyl chloride hydrochloride was reacted with the appropriate asymmetric hydrazine in the presence of pyridine to give the desired product. Where, however, two different R substituents were desired, the above method was not feasible and recourse was had to the alternative procedure in which 1-isonicotinyl-2-alkylhydrazine was treated with the appropriate alkyl halide in the presence of sodium ethoxide.

[1] This paper was presented at the 126th Meeting of the American Chemical Society, before the Division of Medicinal Chemistry.



The compounds of Type B were prepared by reacting isonicotinyl chloride hydrochloride with the appropriate symmetrical hydrazine or pyrazole in the



presence of pyridine. However, 1-isonicotinyl-3,5-dimethylpyrazole (I) was also prepared by condensing isonicotinylhydrazine with acetylacetone.

The compounds prepared in this study are listed in Tables I and II. The preparative details are given in the Experimental section.

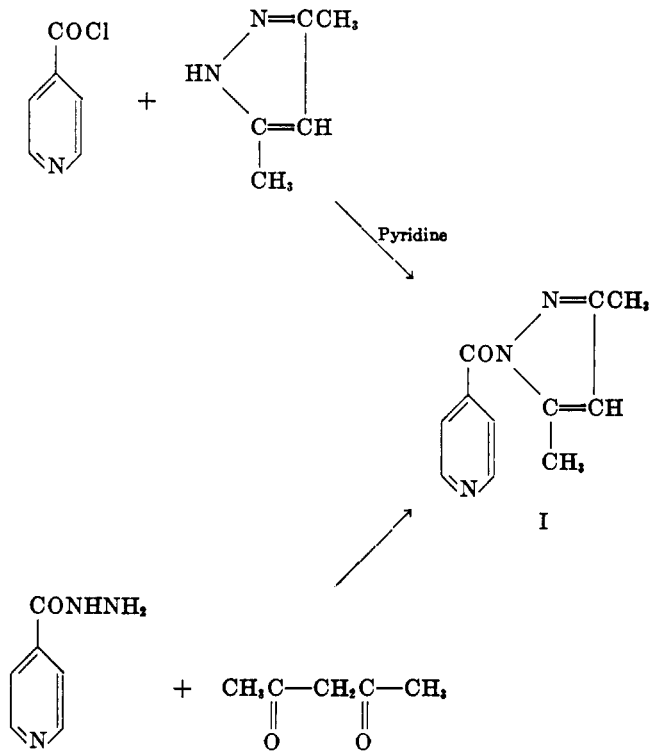
Acknowledgment. The authors are indebted to Dr. A. Steyermark and his staff for the microanalyses and to Drs. R. J. Schnitzer and E. Grunberg and the staff of the Roche Chemotherapy Laboratory for testing the compounds. Thanks are also due to Mr. B. Pecherer for generously providing the pyrazole, the N-aminomorpholine hydrochloride and the N-aminopiperidine used in this study.

EXPERIMENTAL

All the melting points are corrected.

N^2,N^2-DIALKYL DERIVATIVES

1) *1-Isonicotinyl-2,2-dimethylhydrazine.* To a solution of 36. g of isonicotinyl chloride hydrochloride in 150–200 ml. of pyridine was added 18 g. of *asymmetric* dimethylhydrazine,



prepared according to a previously described method (6). The reaction mixture which became hot during the addition was permitted to cool and the excess of pyridine was removed under a vacuum. The residue was treated with an excess of saturated potassium carbonate solution and the resulting mixture was extracted with chloroform. The chloroform solution on evaporation under a vacuum left a solid residue which upon recrystallization from benzene gave 1-isonicotinyl-2,2-dimethylhydrazine in the form of colorless spires and diamonds melting at 120–121°; yield 20 g. The product was very soluble in water and in most of the common polar organic solvents and was only slightly soluble in benzene and ligroin.

Anal. Calc'd for $C_8H_{11}N_3O$: C, 58.2; H, 6.7.
Found: C, 58.5; H, 6.4.

A portion of the free base was converted to the dihydrochloride by solution in 2-propanol and treatment with ethanolic hydrogen chloride. Upon recrystallization from a mixture of methanol and 2-propanol, the *dihydrochloride* was obtained in the form of pale yellow crystals soluble in water and in methanol and insoluble in most of the other common organic solvents; m.p. 210–211° (dec.).

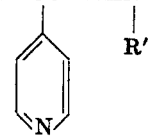
Anal. Calc'd for $C_8H_{11}N_3O \cdot 2HCl$: C, 40.3; H, 5.5.
Found: C, 40.8; H, 5.1.

2) *1-Isonicotinyl-2,2-diethylhydrazine.* Isonicotinyl chloride hydrochloride (97 g.), 48 g. of *asymmetric* diethylhydrazine prepared as described by Fischer (7), and 200 ml. of pyridine were reacted according to the procedure outlined in Experiment 1 above to yield 50 g. of 1-isonicotinyl-2,2-diethylhydrazine. Upon recrystallization from benzene, the product was obtained in the form of colorless prisms, soluble in water and most organic solvents and insoluble in cold benzene and petroleum ether; m.p. 89.5–90.5°.

Anal. Calc'd for $C_{10}H_{15}N_3O$: C, 62.1; H, 7.8.
Found: C, 62.4; H, 7.6.

TABLE I

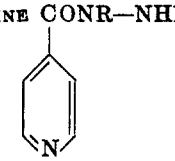
N^2,N^2-Dialkyl Derivatives of Isonicotinylhydrazine



R	R′	Melting Points, °C. (corr.)	
		Base	Salt
$-CH_3$	$-CH_3$	120–121	2HCl 210–211 (dec.)
$-CH_2CH_3$	$-CH_2CH_3$	89.5–90.5	2HCl 205–208 (dec.)
$-CH_3$	$-CH_2CH_3$		2HCl 196–197 (dec.)
$-CH_3$	$-CH_2CH{=}CH_2$		2HCl 162.5–163.5 (dec.)
$-CH_3$	$-CH(CH_3)_2$	95–96	
$-CH_2CH_3$	$-CH_2CH{=}CH_2$		2HCl 176.5–177.5 (dec.)
$-CH(CH_3)_2$	$-CH(CH_3)_2$	110–111	2HCl 202–203 (dec.)
$-CH(CH_3)_2$	$-CH_2CH{=}CH_2$		2HCl 188.5–189.5 (dec.)
$-CH(CH_3)_2$	$-CH_2CH_2CH_2CH_3$		2HCl 203–205 (dec.)
$-CH_3$	$-CH_2C_6H_5$		2HCl 183.5–184.5
$-CH_2CH_3$	$-CH_2C_6H_5$		2HCl 196–197
$-CH_2C_6H_5$	$-CH_2C_6H_5$	161–162	
$-C_6H_5$	$-C_6H_5$	183.5–184.5	HCl 208–212
$-CH_2CH_2CH_2CH_2CH_2-$		174.5–175.5	
$-CH_2CH_2OCH_2CH_2-$		195.5–196.5	

TABLE II

N^1,N^2-Dialkyl Derivatives of Isonicotinylhydrazine



R	R′	Melting Points, °C. (corr.)	
		Base	Salt
$-CH_3$	$-CH_3$		$H_2C_2O_4$ 142–143
$-CH(CH_3)_2$	$-CH(CH_3)_2$		HCl 155–156.5
$-CH_2C_6H_5$	$-CH_2C_6H_5$	102–103	HCl 220–221
$-CH_2C_6H_5$	$=CHC_6H_5$	126–127	HCl 234–239
$-CH{=}CH-CH{=}$		sublimes *ca* 300	
$CH_3-C{=}CH-C-CH_3$		86.5–87.5	

The *dihydrochloride* was prepared by treating a 2-propanol solution of the base with ethanolic hydrogen chloride. White needles from a mixture of methanol and 2-propanol; m.p. 205–208° (dec.).

Anal. Calc'd for $C_{10}H_{15}N_3O{\cdot}2HCl$: C, 45.1; H, 6.4.

Found: C, 44.6; H, 6.6.

3) *1-Isonicotinyl-2-methyl-2-ethylhydrazine dihydrochloride.* To a solution of 2.3 g. of sodium in 100 ml. of ethanol was added with stirring, 16.5 g. of 1-isonicotinyl-2-ethylhydra-

zine (4) and then, portionwise, 6.2 ml. of methyl iodide. Heat was liberated during the methyl iodide addition. The mixture was then refluxed for *ca* 2 hours, the ethanol was removed under a vacuum, and the residue was treated with an excess of concentrated ammonium hydroxide. The alkaline solution was evaporated to dryness under a vacuum and the residue was extracted 3 times with chloroform. The chloroform solution was decolorized with charcoal and then evaporated on a steam-bath to yield 1-isonicotinyl-2-methyl-2-ethylhydrazine in the form of an oil. Conversion to the dihydrochloride was effected by treating a 2-propanol solution of the base with ethanolic hydrogen chloride. Upon recrystallization from ethanol, the dihydrochloride was obtained in the form of white crystals; m.p. 196–197° (dec.); yield 5 g.

Anal. Calc'd for $C_9H_{13}N_3O \cdot 2HCl$: C, 42.8; H, 6.0.
Found: C, 43.1; H, 5.8.

4). *1-Isonicotinyl-2-allyl-2-methylhydrazine dihydrochloride.* 1-Isonicotinyl-2-methylhydrazine (4) (15 g.), was dissolved in a solution containing 2.3 g. of sodium in 100 ml. of ethanol. Allyl chloride (8.5 ml.) then was added and the mixture was refluxed with stirring for one half hour; cooled, and filtered to remove sodium chloride and then evaporated under a vacuum to remove the solvent. The residue was extracted with chloroform and the chloroform extracts, on evaporation, yielded the desired product in the form of an oily base. Conversion to the dihydrochloride was effected as described in Experiment 3 above. Recrystallization from 2-propanol gave 19.5 g. of white crystals of the dihydrochloride; m.p. 162.5–163.5° (dec.).

Anal. Calc'd for $C_{12}H_{19}N_3O \cdot 2HCl$: C, 45.4; H, 5.7.
Found: C, 45.3; H, 5.8.

5). *1-Isonicotinyl-2-isopropyl-2-methylhydrazine.* A mixture of 35.8 g. of 1-isonicotinyl-2-isopropylhydrazine (4), 12.4 ml. of methyl iodide, 4.6 g. of sodium, and 200 ml. of ethanol was reacted as described in Experiment 3 above, except that the mixture was refluxed only one hour. The oil obtained after removal of the chloroform was dissolved in benzene; the benzene solution was decolorized and ligroin (b.p. 60–72°) was added to yield 10 g. of the desired product. Recrystallization from benzene gave small, colorless prisms; m.p. 95–96°; soluble in most organic solvents and water, insoluble in ligroin and cold benzene.

Anal. Calc'd for $C_{12}H_{19}N_3O$: C, 62.2; H, 7.8.
Found: C, 62.1; H, 7.5.

6). *1-Isonicotinyl-2-allyl-2-ethylhydrazine dihydrochloride.* A mixture of 16.5 g. of 1-isonicotinyl-2-ethylhydrazine (4), 8.5 ml. of allyl chloride, 2.3 g. of sodium, and 100 ml. of ethanol was reacted as described in Experiment 4 above to give 22 g. of 1-isonicotinyl-2-allyl-2-ethylhydrazine dihydrochloride. Upon recrystallization from a mixture of methanol and 2-propanol the product was obtained in the form of cream-colored crystals; m.p. 176.5–177.5° (dec.).

Anal. Calc'd for $C_{11}H_{18}N_3O \cdot 2HCl$: C, 47.5; H, 6.1.
Found: C, 47.7; H, 6.4.

7). *1-Isonicotinyl-2,2-diisopropylhydrazine dihydrochloride.* A mixture of 17.9 g. of 1-isonicotinyl-2-isopropyl hydrazine (4), 17 g. of isopropyl iodide, 2.3 g. of sodium, and 100 ml. of ethanol was reacted as described in Experiment 3 above (except that the mixture was refluxed for only one hour) to give 20 g. of 1-isonicotinyl-2,2-diisopropylhydrazine dihydrochloride. Upon recrystallization from 2-propanol the product was obtained in the form of white crystals; m.p. 202–203° (dec.); soluble in water, methanol, ethanol and hot 2-propanol.

Anal. Calc'd for $C_{17}H_{19}N_3O \cdot 2HCl$: C, 49.0; H, 7.1.
Found: C, 49.2; H, 7.3.

The same compound was also obtained when one equivalent of isonicotinylhydrazine and two equivalents of isopropyl iodide were refluxed in ethanol for 17 hours in the presence of two equivalents of sodium ethoxide. The dihydrochloride of the product so obtained melted at 201–202° (dec.) and gave a mixture melting point of 200–201° (dec.) with an authentic sample of 1-isonicotinyl-2,2-diisopropylhydrazine dihydrochloride.

The *free base* was obtained from the dihydrochloride by treatment with aqueous sodium

hydroxide. It was soluble in all the common solvents including hot water and hot ligroin. Upon recrystallization from a mixture of carbon tetrachloride and ligroin (b.p. 60–72°) it was obtained in the form of white needles; m.p. 110–111°.

Anal. Calc'd for $C_{12}H_{19}N_3O$: C, 65.2; H, 8.6.
Found: C, 65.1; H, 8.5.

8). *1-Isonicotinyl-2-allyl-2-isopropylhydrazine dihydrochloride.* A mixture of 17.9 g. of 1-isonicotinyl-2-isopropylhydrazine (4), 9.6 ml. of allyl chloride, 2.3 g. of sodium, and 100 ml. of ethanol was reacted as described in Experiment 4 above (except that the mixture was refluxed for only 10 minutes) to give 21 g. of the desired dihydrochloride. Upon recrystallization from ethanol the product was obtained in the form of white needles; m.p. 188.5–189.5° (dec.).

Anal. Calc'd for $C_{12}H_{17}N_3O \cdot 2HCl$: C, 49.3; H, 6.5.
Found: C, 49.4; H, 6.7.

9). *1-Isonicotinyl-2-n-butyl-2-isopropylhydrazine dihydrochloride.* To a solution of 2.3 g. of sodium in 200 ml. of ethanol was added 17.9 g. of 1-isonicotinyl-2-isopropylhydrazine (4) and 9.4 ml. of *n*-butyl chloride. The mixture was refluxed overnight and then filtered to remove the precipitated sodium chloride. Upon evaporation of the ethanol under a vacuum, a red gummy residue was obtained which was dissolved in a little water and then salted out by the addition of 6 *N* sodium hydroxide to give a red oil which could not be made to solidify. The red oil was extracted with ether; the ether extracts were dried and then treated with dry hydrogen chloride. The resulting dihydrochloride of 1-isonicotinyl-2-*n*-butyl-2-isopropylhydrazine upon recrystallization from a mixture of methanol and acetone was obtained in the form of small white needles; m.p. 203–205° (dec.); very soluble in water, soluble in methanol, ethanol and 2-propanol and insoluble in chloroform and dioxane.

Anal. Calc'd for $C_{13}H_{21}N_3O \cdot 2HCl$: C, 50.6; H, 7.5.
Found: C, 50.6; H, 7.5.

10). *1-Isonicotinyl-2-benzyl-2-methylhydrazine dihydrochloride.* A mixture of 10 g. of 1-isonicotinyl-2-methylhydrazine (4), 7.5 ml. of benzyl chloride, 1.5 g. of sodium, and 100 ml. of ethanol was reacted as described in Experiment 4 above. The residue obtained upon removal of the ethanol was dissolved in 2-propanol; the resulting solution was filtered to remove a small quantity of insoluble material and an excess of ethanolic hydrogen chloride then was added to give 16 g. of the desired dihydrochloride. Recrystallization from ethanol gave white needles; m.p. 183.5–184.5° (dec.).

Anal. Calc'd for $C_{14}H_{15}N_3O \cdot 2HCl$: C, 53.5; H, 5.4.
Found: C, 53.2; H, 5.5.

11). *1-Isonicotinyl-2-benzyl-2-ethylhydrazine dihydrochloride.* A mixture of 16.5 g. of 1-isonicotinyl-2-ethylhydrazine (4), 12 ml. of benzyl chloride, 2.3 g. of sodium, and 100 ml. of ethanol was reacted as described in Experiment 10 above to give 28 g. of the desired dihydrochloride. Upon recrystallization from a mixture of methanol and 2-propanol mixture, the product was obtained in the form of white crystals; m.p. 196–197°.

Anal. Calc'd for $C_{15}H_{17}N_3O \cdot 2HCl$: C, 55.0; H, 5.8.
Found: C, 54.6; H, 5.9.

12). *1-Isonicotinyl-2,2-dibenzylhydrazine.* To a solution containing 4.6 g. of sodium in 100 ml. of ethanol was added 13.7 g. of isonicotinylhydrazine followed by 24 ml. of benzyl chloride. The mixture was stirred for 20 minutes after the addition of the benzyl chloride and then was refluxed for 5 minutes, cooled and filtered. The filtrate was treated with water to give a precipitate of the desired product. Upon recrystallization from dilute ethanol, 24 g. of the dibenzyl derivative was obtained in the form of white needles; m.p. 161–162°; soluble in the common organic solvents and dilute hydrochloric acid and insoluble in water.

Anal. Calc'd for $C_{20}H_{19}N_3O$: C, 75.7; H, 6.0; Mol. Wt., 317.
Found: C, 75.9; H, 5.9; Mol. Wt. (by $HClO_4$ titration in glacial acetic acid), 309.9.

The dibenzyl derivative was also obtained by refluxing for 40 minutes a solution of 13.6 g. of isonicotinylhydrazine and 24 ml. of benzyl chloride in 150 ml. of pyridine. The pyridine

was removed under a vacuum and the residue was treated with dilute ammonium hydroxide to give the desired product. Recrystallization from dilute ethanol gave white crystals melting at 160–161°. A mixture with an authentic sample of the dibenzyl derivative melted at 160–162°.

13). *1-Isonicotinyl-2,2-diphenylhydrazine.* To a mixture of 12 g. of isonicotinyl chloride hydrochloride in 100 ml. of pyridine was added, portionwise, with stirring, 14.5 g. of diphenylhydrazine, prepared according to the method of Fischer (8). Heat was evolved and the elevated temperature was maintained by heating the reaction mixture on a steam-bath for about 15 minutes following the addition. The pyridine then was removed under a vacuum and the residue was treated with an excess of potassium carbonate solution to give 18 g. of a brown crystalline precipitate of the diphenyl derivative. Recrystallization from benzene resulted in pale yellow needles; m.p. 183.5–184.5°; soluble in the alcohols, slightly soluble in hot benzene and hot xylene, and insoluble in water and ligroin.

Anal. Calc'd for $C_{18}H_{15}N_3O$: C, 74.7; H, 5.2.
Found: C, 75.0; H, 4.9.

A portion of the free base dissolved in 2-propanol was converted to the hydrochloride by treatment with an excess of ethanolic hydrogen chloride. On recrystallization from a mixture of methanol and ethyl acetate, the product which proved to be the monohydrochloride was obtained in the form of yellow needles; m.p. 208–212°.

Anal. Calc'd for $C_{18}H_{15}N_3O \cdot HCl$: C, 66.4; H, 4.9.
Found: C, 66.1; H, 5.0.

14. *1-Isonicotinyl-2,2-pentamethylenehydrazine.* To a suspension of 21 g. of isonicotinyl chloride hydrochloride in 100 ml. of pyridine was added portionwise, with stirring, 10 g. of N-aminopiperidine. Heat was evolved and the mixture was allowed to cool spontaneously. The excess of pyridine was removed under a vacuum and the residue was made strongly alkaline with 6 *N* sodium hydroxide and extracted with chloroform. Removal of the chloroform gave 15 g. of the product which on recrystallization from toluene and decolorization with charcoal was obtained in the form of pale yellow crystal clusters; m.p. 174.5–175.5°; soluble in water and most of the common organic solvents including hot benzene and insoluble in ligroin.

Anal. Calc'd for $C_{11}H_{15}N_3O$: C, 64.4; H, 7.3.
Found: C, 64.8; H, 7.4.

15). *N-(4-Morpholinyl)isonicotinamide.* A mixture of 15 g. of N-aminomorpholine hydrochloride, 19.2 g. of isonicotinyl chloride hydrochloride, and 100 ml. of pyridine was reacted as described in Experiment 13 above. The residue left after removal of the pyridine was made alkaline with saturated potassium carbonate solution and then was extracted with chloroform. The chloroform solution was evaporated to dryness under a vacuum and the residue was recrystallized from ethyl acetate to give 12 g. of the desired product in the form of long white needles; m.p. 195.5–196.5°; very soluble in water, methanol and ethanol, soluble in 2-propanol, hot ethyl acetate, and benzene.

Anal. Calc'd for $C_{10}H_{13}N_3O_2$: C, 58.0; H, 6.3.
Found: C, 58.3; H, 6.2.

N^1,N^2-DIALKYL DERIVATIVES

16). *1-Isonicotinyl-1,2-dimethylhydrazine oxalate.* To 26.6 g. of *sym*-dimethylhydrazine dihydrochloride [prepared according to the procedure outlined by Thiele (9)] in 300 ml. of pyridine was added dropwise, with stirring, over a period of one-half hour, 17.8 g. of isonicotinyl chloride hydrochloride in 300 cc. of pyridine. The mixture was stirred for one-half hour and then heated on a steam-bath for one-half hour. Removal of the pyridine under a vacuum left a residue which was dissolved in concentrated ammonium hydroxide. The alkaline solution was evaporated to dryness under a vacuum and the residue was extracted with chloroform. The chloroform was removed and the small quantity of residual oil was distilled to give a fraction, b.p./5 mm. 130–140°. The distillate was dissolved in 2-propanol and anhydrous oxalic acid was added to give a precipitate of 1-isonicotinyl-1,2-dimethyl-

hydrazine oxalate. Recrystallization from 2-propanol gave cream-colored needles; m.p. 142–143°.

Anal. Calc'd for $C_8H_{11}N_3O \cdot H_2C_2O_4$: C, 47.1; H, 5.1.
Found: C, 47.4; H, 5.4.

17). *1-Isonicotinyl-1,2-diisopropylhydrazine monohydrochloride.* To 7.5 g. of *sym*-diisopropylhydrazine hydrochloride (10) dissolved in 50 ml. of hot pyridine was added portionwise, 9 g. of isonicotinyl chloride hydrochloride. Heat was liberated and the mixture was permitted to cool spontaneously. The precipitated pyridine hydrochloride was filtered off and the filtrate was concentrated under a vacuum to a thick residue which then was extracted with chloroform. Removal of the chloroform left an oil which was treated with dilute ammonium hydroxide. The ammonium hydroxide was evaporated under a vacuum and the residual oil was dissolved in ether. The ether solution was dried and dry hydrogen chloride was passed through to give a precipitate of the desired product. Recrystallization from ethyl acetate resulted in colorless prisms; m.p. 155–156.5°; very soluble in the alcohols and slightly soluble in hot ethyl acetate.

Anal. Calc'd for $C_{12}H_{19}N_3O \cdot HCl$: C, 55.9; H, 7.8.
Found: C, 55.8; H, 7.6.

A portion of the monohydrochloride was dissolved in 2-propanol and treated with ethanolic hydrogen chloride to give a product melting at 119–120° which was probably the dihydrochloride.

18). *1,2-Dibenzylhydrazine hydrochloride.* A mixture of 21 g. of benzalazine and 12.5 ml. of 8 *N* ethanolic hydrogen chloride in methanol, was catalytically reduced in the presence of platinum at room temperature and 50 p.s.i. The reduction was stopped when the requisite quantity of hydrogen had been used up (2 molar equivalents). The mixture then was heated to dissolve the product and filtered hot to remove the catalyst. On cooling, an excellent yield of the desired product was obtained which melted with decomposition at 221–223° after recrystallization from methanol. This compared satisfactorily with the melting point of 225° reported by Curtius (11).

19). *1-Isonicotinyl-1,2-dibenzylhydrazine.* A mixture of 25 g. of *sym*-dibenzylhydrazine hydrochloride, 17.8 g. of isonicotinyl chloride hydrochloride, and 200 ml. of pyridine was heated on a steam-bath for 45 minutes. The pyridine then was removed under a vacuum and the residue was treated with 200 ml. of water to give a tan product which was filtered off, washed with water and dried. Upon recrystallization from a mixture of benzene and ligroin (b.p. 60–72°) and decolorization with charcoal, 14 g. of the dibenzyl derivative was obtained in the form of white prisms; m.p. 102–103°; soluble in most of the common organic solvents except ligroin and insoluble in water.

Anal. Calc'd for $C_{20}H_{19}N_3O$: C, 75.7; H, 6.0.
Found: C, 75.9; H, 6.3.

A solution of the free base in 2-propanol was treated with ethanolic hydrogen chloride to give a monohydrochloride which on recrystallization from ethanol melted at 220–221°; insoluble in cold water and cold alcohols.

Anal. Calc'd for $C_{20}H_{19}N_3O \cdot HCl$: C, 67.9; H, 5.7.
Found: C, 67.9; H, 5.9.

20). *N^1-Benzyl-N^2-benzylidenehydrazine.* A mixture of 21 g. of benzalazine and 15 ml. of 8 *N* ethanolic hydrogen chloride in methanol was catalytically reduced as in Experiment 18 above, except that the reduction was stopped when 1 *molar*-equivalent of hydrogen had been taken up. The reaction mixture was filtered; the methanol was removed under a vacuum and the residue was extracted twice with hot benzene. On cooling, 11 g. of the benzylbenzylidenehydrazine hydrochloride precipitated out. The *hydrochloride* could be purified by recrystallization from benzene to give white flakes; m.p. 146–148°. Curtius reported 153° (11).

21). *1-Isonicotinyl-1-benzyl-2-benzylidenehydrazine mononhydrochloride.* To a solution of 16 g. of N^1-benzyl-N^2-benzylidenehydrazine in 100 ml. of pyridine was added 14 g. of isonicotinyl chloride hydrochloride. The mixture was heated on a steam-bath for about

one-half hour and the pyridine then was removed under a vacuum. The residue was dissolved in about 500 ml. of 2-propanol and ethanolic hydrogen chloride was added to give a precipitate of the desired product. Recrystallization from hot dilute (0.2 *N*) hydrochloric acid gave yellow needles; m.p. 234–239°; soluble in methanol, hot ethanol, insoluble in water.

Anal. Calc'd for $C_{20}H_{17}N_3O \cdot HCl$: C, 68.3; H, 5.1.
Found: C, 67.8; H, 5.1.

The *hydrochloride* on heating in water decomposed to give the *free base* which on recrystallization from dilute methanol was obtained in the form of colorless needles; m.p. 126–127°; very soluble in the alcohols and insoluble in water.

Anal. Calc'd for $C_{20}H_{17}N_3O$: C, 76.2; H, 5.4.
Found: C, 76.3; H, 5.4.

22). *1-Isonicotinylpyrazole.* A mixture of 5 g. of pyrazole, 14 g. of isonicotinyl chloride hydrochloride, and 50 ml. of pyridine was refluxed for one-half hour. The excess of pyridine was removed under a vacuum; water was added to the residue and the mixture was filtered. The insoluble material was the desired 1-isonicotinylpyrazole. On recrystallization from water it was obtained in the form of white crystals which sublimed at about 300° without melting.

Anal. Calc'd for $C_9H_7N_3O$: C, 62.4; H, 4.0.
Found: C, 62.8; H, 4.1.

23). *1-Isonicotinyl-3,5-dimethylpyrazole.* A mixture of 19.2 g. of 3,5-dimethylpyrazole, 35.6 g. of isonicotinyl chloride hydrochloride, and 100 ml. of pyridine was refluxed for one hour; the pyridine was removed under a vacuum and the residue was treated with water and filtered to give 25 g. of the desired product. The product was soluble in all of the organic solvents tested, including hot ligroin and was also soluble in hot water, dilute ammonium hydroxide, dilute pyridine, and dilute acetic acid. Recrystallization from ligroin (60–70°) gave long colorless needles melting at 86.5–87.5°.

Anal. Calc'd for $C_{11}H_{11}N_3O$: C, 65.7; H, 5.5.
Found: C, 65.7; H, 5.6.

1-Isonicotinyl-3,5-dimethylpyrazole was also prepared by condensing isonicotinyl hydrazine and acetylacetone according to the following procedure:

A mixture of 13.7 g. of isonicotinylhydrazine, 10 g. of acetylacetone, 0.5 ml. of 3 *N* hydrochloric acid, and 100 ml. 2-propanol was heated to solution. The solvent then was removed under a vacuum and the viscous residue was treated with water to give a white crystalline product which was recrystallized from petroleum ether to yield white crystals; m.p. 84.5–86°. A mixture with an authentic sample of 1-isonicotinyl-3,5-dimethylpyrazole melted at 85–86°.

Anal. Calc'd for $C_{11}H_{11}N_3O$: C, 65.7; H, 5.5.
Found: C, 66.1; H, 5.4.

CONCLUSION

In extending the study of derivatives of isonicotinylhydrazine to disubstitution products, two series of compounds were synthesized and studied for tuberculostatic activity. One of these series consists in the main of N^2,N^2-dialkyl derivatives and retains in some of its members a high order of activity in mice infected with human tuberculosis strain H37Rv. The other series of N^1,N^2-dialkyl derivatives shows markedly diminished activity which may well be related to the presence of a substituent in the N^1 position.

SUMMARY

A number of N^2,N^2-disubstituted and N^1,N^2-disubstituted derivatives of isonicotinylhydrazine were prepared and studied for tuberculostatic activity.

None of the compounds is as active *in vivo* as is the parent isonicotinylhydrazine itself.

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