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ANTITUBERCULAR AGENTS. DERIVATIVES OF PYRIDINECARBOXYLIC ACID HYDRAZIDES

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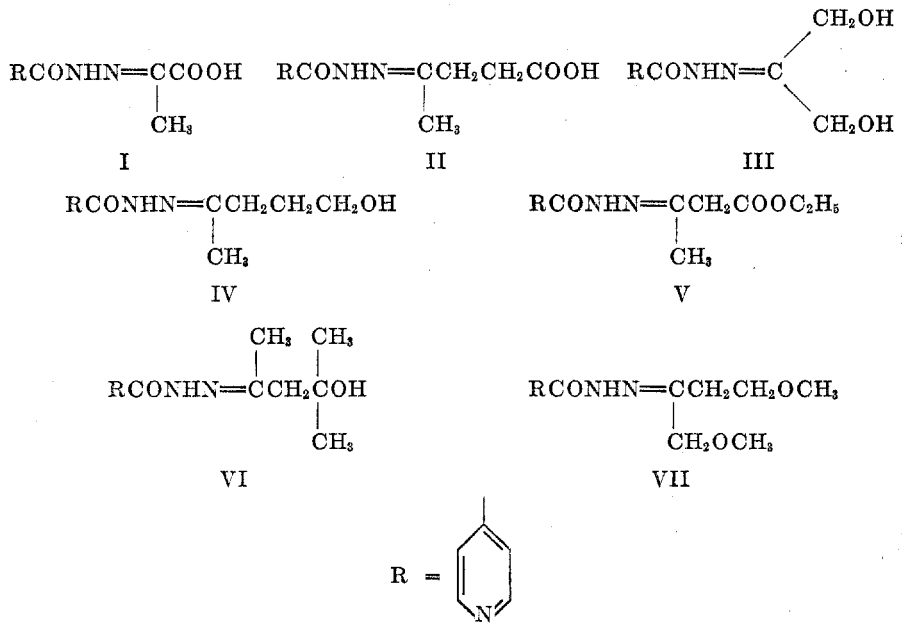
The finding of Grunberg and Schnitzer (1) that isonicotinic acid hydrazide ("Rimifon"® Roche) is a potent antitubercular drug prompted the investigation of derivatives of the hydrazide.

The present paper describes derivatives which result from the condensation of isonicotinic acid hydrazide with carbonyl compounds containing hydroxy and carboxyl groups. In this manner the following crystalline derivatives were obtained:

I 2-(Isonicotinylhydrazono)propionic acid[1]
II 4-(Isonicotinylhydrazono)valeric acid[1]
III 2-(Isonicotinylhydrazono)-1,3-propanediol
IV 4-(Isonicotinylhydrazono)-1-pentanol

The condensation products of isonicotinic acid hydrazide with ethyl acetoacetate (V), diacetone alcohol (VI), 1,4-dimethoxy-2-butanone (VII), were obtained as viscous liquids.

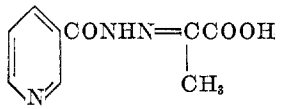


The properties of the new derivatives vary widely depending upon the substituting radicals. The compounds I and II are comparatively little soluble in

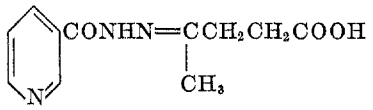
[1] Compounds I and II have been prepared in the meantime also by Carrara, *et al.* (2).

water, as is the dihydroxy derivative III. The low solubility of these alkylidene derivatives is quite unexpected, since groups such as hydroxyl and carboxyl in general enhance water solubility. Compound I appears to be a useful reagent for the detection of isonicotinic acid hydrazide. The non-crystalline derivatives V, VI, and VII are quite easily soluble in water.

In the nicotinic acid series, the unsaturated compounds VIII and IX are somewhat more soluble in water than the corresponding isonicotinic acid derivatives. However, they still crystallize from aqueous solutions.



VIII



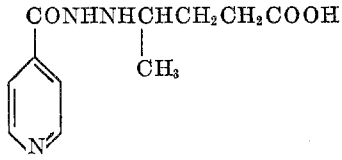
IX

Catalytic hydrogenation of compounds I–VII yielded the corresponding saturated compounds. In this manner the following compounds were obtained:

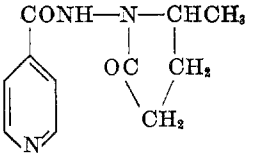
X 2-(Isonicotinylhydrazino)propionic acid (from I)
XI 4-(Isonicotinylhydrazino)valeric acid (from II)
XII 2-(Isonicotinylhydrazino)-1,3-propandiol (from III)
XIII 4-(Isonicotinylhydrazino)-1-pentanol (from IV)
XIV Ethyl 3-(Isonicotinylhydrazino)butyrate (from V)
XV 4-(Isonicotinylhydrazino)-2-methyl-2-pentanol (from VI)
XVI 1-Isonicotinyl-2-(1-methoxymethyl-3-methoxy-propyl)hydrazine (from VII)

The catalytic hydrogenation at temperatures below 100° stops after absorption of 1 mole of hydrogen. Only compound XII was obtained in crystalline form. The others gave crystalline salts with mineral acids. The isolation of compounds XIV, XV, and XVI is evidence for the constitution of the respective parent compounds, V, VI, and VII which, as mentioned above, could not be crystallized.

The acid XI gave a dihydrochloride which on warming was easily converted into the monohydrochloride of the pyrrolidone derivative XVII.



XI



XVII

According to the tests of Dr. R. J. Schnitzer and Dr. E. Grunberg, the new compounds are active against *M. tuberculosum* H37Rv. The unsaturated derivatives I–VII are more potent, perhaps because they can be hydrolyzed *in vivo* to isonicotinic acid hydrazide.

EXPERIMENTAL

The melting points are uncorrected.

1. *2-(Isonicotinylhydrazono)propionic acid* (I). A solution of 13.7 g. (0.1 mole) of isonicotinic acid hydrazide in 200 ml. of water was mixed with a solution of 10 g. (0.11 mole)

of pyruvic acid in 20 ml. of water. The mixture warmed up and almost immediately the condensation product crystallized. The yield of the colorless product of m.p. 213° was 20 g. (96%). It is very little soluble in hot water.

Anal. Calc'd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38.

Found: C, 51.88; H, 4.27.

The compound is so little soluble in water that the reaction may be used as a convenient test for the presence of isonicotinic acid hydrazide. A 0.2% solution of isonicotinic acid hydrazide in water gives, within a minute, a fine crystalline precipitate when mixed with a drop of pyruvic acid. With lower concentrations of the hydrazide this reaction is not reliable.

Compound I dissolves in hot methanol. However, from such solutions it did not crystallize unchanged. The resulting material always melted lower than the starting material.

2. *4-(Isonicotinylhydrazono)valeric acid* (II). To a warm solution of 13.7 g. (0.1 mole) of isonicotinic acid hydrazide in 150 ml. of water, a freshly prepared solution of 13 g. (0.11 mole) of levulinic acid in 50 ml. of water was added slowly. Before addition was complete crystallization of the condensation product started. After 3 hours the compound was filtered and washed with cold water. The yield was 23 g. (97%) of m.p. 221–222°. The material is practically pure. It can be purified further by crystallization from hot water, in which it is not very soluble.

Anal. Calc'd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86.

Found: C, 56.17; H, 5.20; N, 18.02.

3. *2-(Isonicotinylhydrazono)-1,3-propanediol* (III). A solution of 20 g. (0.146 mole) of isonicotinic acid hydrazide in 100 ml. of hot water (about 80°) was added slowly to a solution of 9 g. (0.15 mole) of dihydroxyacetone in 50 ml. of water kept at about 25°. After a few minutes, crystallization started. The material was recrystallized from water, yielding 20 g. (65%) of compound III, m.p. 154°.

Anal. Calc'd for $C_9H_{13}N_3O_3$: C, 51.67; H, 5.30.

Found: C, 51.73; H, 5.27.

When the condensation was carried out in alcohol the product was yellow and the yield was lower.

4. *4-(Isonicotinylhydrazono)-1-pentanol* (IV). Solutions of 27.4 g. (0.2 mole) of isonicotinic acid hydrazide in 200 ml. of alcohol and of 22 g. (0.215 mole) of 4-pentanone-1-ol in 50 ml. of alcohol were mixed at room temperature. After standing overnight at room temperature the solution was distilled to dryness *in vacuo*. The crystalline residue was recrystallized from benzene yielding 22 g. (50%) of compound IV, m.p. 121°. It is quite soluble in water.

Anal. Calc'd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99.

Found: C, 59.63; H, 6.89; N, 18.65.

5. *2-(Isonicotinylhydrazino)propionic acid* (X). Compound I (40 g., 0.193 mole) was hydrogenated at 400 lbs. pressure and 50° in 200 ml. of methanol with 0.5 g. of platinum oxide. The solution was filtered hot from the catalyst. The filtrate on standing in the refrigerator yielded colorless crystals. The material was purified by crystallization from ethanol. A small amount of high-melting material remained undissolved and was filtered off. On cooling, the acid X crystallized slowly. The yield was 12 g. (30%) of m.p. 179–180°.

Anal. Calc'd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09.

Found: C, 51.90; H, 5.02; N, 20.44.

6. *4-(Isonicotinylhydrazino)valeric acid* (XI). The hydrogenation of compound II (Exp. 2) proceeded very slowly and was always incomplete. A typical experiment ran as follows: 30 g. (0.127 mole) of compound II was suspended in 400 ml. of methanol and hydrogenated with 0.5 g. of platinum oxide at 30°. The resulting solution was filtered from the catalyst and the clear filtrate was distilled to dryness. The syrupy residue was stirred up with 100 ml. of water. On standing in the refrigerator, 9 g. of unchanged starting material of m.p. 215–218° crystallized and was filtered off. The filtrate was again evaporated to dryness, leaving a clear colorless viscous oil. Since this could not be crystallized, it was dissolved in 200 ml. of ethanol. The solution was cooled to about +5° and was cautiously neutralized with alcoholic

hydrochloric acid. On standing, 7 g. of crystals of m.p. 166–168° were obtained. The compound is not very stable and the analyses are therefore not entirely satisfactory.

Anal. Calc'd for $C_{11}H_{15}N_3O_3 \cdot 2HCl$: C, 42.59; H, 5.52; Cl 22.86; N, 13.55.

Found: C, 44.42; H, 5.73; Cl 21.77; N, 13.43.

The dihydrochloride was dissolved in 150 ml. of boiling alcohol. The filtered solution did not yield crystals on standing at room temperature. The solution was concentrated to about 50 ml. and about 250 ml. of ether was added. On standing, 3.5 g. of needle-shaped crystals separated and were filtered. The compound melted at 195–197° and is according to the analysis N-(2-oxo-5-methyl-1-pyrrolidyl)isonicotinamide hydrochloride (XVII).

Anal. Calc'd for $C_{11}H_{13}N_3O_2 \cdot HCl$: C, 51.67; H, 5.52; N, 16.43.

Found: C, 51.34; H, 5.62; N, 16.24.

7. *2-(Isonicotinylhydrazino)-1,3-propanediol* (XII). Compound III (Exp. 3) (19 g., 0.09 mole) was hydrogenated in 280 ml. of methanol at 26° and 500 lbs. pressure with 0.5 g. of platinum oxide. The filtered solution was distilled *in vacuo* to dryness, leaving a yellowish oil which slowly solidified. Recrystallization from 150 ml. of isopropyl alcohol gave 14 g. (70%) of compound XII of m.p. 122–123°.

Anal. Calc'd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.90.

Found: C, 51.58; H, 6.28; N, 20.40.

8. *4-(Isonicotinylhydrazino)-1-pentanol* (XIII). A solution of 41 g. (0.3 mole) of isonicotinic acid hydrazide and of 34 g. (0.33 mole) of 4-pentanone-1-ol in 200 ml. of methanol was warmed to 50° for two hours to effect formation of the condensation product. The solution was then hydrogenated at 400 lbs. pressure at 30–40° with 0.5 g. of platinum oxide. The solution was evaporated and the oily residue was dissolved in 250 ml. of ethanol. The calculated amount of alcoholic hydrochloric acid was added, causing crystallization of the dihydrochloride of XIII. The material was filtered, washed thoroughly with alcohol and acetone, and dried over potassium hydroxide. The yield was 60 g. (79%) of m.p. 153–155°.

Anal. Calc'd for $C_{11}H_{17}N_3O_2 \cdot 2HCl$: C, 44.91; H, 5.83; N, 14.28.

Found: C, 45.24; H, 6.06; N, 13.97.

9. *Ethyl 3-(isonicotinylhydrazino)butyrate* (XIV). Isonicotinic acid hydrazide and ethyl acetoacetate condense in methanol to a non-crystalline compound (V). The hydrogenation product was prepared in the following manner: 13.7 g. (0.1 mole) of isonicotinic acid hydrazide and 14 g. (0.107 mole) of ethyl acetoacetate were dissolved in 50 ml. of methanol. The mixture was warmed for 2 hours to 50° to ensure condensation. After cooling, 0.1 g. of platinum oxide was added and the mixture was hydrogenated at 60° and 500 lbs. pressure. The solution was distilled to dryness. The oily residue was dissolved in 200 ml. of alcohol and was carefully neutralized at 5° with stirring with alcoholic hydrochloric acid. The hydrochloride of XIV crystallized immediately. It was filtered and recrystallized from about 700 ml. of abs. alcohol, yielding 15 g. (46%) of the pure dihydrochloride of m.p. 192–193°.

Anal. Calc'd for $C_{12}H_{17}N_3O_3 \cdot 2HCl$: C, 44.45; H, 5.91; N, 12.96.

Found: C, 44.48; H, 6.07; N, 12.99.

10. *4-(Isonicotinylhydrazino)-2-methyl-2-pentanol* (XV). To a solution of 26 g. (0.224 mole) of diacetone alcohol in 150 ml. of alcohol, 27.4 g. (0.2 mole) of isonicotinic acid hydrazide was added. On warming, a homogeneous solution formed which contained the non-crystalline compound VI. The solution was hydrogenated with 0.5 g. of platinum oxide at 30° and 500 lbs. pressure. The catalyst was filtered off and the solution was neutralized with alcoholic hydrochloric acid. The dihydrochloride of XV crystallized immediately. It was filtered and dried. The yield was 48 g. (77%) of m.p. 213–215°.

Anal. Calc'd for $C_{12}H_{19}N_3O_2 \cdot 2HCl$: C, 46.76; H, 6.21; N, 13.63.

Found: C, 47.33; H, 6.54; N, 13.97.

11. *1-Isonicotinyl-2-(1-methoxymethyl-3-methoxy-propyl)hydrazine* (XVI). Isonicotinic acid hydrazide (20 g., 0.146 mole) and 20 g. (0.15 mole) of 1,4-dimethoxy-2-butanone were warmed in 200 ml. of methanol. The solution, which contains the oily condensation product VII, was hydrogenated at 500 lbs. pressure and 50° with 0.5 g. of platinum oxide. On evapo-

ration, 76 g. of an oily material was obtained. This was dissolved in 400 ml. of acetone. Alcoholic hydrochloric acid was added until the yellow solution turned colorless. The hydrochloride of XVI crystallized and was filtered, washed with acetone, and dried. The yield of dihydrochloride of m.p. 180–181° was 40 g. (84%).

Anal. Calc'd for $C_{12}H_{19}N_3O_3 \cdot 2HCl$: C, 44.18; H, 6.49; N, 12.88.
Found: C, 44.06; H, 6.37; N, 12.70.

12. *2-(Nicotinylhydrazono)propionic acid* (VIII). A solution of 13.7 g. (0.1 mole) of nicotinic acid hydrazide in 200 ml. of water was mixed with a solution of 10 g. (0.11 mole) of pyruvic acid in 40 ml. of water. After a few seconds, the condensation product VIII crystallized. It was filtered, washed with ice-cold water, and dried. The yield was 17 g. (87%) of acid of m.p. 213–214°.

Anal. Calc'd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.78.
Found: C, 52.27; H, 4.34; N, 19.90.

13. *4-(Nicotinylhydrazono)valeric acid* (IX). Levulinic acid (13 g., 0.11 mole) was added to a solution of 13.6 g. (0.1 mole) of nicotinic acid hydrazide in 100 ml. of water. After a few minutes, crystallization of IX started. The mixture was filtered after 4 hours and the crystals were washed thoroughly, first with water, then with alcohol. Yield, 21 g. (89%) of m.p. 158–159°.

Anal. Calc'd for $C_{11}H_{13}N_3O_3$: C, 56.15; H, 5.57; H, 17.86.
Found: C, 56.13; H, 5.39; N, 17.83.

Acknowledgment. I wish to thank Dr. Steyermark and his staff for the microanalyses.

SUMMARY

A number of condensation products of isonicotinic acid hydrazide with acrbonyl compounds carrying hydroxy and carboxyl groups are described. Hydrogenation yielded the corresponding saturated derivatives.

NUTLEY 10, NEW JERSEY.

REFERENCES

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(2) CARRARA, CHIANCONE, D'AMATO, GINOULHIAC, MARTINUZZI, TEOTINO, AND VISCONTI, *Gazz. chim. ital.*, **82**, 652, 656 (1952).