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Synthetic Tuberculostats. XI. Trialkyl and Other Derivatives of Isonicotinylhydrazine

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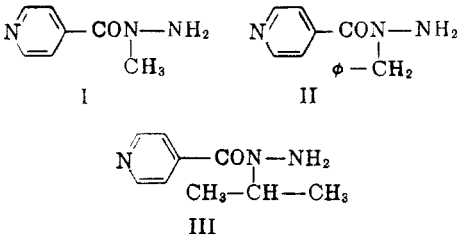
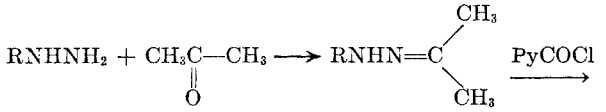
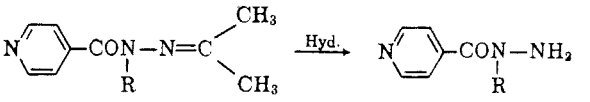
In previous studies with derivatives of isonicotinylhydrazine, one or two of the remaining three hydrogen atoms of the hydrazine moiety had been replaced by various groups.[1-5] To determine the effect of replacing all three hydrogen atoms, a series of trialkyl derivatives was prepared and studied. The compounds proved to be either inactive or weakly active in mice infected with *M. tuberculosis*, human strain H37Rv. This result was not entirely unexpected inasmuch as past experience had indicated that the presence of a group in the N^1 position appeared to be detrimental to tuberculostatic activity.[5] Partial confirmation of this concept was obtained by the preparation of N^1 monoalkyl derivatives. Of the three such compounds prepared, the methyl (I) and benzyl (II) derivatives were much less active than their N^2 counterparts.[3] On the other hand the isopropyl (III) derivative retained a high order of activity—indicating that no hard and fast rule exists concerning the effect of N^1 substitution on activity.



I II III

Preparation of the N^1 methyl and isopropyl derivatives was effected by treating the appropriate monoalkylhydrazine with acetone to give the corresponding hydrazone which then was acylated with isonicotinyl chloride and finally hydrolyzed to give the desired compound.

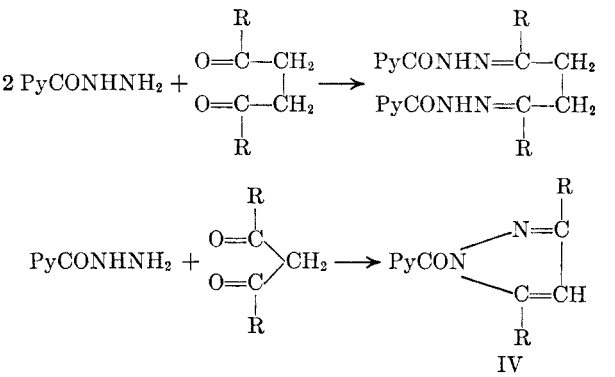




The benzyl derivative was similarly prepared from N^1-benzyl-N^2-benzylidenehydrazine. These and the other alkyl compounds prepared in this study are listed in Table I.

Table II lists some alkylidene derivatives which were prepared in an extension of the work of a previous study.[1]

Compounds with two aldehydic or ketonic groups *alpha* or *gamma* to each other readily react with two molar proportions of isonicotinylhydrazine to give highly active derivatives of the type listed in Table III. This is in contradistinction to the *beta*-diketone, acetylacetone, which we have shown cyclizes with the hydrazine nitrogens to form an inactive pyrazole derivative (IV).[5]



IV

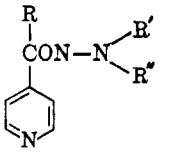
In a previous study[1] it was pointed out that alloxan forms a very insoluble derivative with isonicotinylhydrazine and that this property can be utilized to detect and separate small quantities of isonicotinylhydrazine from its water-soluble N^2 derivatives such as 1-isonicotinyl-2-isopropylhydrazine. Further investigation has shown, however, that the latter also combines with alloxan when concentrated solutions of the two are mixed and cooled. The compound formed is water-soluble, unstable, and has a high activity which is probably due to the fact that it readily decomposes to regenerate 1-isonicotinyl-2-isopropylhydrazine.

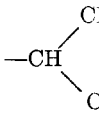
In the accompanying tables the notations in the column marked "Activity" are merely designed to give rough estimations of relative *in vivo* tuber-

(1) Fox and Gibas, *J. Org. Chem.*, **18**, 983 (1953).
(2) Fox, *J. Org. Chem.*, **18**, 990 (1953).
(3) Fox and Gibas, *J. Org. Chem.*, **18**, 994 (1953).
(4) Fox and Gibas, *J. Org. Chem.*, **18**, 1375 (1953).
(5) Fox and Gibas, *J. Org. Chem.*, **20**, 60 (1955).

TABLE I

ALKYL DERIVATIVES OF ISONICOTINYLHYDRAZINE



R	R′	R″	M.P., °C. (Corr.) Base	Salt	Activity
Trialkyl					
—CH_3	—CH_3	—CH_3	191.5–193.5	—	—
—$CH_2CH{=}CH_2$	—CH_3	—CH_3	113–114	—	—
—$CH_2CH_2CH_2CH_3$	—CH_3	—CH_3	—	($1^1/_2$ $H_2C_2O_4$) 132–133	±
—$CH_2C_6H_6$	—CH_3	—CH_3	108–109	—	±
	—CH_3	—CH_3	—	($1^1/_2$ $H_2C_2O_4$) 165.5–166.5	±
—$CH_2CH{=}CH_2$	—C_2H_5	—C_2H_5	—	(2 HCl) 142–143	+
Monoalkyl					
—CH_3	—	—	95–96	(2 HCl) 207–208 (d) ($H_2C_2O_4$) 134–135	±
	—	—	105–106	(2 HCl) 191–193 (d)	++
—$CH_2C_6H_5$	—	—	99.5–100	($H_2C_2O_4$) 148–149 (d)	±
Alkyl-acyl					
—CH_3	—CH_3	PyCO—[a]	148–149	—	—
—	—CH_3	PyCO—	165–166.5	—	±
—	—$CH_2COOC_2H_5$	PyCO—	—	(2 $H_2C_2O_4$) 197–197.5	

[a] Py = 

culostatic activity: ++ means marked activity; + means moderate activity; ± means weak or doubtful activity; − means no activity.

The preparative details for the compounds prepared in this study 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.

EXPERIMENTAL

All the melting points are corrected.

TRIALKYL DERIVATIVES

1. *1-Isonicotinyl-1-methyl-2,2-dimethylhydrazine.* To a solution of 1.15 g. of sodium in 100 ml. of ethanol (absolute) is added 8.2 g. of 1-isonicotinyl-2,2-dimethylhydrazine[6] followed by 7.1 g. (3.05 cc.) of methyl iodide. The mixture is refluxed until the solution is at *p*H 7–8. The ethanol is removed and the residue is treated with an excess of concentrated ammonium hydroxide which, in turn, is removed under a vacuum. The resulting residue is extracted with chloroform and the chloroform solution is evaporated to dryness to yield the desired product which, on recrystallization from benzene using decolorizing carbon, is obtained in the form of white feathery crystals melting at 191.5–193.5°. The product is very soluble in water and in alcohol and is insoluble in ether and in ligroin.

Anal. Calc'd for $C_9H_{13}N_3O$: C, 60.4; H, 7.3. Found: C, 60.4; H, 7.5.

2. *1-Isonicotinyl-1-allyl-2,2-dimethylhydrazine.* A mixture of 2.3 g. of sodium, 100 ml. of ethanol (absolute), 16.5 g. of 1-isonicotinyl-2,2-dimethylhydrazine, and 9 g. (9.6 cc.) of allyl chloride is reacted substantially as described in Experiment 1 above to give 14 g. of the desired product. Upon recrystallization from carbon tetrachloride, it is obtained in the form of colorless spires which melt at 113–114°.

Anal. Calc'd for $C_{11}H_{15}N_3O$: C, 64.4; H, 7.3. Found: C, 64.7; H, 7.3.

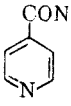
3. *1-Isonicotinyl-1-butyl-2,2-dimethylhydrazine sesquioxalate.* A mixture of 16.5 g. of the dimethyl compound, 2.3 g. of sodium, 100 ml. of ethanol (absolute), and 9.35 cc. of butyl chloride is reacted as in Experiment 1 above. The free base remaining after removal of the chloroform, is too soluble in the common organic solvents for convenient handling. Therefore it is dissolved in 2-propanol and precipitated as the oxalate. Recrystallization from 2-propanol containing oxalic acid gives 16 g. of the desired product in the form of small white needles melting at 132–133°.

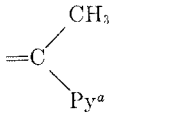
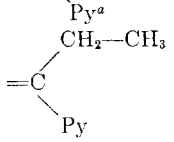
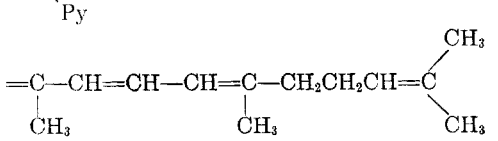
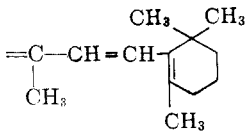
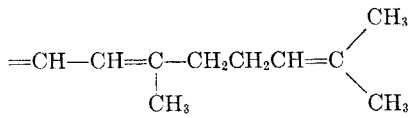
Anal. Calc'd for $C_{12}H_{19}N_3O \cdot 1^1/_2H_2C_2O_4$: C, 50.6; H, 6.2. Found: C, 50.7; H, 5.9.

4. *1-Isonicotinyl-1-benzyl-2,2-dimethylhydrazine.* A mixture containing 16.5 g. of the dimethyl compound, 2.3 g. of sodium, 100 ml. of absolute ethanol, and 12.7 g. (11.5 cc.)

Table II

ALKYLIDENE DERIVATIVES OF ISONICOTINYLHYDRAZINE

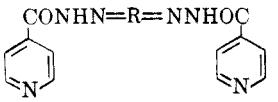


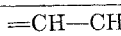
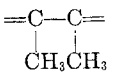
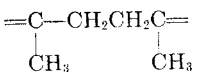
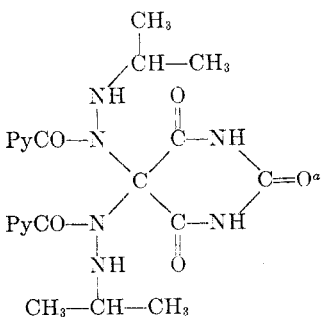
R	M.P., °C. (Corr.)	Activity
	171–172	++
	186.5–188.5	++
	145–146	++
	175.5–176.5	++
	126–127	++

[a] Py = 

TABLE III

BIS(ISONICOTINYLHYDRAZINE) DERIVATIVES



R	M.P., °C. (Corr.)	Activity
	>320	++
	280.5–281.5	++
	(hemihydrate) 165.5–167.5	++
	(dihydrate) 130–131 (d)	++

[a] Py = 

of benzyl chloride is reacted as described in Experiment 1 above. The desired product upon recrystallization from carbon tetrachloride is obtained in the form of white prisms which melt at 108–109°. It is soluble in water, alcohol, benzene, and in chloroform and is insoluble in ligroin and in ether.

Anal. Calc'd for $C_{15}H_{17}N_3O$: C, 70.6; H, 6.7. Found: C, 70.6; H, 6.3.

5. *1-Isonicotinyl-1-cyclohexyl-2,2-dimethylhydrazine sesquioxalate.* A mixture of 8.2 g. of the dimethyl compound, 1.15 g. of sodium, 6.3 ml. (8.1 g.) of cyclohexyl bromide, and 100 ml. of absolute ethanol is reacted as in Experiment 1 above. The free base remaining after removal of the chloroform is dissolved in 2-propanol and reprecipitated as the oxalate. Upon recrystallization from 2-propanol containing dissolved oxalic acid, it is obtained in the form of small white needles which melt at 165.5–166.5°.

Anal. Calc'd for $C_{14}H_{21}N_3O \cdot 1^1/_2H_2C_2O_4$: C, 53.4; H, 6.3; equiv. wt., 127.3. Found: C, 53.3; H, 6.4; equiv. wt., 130.4.

6. *1-Isonicotinyl-1-allyl-2,2-diethylhydrazine dihydrochloride.* A mixture of 9.7 g. of 1-isonicotinyl-2,2-diethylhydrazine,[5] 1.15 g. of sodium, 100 ml. of absolute alcohol, and 6 ml. of allyl chloride is reacted as described in Experiment 1 above. The thick oily residue left after removal of the ethanol is dissolved in 2-propanol and then is treated with an excess of ethanolic hydrogen chloride. Some dihydrochloride of the original diethyl compound precipitates and is removed at this point. The clear filtrate on dilution with ether gives 5 g. of the desired product. Upon recrystallization from 2-propanol or a 2-propanol-ethyl acetate mixture the product is obtained in the form of colorless feathery clusters which melts at 142–143°.

Anal. Calc'd for $C_{13}H_{19}N_3O \cdot 2HCl$: C, 51.0; H, 6.9; equiv. wt., 153. Found: C, 50.3; H, 6.9; equiv. wt., 153.

MONOALKYL DERIVATIVES

7. *1-Isonicotinyl-1-methylhydrazine dihydrochloride.* A mixture of 4.6 g. of methylhydrazine and 11 ml. of acetone is refluxed for about 10 minutes, cooled, and then is diluted with ether. The ether solution is dried over sodium sulfate; the ether is removed and the residue is dissolved in about 50 ml. of dry pyridine. To the pyridine solution is added 17.8 g. of isonicotinyl chloride hydrochloride. Heat is liberated and the mixture is warmed for 30 minutes on a steam-bath. The pyridine then is removed under a vacuum and the residue is heated with 3 *N* hydrochloric acid for 15 minutes on a steam-bath. The mixture is made alkaline with concentrated ammonium hydroxide and then is evaporated to dryness and extracted with chloroform. The oil obtained upon removal of the chloroform is dissolved in 2-propanol and is precipitated as a hydrochloride with ethanolic hydrogen chloride. Recrystallization from a water-methanol-ethanolic hydrogen chloride mixture gives white needles of the product which melt with decomposition at 207–208°.

Anal. Calc'd for $C_7H_9N_3O \cdot 2\ HCl$: C, 37.5; H, 4.9. Found: C, 37.7; H, 4.5.

A portion of the dihydrochloride is converted to the free base which on recrystallization from a benzene-ligroin (70°) mixture is obtained in the form of white needles melting at 95–96°.

Anal. Calc'd for $C_7H_9N_3O$: C, 55.7; H, 6.0. Found: C, 56.0; H, 6.2.

The *oxalate* is prepared by treating a 2-propanol solution of the free base with oxalic acid. Upon recrystallization from methanol, it is obtained in the form of cream-colored crystals which melt with decomposition at 134–135°.

Anal. Calc'd for $C_7H_9N_3O \cdot H_2C_2O_4$: C, 44.8; H, 4.6. Found: C, 45.0; H, 4.4.

8. *1-Isonicotinyl-1-isopropylhydrazine dihydrochloride.* A mixture of 15 g. of isopropylhydrazine hydrochloride,[6] 75 ml. of acetone, and 10 ml. of methanol is refluxed for 30 minutes. The excess solvents are removed under a vacuum and the residue is dissolved in 150 ml. of pyridine. Isonicotinyl chloride hydrochloride (25 g.) is added to the pyridine solution and the mixture is heated on a steam-bath for 30 minutes. The pyridine is removed under a vacuum and the residue is made alkaline with concentrated ammonium hydroxide. The mixture is evaporated to dryness and the residue is extracted with chloroform. The chloroform solution is distilled and the fraction boiling at 130–140° at 0.3 mm. is collected, dissolved in 2-propanol, filtered, and treated with ethanolic hydrogen chloride to precipitate 11 g. of the desired dihydrochloride. Upon recrystallization from a methanol-propanol-2 mixture, it is obtained in the form of white crystals which melt with decomposition at 191–193°.

Anal. Calc'd for $C_9H_{13}N_3O \cdot 2\ HCl$: C, 42.9; H, 6.0. Found: C, 43.0; H, 6.3.

The *free base* is obtained in the form of white needles from ligroin; m.p. 105–106°.

Anal. Calc'd for $C_9H_{13}N_3O$: C, 60.4; H, 7.3. Found: C, 60.6; H, 7.1.

9. *1-Isonicotinyl-1-benzylhydrazine.* In an open flask, a mixture of 3 g. of 1-isonicotinyl 1-benzyl-2-benzylidenehydrazine[5] and 40 ml. 0.5 *N* hydrochloric acid is boiled until the odor of benzaldehyde is gone (2–3 hours). Water is added to the mixture during the boiling to maintain the original liquid level. When no more benzaldehyde odor is detectable, the mixture is evaporated to dryness and 10 ml. of concentrated ammonium hydroxide is added to the residue. An oily layer is formed which is extracted with chloroform, partially clarified with decolorizing carbon, and heated under a vacuum to remove the chloroform. The gummy solid which remains is recrystallized from carbon tetrachloride to give white crystals of the desired base melting at 99.5–100°.

Anal. Calc'd for $C_{13}H_{13}N_3O$: C, 68.7; H, 5.7. Found: C, 68.4; H, 5.3.

A solution of the free base in ethanol, on treatment with oxalic acid, gives white crystals of the *monoöxalate* which melt with decomposition at 148–149°.

Anal. Calc'd for $C_{13}H_{13}N_3O \cdot H_2C_2O_4$: C, 56.7; H, 4.7. Found: C, 56.7; H, 4.8.

ALKYL-ACYL DERIVATIVES

10. *1,2-Diisonicotinyl-1,2-dimethylhydrazine.* To a solution of 13.6 g. of 1,2-dimethylhydrazine[7] in 100 ml. of dry pyridine is added 17.8 g. of isonicotinyl chloride hydrochloride. Heat is liberated and heating is continued on a steam-bath for 30 minutes. The pyridine then is removed under a vacuum and the solid residue is treated with saturated potassium carbonate solution. The oily phase which separates is removed and the aqueous layer is extracted four times with chloroform. The combined oil and chloroform extracts are evaporated under a vacuum and the residue is redissolved in chloroform; the chloroform solution is filtered and the chloroform is removed to yield 14 g. of the desired product. On recrystallization from ethyl acetate and then from a benzene-ligroin (70°) mixture, the substance is obtained in the form of colorless needles which melt at 148–149°.

Anal. Calc'd for $C_{14}H_{14}N_4O_2$: C, 62.2; H, 5.2. Found: C, 62.2; H, 5.2.

11. *1,2-Diisonicotinyl-1-methylhydrazine.* To a solution of 4.6 g. of methylhydrazine in 200 ml. of dry pyridine is added, portionwise, 35 g. of isonicotinyl chloride hydrochloride. Heat is liberated and heating is continued on a steam-bath for one hour. The pyridine is removed under a vacuum and the residue is dissolved in concentrated ammonium hydroxide. The solid left after removal of the ammonium hydroxide is extracted with chloroform and the chloroform solution is evaporated to dryness. Upon recrystallization from 2-propanol, 14 g. of the desired product is obtained in the form of cream-colored crystals which melt at 165–166.5° and are soluble in benzene, ethyl acetate, and in ether.

Anal. Calc'd for $C_{13}H_{12}N_4O_2$: C, 61.0; H, 4.7. Found: C, 60.9; H, 4.3.

The compound was also prepared by treating a pyridine solution of 1-isonicotinyl-2-methylhydrazine with isonicotinyl chloride hydrochloride.

12. *1,2-Diisonicotinyl-2-carbethoxymethylhydrazine dioxalate.* A mixture of 10 g. of ethyl hydrazinoacetate hydrochloride,[8] 100 ml. of dry pyridine, and 11.6 g. of isonicotinyl chloride hydrochloride is interacted as described in Experiment 10 above. The residue remaining after removal of the chloroform is dissolved in 2-propanol and precipitated as the oxalate with oxalic acid. Upon recrystallization from 2-propanol the desired product is obtained in the form of white crystals which are soluble in water and in hot alcohol; insoluble in benzene and in ethyl acetate and melt at 197–197.5°.

Anal. Calc'd for $C_{16}H_{16}N_4O_4 \cdot 2\ H_2C_2O_4$: C, 47.2; H, 3.9; equiv. wt., 127. Found: C, 47.2; H, 4.1; equiv. wt., 130.

ALKYLIDENE DERIVATIVES

The compounds in this category are all prepared by the same general method: a mixture of 0.1 mole of isonicotinylhydrazine, 0.1 mole of the ketone or aldehyde, and 100 ml. of 2-propanol is refluxed for about 3 hours. The solvent then is removed and the product is recrystallized from the appropriate solvent.

(6) Lochte, Noyes, and Bailey, *J. Am. Chem. Soc.*, **44**, 2562 (1922).

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

(8) Bailey and Read, *J. Am. Chem. Soc.*, **36**, 1756 (1914).

13. *1-Isonicotinyl-2-[1-(4-pyridyl)ethylidene]hydrazine.* Isonicotinylhydrazine and methyl 4-pyridyl ketone[9] are interacted as described above. The product crystallizes from 2-propanol in the form of white needles which melt at 171–172° and are soluble in warm alcohol, warm dioxane, and in dilute hydrochloric acid. The substance is very slightly soluble in water, and is insoluble in benzene and in acetone.

Anal. Calc'd for $C_{13}H_{12}N_4O$: C, 65.0; H, 5.0. Found: C, 65.2; H, 5.0.

14. *1-Isonicotinyl-2-[1-(4-pyridyl)propylidene]hydrazine.* Isonicotinylhydrazine and ethyl 4-pyridyl ketone[10] are interacted as described above. The product crystallizes from dioxane in the form of white granular crystals which melt at 186.5–188.5° and are soluble in the common alcohols and are insoluble in water, benzene, and in ether.

Anal. Calc'd for $C_{14}H_{14}N_4O$: C, 66.2; H, 5.5. Found: C, 66.1; H, 5.3.

15. *1-Isonicotinyl-2-[1-methyl-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)allylidene]hydrazine.* Isonicotinylhydrazine and β-ionone are interacted as described above. The product crystallizes from 2-propanol in the form of white needles which melt at 175.5–176.5° and which are soluble in warm alcohols and in warm ethyl acetate and are insoluble in ether and in water.

Anal. Calc'd for $C_{19}H_{25}N_3O$: C, 73.4; H, 8.1. Found: C, 73.1; H, 7.7.

16. *1-Isonicotinyl-2-(1,5,9-trimethyl-2,4,8-decatrien-1-ylidene)hydrazine.* Isonicotinylhydrazine and pseudoionone are interacted as described above. The product crystallizes from ethyl acetate in the form of yellow crystals which melt at 145–146° and which are soluble in warm alcohol and are insoluble in water, benzene, and in ether.

Anal. Calc'd for $C_{19}H_{25}N_3O$: C, 73.4; H, 8.1. Found: C, 73.1; H, 7.8.

17. *1-Isonicotinyl-2(3,7-dimethyl-2,6-octadien-1-ylidene)-hydrazine.* Isonicotinylhydrazine and citral are interacted as described above. The product crystallizes from ethyl acetate in the form of white needles which melt at 126–127° and which are soluble in warm alcohol and in benzene and are insoluble in ligroin.

Anal. Calc'd for $C_{16}H_{21}N_3O$: C, 70.9; H, 7.8. Found: C, 70.9; H, 7.4.

BIS(ISONICOTINYLHYDRAZINE) DERIVATIVES

The compounds in this category are prepared by the same general method: a mixture of 0.2 mole of isonicotinylhydrazine and 0.1 mole of the dialdehyde or diketone in about 300 ml. of a solvent such as 2-propanol or methanol containing a trace of acid (*ca.* 1 ml. dilute hydrochloric acid) is heated on a steam-bath. The product precipitates out practically quantitatively and in pure form as the reaction proceeds.

18. *N,N'-Ethylidene bis(isonicotinylhydrazine).* Isonicotinylhydrazine and aqueous glyoxal are interacted as described above. The white microcrystalline product does not melt under 320° and is insoluble in all common solvents except dilute hydrochloric acid and dilute sodium hydroxide.

Anal. Calc'd for $C_{14}H_{12}N_6O_2$: C, 56.8; H, 4.1. Found: C, 57.2; H, 4.0.

19. *N,N'-(1,2-Dimethylethylenidene)bis(isonicotinylhydrazine).* Isonicotinylhydrazine and diacetyl are interacted as described above. The white crystalline product melts at 280.5–281.5° and is insoluble in all common solvents except dilute hydrochloric acid and dilute sodium hydroxide.

Anal. Calc'd for $C_{16}H_{16}N_6O_2$: C, 59.3; H, 4.9. Found: C, 59.7; H, 4.6.

20. *N,N'-(1,4-Dimethyltetramethylenidene)bis(isonicotinylhydrazine) hemihydrate.* Isonicotinylhydrazine and acetonylacetone are interacted as described above. The white microcrystalline product melts at 165.5–167.5° and is insoluble in water and in all common organic solvents. It can be dissolved in mixtures such as water-ethanol and water-pyridine but does not come out of such solutions.

Anal. Calc'd for $C_{18}H_{20}N_6O_2 \cdot {}^1/_2\,H_2O$: C, 59.8; H, 5.8. Found: C, 59.4; H, 5.6.

21. *5,5-Bis(1-isopropyl-2-isonicotinylhydrazino)barbituric acid dihydrate.* A clear solution of 17.9 g. of 1-isonicotinyl-2-isopropylhydrazine in 60 ml. of water is mixed with a solution of 8 g. of alloxan in 40 ml. of water. The mixture is cooled and the white crystalline product, which melts with decomposition at 130–131°, precipitates.

Anal. Calc'd for $C_{22}H_{26}N_8O_5 \cdot 2H_2O$: C, 51.0; H, 5.8. Found: C, 51.1; H, 5.8.

CONCLUSION

From previous studies[1–5] in this series, it is clear that the powerful *in vivo* tuberculostatic activity of isonicotinylhydrazine is largely maintained through a wide variation in structure. We have shown that one or both N^2 hydrogens of the hydrazine moiety can be replaced by a variety of groups with—most often—but little loss of activity. On the other hand, replacement of the N^1 hydrogen appears to be largely detrimental.[5] This has been partially confirmed in the present study since the trialkyl derivatives of isonicotinylhydrazine described here are either inactive or weakly active and of the three N^1 monoalkyl derivatives, two are much less active than their N^2 substitution isomers. The notable exception to the rule is 1-isonicotinyl-1-isopropylhydrazine which maintains a high order of activity.

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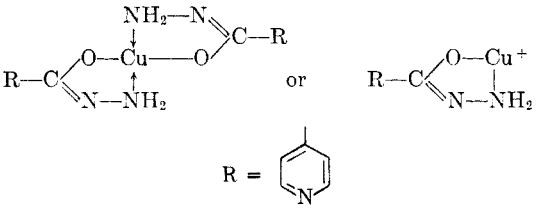
ADDENDUM

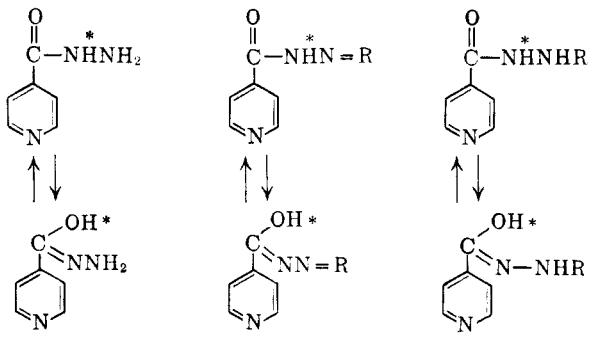
Subsequent to the completion of this paper, our attention was called to the report of J. Cymerman-Craig, D. Willis, S. D. Rubbo, and Janice Edgar, in *Nature*, **176**, 34(July 2, 1955) which attempts to relate the anti-tuberculous activity of isoniazid (isonicotinylhydrazine) to its ability to form chelates of the following type with copper:



The idea that copper chelation might be responsible for the activity of isoniazid has been advanced repeatedly on purely speculative grounds. In support of this idea, Cymerman-Craig and his co-workers point out that isoniazid and its N^2-alkylidene and N^2-alkyl derivatives are all highly active compounds which form complexes with copper and have a labile hydrogen atom on the N^1 nitrogen which can engage in tautomeric interchange with the carbonyl oxygen.

(9) Kolloff and Hunter, *J. Am. Chem. Soc.*, **63**, 490 (1941).

(10) Burrus and Powell, *J. Am. Chem. Soc.*, **67**, 1470 (1945).



On this basis, they state, "It is therefore clear that the ability to form chelate complexes ..... depends on the asterisked hydrogen atom ... and the substitution of this hydrogen, for example by methyl, will produce compounds unable to form such complexes." To substantiate this experimentally, they prepared 1-isonicotinyl-1-methylhydrazine (which we have reported in this paper as compound I) and two of its alkylidene derivatives. Since all three compounds proved to be comparatively inactive, they suggest "that the anti-tuberculous action of isoniazid compounds may be related to their ability to form chelate complexes ..... and that inability to form such complexes results in disappearance of activity."

This judgment is substantially in accord with our own findings. In a previous paper,[5] we showed that amongst the dialkyl derivatives of isonicotinylhydrazine, those with N^1 substitution were of a much lower order of activity. Similarly, in the present paper, we have shown that the trialkyl derivatives are uniformly weak or inactive and that in addition to the N^1-methyl, the N^1-benzyl derivative (compound II) is also relatively inactive.

Up to this point, all the evidence coincides remarkably well with the theory. Unfortunately (for the theory, that is) the N^1-isopropyl derivative (compound III) is highly active and yet has no labile hydrogen atom in the N^1 position, nor does it form a copper complex.

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