[CONTRIBUTION NO. 346 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LAROCHE, INC.]

SYNTHETIC TUBERCULOSTATS. VIII. ACYL DERIVATIVES OF ISONICOTINYL HYDRAZINE

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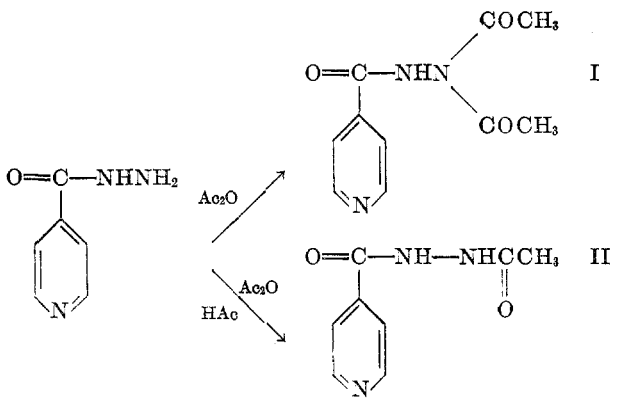
The *in vivo* tuberculostatic activity of 1,2-diisonicotinyl hydrazine (1) indicated that acylation of isonicotinyl hydrazine did not necessarily destroy activity. In continuation of the study of derivatives of isonicotinyl hydrazine (2–4), therefore, a series of acyl derivatives were prepared and tested. In the main, the acyl derivatives proved to be highly tuberculostatic though somewhat less so than isonicotinyl hydrazine itself.

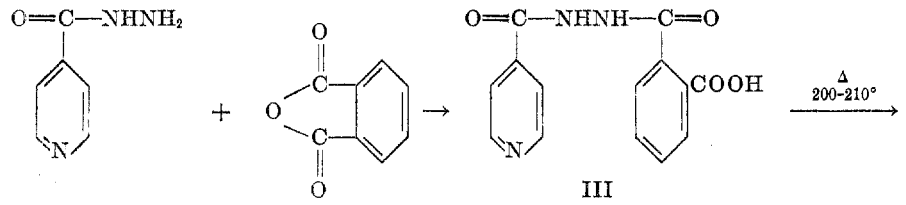
Most of the compounds in this series were prepared by the action of the appropriate acid chloride or acid anhydride on isonicotinyl hydrazine. When, however, isonicotinyl hydrazine was treated with an excess of acetic anhydride a diacetyl derivative, namely, 1-isonicotinyl-2,2(?)-diacetylhydrazine (I), was obtained. To obtain the monoacetyl derivative II the isonicotinyl hydrazine was treated with slightly more than one equivalent of acetic anhydride with glacial acetic acid as a diluent.



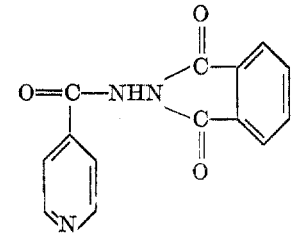
The two compounds could not readily be distinguished from each other since they had similar physical properties and the same melting points. A mixture of the two, however, gave a depressed melting point.

Treatment of isonicotinyl hydrazine with phthalic anhydride did not give the phthaloyl derivative directly. Instead, 1-isonicotinyl-2-(*o*-carboxybenzoyl) hydrazine (III) was formed which could be cyclized to 1-isonicotinyl-2-phthaloyl hydrazine (IV) by heating at 200–210°.

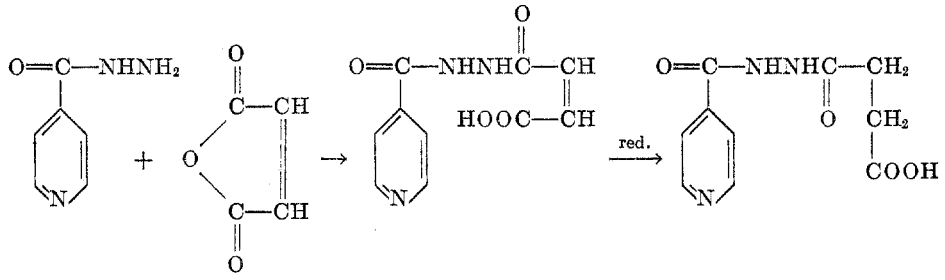
Similarly, maleic anhydride gave 1-isonicotinyl-2-(β-carboxyacrylyl) hydrazine (V) which, however, could not be made to cyclize on heating. Reduction of V gave 1-isonicotinyl-2-(β-carboxypropionyl) hydrazine (VI).



III

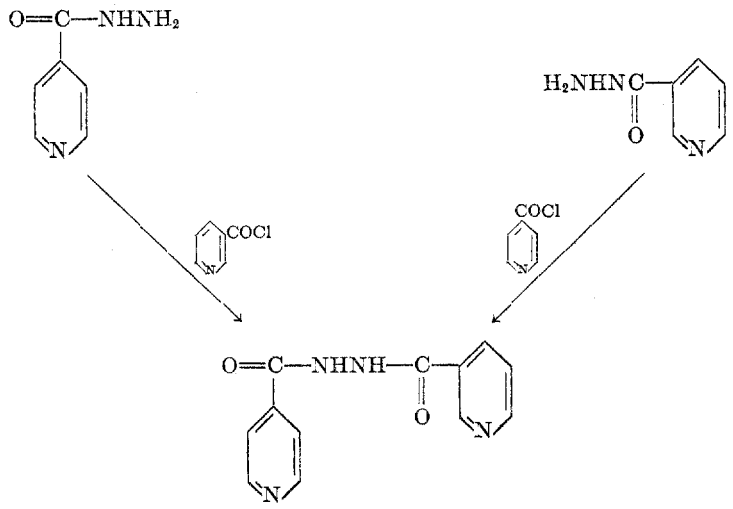


IV



V VI

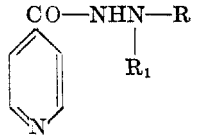
1-Isonicotinyl-2-nicotinyl hydrazine (VII) was prepared both by the action of isonicotinyl chloride on nicotinyl hydrazine and by the action of nicotinyl chloride on isonicotinyl hydrazine.

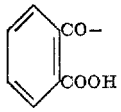
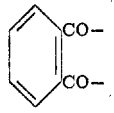
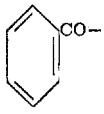
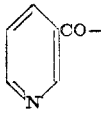
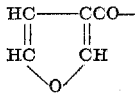


VII

TABLE I

Acyl Derivatives of Isonicotinyl Hydrazine



R	R_1	M.P., °C. (corr.)	Analyses						Preparation[a]	Remarks
			Calc'd			Found				
			C	H	N	C	H	N		
CH_3CO-	H	162–163	53.6	5.0	23.5	53.9	4.9	23.5	E	Colorless needles. V. sol. H_2O, alcohol; sol. hot ethyl acetate
CH_3CO-	$CH_3C(=O)-O$	161–163			19.0			19.1	A	Colorless needles. M. W. calc'd, 221; M. W. found, 222 (perchloric acid titration). V. sol. H_2O, alcohol; sol. hot ethyl acetate
CH_3CH_2CO-	H	130.5–131.5	56.0	5.7		56.2	5.6		A	Colorless flakes. V. sol. H_2O, alcohol; sol. hot ethyl acetate
$CH_3CH_2CH_2CO-$	H	139–139.5	58.0	6.2		58.3	6.1		A & B	White needles. Sol. H_2O, alcohol, hot ethyl acetate
$CH_3(CH_2)_{16}CO-$	H	125–126	71.5	10.2		71.4	10.4		B	White needles or flakes. Sol. alcohol, $CHCl_3$, hot benzene. Insol. H_2O
$CH_3(CH_2)_{14}CO-$	H	117–119	70.4	9.9		70.7	9.5		B	Colorless flakes. Sol. alcohol, $CHCl_3$, hot benzene, insol. H_2O
	H	178.5	59.0	3.9		58.9	3.6		A	White crystals Insol. all common solvents. Sol. dil. HCl, dil. NaOH
		223.5–225.5	62.9	3.4		62.9	3.4		E	White granules. Insol. H_2O. Sol. alcohol
HOOCCH=CHCO—	H	Indef.	51.0	3.8		51.3	3.9		A	White crystals. Sol. dil. HCl, dil. $NaHCO_3$ solution. Sl. sol. methanol. Insol. all other common solvents
$HOOCCH_2CH_2CO-$	H	223.5–224.5	50.6	4.6		50.0	4.4		E	White needles. Sol. pyridine, hot H_2O. Insol. alcohol, cold H_2O
	H	227.5–228.5	64.6	4.6		64.5	4.6		A	White needles. Insol. H_2O, cold alcohol. Sol. hot H_2O, hot methanol
	H	225–226	59.5	4.1		59.1	4.1		E	White needles. Sol. hot H_2O, methanol, hot butyl acetate. Insol. cold H_2O, cold butyl acetate
	H	219.5–220	57.1	3.9		56.9	4.5		B	White needles. Sol. dil. HCl, dil. NH_4OH, hot butyl acetate. Sl. sol. alcohol, H_2O

[a] Note. A refers to Method A, B to Method B; E, see experimental for details.

The compounds prepared in this series are listed in Table I. All the melting points are corrected.

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EXPERIMENTAL

The acyl derivatives of isonicotinyl hydrazine were prepared in the main by acylation (A) with acid anhydrides and (B) with acid chlorides. The general procedure used with each of these mthods was as follows:

(*A*). *Acylation with acid anhydrides.* Isonicotinyl hydrazine was added portionwise to about a 50–100% excess of the anhydride. If the anhydride was liquid, no solvent was used; if solid, the anhydride was dissolved in dioxane. Heat was frequently liberated as the reactants were mixed. When addition was complete, the reaction mixture was heated on a steam bath for 15–30 minutes and then cooled. In most cases, the product precipitated spontaneously though sometimes it was found desirable to precipitate the product with benzene or ether.

(*B*). *Acylation with acid chlorides.* One equivalent of the acid chloride in dry dioxane solution was added slowly with stirring to a refluxing mixture of isonicotinyl hydrazine in approximately 10 volumes of dry dioxane. When the addition was complete, heating was continued for ½ to 1 hour. The precipitate was filtered, dissolved in water, and the water solution was made alkaline with dilute ammonium hydroxide. On acidification with dilute acetic acid the desired product precipitated.

1-Isonicotinyl-2-acetylhydrazine. To 20 g. of isonicotinyl hydrazine suspended in warm glacial acetic acid was added 15 cc. of acetic anhydride. The resulting solution was heated on a steam-bath for ½ hour and was then treated with 180 cc. of benzene. On cooling and scratching, the product precipitated. Recrystallization from a mixture of propanol-2 and ethyl acetate gave colorless needles, m.p. 162–163°. A mixture melt with the diacetyl derivative melted at 150–154° with previous softening.

1-Isonicotinyl-2-phthaloyl hydrazine. 1-Isonicotinyl-2-(*o*-carboxybenzoyl) hydrazine (5 g.) was heated in an oil-bath at 200–210° (bath temperature) for 15 minutes. The melt on cooling solidified to give the cyclized product. Recrystallization from propanol-2 gave white granular crystals, m.p. 223.5–225.5°.

1-Isonicotinyl-2-(β-carboxypropionyl)hydrazine. A methanolic solution of 4.8 g. of 1-isonicotinyl-2-(β-carboxyacrylyl)hydrazine was reduced with hydrogen at 50 p.s.i. and 60° in the presence of a platinum catalyst. When one mole-equivalent of hydrogen had been absorbed the mixture was filtered, the methanol was removed under a vacuum, and the solid residue was recrystallized from water to give fine white needles, m.p. 223.5–224.5°.

1-Isonicotinyl-2-nicotinyl hydrazine. To a suspension of 16 g. of isonicotinyl hydrazine in about 100 cc. of dry pyridine was added, portionwise, a solution of 16 g. of nicotinyl chloride in 30 cc. of dry pyridine. Heat was evolved spontaneously. When the addition was complete, the pyridine was removed under a vacuum. The solid residue on recrystallization from butyl acetate gave fine white needles of the product, m.p. 225–226°.

The same product was also obtained as follows: To 16 g. of nicotinyl hydrazine in 100 cc. of hot pyridine was added, dropwise, 25 g. of isonicotinyl chloride hydrochloride in 300 cc. of pyridine. The mixture was refluxed for 15 minutes and the pyridine was removed under a vacuum after 10 cc. of concentrated ammonium hydroxide had first been added. The residue was recrystallized from water to give 25 g. of 1-isonicotinyl-2-nicotinyl hydrazine, m.p. 224.5–225.5°.

CONCLUSION AND SUMMARY

A series of acyl derivatives of isonicotinyl hydrazine was prepared and studied for tuberculostatic activity. None of the compounds was as active as isonicotinyl hydrazine itself in mice infected with human strain H37Rv.

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(1) FOX AND GIBAS, *J. Org. Chem.*, **17,** 1653 (1952).
(2) FOX AND GIBAS, *J. Org. Chem.*, **18,** 983 (1953).
(3) FOX, *J. Org. Chem.*, **18,** 990 (1953).
(4) FOX AND GIBAS, *J. Org. Chem.*, **18,** 994 (1953).