The Chemotherapy of Tuberculosis. Part VI. Some Derivatives of* iso*Nicotinic Acid.*

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N- and *N'*-Methyl-*N*-*iso*nicotinoylhydrazine, and *N*-methyl- and *NN'*-dimethyl-*NN'*-di*iso*nicotinoylhydrazine, have been prepared to test a possible correlation between antituberculous activity and chelating ability in this series.

The reaction of *iso*nicotinoylhydrazine with diketones has been found, in two cases, to give results differing from those of Yale *et al.* (*loc. cit.*); attempted preparation of aminomethyl 4-pyridyl ketone gave only 2 : 5-di-4'-pyridylpyrazine.

The high specific activity of *iso*nicotinoylhydrazine against *Mycobact. tuberculosis* has given rise to a number of hypotheses regarding its mode of action. *iso*Nicotinoylhydrazine is known to form metal complexes (cf. *inter al.*, Albert, *Experientia*, 1953, **9**, 370) and the accompanying fall in pH suggests salt formation *via* a *pseudo*-acid (II). It was therefore of interest to examine *N*-methyl-*N*-*iso*nicotinoylhydrazine which will be unable to form such complexes. At the same time the preparation of *N'*-methyl- and *NN'*-dimethyl-*N*-*iso*nicotinoylhydrazine was investigated.

Methyl *iso*nicotinate and methylhydrazine at 100° gave *N'*-methyl-*N*-*iso*nicotinoylhydrazine (I; $R^1 = R^2 = H$, $R^3 = Me$); use of *iso*nicotinoyl chloride gave the same substance, together with *N*-methyl-*NN'*-di*iso*nicotinoylhydrazine (III; $R^1 = H$, $R^2 = Me$). Meyer and Graf's method (*Ber.*, 1928, **61**, 2202) for the preparation of *iso*nicotinoyl chloride was unsatisfactory; pure material was obtained by treatment of *iso*nicotinoyl chloride hydrochloride (Spath and Spitzer, *Ber.*, 1926, **59**, 1477) with triethylamine. The structure of the derivative (I; $R^1 = R^2 = H$, $R^3 = Me$) was established by its failure to condense with acetone; the parent compound, possessing a primary amino-group, readily undergoes this reaction (Fox and Gibas, *J. Org. Chem.*, 1953, **18**, 983). While this work was in progress Fox and Gibas (*J. Org. Chem.*, 1953, **18**, 994) reported the synthesis of this compound (I; $R^1 = R^2 = H$, $R^3 = Me$) in unstated yield from methylhydrazine and methyl *iso*nicotinate at 130°.

Condensation of *iso*nicotinoyl chloride with *NN*-dimethylhydrazine gave a hygroscopic product [cf. the preparation of *N*-2-furoyl-*NN'*-dimethylhydrazine from *NN*-dimethylhydrazine and 2-furoyl chloride by Yale, Losee, Martins, Holsing, Perry, and Bernstein (*J. Amer. Chem. Soc.*, 1953, **75**, 1933)]. *iso*Nicotinic acid was the only product obtained from this by treatment with aqueous formaldehyde and formic acid, or by hydrochloric acid or aqueous formic acid alone.

No reaction occurred between *NN'*-dimethylhydrazine and methyl *iso*nicotinate under mild conditions, while more vigorous treatment cleaved the hydrazine giving methylamine, *iso*nicotinic acid, and *N'*-methyl*iso*nicotinamide. The latter was synthesised from methyl *iso*nicotinate and methylamine. Attempted preparation of *NN'*-dimethyl-*N*-*iso*nicotinoylhydrazine by reaction of *iso*nicotinoyl chloride with excess of *NN'*-dimethylhydrazine in triethylamine gave tars, while the same reagents with addition of pyridine gave only *NN'*-dimethyl-*NN'*-di*iso*nicotinoylhydrazine, also readily obtained from *NN'*-dimethylhydrazine and 2 mols. of the acid chloride.

To the authors' knowledge, no *N*-substituted *N*-*iso*nicotinoylhydrazine has been reported to date. Attempted methylation of *iso*nicotinoylhydrazine by the Eschweiler–Clarke method (Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571) gave only *iso*nicotinic acid, also obtained by using aqueous formic acid alone even at 0°. Yale *et al.* report formylation of *iso*nicotinoylhydrazine by anhydrous formic acid, but a suitable anhydrous solvent to induce *N*-methylation without *N*-formylation could not be found. The desired *N*-methyl-*N*-*iso*nicotinoylhydrazine was, however, obtained *via* its benzylidene

* Part V, preceding paper.

derivatives. Condensation of *N*-methyl-*N'*-4-nitrobenzylidenehydrazine (Brady and McHugh, *J.*, 1922, 1648) with methyl *iso*nicotinate, in dimethylformamide or without solvent, was unsuccessful; however, reaction with *iso*nicotinoyl chloride readily gave *N*-methyl-*N*-*iso*nicotinoyl-*N'*-4-nitrobenzylidenehydrazine, and the unstable *N*-methyl-*N'*-veratrylidenehydrazine afforded the veratrylidene analogue. Attempted condensation of *iso*nicotinoyl chloride and *N*-*cyclo*hexylidene-*N'*-methylhydrazine (Todd, *J. Amer. Chem. Soc.*, 1949, **71**, 1353) gave intractable tars.

The 4-nitrobenzylidene compound was relatively stable to hydrolysis, hydrochloric acid forming the Schiff's base hydrochloride while 2 : 4-dinitrophenylhydrazine hydrochloride under more drastic conditions gave *iso*nicotinic acid and the derivative of the aldehyde. However, the same reagent readily hydrolysed the veratrylidene analogue, removal of the aldehyde derivative affording *N*-methyl-*N*-*iso*nicotinoylhydrazine dihydrochloride.

In view of the tuberculostatic activity of 5-acetamidothiophen-2-aldehyde thiosemicarbazone (Cymerman-Craig and Willis, *J.*, 1955, 1071) the parent aldehyde was condensed with *iso*nicotinoylhydrazine to give the Schiff's base. Condensation of *iso*nicotinoylhydrazine with several diketones was also examined before the publication by Yale *et al.* (*loc. cit.*) came to hand. Our results are reported in so far as they differ from these authors' findings.

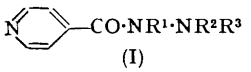
Yale *et al.* report reaction of acetylacetone mono*iso*nicotinoylhydrazone and *iso*nicotinoylhydrazine to give acetylacetone bis*iso*nicotinoylhydrazone, m. p. 254—256°. We found however, that this diketone with *iso*nicotinoylhydrazine (2 mols.) gave only *NN'*-di*iso*nicotinoylhydrazine (m. p. 256°) identical with an authentic sample, while the mother-liquors afforded 3 : 5-dimethylpyrazole. Repetition of the experiment of Yale *et al.* showed that their product was also identical with *NN'*-di*iso*nicotinoylhydrazine, obtained in aqueous or alcoholic solution, and 3 : 5-dimethylpyrazole was also isolated. These two compounds may be formed from the bis-acetylacetone compound (IV) by the changes illustrated.

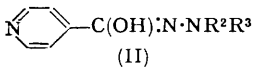
Yale *et al.* report acetonylacetone and *iso*nicotinoylhydrazine as giving solely 2 : 5-dimethyl-1-*iso*nicotinamidopyrrole. We find that acetonylacetone bis*iso*nicotinoylhydrazone is readily obtainable from this reaction, with only a small amount of the pyrrole, arising presumably by internal cyclisation of the monohydrazone first formed. Fission of the bishydrazone occurs readily, on crystallisation from nitrobenzene, on treatment with picric acid, or on heating in ethylene glycol, the products being *iso*nicotinoylhydrazine and 2 : 5-dimethyl-1-*iso*nicotinamidopyrrole. The mechanism of fission may be a preliminary loss of a proton, followed by intramolecular rearrangement and loss of an anion, as shown in (V).

Aminomethyl 4-pyridyl ketone, an analogue of *iso*nicotinoylhydrazine in which the *N*-nitrogen atom is replaced by a methylene group, has been prepared by Burrus and Powell (*J. Amer. Chem. Soc.*, 1945, **67**, 1468) who obtained an unstable dihydrochloride from ethyl hydroxyimino*iso*nicotinoyl acetate. The Neber rearrangement (Neber and Huh, *Annalen*, 1935, **515**, 283; Hatch and Cram, *J. Amer. Chem. Soc.*, 1953, **75**, 38) has been used (Clemo, Holmes, and Leitch, *J.*, 1938, 753) for the synthesis of aminomethyl 2-pyridyl ketone, and the application of this method to methyl 4-pyridyl ketoxime was investigated. The ketoxime was converted into its toluene-*p*-sulphonate which with potassium ethoxide gave an unstable hydrochloride. Attempted liberation of the free base gave only 2 : 5-di-4'-pyridylpyrazine (VI). Formation of 2 : 5-diarylpyrazines from aminomethyl aryl ketones is well known (Neber and Huh, *loc. cit.*; Gabriel, *Ber.*, 1908, **41**, 1127; Burrus and Powell, *loc. cit.*) and the substance (VI) showed ultraviolet absorption resembling that of 2 : 2'-dipyridyl (Gillam, Hey, and Lambert, *J.*, 1941, 364), with the expected bathochromic shift.

It was of interest to prepare a 4-basically substituted benzoylhydrazine. *p*-Diethylaminobenzoic acid could not be obtained, even under drastic conditions, by Pearl's method (*J. Org. Chem.*, 1947, **12**, 85); it was prepared by Rousset's method (*Bull. Soc. chim., France*, 1894, **11**, 318) and converted, *via* the ester, into *NN'*-di-(*p*-diethylaminobenzoyl)-hydrazine.

The hydrazides were kindly examined by Professor S. D. Rubbo for activity against *Mycobact. tuberculosis* H 37 Rv *in vitro* in presence of 10% of serum. *N*-Methyl-*N'-iso*nicotinoyl- and *NN'*-di*iso*nicotinoyl-hydrazine and its monomethyl derivative had some, though reduced, activity (active at *ca.* M/32,000); Fox and Gibas (*loc. cit.*) report *N*-methyl-*N'-iso*nicotinoylhydrazine to be active *in vivo*. However, while *iso*nicotinoylhydrazine and all Schiff's bases derived from this were active at M/1,200,000—M/4,800,000, *NN'*-dimethyl-*NN'*-di*iso*nicotinoylhydrazine, *N*-methyl-*N-iso*nicotinoylhydrazine, and both


(I)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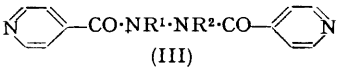
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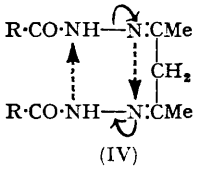
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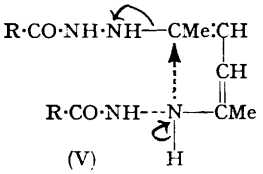
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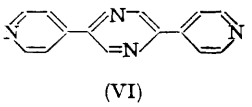
(VI)

its benzylidene derivatives were virtually inactive (M/250—M/2000). Since the *N*-methyl compounds are incapable of chelation *via* the *pseudo*-acid (II) and give, in fact, neither a colour change nor a precipitate with cupric ion, a direct connection between chelating ability and antituberculous activity in this series appears likely. The bacteriological aspects will be discussed in full elsewhere.

Experimental

iso*Nicotinoyl Chloride.*—*iso*Nicotinoyl chloride hydrochloride (Spath and Spitzer, *Ber.*, 1926, **59**, 1477), from *iso*nicotinic acid (24·6 g.), was distilled from triethylamine (80 g.), giving a red oil, b. p. 80—120°/25 mm., which on redistillation yielded *iso*nicotinoyl chloride (6 g.), b. p. 80°/15 mm.

N-*Methyl*-N'-iso*nicotinoylhydrazine.*—(*a*) Reaction of methylhydrazine (1·84 g.; Hatt, *Org. Synth.*, Coll. Vol. II, 1943, p. 395) and methyl *iso*nicotinate (2·74 g.) at 100° for 2 hr., followed by concentration *in vacuo*, left a glass from which acetone precipitated *iso*nicotinic acid (0·29 g.). Addition of ether to the acetone-soluble portion gave *N*-methyl-*N'-iso*nicotinoylhydrazine (1·21 g., 40%), m. p. 75—79°, converted into the dihydrochloride, m. p. 226—227° (from methanol) (Found: N, 18·8. Calc. for $C_7H_9ON_3$,2HCl: N, 18·8%). The acetone–ether mother liquors gave the *picrate* (1·64 g., 21·5%), m. p. 173·5—174·5° (decomp.) (from aqueous alcohol) (Found: C, 41·3; H, 3·3; N, 21·9. $C_7H_9ON_3$,$C_6H_3O_7N_3$ requires C, 41·1; H, 3·2; N, 22·1%). The dioxalate had m. p. 196°. Fox and Gibas (*J. Org. Chem.*, 1953, **18**, 994) report the dihydrochloride, m. p. 225·5—226·5°, and the dioxalate, m. p. 196—197°.

(*b*) *iso*Nicotinoyl chloride (4·85 g.) in dry benzene (25 c.c.) was treated at 20° with methylhydrazine (1·58 g.) in benzene (25 c.c.). The temperature rose to 50°; after 5 minutes' refluxing, evaporation and treatment with acetone gave N-*methyl*-NN'-*diisonicotinoylhydrazine dihydrochloride* (2·4 g., 42%), m. p. 257—258° (from methanol) (Found: C, 47·5; H, 4·45; N, 17·5. $C_{13}H_{18}O_2N_4$,2HCl requires C, 47·4; H, 4·3; N, 17·0%); the *dipicrate* separated from water as yellow plates, m. p. 252° (Found: C, 42·1; H, 2·55; N, 19·7. $C_{13}H_{18}O_2N_4$,$2C_6H_3O_7N_3$ requires C, 42·0; H, 2·55; N, 19·6%). The acetone mother-liquors on treatment with alcoholic hydrogen chloride gave *N*-methyl-*N'-iso*nicotinoylhydrazine dihydrochloride (2·26 g., 30%), m. p. and mixed m. p. 225—226°.

Attempted Preparation of NN'-*Dimethyl*-N-iso*nicotinoylhydrazine.*—(*a*) A mixture of *NN'*-dimethylhydrazine (13·5 g.) and methyl *iso*nicotinate (13·7 g.) was heated for 3 hr. at 130° in a sealed tube. Methylamine was evolved, leaving a dark oil from which, after removal of volatile products *in vacuo*, cold ethanolic hydrogen chloride precipitated *iso*nicotinic acid hydrochloride (13·6 g., 80%), m. p. and mixed m. p. 282°. The mother-liquors were made alkaline (ammonia in chloroform) and chromatographed on alumina, giving an oil which with ethanolic hydrogen chloride furnished *N'*-methyl*iso*nicotinamide hydrochloride (1·34 g., 8%), m. p. 206°, converted into the picrate, m. p. 165°, both identical with authentic specimens (see below).

(*b*) A solution of *iso*nicotinoyl chloride hydrochloride (5·34 g., 1 mol.) in pyridine (50 c.c.)

at 50° was slowly added with vigorous stirring to *NN'*-dimethylhydrazine dihydrochloride (8 g., 2 mols.; Hatt, *Org. Synth.*, Coll. Vol. II, 1943, p. 208) in pyridine (50 c.c.) and triethylamine (50 c.c.), and the mixture heated at 100° for 1 hr. Cooling to 0° gave triethylamine hydrochloride which was filtered off, and the filtrate was concentrated, washed with potassium carbonate solution, and extracted with chloroform. Crystallisation from benzene gave *NN'*-dimethyl-*NN'*-di*iso*nicotinoylhydrazine (1 g., 27%), m. p. and mixed m. p. 145—147°.

NN'-*Dimethyl*-NN'-*di*iso*nicotinoylhydrazine*.—*NN'*-Dimethylhydrazine dihydrochloride (2·7 g.) was slowly added with efficient stirring to *iso*nicotinoyl chloride hydrochloride (7·5 g., 2 mols.) in pyridine (100 c.c.) and triethylamine (25 c.c.) at 40°. After 1 hour's heating at 100°, working-up as described above gave NN'-*dimethyl*-NN'-*di*iso*nicotinoylhydrazine* (2·9 g., 54%) as needles (from benzene), m. p. 147° (Found: C, 62·1; H, 5·15; N, 20·4. $C_{14}H_{14}O_2N_4$ requires C, 62·2; H, 5·2; N, 20·7%).

N'-*Methyl*iso*nicotinamide*.—Reaction of methyl *iso*nicotinate (2·74 g.) and aqueous methylamine (10 c.c., 30% w/v) for 1 hr. at 100°, and trituration with alcohol–ether of the oil left on removal of solvent, gave the amide (2·6 g., 95%), m. p. 112—113°. The *hydrochloride* crystallised from alcoholic hydrogen chloride as plates, m. p. 205—206° (Found: C, 48·7; H, 5·3; N, 16·3. $C_7H_8ON_2$,HCl requires C, 48·7; H, 5·25; N, 16·2%), and the *picrate* formed needles (from ethanol), m. p. 165° (Found: C, 42·8; H, 3·05. $C_7H_8ON_2,C_6H_3O_7N_3$ requires C, 42·7; H, 3·05%).

N-*Methyl*-N-iso*nicotinoyl*-N'-4-*nitrobenzylidenehydrazine*.—*iso*Nicotinoyl chloride hydrochloride (7·5 g.) in pyridine (75 c.c.) at 50° was added to a well-stirred suspension of *N*-methyl-*N'*-4-nitrobenzylidenehydrazine (7·5 g.; Brady and McHugh, *J.*, 1922, 1652) in triethylamine (50 c.c.) and heated under reflux for 2 hr. The solid *hydrazine* separating on cooling was washed with water and crystallised from pyridine as needles, m. p. 276—277° (8·6 g., 72%) (Found: C, 59·1; H, 4·25; N, 19·8. $C_{14}H_{12}O_3N_4$ requires C, 59·1; H, 4·25; N, 19·7%).

N-*Methyl*-N'-*veratrylidenehydrazine*.—Veratraldehyde (10 g.), methylhydrazine (2·78 g.), and ethanol (30 c.c.) were heated for 3 hr. at 100°. Concentration *in vacuo* and one crystallisation from alcohol afforded the hydrazine (10·1 g., 85%) as prisms, m. p. 95—98°, decomposing rapidly on further purification or storage.

N-*Methyl*-N-iso*nicotinoyl*-N'-*veratrylidenehydrazine*.—The foregoing hydrazine (9 g.), suspended in triethylamine (100 c.c.), was treated with a solution of *iso*nicotinoyl chloride hydrochloride (8·5 g.) in pyridine (100 c.c.) at 50° and left overnight. The solid was filtered off, washed with water and aqueous sodium hydrogen carbonate, and crystallised from methanol as needles, m. p. 163°, of N-*methyl*-N-iso*nicotinoyl*-N'-*veratrylidenehydrazine* (6·4 g., 46%) (Found: C, 64·2; H, 5·75. $C_{16}H_{17}O_3N_3$ requires C, 64·2; H, 5·75%).

N-*Methyl*-N-iso*nicotinoylhydrazine*.—Treatment of the above Schiff's base (1·57 g.) in alcohol (150 c.c.) with 2 : 4-dinitrophenylhydrazine (0·99 g.) in alcoholic N-hydrogen chloride (150 c.c.) at 60° gave veratraldehyde 2 : 4-dinitrophenylhydrazone (1·67 g., 96%), which was removed from the cooled solution after 1 hr. Evaporation *in vacuo* of the filtrate and extraction of the residue with water gave N-*methyl*-N-iso*nicotinoylhydrazine dihydrochloride* (1·1 g., 94%), m. p. 224° (decomp.) (from methanol–chloroform) (Found: C, 37·6; H, 4·95. $C_7H_9ON_3$,2HCl requires C, 37·5; H, 4·95%).

N-(5-*Acetamido*-2-*thenylidene*)-N'-iso*nicotinoylhydrazine*.—A solution of *iso*nicotinoylhydrazine (0·48 g.) and 5-acetamidothiophen-2-aldehyde (0·59 g.; Cymerman-Craig and Willis, *J.*, 1955, 1071) in boiling methanol (10 c.c.) deposited the *Schiff's base* (0·90 g., 90%) within 10 min., forming from nitrobenzene yellow crystals, m. p. 273—275° (Found: C, 54·0; H, 4·25; N, 19·0; S, 10·8. $C_{13}H_{12}O_2N_4S$ requires C, 54·1; H, 4·2; N, 19·4; S, 11·1%).

Methyl iso*Nicotinate Hydrochloride*.—This hydrochloride crystallised from alcohol as hygroscopic plates, m. p. 143—144°. Ternajgo (*Monatsh.*, 1900, **21**, 451) reports m. p. 257° but was probably dealing with *iso*nicotinic acid hydrochloride.

iso*Nicotinamide Picrate*.—The *picrate* crystallised from aqueous alcohol as yellow needles, m. p. 214—215° (Found: C, 41·2; H, 2·55; N, 19·8. $C_6H_6ON_2,C_6H_3O_7N_3$ requires C, 41·0; H, 2·6; N, 19·9%).

*Diacetyl Bis*iso*nicotinoylhydrazone*.—Diacetyl (0·86 g., 1 mol.) and *iso*nicotinoylhydrazine (2·74 g., 2 mols.) were refluxed in alcohol (25 c.c.) for 2 hr., giving the bishydrazone (3·07 g., 95%) which, crystallised from methanol (Soxhlet), had m. p. 287° (decomp.) (Found: C, 59·0; H, 5·0. Calc. for $C_{16}H_{16}O_2N_6$: C, 59·25; H, 5·0%). Yale, Losee, Martins, Holsing, Perry, and Bernstein (*J. Amer. Chem. Soc.*, 1953, **75**, 1933) give m. p. >300° (60% yield).

Condensation with Acetylacetone.—(*a*) Acetylacetone (3 g., 3 mols.) and *iso*nicotinoylhydrazine (2·74 g., 2 mols.) were heated under reflux in methanol (12 c.c.) for 30 min. Removal of solvent gave acetylacetone mono*iso*nicotinoylhydrazone (4·2 g., 95%), needles (from ethyl acetate),

m. p. 133° (Found : C, 60·2; H, 5·95; N, 19·4. Calc. for $C_{11}H_{13}O_2N_3$: C, 60·3; H, 6·0; N, 19·2%). Yale *et al.* (*loc. cit.*) give m. p. 131—133° (49% yield).

(*b*) *iso*Nicotinoylhydrazine (2·74 g., 2 mols.) and acetylacetone (1 g., 1 mol.) were refluxed for 2 hr. in ethanol (10 c.c.). The resultant gum, taken up in ethyl acetate, deposited *NN'*-di-*iso*nicotinoylhydrazine (2·1 g., 86%), crystallising from water as needles, m. p. 256°, undepressed on admixture with an authentic sample (Graf, *J. prakt. Chem.*, 1933, **138**, 289) (Found : C, 59·3; H, 4·2; N, 23·3. Calc. for $C_{12}H_{10}O_2N_4$: C, 59·5; H, 4·15; N, 23·1%). The ethyl acetate mother-liquors afforded an oil which on sublimation (100—120°/15 mm.) gave 2 : 5-dimethylpyrazole (0·48 g., 50%), m. p. and mixed m. p. 106° (Knorr and Rosengarten, *Annalen*, 1894, **279**, 237) (Found : C, 62·3; H, 8·0. Calc. for $C_5H_8N_2$: C, 62·5; H, 8·4%).

(*c*) To *iso*nicotinoylhydrazine (0·69 g., 1 mol.) in boiling alcohol (15 c.c.) was added acetylacetone mono*iso*nicotinoylhydrazone (1·1 g., 1 mol.). After 30 min., evaporation furnished recovered *iso*nicotinoylhydrazine (0·46 g.), and the filtrate with ethyl acetate gave *NN'*-di*iso*nicotinoylhydrazine (0·31 g., 26%), m. p. and mixed m. p. 256°. The soluble fraction on sublimation gave 2 : 5-dimethylpyrazole (0·025 g., 5%), identical in m. p. and mixed m. p. with the material described above.

(*d*) Acetylacetone mono*iso*nicotinoylhydrazone (2·19 g., 1 mol.) was heated at 100° with *iso*nicotinoylhydrazine (1·37 g., 1 mol.) in water (20 c.c.) until dissolution was complete. On cooling, *NN'*-di*iso*nicotinoylhydrazine (1·3 g., 53%) separated, having m. p. and mixed m. p. 256°.

Condensation with Acetonylacetone.—(*a*) Acetonylacetone (4·56 g.) was added to a refluxing solution of *iso*nicotinoylhydrazine (11 g.) in ethanol (200 c.c.). After 1 hr., the product which separated crystallised from methanol (Soxhlet), yielding *acetonylacetone bisisonicotinoylhydrazone* (11·1 g., 79%), m. p. 182° (Found : C, 61·0; H, 5·75. $C_{18}H_{20}O_2N_6$ requires C, 61·4; H, 5·7%). The alcoholic solution gave 2 : 5-dimethyl-1-*iso*nicotinamidopyrrole (1·1 g., 13%), crystallising from benzene as needles, m. p. 146° (Found : C, 66·7; H, 6·05. Calc. for $C_{12}H_{13}ON_3$: C, 66·9; H, 6·1%). Yale *et al.* (*loc. cit.*) give m. p. 147—148°.

(*b*) Dissolution of acetonylacetone bis*iso*nicotinoylhydrazone (0·35 g.) in boiling nitrobenzene gave *iso*nicotinoylhydrazine (0·108 g., 79%) (m. p. and mixed m. p.).

(*c*) Reaction of acetonylacetone bis*iso*nicotinoylhydrazone with picric acid gave only *isonicotinoylhydrazine dipicrate*, separating from water as yellow needles, m. p. 185° (Found : C, 36·3; H, 2·45. $C_6H_7ON_3,2C_6H_3O_7N_3$ requires C, 36·5; H, 2·2%).

(*d*) Acetonylacetone bis*iso*nicotinoylhydrazone (1·6 g.) was refluxed in ethylene glycol (10 c.c.) for 5 min. Addition of water and crystallisation of the precipitate from benzene gave 2 : 5-dimethyl-1-*iso*nicotinamidopyrrole (0·4 g., 41%), m. p. and mixed m. p. 145°.

4-Acetylpyridine Oxime.—The oxime crystallised from aqueous alcohol as white laths, m. p. 158° (Found : C, 61·7; H, 6·05. Calc. for $C_7H_8ON_2$: C, 61·7; H, 5·95%). Pinner (*Ber.*, 1901, **34**, 4250) records m. p. 142°.

This (5 g.) in pyridine (10 c.c.) was treated at 0—5° with finely powdered toluene-*p*-sulphonyl chloride (7·65 g.) and set aside for 24 hr. Addition of ice and isolation in the usual manner gave the *ketoxime toluene*-p-*sulphonate* (9·7 g., 90%) as prisms, m. p. 80° (from aqueous alcohol) (Found : C, 57·9; H, 4·85. $C_{14}H_{14}O_3N_2S$ requires C, 57·9; H, 4·85%).

Rearrangement. A solution of potassium (0·49 g.) in ethanol (12 c.c.) was treated with the above toluene-*p*-sulphonate (3·1 g.) in ethanol (8 c.c.) under nitrogen. Potassium toluene-*p*-sulphonate separated almost immediately and was removed (2·12 g., 95%) after addition of ether (160 c.c.) 1 hr. later. Extraction of the ethereal solution with 2N-hydrochloric acid (4 × 40 c.c.), evaporation at $<40°$ of the extracts *in vacuo*, and crystallisation of the residue from methanol gave a hydrochloride (1·15 g.), m. p. 230—235° (decomp.), rapidly darkening in air, on heating, or on attempted recrystallisation. Burrus and Powell (*J. Amer. Chem. Soc.*, 1945, **67**, 1468) record m. p. 240—245° (decomp.) for aminomethyl 4-pyridyl ketone dihydrochloride.

The hydrochloride (0·9 g.), on dissolution in sodium hydrogen carbonate solution and extraction with benzene, gave 2 : 5-*di*-4'-*pyridylpyrazine* (0·02 g.), as prisms, m. p. 231—232°, after sublimation and crystallisation from alcohol (Found : C, 71·3; H, 4·6. $C_{14}H_{10}N_4$ requires C, 71·7; H, 4·3%), showing $\lambda_{max.}$ 2600 (ε 13,200), 3070 (ε 20,400), and $\lambda_{min.}$ 2300 (ε 4000), 2750 A (ε 9550) in EtOH.

Methyl p-*Diethylaminobenzoate.*—Obtained by esterification of *p*-diethylaminobenzoic acid (Rousset, *Bull. Soc. chim. France*, 1894, **11**, 318) with methanol, sulphuric acid, and benzene, the *ester* had m. p. 45—47°, b. p. 94—98°/0·001 mm. (Found : C, 69·8; H, 8·25; N, 6·65. $C_{12}H_{17}O_2N$ requires C, 69·5; H, 8·25; N, 6·75%).

Di-(p-*diethylaminobenzoyl*)*hydrazine.*—The above ester (2 g.), hydrazine hydrate (8 g.,

100%), and 2-ethoxyethanol (5 c.c.) were refluxed for 11 hr. Trituration of the oil with benzene gave *di*-(p-*diethylaminobenzoyl*)*hydrazine* (1·2 g., 69%), crystallising from pyridine as needles, m. p. 267° (Found : C, 69·0; H, 7·85; N, 14·4. $C_{22}H_{30}O_2N_4$ requires C, 69·1; H, 7·9; N, 14·6%)

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