PREPARATION OF A PARTIALLY HYDROGENATED DIBENZO[*c*,*h*][1,2,6,7]TETRAZECINE AND ITS PYRIDINE ANALOGUE

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Heating of hydrazides of salicylic acid and/or 3-hydroxyisonicotinic acid gave rise to a partially hydrogenated dibenzo[*c*,*h*][1,2,6,7]tetrazecine and its pyridine analogue.

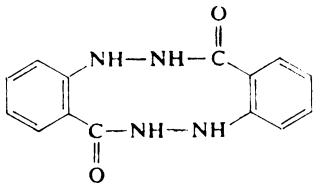
Isonicotinoylhydrazide is one of the most efficacious antituberculous drugs. It was chemically modified to a number of compounds in order to get some insight into the relation of their antituberculous activity to their structures. The present paper deals with the effect of a hydrazide group incorporated in the ring.

The study started with the preparation of hydrazide of 3-hydroxyisonicotinic acid, previously synthetized by Fox and Gibas[1] by heating an ester of the acid with hydrazine. The authors reported a melting point of 320°C, but the hydrazide prepared by ourselves melted at 195°C. In a paper by Roe and Selingman[2], who obtained the same compound by heating ethyl 3-fluoroisonicotinate hydrochloride with hydrazine hydrate, the melting point is not given. Heating the hydrazide we prepared above the melting point resulted in a loss of water and conversion into a new product, melting at the temperature stated by Fox and Gibas. We assumed that the reaction was an intramolecular elimination of water, with the formation of 3*H*,4*H*-pyrazolo-[3,4,*c*]pyridine-5-one. This compounds was synthetized by Sekikawa and coworkers[3] by heating 3-hydrazinoisonicotinic acid dihydrochloride; they also synthetized some other similar compounds, whose structures were inferred from their IR and NMR spectra. The reaction had been demonstrated before on dehydration of salicylic acid hydrazide[4].

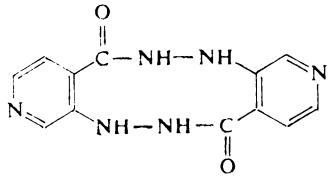
Several hydrazides of aromatic hydroxy acids with functional groups at the *ortho* position were prepared. Thus hydrazinolysis of ethyl salicylate gave hydrazide of salicylic acid[5]. Hydrazide of 3-hydroxyisonicotonic acid was prepared from 3-bromoisonicotinic acid[6]; the latter was converted by a solution of sodium hydroxide, in the presence of cupric ions, into 3-hydroxyisonicotinic acid; reaction of its ester with hydrazine hydrate afforded the hydrazide. Hydrazide of 2-hydroxynicotinic acid was synthetized from nicotinamide; this was converted into an N-oxide, whose

reaction with phosphorus pentachloride afforded 2-chloro-3-cyanopyridine[7]. Its alkaline hydrolysis, catalysed by cupric ions, gave 2-hydroxynicotinic acid[8] and hydrazinolysis of its ester yielded the corresponding hydrazide. Hydrazide of 3-hydroxypicolinic acid was obtained from imide of quinolinic acid, whose Hofmann reaction afforded 3-aminopicolinic acid[9]. Its diazotation, followed by hydrolysis of the diazonium salt, produced 3-hydroxypicolinic acid[10]. Hydrazide of this acid was obtained by the usual procedure.

In heating hydrazides of salicylic acid and/or 3-hydroxyisonicotinic acid reaction between two molecules of either compound released two molecules of water and gave rise to 5,6,7,12,13,14-hexahydrodibenzo[*c*,*h*] [1,2,6,7]tetrazecine-7,14-dione (*I*) and 5,6,7,12,13,14-hexahydrodipyrido[3,4-*c*,*h*] [1,2,6,7]tetrazecine-5,12-dione (*II*), respectively.



I



II

An analogous conversion of 3-hydroxypicolinic acid hydrazide did not occur. Heating of hydrazide of 2-hydroxynicotinic acid probably gave a linear polycondensate, since the hydrazide can be expected to react in its 2-pyridone form.

The compounds prepared were tested for the inhibitory effect *in vivo* on the strain *Mycobacterium tuberculosis* $H_{37}R_v$ and atypical strains *M. avium* and *M. kansasii*. None has shown a strong activity. The most efficacious were hydrazides of 3-hydroxyisonicotinic and 2-hydroxynicotinic acids, which killed *M. tuberculosis* $H_{37}R_v$ at a concentration of $32 . 10^{-9}$ g/ml. The other compounds were efficacious against all the strains if employed in a two-fold concentration, *i.e.* $64 . 10^{-9}$ g/ml. It can be concluded that incorporation of a hydrazide group into the ring does not increase the activity of the compounds.

EXPERIMENTAL

The melting points, determined on the Kofler stage, are not corrected. The samples to be analysed were dried over P_2O_5 at a pressure of *c.* 100 Pa and room temperature. The IR spectra (KBr) were recorded with a spectrophotometer Perkin–Elmer 577, the ^1H NMR spectra (in hydrofluoric acid) with a spectrometer Tesla BS 497 (100 MHz) and the mass spectra with a spectrometer Jeol D 100.

Hydrazide of 3-Hydroxyisonicotinic Acid

Ethyl 3-hydroxyisonicotinate (3·3 g, 0·02 mol) was dissolved in ethanol (10 ml) and 80% hydrazine hydrate (3·2 g) was added. The mixture was kept at a temperature of 30°C for 20 min and cooled down. The crystalline product was collected on a filter and recrystallized from ethanol; yield 1·0 g (35%), m.p. 110–118°C. Mass spectrum (*m*/*z*): 154 M^+; IR spectrum: 1 640 cm^{-1} ($CONH_2$) ^1H NMR spectrum: $\tau_{(a)} = 1{\cdot}35$ ppm, $\tau_{(b)} = 1{\cdot}50$ ppm, $\tau_{(c)} = 1{\cdot}65$ ppm, $J_{b,c} = 6$ Hz. For $C_6H_7N_3O_2$ (153·0) calculated: 47·08% C, 4·57% H, 27·44% N; found: 47·11% C, 4·63% H, 27·51% N.

5,6,7,12,13,14-Hexahydrodipyrido[3,4-*c*,*h*][1,2,6,7]tetrazecine-5,12-dione (*II*)

Hydrazide of 3-hydroxyisonicotinic acid (5 g, 0·03 mol) was heated to 180°C for 2 h, then to 210°C for 3 h. The melt was washed in boiling water, then with hot ethanol; yield 2·3 g (60%), m.p. 319–321°C. Mass spectrum (*m*/*z*): 271 M^+; IR spectrum 1 610 cm^{-1} ($CONH_2$); ^1H NMR spectrum: $\tau_{(a)} = 1{\cdot}25$ ppm, $\tau_{(b)} = 1{\cdot}32$ ppm, $\tau_{(c)} = 1{\cdot}53$ ppm, $J_{c,b} = 6$ Hz. For $C_{12}H_{10}N_6O_2$ (270·1) calculated: 53·35% C, 3·70% H, 31·10% N; found: 53·43% C, 3·78% H, 30·99% N.

5,6,7,12,13,14-Hexahydrodibenzo[*c*,*h*][1,2,6,7]tetrazecine-7,14-dione (*I*)

The procedure starting from salicylic acid hydrazide (5 g, 0·032 mol), was analogous to the preceding one; yield 3·88 g (80%), m.p. 242–243°C. Mass spectrum (*m*/*z*): 271 M^+; IR spectrum: 1 604 cm^{-1} ($CONH_2$); ^1H NMR spectrum: $\tau_{(a)} = 1{\cdot}98$ ppm, $\tau_{(b)} = 2{\cdot}48$ ppm, $\tau_{(c)} = 2{\cdot}95$ ppm, $\tau_{(d)} = 2{\cdot}82$ ppm, $J_{a,d} = 8$ Hz, $J_{a,b} = 2$ Hz. For $C_{14}H_{12}N_4O_2$(268·1) calculated: 62·71% C, 4·48% H, 20·89% N; found: 62·84% C, 4·56% H, 20·95% N.

Acid hydrolysis: 1 g of compound *I* was heated with 20 ml of concentrated hydrochloric acid for 12 h. The product melted at 245°C, which corresponds to 2-hydrazinobenzoic acid (reported[12] m.p. 245–246°C). The identity of the product was corroborated chromatographically (its R_F and that of an authentic sample were the same, 0·81) and by IR spectroscopy (both samples had a common IR spectrum (3 195 cm^{-1} N—H, 1 695 cm^{-1} C=O carboxyl).

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