[CONTRIBUTION NO. 340 FROM THE RESEARCH LABORATORIES, HOFFMAN LA-ROCHE, INC.]

SYNTHETIC TUBERCULOSTATS. VII. MONOALKYL DERIVATIVES OF ISONICOTINYLHYDRAZINE

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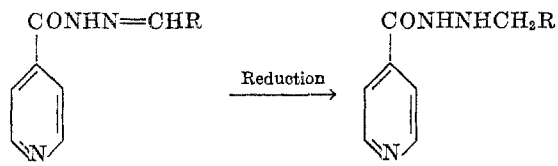
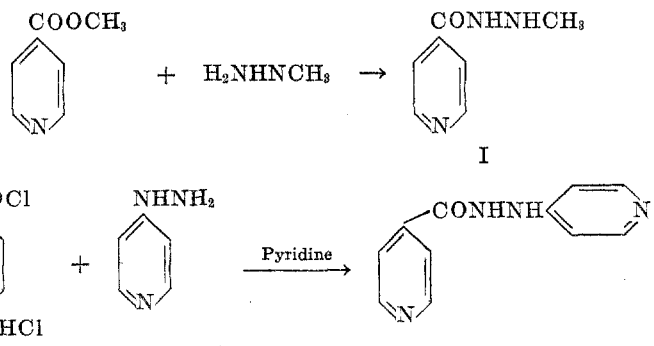
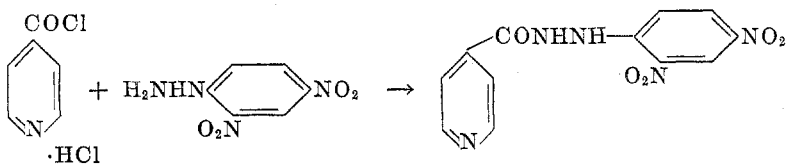
The advantages to be derived from the remarkable *in vivo* activity and relative atoxicity of the alkylidene, arylalkylidene, and the sugar derivatives of isonicotinylhydrazine (1, 2) are offset to some degree by the lability inherent in the double bond of the —C=N— or Schiff's base linkage. It was decided therefore to eliminate this double bond to form more stable alkyl derivatives. That stability could thus be achieved was hardly to be doubted. It was a moot question, however, as to whether the activity would survive the structural change because the possibility existed that the activity of the alkylidenes was due to their scission to the parent isonicotinylhydrazine. If the latter concept were true, it appeared probable that stabilization of the molecules by conversion to the corresponding alkyl derivatives would abolish or, at the very least, markedly reduce the activity. This was not the case. The alkyl, cycloalkyl, and arylalkyl derivatives prepared in this study were actively tuberculostatic *in vivo*.

Most of the compounds were prepared by catalytic reduction, under very mild conditions, of the corresponding alkylidene or arylalkylidene derivatives.



As exceptions to the rule, 1-isonicotinyl-2-methylhydrazine (I) was prepared by the action of methylhydrazine on methyl isonicotinate and 1-isonicotinyl-2-(4-pyridyl)hydrazine (II) and 1-isonicotinyl-2-(2,4-dinitrophenyl)hydrazine (III) were prepared by the action of isonicotinyl chloride hydrochloride on *gamma*-pyridylhydrazine and 2,4-dinitrophenylhydrazine respectively.



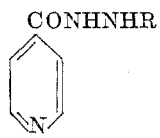


III

A platinum catalyst was used in all the reductions since every attempt to use Raney nickel was unsuccessful. The straight and branched-chain alkylidene and the cycloalkylidene derivatives were most easily reduced, whereas the benzylidene derivatives would not reduce under the same conditions and required the presence of an acid medium.

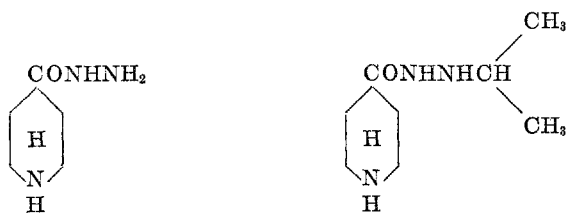
TABLE I

STRAIGHT-CHAIN ALKYL DERIVATIVES OF ISONICOTINYLHYDRAZINE



R	SALT	M.P., °C.	ACTIVITY
$-CH_3$	—	83.5–84.5	
$-CH_3$	2 HCl	225.5–226.5	+
$-CH_3$	2 $H_2C_2O_4$	196–197	
$-CH_2CH_3$	—	105–107	
$-CH_2CH_3$	2 HCl	220–222	+
$-CH_2CH_2CH_3$	—	60–60.5	+
$-CH_2CH_2CH_2CH_3$	—	76–77	+
$-CH_2CH_2CH_2CH_3$	2 HCl	227–229	
$-CH_2(CH_2)_4CH_3$	2 HCl	214–215	+
$-CH_2(CH_2)_5CH_3$	2 HCl	222.5–224.5	+

To ascertain the effect of reducing the pyridine ring on the activity of the isonicotinylhydrazines, isonipecotic acid hydrazine (IV) and 1-isonipectoyl-2-isopropylhydrazine (V) were prepared. Both compounds were inactive.

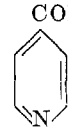


IV V

The compounds prepared in this study are listed in Tables I, II, and III. Under the column headed, "Activity", only the presence or absence of *in vivo* activity is noted. All the melting points in Tables I, II, and II are corrected.

TABLE II

BRANCHED-CHAIN AND CYCLOALKYL DERIVATIVES OF ISONICOTINYLHYDRAZINE



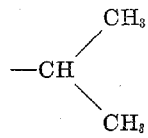
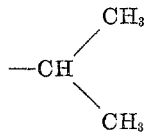
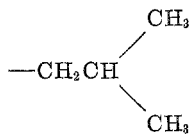
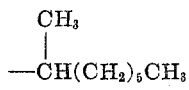
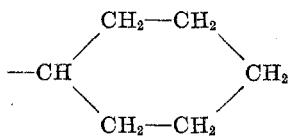
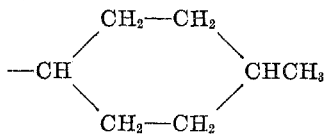
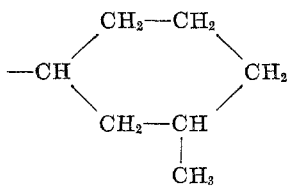
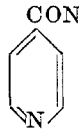
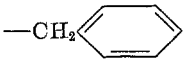
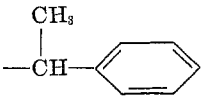
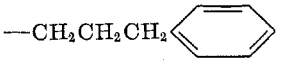
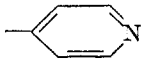
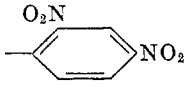
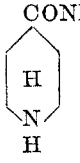
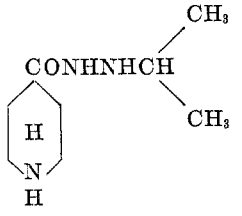
R	SALT	M.P., °C.	ACTIVITY
	—	112–113	+
	2 HCl	227–228	+
	2 HCl	223.5–224.5	+
	2 HCl	221.5–223.5	+
	—	148.5–149	+
	2 HCl	227–228	+
	—	114–116	+

TABLE III

ARYLALKYL AND MISCELLANEOUS DERIVATIVES OF ISONICOTINYLHYDRAZINE



R	SALT	M.P., °C.	ACTIVITY
	—	119.5–120.5	+
	—	116–117	+
	2 HCl	222–223	+
	—	118–119	+
$-CH_2(CHOH)_4CH_2OH$	—	indef. 100	+
	—	245–246	−
	HCl	248–248.5	−
	2 HCl	244.5	−
	2 HCl	254.5–255.5	−

Acknowledgment. The authors are indebted to Drs. R. J. Schnitzer and E. Grunberg and the staff of the chemotherapy laboratory for the chemotherapeutic results and to Dr. A. Steyermark and his staff for the microanalyses.

EXPERIMENTAL

All melting points are corrected.

1. *1-Isonicotinyl-2-methylhydrazine.* A mixture of 13.7 g. of methyl isonicotinate and 6 g. of methylhydrazine was heated at 130° for 3 hours. The volatile fractions were removed under a vacuum, the viscous residue was dissolved in propanol-2 and the clear solution was treated with an excess of ethanolic hydrogen chloride. The 1-isonicotinyl-2-methylhydrazine dihydrochloride which precipitated was recrystallized from a mixture of water-methanol-propanol-2. Colorless needles; m.p. 225.5–226.5° (with decomposition).

Anal. Calc'd for $C_7H_9N_3O \cdot 2HCl$: C, 37.5; H, 4.9.
Found: C, 37.7; H, 5.0.

The *free base* was obtained by heating the dihydrochloride with ammonium hydroxide, evaporating the mixture to dryness under a vacuum, and extracting the residue with chloroform. Removal of the chloroform gave white crystals soluble in water and melting at 83.5–84.5°.

Anal. Calc'd for $C_7H_9N_3O$: C, 55.7; H, 6.0.
Found: C, 55.7; H, 5.9.

The *dioxalate* was obtained by treating the base with oxalic acid. Recrystallization from dilute ethanol gave white crystals. m.p. 196–197° (with decomposition).

Anal. Calc'd for $C_7H_9N_3O \cdot 2H_2C_2O_4$: C, 39.9; H, 3.9.
Found: C, 40.1; H, 3.8.

2. *1-Isonicotinyl-2-ethylhydrazine dihydrochloride.* A methanolic solution of 4.89 g. of 1-isonicotinyl-2-ethylidenehydrazine was reduced with hydrogen at room temperature and 40–50 p.s.i. using a platinum catalyst. The reduction was stopped when 1 molar-equivalent of hydrogen had been used. The reaction mixture was filtered, the methanol was removed and the residue was dissolved in propanol-2 and then treated with an excess of ethanolic hydrogen chloride. A precipitate of the dihydrochloride of 1-isonicotinyl-2-ethylhydrazine was obtained which could be purified by recrystallization from a methanol-acetone mixture to give colorless feathery crystals which decomposed at 220–222°.

Anal. Calc'd for $C_8H_{11}N_3O \cdot 2HCl$: C, 40.4; H, 5.5.
Found: C, 40.3; H, 5.2.

The *free base* was prepared by dissolving the hydrochloride in concentrated ammonium hydroxide, evaporating the solution to dryness under a vacuum and extracting the residue with chloroform. Upon removal of the chloroform, the free base was obtained in the form of white crystals which were very soluble in water and the alcohols and which melted at 105–107°.

Anal. Calc'd for $C_8H_{11}N_3O$: C, 58.2; H, 6.7.
Found: C, 58.6; H, 6.8.

3. *1-Isonicotinyl-2-propylhydrazine.* A methanolic solution of 17.7 g. of the corresponding propylidene derivative was reduced as described in Experiment 2, and the methanol was removed to yield an oil which crystallized on standing. Upon recrystallization from a mixture of benzene and petroleum ether, the 1-isonicotinyl-2-propylhydrazine was obtained in the form of soft white needles which melted at 60–60.5°; yield 9.5 g. The product was very soluble in water and in most of the common organic solvents.

Anal. Calc'd for $C_9H_{13}N_3O$: C, 60.4; H, 7.3.
Found: C, 60.1; H, 7.3.

4. *1-Isonicotinyl-2-isopropylhydrazine.* This compound could be made by reducing the corresponding isopropylidene derivative according to the procedure outlined in Experiment 2. It was also more conveniently prepared according to the following procedure:

A mixture of 96 g. of isonicotinylhydrazine, 55 cc. of acetone, and 200 cc. of propanol-2 was heated to solution and then diluted with an additional 350 cc. of propanol-2. The reaction mixture was cooled, 200 mg. of platinum oxide was added, and the whole was reduced at room temperature and about 300 p.s.i. of hydrogen. When the hydrogen uptake ceased, the catalyst was filtered off, the solvent was removed and the residual oil was treated with

700 cc. of benzene. On standing, 81 g. of pure 1-isonicotinyl-2-isopropylhydrazine precipitated out. A further quantity of practically pure product was obtained by concentrating the benzene filtrate to about 300 cc. White needles; m.p. 112–113°; very soluble in water and in alcohol.

Anal. Calc'd for $C_9H_{13}N_3O$: C, 60.3; H, 7.3.
Found: C, 60.4; H, 7.3.

The *dihydrochloride* precipitated out in the form of white rhomboids from a propanol-2 solution of the free base on treatment with ethanolic hydrogen chloride; m.p. 227–228° (dec.).

Anal. Calc'd for $C_9H_{13}N_3O \cdot 2HCl$: C, 42.9; H, 6.0.
Found: C, 42.7; H, 6.0.

5. *1-Isonicotinyl-2-butylhydrazine.* A methanolic solution of 19.1 g. of the corresponding butylidene derivative was reduced as described in Experiment 2 except that the reduction was carried out at 50–60°. The free base was obtained in the form of white needles upon recrystallization from xylene; m.p. 76–77°.

Anal. Calc'd for $C_{10}H_{15}N_3O$: C, 62.3; H, 7.8.
Found: C, 62.3; H, 7.7.

The *dihydrochloride* decomposed at 227–229°.

6. *1-Isonicotinyl-2-isobutylhydrazine dihydrochloride.* A methanolic solution of 14 g. of the corresponding isobutylidene derivative was reduced as described in Experiment 5. The reduction product, after removal of the methanol, was dissolved in propanol-2 and was converted to the dihydrochloride with ethanolic HCl. Upon recrystallization from a methanol-propanol-2 mixture, the 1-isonicotinyl-2-isobutylhydrazine dihydrochloride was obtained in the form of white crystals which melted at 223.5–224.5°.

Anal. Calc'd for $C_{10}H_{15}N_3O \cdot 2HCl$: C, 45.1; H, 6.4.
Found: C, 44.9; H, 6.3.

The *free base* was an oil which could not be crystallized.

7. *1-Isonicotinyl-2-hexylhydrazine dihydrochloride.* A methanolic solution of 20 g. of the corresponding hexylidene derivative was treated as described in Experiment 2 to give 1-isonicotinyl-2-hexylhydrazine dihydrochloride. White plates from glacial acetic acid decomposed at 214–215°.

Anal. Calc'd for $C_{12}H_{19}N_3O \cdot 2HCl$: C, 49.0; H, 7.1.
Found: C, 48.8; H, 7.0.

8. *1-Isonicotinyl-2-heptylhydrazine dihydrochloride.* A methanolic solution of 14 g. of the corresponding heptylidene derivative was treated as described in Experiment 2 to give 1-isonicotinyl-2-heptylhydrazine dihydrochloride. Lustrous flakes from methanol-propanol-2 mixture; m.p. 222.5–224.5°.

Anal. Calc'd for $C_{13}H_{21}N_3O \cdot 2HCl$: C, 50.6; H, 7.5.
Found: C, 50.7; H, 7.7.

9. *1-Isonicotinyl-2-(1-methylheptyl)hydrazine dihydrochloride.* A methanolic solution of 15 g. of the corresponding 1-methylheptylidene derivative was treated as described in Experiment 6 to give 1-isonicotinyl-2-(1-methylheptyl)hydrazine dihydrochloride in the form of lustrous white flakes which decomposed at 221.5–223.5°.

Anal. Calc'd for $C_{14}H_{23}N_3O \cdot 2HCl$: C, 52.2; H, 7.8.
Found: C, 52.3; H, 7.5.

10. *1-Isonicotinyl-2-cyclohexylhydrazine.* A mixture of 21 g. of isonicotinylhydrazine and 15 g. (16 cc.) of cyclohexanone in 150 cc. of methanol was reduced with hydrogen in the presence of a platinum catalyst at room temperature and 50 p.s.i. As the reduction proceeded, the product precipitated out. When the theoretical quantity of hydrogen was taken up, the reduction was stopped and the reaction mixture was heated to solution and filtered. The clear filtrate on cooling gave colorless needles of 1-isonicotinyl-2-cyclohexylhydrazine; m.p. 148.5–149°; yield 24 g.

Anal. Calc'd for $C_{12}H_{17}N_3O$: C, 65.8; H, 7.8.
Found: C, 65.6; H, 7.4.

The same product could also be obtained by reducing the corresponding cyclohexylidene derivative according to the procedure described in Experiment 2.

11. *1-Isonicotinyl-2-(4-methylcyclohexyl)hydrazine dihydrochloride.* A mixture of 21 g. of isonicotinylhydrazine and 18.7 g. of 4-methylcyclohexanone was reduced as in Experiment 10 above. When the theoretical quantity of hydrogen had been taken up, the reduction was stopped, the reaction mixture was filtered, and the methanol was removed under a vacuum to leave an oily base. The oil was dissolved in propanol-2 and converted to the hydrochloride with ethanolic HCl. Recrystallization from a methanol-propanol-2 mixture gave white crystals of 1-isonicotinyl-2-(4-methylcyclohexyl)hydrazine dihydrochloride, m.p. 227–228°.

Anal. Calc'd for $C_{13}H_{19}N_3O \cdot 2HCl$: C, 51.0; H, 6.9.

Found: C, 51.0; H, 6.6.

12. *1-Isonicotinyl-2-(3-methylcyclohexyl)hydrazine.* A mixture of 21 g. of isonicotinylhydrazine and 18.7 g. of 3-methylcyclohexanone was reduced as in Experiment 11 above. The oil left upon removal of the methanol solvent solidified on standing and was recrystallized from toluene to yield white needles, m.p. 114–116°.

Anal. Calc'd for $C_{13}H_{19}N_3O$: C, 67.0; H, 8.2.

Found: C, 67.2; H, 8.2.

13. *1-Isonicotinyl-2-sorbitylhydrazine.* An aqueous solution of 15 g. of 1-isonicotinyl-2-glucosylhydrazine was reduced as described in Experiment 2. The reaction mixture was filtered, and the water was removed under a vacuum to leave a viscous residue which was dissolved in 400 cc. of methanol. The methanolic solution, after decolorization with charcoal, was added with stirring to 600 cc. of acetone to yield the sorbityl compound as a yellow powder of indefinite melting point.

Anal. Calc'd for $C_{12}H_{19}N_3O_6 \cdot 1CH_3OH$: C, 46.8; H, 6.9.

Found: C, 46.6; H, 6.9.

In another run the sorbityl derivative was precipitated from methanolic solution by the addition of propanol-2. It was thus obtained in the form of tan crystals of variable melting point which proved to be the dimethanolate.

Anal. Calc'd for $C_{12}H_{19}N_3O_6 \cdot 2CH_3OH$: C, 46.0; H, 7.4.

Found: C, 45.9; H, 7.2.

14. *1-Isonicotinyl-2-benzylhydrazine.* A methanolic solution of 4.5 g. of the corresponding benzylidene derivative was treated with 20 cc. of concentrated ethanolic HCl and was then reduced as described in Experiment 2. The hydrochloride of the product precipitated as the reduction proceeded. To facilitate removal of the catalyst sufficient water was added to the reaction mixture after reduction was complete to dissolve the precipitate. The mixture was filtered, concentrated to a small volume and then made alkaline with ammonium hydroxide to give a precipitate of the free base. Upon recrystallization from benzene, the 1-isonicotinyl-2-benzylhydrazine was obtained in the form of white needles which melted at 119.5–120.5°. The product was soluble in alcohol, chloroform, and in mineral acids and bases and was insoluble in water, cold benzene, and ligroin.

Anal. Calc'd for $C_{13}H_{13}N_3O$: C, 68.7; H, 5.7.

Found: C, 68.7; H, 5.6.

15. *1-Isonicotinyl-2-(p-methoxybenzyl)hydrazine.* The corresponding *p*-methoxybenzylidene derivative (5.1 g.) was reduced as described in Experiment 12. The insoluble product (hydrochloride) was filtered off together with the catalyst and then dissolved in water and filtered again to remove the catalyst. The aqueous filtrate was made alkaline with dilute ammonium hydroxide and then neutralized with acetic acid to give the desired compound in the form of its free base. White needles from benzene; m.p. 116–117°.

Anal. Calc'd for $C_{14}H_{15}N_3O_2$: C, 65.5; H, 5.8.

Found: C, 65.4; H, 5.8.

16. *1-Isonicotinyl-2-(α-methylbenzyl)hydrazine dihydrochloride.* The corresponding α-methylbenzylidene derivative (4.8 g.) was reduced as described in Experiment 12. The reaction mixture was then filtered, the methanol was removed under a vacuum, and the solid hydrochloride thus obtained was recrystallized from a methanol-propanol-2 mixture to give white needles; m.p. 222–223° (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.

The *free base* was an oil which could not be crystallized.

17. *1-Isonicotinyl-2-(3-phenylpropyl)hydrazine.* A methanolic solution of 20 g. of the corresponding cinnamylidene derivative was treated as described in Experiment 2 except that 2 molar equivalents of hydrogen were taken up. The resulting 1-isonicotinyl-2-(3-phenylpropyl)hydrazine upon recrystallization from benzene melted at 118–119°.

Anal. Calc'd for $C_{15}H_{17}N_3O$: C, 70.6; H, 6.7.
Found: C, 70.6; H, 6.7.

18. *1-Isonicotinyl-2-(4-pyridyl)hydrazine dihydrate.* To 17.8 g. of isonicotinyl chloride-hydrochloride in 100 cc. of dry pyridine there was added 27.1 g. of γ-pyridylhydrazine. The mixture evolved heat and was stirred and heated on a steam-bath for about ½ hour or until solution was practically complete. The pyridine was removed under a vacuum, and the residue was made alkaline with a saturated solution of potassium carbonate. An oily layer formed which solidified on standing. It was filtered off and recrystallized from water to yield golden yellow flakes of the 4-pyridyl derivative which partially melted at about 115° and resolidified to melt again at 245–246°.

Anal. Calc'd for $C_{11}H_{10}N_4O \cdot 2H_2O$: C, 52.8; H, 5.6; N, 22.4.
Found: C, 52.2; H, 5.0; N, 22.5.

A sample of the material when dried at 100° lost 1 mole of water to give the *monohydrate.*

Anal. Calc'd for $C_{11}H_{10}N_4O \cdot 1H_2O$: C, 56.9; H, 5.2.
Found: C, 57.5; H, 4.4.
Calc'd for $C_{11}H_{10}N_4O \cdot 2H_2O$: M.W., 250.
Found (perchloric acid titration): M.W., 252.

19. *Isonipecotylhydrazine dihydrochloride.* A methanolic solution of 28 g. of methyl isonicotinate hydrochloride was reduced as described in Experiment 5, except that the reduction was permitted to go to completion. The resulting methyl isonipectotate hydrochloride on recrystallization from propanol-2 melted at 165.5–166.5°.

To 10 g. of methyl isonipecotate hydrochloride there was added with stirring 10 cc. of 85% hydrazine hydrate. Heat was liberated spontaneously. After heating the mixture on the steam-bath for ½ hour, the excess hydrazine hydrate was removed under a vacuum and the residue was recrystallized from a mixture of methanol (containing a little aqueous 3 *N* hydrochloric acid) and propanol-2 to yield white needles of isonipectoyl hydrazine dihydrochloride, m.p. 244–245° (dec.).

Anal. Calc'd for $C_6H_{13}N_3O \cdot 2HCl$: C, 33.4; H, 6.9.
Found: C, 33.2; H, 7.3.

20. *1-Isonipecotyl-2-isopropylhydrazine dihydrochloride.* A methanolic solution containing 6.5 g. of 1-isonicotinyl-2-isopropylhydrazine and 10 cc. of saturated ethanolic HCl was reduced as in Experiment 17 above. Water was added to the reaction mixture to dissolve the product and permit removal of the catalyst. The mixture was then evaporated to dryness under a vacuum, the residue was dissolved in methanol, ethanolic HCl was added, and finally an excess of propanol-2 to give white needles of 1-isonipecotyl-2-isopropyl hydrazine dihydrochloride, m.p. 254.5–255.5°.

Anal. Calc'd for $C_7H_{19}N_3O \cdot 2HCl$: C, 41.8; H, 8.1.
Found: C, 42.0; H, 8.2.

21. *1-Isonicotinyl-2-(2,4-dinitrophenyl)hydrazine hydrochloride.* To a suspension of 4.5 g. of isonicotinyl chloride hydrochloride in 25 cc. of pyridine was added 5 g. of 2,4-dinitrophenylhydrazine in 25 cc. of pyridine. Heat was evolved and the mixture was heated on the steam-bath for about 15 minutes longer and then cooled. The precipitate was filtered off and on recrystallization from dilute hydrochloric acid gave orange needles of 1-isonicotinyl-2-(2,4-dinitrophenyl)hydrazine, m.p. 248–248.5°. The crystals turn black in water or alkali.

Anal. Calc'd for $C_{12}H_9N_5O_5 \cdot HCl \cdot H_2O$: C, 40.4; H, 3.4.
Found: C, 40.7; H, 3.5.

Conclusion. The preparation in this study of stable derivatives of isonicotinylhydrazine in which one of the terminal hydrogen atoms of the hydrazide moiety is replaced by an alkyl, cycloalkyl, or aralkyl group leads to a broad series of highly active tuberculostats. The stability of these compounds suggests that their *in vivo* activity is not due to scission to the parent compound as might be postulated for the alkylidene derivatives but is rather a function of the molecule as a whole. This is borne out to some degree by the fact that 1-isonicotinyl-2-(4-pyridyl)hydrazine (II) and 1-isonicotinyl-2-(2,4-dinitrophenyl)hydrazine (III) are both inactive. Reduction of the pyridine ring is incompatible with activity.

SUMMARY

A series of alkyl, cycloalkyl, and aralkyl derivatives of isonicotinylhydrazine has been prepared and studied. With two exceptions, all of the compounds show marked *in vivo* activity. Upon complete reduction of the pyridine ring, activity is lost.

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