# Diazaindenes (Azaindoles). Part 7.[1] Formation of Imidazo[1,2-*a*]pyridinium-8-carboxylate in an Attempt to prepare Pyrrolo[2,3-*b*]pyridin-3-one

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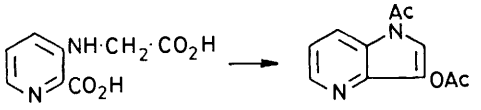
Attempts to obtain *N*-(3-carboxy-2-pyridyl)glycine (5) from 2-chloro-3-cyanopyridine are described. The ring–chain tautomerism of certain *N*-(2-pyridyl)aminoacetaldehydes is discussed. Three preparations of *N*-3-(carboxy-2-pyridyl)aminoacetaldehyde (20) and its cyclisation to the zwitterionic imidazo[1,2-*a*]pyridinium-8-carboxylate (23) are given.

THOSE pyrrolopyridines (azaindoles) containing one carbonyl function in the five-membered ring (azaoxindoles and azaindoxyls) are of interest as potential intermediates in the synthesis of pyrrolopyridines and their 2,3-dione derivatives (azaisatins). A few examples of each of these systems are known.[2,3] In particular, Willette has reported the preparation of 3-acetoxy-1-



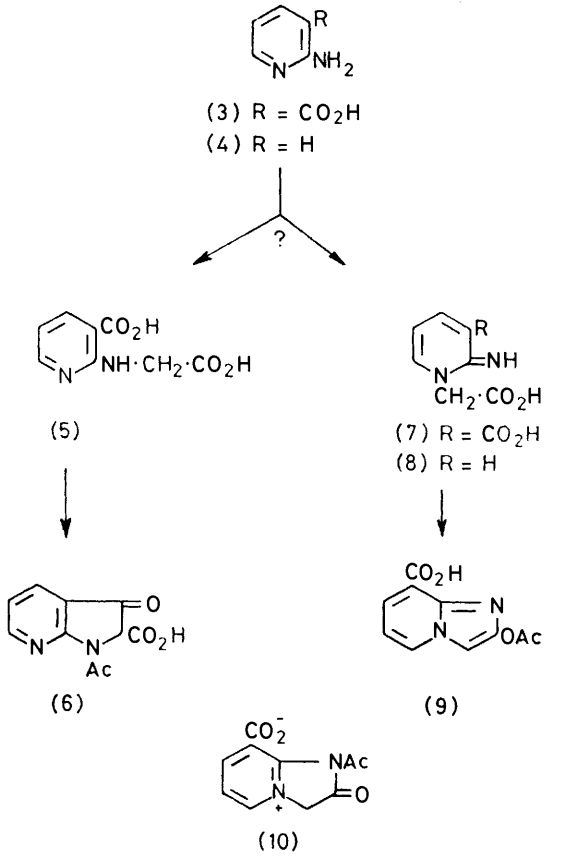
(2)

acetylpyrrolo[3,2-*b*]pyridine (2) (a derivative of 4-azaindoxyl) by cyclisation of the appropriately disubstituted pyridine (1). However, the reaction of 2-aminonicotinic acid (3) with chloroacetic acid and cyclisation of the intermediate product in the presence of acetic anhydride would lead to 1-acetyl-3-oxo-2,3-dihydropyrrolo[2,3-*b*]pyridine-2-carboxylic acid (6), as claimed by Willette,[4] only if the intermediate has the structure (5) originally suggested by Sucharda.[5] It is more likely, however, that the amine (3) reacts with chloroacetic acid to give the imine (7) [6,7] just as 2-aminopyridine (4) gives the imine (8) and that the cyclised product is an imidazopyridine [*e.g.* (9) or (10)].

We were unable to repeat Willette's preparation of (6), and record here our results from investigations of related reactions.

Attempts to cause reaction between 2-chloro-3-cyanopyridine (11) and glycine in the presence of aqueous base gave 2-(carboxymethylamino)nicotinamide (12) (Scheme 2). However the reaction was difficult to reproduce and 2-chloronicotinic acid was the usual isolable product. Several attempts to obtain the *N*-(3-cyano-2-pyridyl)-glycine ester from (11) and ethyl glycinate hydrochloride in the presence of base were unsuccessful, as were efforts to obtain a reaction between aminoacetaldehyde dimethyl acetal and 2-chloronicotinic acid. A lack of reactivity of the halogen in 2-chloro-3-cyanopyridine and 2-chloronicotinic acid has been found by other workers.[8]

2-Chloro-3-cyanopyridine does undergo reaction with the more nucleophilic amines, *e.g.* benzylamine [9] and aminoacetaldehyde dimethyl acetal. The latter readily yielded *N*-(3-cyano-2-pyridyl)aminoacetaldehyde dimethyl acetal (13), which underwent hydrolysis in dilute acid to give the aldehyde, isolated as its hydrochloride (14). The amino-acetal (13) was the starting material for the preparation of a number of other compounds. Hydrolysis of the acetal with hot sodium hydroxide solution followed by acidification of the hot solution with



SCHEME 1

hydrochloric acid yielded 2-chloronicotinic acid, but the aldehyde-acid (20) was obtained when the cold alkaline mixture from (13) was acidified with dilute hydrochloric acid and then warmed. Isolation of this aldehyde-acid (20) proved to be difficult and alternative routes from the acetal (13) were investigated.

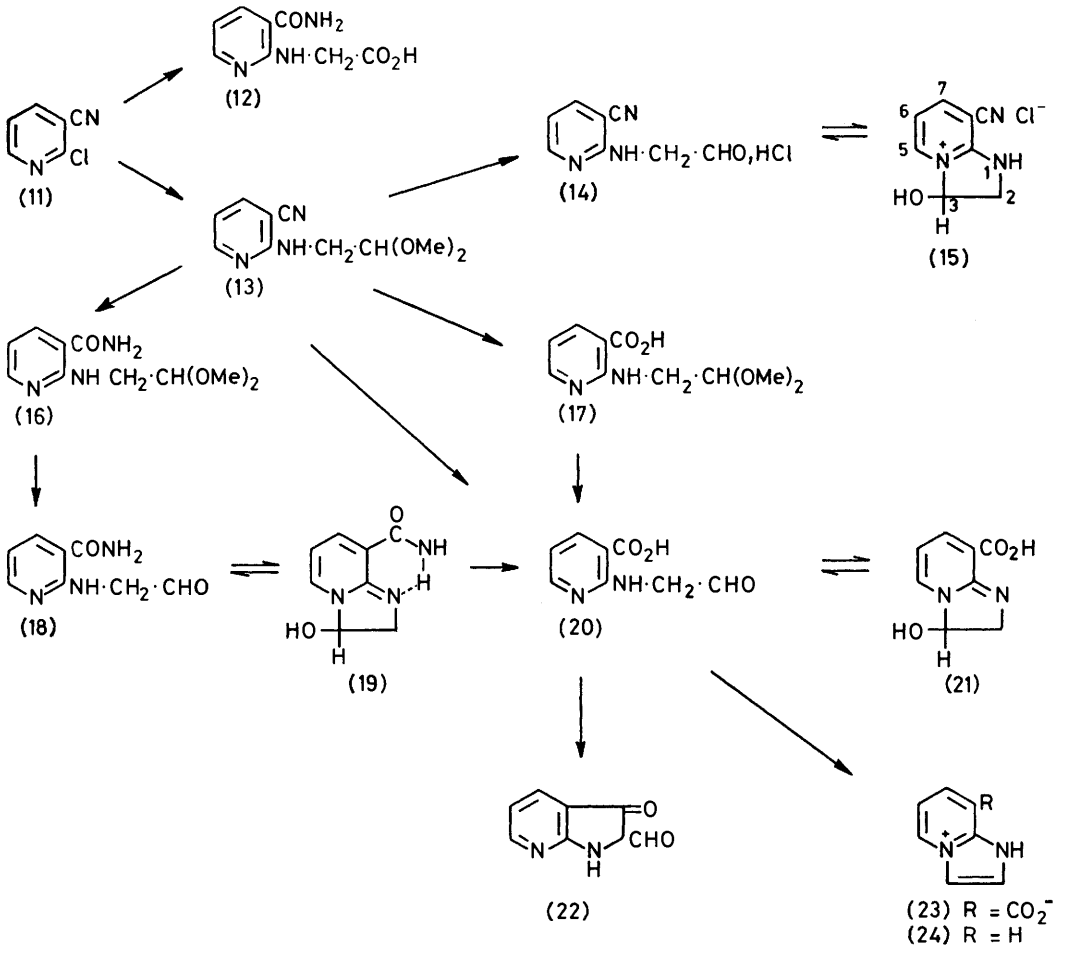
Hydrolysis of (13) with barium hydroxide solution gave the acid-acetal (17), but again isolation and purification of the compound was troublesome. However, acid hydrolysis of (17) yielded the aldehyde-acid

(20). A better route to (20) was found to be the converion of the cyanide (13) into the amido-acetal (16) (a more readily purified compound) and acidic hydrolysis to (18), followed by treatment of the amide (18) with nitrous acid to give (20). The aldehyde-acid and the other aldehydes in this work, *e.g.* (14) and (18), gave characteristic yellow solutions in alkali.

Certain aspects of the properties of the aldehydes (14), (18), and (20) appeared to be anomalous. The aldehyde-acid (20) was unexpectedly difficult to oxidise to the dicarboxylic acid (5) and we were unable to isolate this compound. Thus it was not possible to make a comparison with the compounds obtained using the route described by Sucharda and Willette. More striking was that, although the $^1$H n.m.r. spectra of the acetals (13), (14), and (17) are first order, the spectra of the expected substituted aldehydes (14), (19), and (20) are not readily interpreted. Most significantly, they do not show a signal at $\delta$ *ca.* 10 attributable to an formyl proton, though the i.r. spectrum of (18) shows peaks at 1 680 and 1 660 cm$^{-1}$ ascribable to the two different carbonyl functions. Similarly, the aldehyde-acid (20) yielded a 2,4-dinitrophenylhydrazone and showed absorptions at 1 705 and 1 650 cm$^{-1}$ in its i.r. spectrum. It seems likely that these compounds exist in both aldehyde, (14), (18), and (20), and bicyclic forms, (15), (19), and (21), respectively, and that the latter are preferred in dimethyl sulphoxide solution. The n.m.r. spectra of the ' aldehydes ' are now more readily understandable, since the ' formyl ' proton is present as part of the non-aromatic methine group.

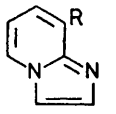
Treatment of the aldehyde-acid (20) with acetic anhydride in the presence of potassium acetate yielded a product which was expected to be either the pyrrolopyridine derivative (22) or the isomeric imidazo[1,2-*a*]-pyridine (23) [or (25)]. The mass spectrum showed the molecular ion at the expected, *m/e* 162, and fragmentation by loss of $CO_2$ and then $C_2H_2$ favoured (23) [or (25)]. Decarboxylation occurred when the compound was heated strongly and the product was imidazo[1,2-*a*]-pyridine (26), thus confirming the nature of the ring system. This finding also lends some support to our postulated 2,3-dihydroimidazopyridine structure for the ' aldehydes '.

The $^1$H n.m.r. spectra of imidazo[1,2-*a*]pyridines and their salts have been the subject of several investigations.[10] Paudler and his co-workers [11,12] have shown that the 3-H is more deshielded than the 2-H in the




SCHEME 2

salts, while the reverse is true for the free bases, and that the cation of the heterocycle hydrochlorides is best represented by (24). A comparison of the $^1H$ n.m.r. spectrum of the cyclised product from the aldehydo-acid shows peaks at δ 8.6 (2-H), 8.1 (3-H), 9.3 (5-H), 7.6 (6-H), and 8.5 (7-H) which closely agrees with the



(25) R = $CO_2H$
(26) R = H

spectrum of the cation of imidazo[1,2-*a*]pyridine hydrobromide (24) [δ 8.8 (2-H), 8.1 (3-H), 9.4 (5-H), and 7.6 (6-H)] but differs from that of imidazo[1,2-*a*]pyridine (26) [δ 7.7 (2-H), 7.6 (3-H), 8.05 (5-H), and 6.5 (6-H)].[12] Thus we favour the zwitterion formulation (23) for the cyclised product.

## EXPERIMENTAL

The i.r. and n.m.r. spectra were recorded on instruments described previously.[13] The mass spectra were recorded on a Perkin-Elmer RMS-4 spectrometer operated at 70 eV.

N-(3-*Carboxamido*-2-*pyridyl*)*glycine* (12).—A solution of glycine (3.75 g) in water (25 cm³) was added to a stirred solution of 2-chloro-3-cyanopyridine [8] (6.9 g) and sodium carbonate (8.5 g) in water (40 cm³), and the mixture was boiled under reflux for 12 h. The cold solution was acidified to pH 3 with concentrated hydrochloric acid and the precipitate was collected. The crude product was dissolved in a slight excess of sodium hydroxide solution and the insoluble impurity removed. Addition of hydrochloric acid to give pH 3 produced a precipitate which was filtered off, washed with water, and crystallised from water as N-(3-*carboxamido*-2-*pyridyl*)*glycine* (1.4 g), m.p. 241—243° (decomp.) (Found: C, 49.5; H, 4.5; N, 21.2. $C_8H_9N_3O_3$ requires C, 49.2; H, 4.6; N, 21.5%), $\nu_{max.}$ 3 420 (OH), 3 150 ($NH_2$), 1 680 (CO), and 1 650 (CO) $cm^{-1}$; δ[$(CD_3)_2SO$] 8.8 (1 H, t, *J* 6 Hz, exchanged in $D_2O$, NH), 8.2 (2 H, m, 4- and 6-H), 7.8br (1 H, s, exchanged in $D_2O$, OH), 6.6 (1 H, q, 5-H), 5.6br (2 H, s, exchanged in $D_2O$, $NH_2$), and 4.2 (2 H, d, *J* 6 Hz, exchanged in $D_2O$, $CH_2$).

N-(3-*Cyano*-2-*pyridyl*)*aminoacetaldehyde Dimethyl Acetal* (13).—2-Chloro-3-cyanopyridine (2 g) and aminoacetaldehyde dimethyl acetal (3 g) were heated gently under reflux to 130° and maintained at that temperature for 5 min. The cooled mixture was poured into water containing sodium hydrogencarbonate. The solid was removed and crystallised from light petroleum (b.p. 60—80°) to give N-(3-*cyano*-2-*pyridyl*)*aminoacetaldehyde dimethyl acetal* (3.8 g), m.p. 73—74° (Found: C, 58.1; H, 6.4; N, 20.2. $C_{10}H_{13}N_3O_2$ requires C, 57.6; H, 6.7; N, 20.2%), $\nu_{max.}$ 3 430 (NH) and 2 230 (CN) $cm^{-1}$; δ[$(CD_3)_2SO$] 8.3 (1 H, q, *J* 5 and 2 Hz, 6-H), 7.9 (1 H, q, *J* 8 and 2 Hz, 4-H), 6.95 (1 H, t, *J* 6 Hz, exchanged in $D_2O$, NH), 6.7 (1 H, q, *J* 5 and 8 Hz, 5-H), 4.6 (1 H, t, *J* 5 Hz, CH), 3.5 (2 H, m, became a doublet with *J* 5 Hz on addition of $D_2O$, $CH_2$), and 3.4 (6 H, s, 2 × Me).

N-(3-*Cyano*-2-*pyridyl*)*aminoacetaldehyde Hydrochloride* (14).—The aforementioned dimethyl acetal (2 g) was warmed with dilute hydrochloric acid (20 cm³) for 1 h and then evaporated to dryness under vacuum. Crystallisation of the solid from aqueous ethanol gave N-(3-*cyano*-2-*pyridyl*)-*aminoacetaldehyde hydrochloride* (1.4 g), m.p. 205—206° (Found: C, 48.6; H, 4.5; Cl, 17.7. $C_8H_8ClN_3O$ requires C, 48.6; H, 4.1; Cl, 18.0%), $\nu_{max.}$ 3 430 (NH), 2 230 (CN), and 1 700 (CO) $cm^{-1}$, δ[$(CD_3)_2SO$] 10.7br (1 H, s, exchanged in $D_2O$, OH), 8.6 {2 H, m which becomes a triplet in $D_2O$, 5- and 7-H [structure (15)]}, 7.2 (1 H, t, C*H*OH), 6.5br (1 H, t which becomes a sharp t in $D_2O$, 6-H), 6.2br (1 H, s, exchanged in $D_2O$, NH), and 4.0 (2 H, t, $CH_2$).

N-(3-*Carboxy*-2-*pyridyl*)*aminoacetaldehyde Dimethyl Acetal* (17).—*N*-(3-Cyano-2-pyridyl)aminoacetaldehyde dimethyl acetal (6 g) and aqueous barium hydroxide [$Ba(OH)_2,8H_2O$ (9 g); 50 cm³] were refluxed until evolution of ammonia had ceased (3—4 h). Carbon dioxide was passed through the cooled solution and the precipitated barium carbonate removed. The filtrate was evaporated to dryness and the residue crystallised from ethanol to give N-(3-*carboxy*-2-*pyridyl*)*aminoacetaldehyde dimethyl acetal* (4.2 g), m.p. 134—135° (Found: C, 52.7; H, 6.3; N, 12.5%; $M^+$, 226. $C_{10}H_{14}N_2O_4$ requires C, 53.1; H, 6.2; N, 12.9%; *M*, 226), $\nu_{max.}$ 3 450 (NH) and 3 150 (OH) $cm^{-1}$.

N-(3-*Carboxamido*-2-*pyridyl*)*aminoacetaldehyde Dimethyl Acetal* (16).—The cyanopyridylaminoaldehyde dimethyl acetal (10 g), in ethanol (500 cm³), was added to aqueous sodium hydroxide (8 cm³, 5M) and hydrogen peroxide solution (500 cm³, 10%) and the mixture maintained at 50° for 1 h. The solution was evaporated to dryness and a small volume of aqueous sodium hydroxide was added. The solid was filtered off, washed with water, and crystallised from aqueous ethanol to give N-(3-*carboxamido*-2-*pyridyl*)*aminoacetaldehyde dimethyl acetal* (8.3 g), m.p. 83—84° (Found: C, 52.9; H, 6.7; N, 18.8. $C_{10}H_{15}N_3O_3$ requires C, 53.3; H, 6.7; N, 18.7%), $\nu_{max.}$ 3 250 ($NH_2$) and 1 670 (CO) $cm^{-1}$; δ[$(CD_3)_2SO$)] 9.4 (1 H, t, *J* 6 Hz, exchanged in $D_2O$, NH), 8.8 (2 H, m, 4- and 6-H), 8.3br (2 H, s, exchanged in $D_2O$, $NH_2$), 7.2 (1 H, q, 5-H), 4.9 (1 H, t, *J* 6 Hz), 3.8 (2 H, m, became a d with *J* 6 Hz in $D_2O$, $CH_2$), and 3.6 (6 H, s, 2 × Me).

N-(3-*Carboxamido*-2-*pyridyl*)*aminoacetaldehyde* (18).—The amido-acetal (2 g) was warmed with dilute hydrochloric acid and evaporated to dryness. Crystallisation of the residue from aqueous ethanol gave N-(3-*carboxamido*-2-*pyridyl*)-*aminoacetaldehyde* (1.6 g), m.p. 213—215° (Found: C, 53.2; H, 5.3; N, 23.6%; $M^+$, 179. $C_8H_9N_2O_2$ requires C, 53.6; H, 5.0; H, 23.5%; *M*, 179), $\nu_{max.}$ 3 500 and 3 350 ($NH_2$), 3 320 (NH), 1 680, and 1 660 (CO and CHO) $cm^{-1}$; δ[$(CD_3)_2SO$] 9.4 (1 H, s, exchanged in $D_2O$, OH), 8.7 (3 H, d, becomes a t equivalent to 2 H in $D_2O$, 5- and 7-H and NH), 8.0br (1 H, s, exchanged in $D_2O$, hydrogen bonded NH), 7.1 (1 H, t, C*H*OH), 6.4br (1 H, s, becomes a dd in $D_2O$, 6-H), and 4.0 (2 H, d, $CH_2$).

N-(3-*Carboxy*-2-*pyridyl*)*aminoacetaldehyde* (20).—This compound was prepared by three routes.

(a) *N*-(3-Carboxamido-2-pyridyl)aminoacetaldehyde dimethyl acetal (2.2 g) was added to dilute hydrochloric acid (25 cm³, 1M) and warmed to 50° for 1 h. Aqueous sodium nitrite (1 g, 5 cm³) was added to the cooled solution until evolution of nitrogen ceased. The mixture was warmed on a boiling water-bath for 30 min and evaporated to dryness. The residue was extracted with hot ethanol and the cooled solution then deposited N-(3-*carboxy*-2-*pyridyl*)*aminoacetaldehyde* (1.2 g), m.p. 262—264° (Found: C, 52.9; H, 4.1; N, 15.4%; $M^+$, 180. $C_8H_7N_2O_3$ requires C, 53.3; H, 4.4; N, 15.6%; *M*, 180), $\nu_{max.}$ 3 450 (NH), 3 300 (OH), 1 705

(CHO), and 1 650 (CO) $cm^{-1}$; δ[$(CD_3)_2SO$] 9.4 {1 H, s, exchanged in $D_2O$, OH, or NH [structure (20)]}, 8.6 (2 H, q, 5- and 7-H), 7.1 (1 H, t, C*H*OH), 6.5 (1 H, t, 6-H), and 3.9 (2 H, q, becomes a d in $D_2O$, $CH_2$). One of the expected exchangeable signals (OH or NH) was not observed.

(b) *N*-(3-Cyano-2-pyridyl)aminoacetaldehyde dimethyl acetal (2.1 g) and aqueous sodium hydroxide (25 $cm^3$, 4M) were refluxed until evolution of ammonia ceased (3—4 h). The solution was evaporated to small volume, acidified with hydrochloric acid and warmed for 10 min, and then evaporated to small volume. Addition of concentrated hydrochloric acid gave a precipitate of sodium chloride, which was removed. The solution was evaporated to dryness under vacuum and the residue crystallised from aqueous ethanol to give the aldehyde-acid (1.3 g).

(c) *N*-(3-Carboxy-2-pyridyl)aminoacetaldehyde dimethyl acetal (2.2 g) was warmed on a water-bath with dilute hydrochloric acid for 15 min. The solution was evaporated to dryness to give the aldehyde-acid (1.7 g).

The aldehyde-acid (0.15 g) was dissolved in a mixture of 2,4-dinitrophenylhydrazine (0.5 g) in dimethylformamide (10 $cm^3$), concentrated hydrochloric acid (2 drops) was added,[14] and the mixture allowed to stand for 15 min. After trituration of the mixture with dilute hydrochloric acid, the solid was collected and crystallised from aqueous ethanol to give N-(*3-carboxy-2-pyridyl*)*aminoacetaldehyde 2,4-dinitrophenylhydrazone*, m.p. 250—252° (Found: C, 46.3; H, 3.4. $C_{14}H_{12}N_6O_6$ requires C, 46.7; H, 3.3%), $\nu_{max.}$ 1 610 $cm^{-1}$ (C:N).

1H-*Imidazo*[1,2-a]*pyridinium-8-carboxylate* (23).—*N*-(3-Carboxy-2-pyridyl)aminoacetaldehyde (1.5 g), sodium acetate (0.5 g), and acetic anhydride (10 $cm^3$) were refluxed for 30 min. Water was carefully added to the cooled solution and the mixture evaporated to dryness. The residue was treated with hydrochloric acid (10 $cm^3$, 18M), the solution evaporated to small volume, and acetic acid added dropwise until precipitation of sodium chloride ceased. The solid was filtered off, the filtrate was diluted with water (10 $cm^3$), boiled with charcoal, and evaporated to small volume. The cold solution deposited 1H-*imidazo*[1,2-a]*pyridinium-8-carboxylate* (0.9 g), m.p. 239—240° (Found: C, 58.9; H, 4.1; N, 17.1%; $M^+$, 162. $C_8H_6N_2O_2$ requires C, 59.3; H, 3.7; N, 17.3%; *M*, 162), $\nu_{max.}$ 1 690 (CO) $cm^{-1}$; δ[$(CD_3)_2SO$] 9.3 (1 H, d, *J* 7 Hz, 5-H), 8.6 (1 H, d, *J* 2 Hz, 2-H), 8.5 (1 H, d, *J* 7 Hz, 7-H), 8.1 (1 H, d, *J* 2 Hz, 3-H), and 7.6 (1 H, t, 6-H).

*Decarboxylation of* 1H-*Imidazo*[1,2-a]*pyridinium-8-carboxylate*.—The acid was heated at 250—270° for 4 h and the resultant oil was purified by column chromatography (alumina–benzene). The product had an i.r. spectrum identical to that of imidazo[1,2-*a*]pyridine prepared by a known route.[15] Both samples gave the same picrate, m.p. 203—205° (lit.,[15] 203—205°).

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