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EXPERIMENTAL CHEMOTHERAPY OF TUBERCULOSIS. I. SUBSTITUTED NICOTINAMIDES

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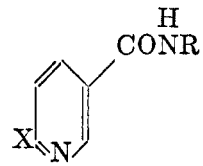
Experimental *in vivo* investigations in our laboratories have shown that many compounds may have tuberculostatic activity. One of these, nicotinamide (I), showed considerable promise and this nucleus was subjected to a two-fold variation. Derivatives of type II were prepared, wherein the amide group was substituted and the ring kept constant. Compounds of this type had some activity but far less than that of free nicotinamide. Of these compounds the most active was N-(2-thiazolyl)nicotinamide, but it was too toxic for further use.



I R, X = H
II R = $C_3H_7\cdots$, heterocycle, etc. X = H
III R = H, X = Cl, NH_2, C_4H_9O, etc.

Compounds of type III were prepared where the amide group was unchanged and ring substitution made. These showed no activity. Many of the compounds used as intermediates in this investigation such as *p*-aminosalicylic acid and 5-amino-2-methylcoumarane (1) which were by themselves active, lost their activity completely when converted to the corresponding nicotinamide.

Evidence presented elsewhere (2) supports the belief that the role of nicotinamide in the treatment of experimentally infected mice is that of a vitamin.

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EXPERIMENTAL

N-Nicotinyl-3-aminopyridine. To a solution of 15 g. (0.16 mole) of 3-aminopyridine and 30 ml. of pyridine was cautiously added 23 g. (0.16 mole) of nicotinyl chloride. After heating for fifteen minutes the reaction mixture was poured onto ice-water, filtered, and washed with water; wt. 21 g., m.p. 186°. After one recrystallization from alcohol it melted at 188°.

Nicotinyldicyandiamide. To a stirred (25–30°) solution of 15 g. (0.18 mole) of dicyandiamide, 20 g. (0.5 mole) of 95% sodium hydroxide, 75 ml. of water, and 75 ml. of acetone was added dropwise 30 g. (0.21 mole) of nicotinyl chloride. A further addition of 20 ml. of water was made and the reaction mixture was acidified with acetic acid. The product was filtered and washed, wt. 12 g. After recrystallization from 50% alcohol it melted at 170–175°.

p-(Nicotinylamino)benzoic acid. To a continuously stirred cold solution of 7 g. (0.18 mole) of sodium hydroxide, 20 g. (0.15 mole) of *p*-aminobenzoic acid, and 300 ml. of water

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TABLE I

SUBSTITUTED NICOTINAMIDES

NO.	PRODUCT	METHOD OF PREPARATION	M.P., °C.	FORMULA	CALCULATED			FOUND			ACTIVITY
					C	H	N	C	H	N	
1	N-nicotinyl-3-aminopyridine	A	188	$C_{11}H_9N_3O$	66.3	4.5	21.1	66.9	5.0	21.1	+
2	N-nicotinyl-2-aminopyridine (3)	A	141–143	$C_{11}H_9N_3O$			21.1			21.1	−
3	N-nicotinyl-1-aminoanthraquinone	A	205	$C_{20}H_{12}N_2O_3$	73.2	3.7	8.5	73.3	3.9	8.6	−
4	N-(2-thiazolyl)nicotinamide	A	211 dec.	$C_9H_7N_3OS$			20.5			20.6	++
5	N-cyclohexylnicotinamide (3)	A	140–142	$C_{12}H_{16}N_2O$			13.7			13.8	−
6	N-dodecoylnicotinamide (3)	A	63– 64.5	$C_{18}H_{30}N_2O$			9.7			9.3	−
7	5-(Nicotinylamino)-2-methylcoumarane	A	140	$C_{16}H_{14}N_2O_2$	70.9	5.5	11.0	70.2	5.9	10.5	−
8	Nicotinyldicyandiamide	A	170–175	$C_8H_7N_5O$			37.3			37.5	−
9	N-nicotinylbenzylamine	A	125–126	$C_{13}H_{12}N_2O$			13.2			13.2	−
10	4-(Nicotinylamino)salicylic acid	A	195 dec.	$C_{13}H_{10}N_2O_4$	60.5	3.9	10.9	60.3	4.0	11.2	−
11	N-nicotinyl-2-amino-5-azoanisole	A	150–152	$C_{20}H_{18}N_4O_2$	66.3	5.0	15.5	66.8	5.0	16.0	−
12	N-(2-pyrimidyl)nicotinamide	A	173–175	$C_{10}H_8N_4O$			28.0			27.8	+
13	2-(Nicotinylamino)-phenol	A	200 dec.	$C_{12}H_{10}N_2O_2$	67.3	4.7	13.1	67.3	4.7	13.0	−−
14	3-(Nicotinylamino)-phenol	A	215–218	$C_{12}H_{10}N_2O_2$	67.3	4.7	13.1	67.7	4.9	13.0	−
15	4-(Nicotinylamino)-phenol	A	203–205	$C_{12}H_{10}N_2O_2$	67.3	4.7	13.1	67.0	4.6	13.3	−
16	2-(Nicotinylamino)-5-carbethoxythiazole	A	187–192	$C_{12}H_{11}N_3O_3S$	52.0	4.0	15.2	51.0	4.0	15.7	−
17	N-propylnicotinamide		89– 92	$C_9H_{12}N_2O$	65.9	7.3	17.1	65.9	7.2	16.8	C
18	N-isopropylnicotinamide		85– 86.5	$C_9H_{12}N_2O$	65.9	7.3	17.1	66.0	7.6	17.1	+
19	N-methoxypropylnicotinamide		B	$C_{10}H_{14}N_2O_2$			14.4			14.0	−
20	N-butylnicotinamide		34– 37	$C_{10}H_{14}N_2O$	67.4	7.9	15.7	67.4	8.0	15.7	+
21	*p*-(Nicotinylamino)acetanilide	A	275–278	$C_{14}H_{13}N_3O_2$	65.9	5.1	16.5	66.3	5.2	16.9	−
22	6-Chloronicotinamide (5)		212–213	$C_6H_5ClN_2O$	46.2	3.2	18.0	46.0	3.5	17.6	−
23	6-Aminonicotinamide		243–244	$C_6H_7N_3O$	52.6	5.1	30.7	52.9	5.3	30.3	−
24	6-Butoxynicotinamide		150–151	$C_{10}H_{14}N_2O_2$	61.9	7.2	14.4	61.9	7.1	14.5	−
25	*p*-(Nicotinylamino)benzoic acid		298–299	$C_{13}H_{10}N_2O_3$	64.5	4.1	11.6	64.0	4.6	11.7	−

A. Prepared in approximately the same manner as N-nicotinyl-3-aminopyridine shown in the Experimental.
Compounds 1, 3, 9, and 21 were recrystallized from alcohol.
Compounds 2, 5, and 6 were recrystallized from acetone.
Compounds 10 and 16 were purified by reprecipitation from an acid solution by alkali.
Compound 7 from benzene-petroleum ether.
Compound 12 from chloroform.
Compound 4 from water.

B. Liquid of b.p. 235–240° at 14 mm.

C. Not tested.
The basis of activity is in relationship to that of streptomycin in mice.
Those compounds with + show approximately 25% activity, while ++ is approximately 50% of streptomycin activity.
The compounds were usually fed in a 0.25% synthetic diet. For complete details see the report of D. McKenzie (2).

was added simultaneously 24 g. (0.17 mole) of nicotinyl chloride and a dilute sodium hydroxide solution, so that the reaction mixture was kept slightly alkaline. The product resulting from acidification was washed successively with water and alcohol. The crude product was dissolved in alkali, treated with Norit, and reprecipitated; wt. 15 g., m.p. 298–299°.

N-Propylnicotinamide. A mixture of 7.5 g. (0.05 mole) of ethyl nicotinate and 15 g. (0.26 mole) of *n*-propylamine was heated for 18 hours at 150°. The excess propylamine was removed in a vacuum and the residue crystallized upon trituration with high-boiling petroleum ether; wt. 8 g., m.p. 89–92°.

N-Isopropylnicotinamide. To a mixture of 12.2 g. (0.02 mole) of isopropylamine and 100 g. of cracked ice was added dropwise 10 g. (0.07 mole) of nicotinyl chloride. The reaction mixture was extracted twice with 200 ml. portions of chloroform and the chloroform was boiled off. The solid residue weighed 7.5 g. After recrystallization from chloroform-petroleum ether it melted at 85–86.5°.

N-Methoxypropylnicotinamide. Forty grams (0.45 mole) of methoxypropylamine and 15.2 g. (1.07 mole) of nicotinyl chloride synthesized in the same manner as the isopropyl analog gave 10 g. of the desired product as a light yellow oil, b.p. 235–240° (14 mm.).

N-Butylnicotinamide. Two and one-half grams of the desired product was obtained using the same procedure with 3 g. (0.04 mole) of *n*-butylamine and 3 g. (0.02 mole) of nicotinyl chloride. The product obtained from the removal of chloroform could be crystallized by cooling in a dry-ice bath and scratching. The product after trituration with low-boiling petroleum ether and a few drops of chloroform was filtered. The compound melted on the microstage at 34–37° w.p.s. It did not lend itself to successful recrystallization.

Methyl coumalate. Coumalic acid was prepared according to the directions of von Pechmann (4). We found it more desirable to form the methyl ester by adding an ethereal solution of diazomethane to an alcohol suspension of the acid than by the vigorous esterification procedure used by von Pechmann.

6-Chloronicotinamide (5). A mixture of 100 g. (0.5 mole) of phosphorus pentachloride, 100 g. (0.67 mole) of phosphorus oxychloride, and 50 g. (0.36 mole) of 6-hydroxynicotinamide (4) (prepared from methyl coumalate and ammonia) was cautiously added to 600 ml. of ice-cold concentrated ammonium hydroxide and 400 ml. of water. The crude washed product weighed 32 g., m.p. 203–205°, and after recrystallization from alcohol it melted at 212–213°.

6-Aminonicotinamide. A mixture of 5 g. (0.03 mole) of 6-chloronicotinamide and 50 ml. of concentrated ammonium hydroxide was heated for 6–8 hours at 170° in a bomb. The crude product weighed 2.5 g.; it melted at 257–260° after recrystallization from water. The ammoniacal filtrate deposited approximately 1 g. of 6-hydroxynicotinic acid upon acidification. Marckwald (6) reports m.p. 243–244°.

6-Butoxynicotinamide. A mixture of 5 g. (0.03 mole) of 6-chloronicotinamide and 3.5 g. (0.04 mole) of sodium butoxide in 25 ml. of butanol was refluxed for thirty minutes on a steam cone. The cooled reaction mixture was filtered and washed with water, wt. 2.5 g. After three recrystallizations from alcohol it melted at 150–151°.

SUMMARY

A series of 25 substituted nicotinamides have been synthesized and tested for tuberculostatic activity. The most active compound prepared N-(2-thiazolyl)-nicotinamide is less active than nicotinamide as a tuberculostatic agent.

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