303. *The Chemotherapy of Tuberculosis. Part IV.*† *Some N-Substituted Nicotinamides and Nicotinamidines.*

By J. N. Baxter and J. Cymerman-Craig.

Two parallel series of six *N*-aryl-nicotinamides and -nicotinamidines have been prepared. Their basic dissociation constants have been determined potentiometrically in 50% alcoholic solution : these bear no visible relations to the relative antituberculous activities.

Because of the well-known antituberculous activity of nicotinamide and its *N*-substituted derivatives, and the relation of basic strength to antibacterial action, the effect of an increase in the basicity of compounds related to nicotinamide on their antituberculous activity has been investigated. A series of six *N*-aryl-nicotinamidines, 3-C_5H_4N·C(:NH)·NHAr, was prepared by Oxley and Short's method (*J.*, 1946, 147), the corresponding nicotinamides being readily obtained for comparison from nicotinoyl chloride and the appropriate amine.

Potentiometric titration in 50% alcoholic solution at 20° ± 1° (procedure : Carswell, Cymerman, and Lyons, *J.*, 1952, 430) was used to obtain the pK_a values (see Table 1). Amides were titrated with N/20-hydrochloric acid, while for the amidines the hydrochlorides

* There is a misquotation in this paper of solution results given previously by Sutton and Hampson (*loc. cit.*). † Part III, *J.*, 1951, 2342.

(or, in the case of benzamidine, the benzenesulphonate) were titrated with N/20-sodium hydroxide. Results were corrected for hydrogen- or hydroxyl-ion concentration. It is seen that the pK_a of nicotinamide lies close to that of the similarly constituted 3-acetylpyridine, in accord with the $+I$ and $+E$ effect of these groups, and the substitution of a phenyl or 4-diphenylyl group for an amide-hydrogen atom lowers the pK_a by 0·39 and 0·66 unit respectively. In both nicotinamidine and benzamidine, substitution of an amino-hydrogen atom by the 4-diphenylyl group reduces the pK_a by 3 units.

Antituberculous activities *in vitro* (Table 2) have been kindly determined by Pro-

TABLE 1. *Ionisation constants.*

Compound	pK_a at 20° ± 1°	Solvent	Compound	pK_a at 20° ± 1°	Solvent
Pyridine	5·19	Water [1]	Nicotinamidine	9·65	50% Alcohol
Nicotinic acid	3·55	,, [2]	*N*-4-Diphenylylnicotinamidine	6·63	,,
3-Acetylpyridine	3·18	,, [1]	Benzamidine	11·6	Water [3]
Nicotinamide	3·15	50% Alcohol		11·23	50% Alcohol
Nicotinanilide	2·76	,,			
N-4-Diphenylylnicotinamide	2·49	,,	*N*-4-Diphenylylbenzamidine	8·10	,, [4]

[1] Hall and Sprinkle, *loc. cit.*; values at 25°. [2] Basic dissociation constant; Hughes, Jellinek, and Ambrose, *J. Phys. Colloid Chem.*, 1949, **53**, 410. [3] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [4] Carswell, Cymerman, and Lyons, *loc. cit.*

TABLE 2.

N-Substituent	Nicotinamides, activity * with 10% serum	Nicotinamides, activity * without serum	Nicotinamidines, activity * with 10% serum	Nicotinamidines, activity * without serum
p-Ethoxyphenyl	—	—	<2000	<2,000
p-Chlorophenyl	2,000	4,000	<2000	<2,000
*p-cyclo*Hexylphenyl	<8,000	<8,000	8000	16,000
4-Diphenylyl	<8,000	<8,000	4000	8,000
p-Phenoxyphenyl	16,000	32,000	4000	8,000
2-Dibenzofuryl	<8,000	<8,000	<2000	<2,000
None	<125	500	<125	125

* Highest dilution expressed as 1/molarity of the substance completely inhibiting growth of *Mycobact. tuberculosis* (H. 37 Rv) in Youmans's medium after 14 days at 37°.

fessor S. D. Rubbo, and a full account of the bacteriological aspects will be given elsewhere. Although the *N*-substituted compounds greatly exceed the parent substances in activity, the highest activity recorded is of a low order, and no clear relation appears between ionisation and activity in this series. Activities were decreased by the presence of serum.

Prolonged evaporation of an aqueous solution of *N*-*p*-chlorophenylnicotinamidinium toluene-*p*-sulphonate at 100° gave *N*-*p*-chlorophenylnicotinamide, accompanied by some of the amidine salt. Such hydrolysis of an amidine in neutral solution may be ascribed to the presence of some free amidine base. The 4-diphenylyl-amidine has pK_a only 6·63 at 20° in 50% alcohol, and the base-weakening influence of substituents is in the order Cl>Ph>OEt; *e.g.*, *p*-chloroaniline, 4-aminodiphenyl, and *p*-phenetidine have pK_a 4·0, 4·27, and 5·25 respectively at 25° in water (Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3472). The *p*-chlorophenyl-amidine will thus have pK_a less than 6·63 at 20° in 50% alcohol, so that a considerable proportion of free amidine will exist in neutral solution, giving rise to the observed hydrolysis. Neutral hydrolysis also occurred with the *p*-ethoxyphenyl-amidine, but only 1% of amide was obtained in this case; the *p*-ethoxyphenyl analogue will have pK_a greater than 6·63 under the same conditions, and the proportion of free base present will therefore be much smaller.

It is seen from Table 1 that the basic strengths of nicotinamidines are 1·5 pK units lower than those of the corresponding benzamidines; this appears to be due to the general electron-withdrawing effect of the ring-nitrogen atom in the former.

EXPERIMENTAL

N-Substituted Nicotinamides.—A solution of nicotinoyl chloride hydrochloride (0·01 mole) in dry pyridine (5 c.c.) was mixed with a solution of the amine (0·01 mole) in dry pyridine (20 c.c.), and the next morning poured into ice-water (150 c.c.). The precipitate crystallised from chloroform or alcohol, giving the *amides* in 55—65% yield as needles or prisms (see Table 3).

N-*Substituted Nicotinamidines*.—The amine toluene-*p*-sulphonate (0·05 mole) and 3-cyanopyridine (0·05 mole plus 15% excess) were heated at 200° for 1·5—2·5 hours, the mixture extracted with ether, and the ether-insoluble solid extacted with boiling water. The amidine salt separated from the aqueous filtrate on cooling or on concentration *in vacuo*, and crystallised from water or *iso*propanol in plates or needles of the *amidinium toluene*-p-*sulphonates* in 25—35% yield (see Table 4). The free base was obtained by basifying an ice-cold aqueous solution of the pure salt. Crystallisation from chloroform–light petroleum (b. p. 40—60°) afforded the amidines as plates or prisms (see Table 5).

TABLE 3. N-*Substituted nicotinamides*.

N-Substituent	M. p.	Formula	Found (%) C	H	N	Requires (%) C	H	N
p-*Chlorophenyl*	169·5—170°	$C_{12}H_9ON_2Cl$	61·9	4·1	11·9	61·9	3·9	12·05
p-cyclo*Hexylphenyl*	203—203·5	$C_{18}H_{20}ON_2$	77·25	7·15	10·45	77·1	7·2	10·0
4-*Diphenylyl* [1]	217	$C_{18}H_{14}ON_2$	79·0	5·25	10·6	78·8	5·15	10·2
p-*Phenoxyphenyl*	149·5—150	$C_{18}H_{14}O_2N_2$	74·6	4·95	9·65	74·5	4·85	9·65
2-*Dibenzofuryl*	220	$C_{18}H_{12}O_2N_2$	74·65	4·05	10·0	75·0	4·2	9·75

[1] The *hydrochloride* formed plates (from alcohol), m. p. 267° (Found: C, 69·3; H, 4·95; N, 8·5. $C_{18}H_{14}ON_2$,HCl requires C, 69·55; H, 4·85; N, 9·0%).

TABLE 4. N-*Substituted nicotinamidinium toluene*-p-*sulphonates*.

N-Substituent	M. p.	Formula	Found N (%)	Requires N (%)
p-*Ethoxyphenyl*	220°	$C_{21}H_{23}O_4N_3S$	9·8 [1]	10·15
p-cyclo*Hexylphenyl*	178	$C_{25}H_{29}O_3N_3S$	— [2]	—
4-*Diphenylyl*	213	$C_{25}H_{23}O_3N_3S$	9·2, 9·45	9·45
p-*Phenoxyphenyl*	170	$C_{25}H_{23}O_4N_3S$	9·3	9·1
2-*Dibenzofuryl*	213	$C_{25}H_{21}O_4N_3S$	9·1	9·15

[1] Found: S, 7·65. Requires S, 7·75%. [2] Found: C, 66·7; H, 6·7. Requires C, 66·5; H, 6·5%.

TABLE 5. N-*Substituted nicotinamidines*.

N-Substituent	M. p.	Formula	Found (%) C	H	N	Requires (%) C	H	N
p-*Ethoxyphenyl*	128—129°	$C_{14}H_{15}ON_3$	69·4	6·1	17·5	69·7	6·25	17·4
p-*Chlorophenyl*	190	$C_{12}H_{10}N_3Cl$	61·9	4·15	17·5	62·2	4·35	18·1
p-cyclo*Hexylphenyl*	172	$C_{18}H_{21}N_3$	—	—	14·8	—	—	15·0
4-*Diphenylyl*	162·5	$C_{18}H_{15}N_3$	78·9	5·7	15·0	79·1	5·5	15·4
p-*Phenoxyphenyl*	163—164	$C_{18}H_{15}ON_3$	—	—	14·1	—	—	14·5
2-*Dibenzofuryl*	217·5	$C_{18}H_{13}ON_3$	—	—	14·4	—	—	14·6

Neutral Hydrolysis of Amidines.—(*a*) Evaporation of an aqueous solution of *N*-*p*-chlorophenylnicotinamidinium toluene-*p*-sulphonate at 100° afforded a solid (A), part of which after repeated crystallisation gave *N*-*p*-chlorophenylnicotinamide, m. p. 170° (Found: N, 12·0. Calc. for $C_{12}H_9ON_2Cl$: N, 12·0%), undepressed on admixture with an authentic sample. Part of (A) was basified at 0° and crystallisation of the base from chloroform gave fractions (i) and (ii). A small fraction (i) consisted of the amidine, m. p. and mixed m. p. 189°. The *amidine dihydrochloride*, crystallised from methanol–ether, had m. p. 258—259° (decomp.) (Found: N, 13·8; equiv., 156. $C_{12}H_{10}N_3Cl$,2HCl requires N, 13·8%; equiv., 152). The *dipicrate*, plates (from alcohol), had m. p. 166° [Found: N, 17·9; equiv. (by titration with sodium hydroxide in presence of thymolphthalein), 339. $C_{12}H_{10}N_3Cl$,$2C_6H_3O_7N_3$ requires N, 18·25%; equiv., 345]. Fraction (ii), m. p. 151—152°, gave a mixture of two picrates, one of which had m. p. 166°, undepressed on admixture with the amidine dipicrate above, while the other crystallised from alcohol in orange prisms. m. p. 204—206° of N-p-*chlorophenylnicotinamide picrate* (Found: C, 47·2; H, 2·3; N, 14·4. $C_{12}H_9ON_2Cl$,$C_6H_3O_7N_3$ requires C, 46·8; H, 2·6; N, 15·2%) (m. p. undepressed by an authentic sample).

(*b*) Evaporation of an aqueous solution of *N*-p-ethoxyphenylnicotinamidinium toluene-*p*-sulphonate gave (i) the amidine toluene-*p*-sulphonate in 35% yield (see Table 3) and (ii) an oil which solidified and crystallised from *iso*propanol to give *N*-*p*-ethoxyphenylnicotinamide (1%), m. p. 171—172° (Found: C, 68·7; H, 5·9; N, 11·8. Calc. for $C_{14}H_{14}O_2N_2$: C, 69·4; H, 5·8; N, 11·6%). Lanfranchi (*Chem. Abs.*, 1947, **41**, 454) gives m. p. 170—171°.

Materials for pK_a *Determinations*.—Nicotinamide: plates, m. p. 129° (lit., m. p. 129—131°). Nicotinanilide: m. p. 119—120° [from benzene–light petroleum (b. p. 40—60°)] (Badgett,

Provost, Ogg, and Woodward, *J. Amer. Chem. Soc.*, 1945, **67**, 1135, give m. p. 117°). The *hydrochloride* crystallised from alcohol in needles, m. p. 201·5—202° (Found: C, 61·2, 61·3; H, 4·7, 4·8; N, 11·5. $C_{12}H_{10}ON_2$,HCl requires C, 61·4; H, 4·75; N, 11·9%).

Nicotinamidine: the hydrochloride crystallised from *iso*propanol–ether and had constant m. p. 186—187° (Barber and Slack, *J. Amer. Chem. Soc.*, 1944, **66**, 1607, give m. p. 190°).

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Organic Chemistry Department, University of Sydney. [*Received, November 3rd*, 1952.]