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SYNTHETIC TUBERCULOSTATS. VI.
SOME SUGAR DERIVATIVES OF ISONICOTINYLHYDRAZINE

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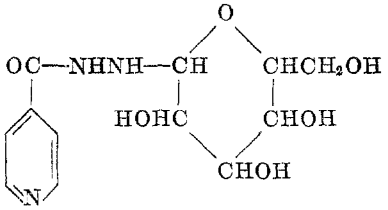
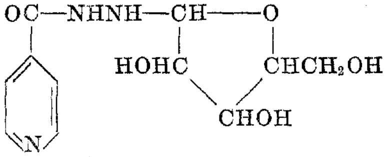
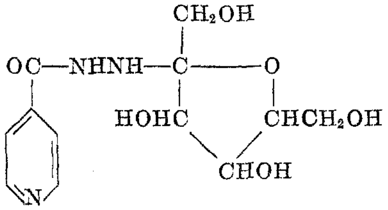
The activity of the 1-isonicotinyl-2-alkylidenehydrazines (1) suggested the desirability of preparing some sugar derivatives in the hope of effecting a decrease in toxicity. Accordingly, isonicotinylhydrazine was condensed with D-glucose (I) and D-galactose (II) as representative of the aldohexoses; with D-xylose (III) and D-ribose (IV) as representative of the aldopentoses and with D(−)fructose (V) as an example of the ketohexoses. All of the sugar derivatives were active and were markedly less toxic than the parent isonicotinyl hydrazine.



I = Glucosyl
II = Galactosyl

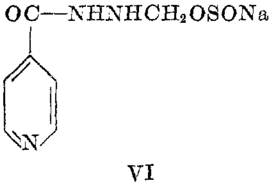


III = Xylosyl
IV = Ribosyl

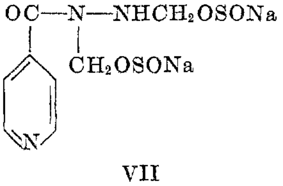


V = Fructosyl

Another method of detoxifying chemotherapeutic substances possessing amino groups which has at times been successful, lay in the use of sodium formaldehyde sulfoxylate. Isonicotinylhydrazine was therefore condensed with one and two moles of sodium formaldehyde sulfoxylate to give sodium isonicotinylhydrazinomethanesulfinate (VI) and disodium α,α'-(?)-(isonicotinylhydrazo)bis(methanesulfinate) (VII) respectively.



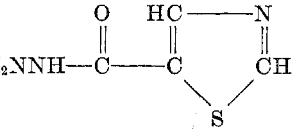
VI



VII

Both compounds were very actively tuberculostatic and relatively atoxic.

The oft-suggested equivalency of sulfur and the ethylenic link was tested by substituting the thiazole for the pyridine ring. The substitution was effected by preparing 5-thiazolecarboxylic acid hydrazide (VIII) which proved to be very toxic and inactive at its tolerated dose.



VIII

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EXPERIMENTAL

All the melting points are corrected.

1. *1-Isonicotinyl-2-*D*-glucosylhydrazine.* A mixture of 137 g. (1 mole) of isonicotinyl hydrazine, 180 g. (1 mole) of anhydrous D-glucose, and 1000 cc. of methanol was refluxed until solution was complete. The reaction mixture was filtered and then cooled to precipitate 1-isonicotinyl-2-D-glucosyl hydrazine in two crystalline forms: (a) fine white needles, and (b) hard colorless granules. The precipitate was removed and on evaporating the filtrate to dryness, the rest of the product was obtained in quantitative yield. The compound decomposed at 160° with previous softening and darkening and was very soluble in water, soluble in methanol, and insoluble in most of the other organic solvents.

Anal. Calc'd for $C_{12}H_{17}N_3O_6$: C, 48.2; H, 5.7.
Found: C, 48.0; H, 5.5.

2. *1-Isonicotinyl-2-*D*-galactosylhydrazine.* A mixture of 13.7 g. (0.1 mole) of isonicotinylhydrazine, 18.0 g. (0.1 mole) of anhydrous D-galactose, and 100 cc. of methanol was refluxed to solution. The solution was then concentrated to about 30 cc. and was allowed to stand in the refrigerator overnight, during which period it gelled. It was therefore heated on a steam-bath and hot propanol-2 was slowly added until crystallization was complete. The small colorless crystals of 1-isonicotinyl-2-D-galactosylhydrazine decomposed at 154.5–156° with previous darkening.

Anal. Calc'd for $C_{12}H_{17}N_3O_6$: C, 48.2; H, 5.7.
Found: C, 48.1; H, 6.0.

3. *1-Isonicotinyl-2-*D*-xylosylhydrazine.* A mixture of 13.7 g. (0.1 mole) of isonicotinylhydrazine, 15 g. of D-xylose, and 100 cc. of methanol was refluxed to solution. The methanol was then removed under a vacuum and the viscous residue was solidified by further drying in a vacuum-desiccator. The 1-isonicotinyl-2-D-xylosylhydrazine was obtained in the form of a hemi-methanolate which had no definite melting point but was completely melted below 100°.

Anal. Calc'd for $C_{11}H_{15}N_3O_5 \cdot \frac{1}{2}CH_3OH$: C, 48.4; H, 6.0.
Found: C, 48.3; H, 6.3.

4. *1-Isonicotinyl-2-*D*-ribosylhydrazine.* A mixture of 13.7 g. (0.1 mole) of isonicotinylhydrazine, 15 g. of D-ribose, and 100 cc. of methanol was reacted as described in Experiment 3 above to give 1-isonicotinyl-2-D-ribosyl hydrazine methanolate which melted indefinitely below 100°.

Anal. Calc'd for $C_{11}H_{15}N_3O_5 \cdot CH_3OH$: C, 47.8; H, 6.3.
Found: C, 48.0; H, 5.7.

5. *1-Isonicotinyl-2-*D*(−)fructosylhydrazine.* A mixture of 13.7 g. (0.1 mole) of isonicotinylhydrazine, 18 g. of D(−)-fructose, and 100 cc. methanol was refluxed to solution. The

methanolic solution was concentrated to a small volume, and was treated with about 150 cc. of propanol-2 and concentrated again. The resulting concentrate was diluted with another 150 cc. of propanol-2 and the solution was then poured into about 700 cc. of ether to give a white flocculent precipitate. The supernatant ethereal solution was decanted and fresh ether was added. The mixture was stirred for about one-half hour, filtered, and the precipitate was quickly transferred to a vacuum-desiccator for drying. The dry 1-isonicotinyl-2-D(−)fructosyl hydrazine monohydrate was obtained as a cream-colored powder which melted indefinitely below 90°.

Anal. Calc'd for $C_{12}H_{17}N_3O_6 \cdot H_2O$: C, 45.5; H, 6.0.
Found: C, 45.6; H, 6.2.

6. *Sodium isonicotinylhydrazinomethanesulfinate.* A mixture of 274 g. (2 moles) of isonicotinylhydrazine and 308 g. (2 moles) of sodium formaldehyde sulfoxylate dihydrate in 1400 cc. of methanol was heated to solution. The slightly hazy solution was filtered through Celite and the practically clear filtrate was slowly added, with vigorous stirring, to 6 liters of acetone to produce a fine flocculent precipitate. When the addition of the methanolic solution was complete, an additional 4 l. of acetone was added and the mixture was stirred for about one-half hour longer. The precipitated sodium isonicotinylhydrazinomethanesulfinate was filtered off, washed with ether, and promptly placed in a vacuum-desiccator to dry. Yield, 448 g. of a cream-colored powder which had no definite melting point. In different batches, the product has been obtained in various states of hydration and in the anhydrous form.

Anal. Calc'd for $C_7H_8N_3NaO_3S$: C, 35.4; H, 3.4; Na, 9.4.
Found: C, 35.3; H, 3.9; Na, 10.1.
Calc'd for $C_7H_8N_3NaO_3S \cdot \frac{1}{2}H_2O$: C, 34.1; H, 3.7; Na, 9.3.
Found: C, 34.2; H, 4.1; Na, 9.5.
Calc'd for $C_7H_8N_3NaO_3S \cdot 1\frac{1}{2}H_2O$: C, 31.8; H, 4.2.
Found: C, 31.8; H, 4.0.
Calc'd for $C_7H_8N_3NaO_3S \cdot 2\frac{1}{2}H_2O$: C, 29.8; H, 4.6.
Found: C, 29.7; H, 3.8.

7. *Disodium α,α′-(isonicotinylhydrazo)bis(methanesulfinate) sesquihydrate.* A mixture of 27.4 g. (0.2 mole) of isonicotinylhydrazine and 6.16 g. (0.4 mole) of sodium formaldehyde sulfoxylate in 200 cc. of methanol was heated to solution and a small quantity of a white crystalline material which failed to dissolve was filtered off. The clear solution was then added with vigorous stirring to 850 cc. of acetone to produce a flocculent precipitate. When addition was complete, 570 cc. of additional acetone was added and the mixture was stirred for about one-half hour longer. The precipitated disodium α,α′-(isonicotinylhydrazo)bis(methanesulfinate) was filtered off, washed with ether and quickly placed in a vacuum-desiccator to dry, since overlong exposure of the wet material to moist air results in marked deliquescence. Yield, 63 g. of a cream-colored powder which decomposed at 206–207°.

Anal. Calc'd for $C_8H_9N_3Na_2O_5S_2 \cdot 1\frac{1}{2}H_2O$: C, 26.4; 3.3.
Found: C, 26.7; H, 4.0.

8. *5-Thiazolecarboxylic acid hydrazide.* To 31 g. of ethyl 5-thiazolecarboxylate prepared according to the method of Erlenmeyer and Marbet [*Helv. Chim. Acta,* **29,** 1946 (1946)] there was added with shaking 16.5 cc. of hydrazine hydrate (85%). Heat was evolved and the mixture solidified. Upon recrystallization from methanol, and then propanol-2, white needles of 5-thiazolecarboxylic acid hydrazide (12 g.) were obtained which melted at 165.5–167.5°.

Anal. Calc'd for $C_4H_5N_3OS$: C, 33.6; H, 3.5.
Found: C, 33.9; H, 3.4.

Conclusion. The aldohexose, aldopentose, and ketohexose derivatives of isonicotinylhydrazine prepared in this study are very active and relatively atoxic tuberculostats. The aldohexose derivatives, namely, 1-isonicotinyl-2-D-glycosylhydrazine (I) and 1-isonicotinyl-2-D-galactosylhydrazine (II) are readily prepared in pure crystalline form. The aldopentose derivatives, 1-isonicotinyl-2-D-xylosylhydrazine (III) and 1-isonicotinyl-2-D-ribosylhydrazine (IV), and the ketohexose, 1-isonicotinyl-2-D(−)-fructosylhydrazine (V) are more difficult to prepare and are less stable.

Sodium isonicotinylhydrazinomethane sulfinate (VI) and the disubstituted, disodium α,α'(?)-(isonicotinylhydrazo)bis(methanesulfinate) (VII) are stable, very active and relatively atoxic compounds.

SUMMARY

A series of aldohexose, aldopentose, ketohexose, and sodium formaldehyde sulfoxylate derivatives of isonicotinyl hydrazine were prepared and studied for *in vivo* activity in mouse tuberculosis. All of the compounds were very active and relatively atoxic.

5-Thiazolecarboxylic acid hydrazide was inactive at its tolerated dose.

NUTLEY 10, N. J.

REFERENCE

1. FOX AND GIBAS, *J. Org. Chem.*, **18**, Paper V, this issue (1953).