1102. *Diazaindenes ("Azaindoles"). Part III.*[1] *Synthetic Approaches (Preliminary Results)*

By Robert E. Willette

Diazaindenes ("azaindoles") are of biological interest as possible metabilite antagonists to naturally-occurring indoles and purines.[2] However, the known syntheses[1-3] of the diazaindenes and their suitably substituted derivatives are inconvenient, and usually give very small yields. Most of the previously attempted syntheses require electron availability in the ring, *e.g.*, the Fischer indole ring closure, or the removal of a proton from its alkyl substituent, *e.g.*, Madelung and Reissert methods.

This Paper describes attempts to prepare diazaindenes from disubstituted pyridines requiring other than base-catalysed ring closures, and from indoxyl intermediates by methods other than those already known.[1-3]

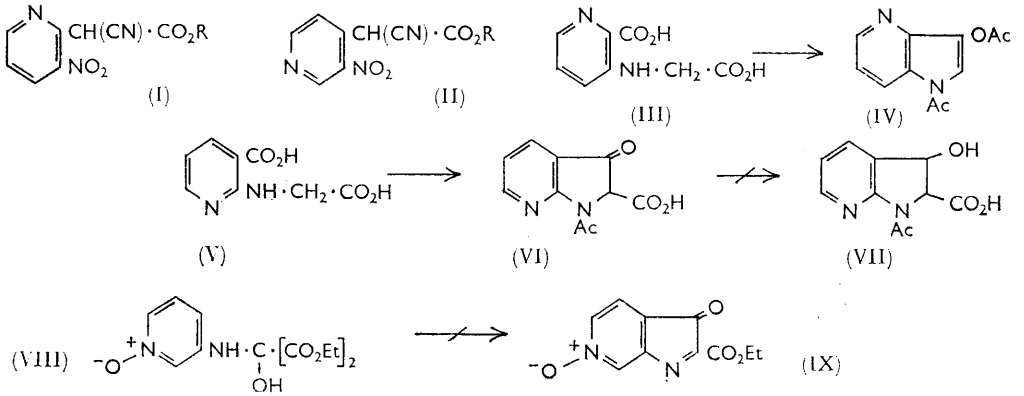
In an endeavour to prepare nitropyridylacetonitriles similar to the *o*-nitrophenylacetonitriles which have given indoles by reductive cyclisation,[4] five new 3-nitro-2- (I; R = Me, Et, CH_2Ph) and -4-pyridylcyanoacetates (II; R = Et, CH_2Ph) were synthesised from 2-chloro-3-nitro- and 4-methoxy-3-nitro-pyridine, respectively, in high yield, by condensation with cyanoacetic esters and potassium t-butoxide in t-butyl alcohol according to a general method.[5] However, these esters resisted hydrogenation, *e.g.*, over 30% palladium–charcoal, Raney nickel (W-2, W-5, and W-7), and platinum oxide at 4—100 atm. and 25—90°. They also failed to hydrolyse under basic or acidic conditions. The methyl ester (I; R = Me) was recovered from treatment with methanolic ammonia containing sodium methoxide. The benzyl esters (I and II; R = CH_2Ph) were prepared in the hope that they might undergo hydrogenolysis to the acids, but they gave the amino-cyanoacetates in 21 and 50% yields, respectively. These amino-esters did not absorb any further hydrogen under more rigorous conditions.

The synthesis of some diazaindanones was undertaken with two aims: (*a*) their possible reduction[6] to diazaindenes, (*b*) their suitability as intermediates for the introduction of substituents into the 3-position by established methods.[7]

Employing the usual conditions for the synthesis of *ON*-diacetylindoxyls,[8] the diacid

[1] Part II, A. Albert and R. E. Willette, *J.*, 1964, 4063.
[2] T. Adler and A. Albert, *J.*, 1960, 1794.
[3] (*a*) W. Herz and D. R. Murty, *J. Org. Chem.*, 1961, **26**, 122; (*b*) M. M. Robison, B. L. Robison, and F. P. Butler, *J. Amer. Chem. Soc.*, 1959, **81**, 743, and references cited therein; (*c*) S. Siddappa, *J. Karnatak Univ.*, 1962, **7**, 26.
[4] G. N. Walker, *J. Amer. Chem. Soc.*, 1955, **77**, 3844; H. Plieninger and I. Nógrádi, *Chem. Ber.* 1955, **88**, 1961; H. R. Snyder, E. P. Merica, C. G. Force, and E. G. White, *J. Amer. Chem. Soc.*, 1958, **80**, 4622.
[5] C. A. Grob and O. Weissbach, *Helv. Chim. Acta*, 1961, **44**, 1748.
[6] U.S.P. 2,365,966 (*Chem. Abs.*, 1946, **40**, 609); T. Komai, *Pharm. Bull.* (*Tokyo*), 1956, **4**, 261.
[7] G. Hallmann, *Chem. Ber.*, 1962, **95**, 1138; J. R. Piper and F. J. Stevens, *J. Org. Chem.*, 1962, **27**, 3134; M. C. Bettembourg and S. David, *Bull. Soc. chim. France*, 1962, 772; C. S. Franklin and A. C. White, *J.*, 1963, 1335; C. D. Nenitzescu and D. Ralleanu, *Chem. Ber.*, 1958, **91**, 1141.
[8] S. J. Holt and A. W. Sadler, *Proc. Roy. Soc.*, 1958, *B*, **148**, 481.

(III) was cyclised to 3-acetoxy-1-acetyl-1,4-diazaindene (IV) in 22% yield. By substituting *fused* potassium acetate for the sodium salt, yields of the indoxyl (IV) were raised to 63%. Decomposition resulted from treatment with dilute alkali, refluxing sodium



sulphide in 50% ethanol, sodium amalgam, or sodium borohydride. All attempts to prepare the 1,5- and 1,6-diazaisomers by the above procedures failed.

Treatment of 2-(carboxymethyl)aminonicotinic acid (V) with acetic anhydride and potassium acetate gave, instead of the expected diacetylindoxyl, the *N*-acetylindoxylic acid (VI). An attempt with the potassium salt of (V) by Holt's procedure [9] failed. The acid (VI) was recovered unchanged from refluxing 2N-sodium hydroxide. Efforts to reduce it to the hydroxy-indoline (VII) also failed, and it decomposed under decarboxylating conditions.

Attempts were then made to prepare the indoxyls by cyclisation of pyridylamino- (or imino-)malonates.[10] Thus, 3-aminopyridine 1-oxide was condensed with ethyl mesoxalate to give the aminohydroxymalonate (VIII). It did not dehydrate in sulphuric acid, or in refluxing toluene or xylene with a few drops of sulphuric acid, and it decomposed upon sublimation. Attempts to cyclise it to the 3-oxo-3*H*-indole (IX) by heating in diphenyl ether under a variety of conditions gave intractable tars.

Experimental

Microanalyses were by Dr. J. E. Fildes and her staff.

Ethyl Pyruvate 3-Pyridylhydrazone 1-Oxide.—3-Hydrazinopyridine 1-oxide [11] (0·1 g.), ethyl pyruvate (0·1 g.), and ethanol (2 ml.) were heated on a steam-bath for 1 hr. Cooling afforded the *hydrazone* (0·1 g., 56%), m. p. 214—216° (from ethanol) (Found: C, 53·7; H, 6·0; N, 18·6. $C_{10}H_{13}N_3O_3$ requires C, 53·8; H, 5·9; N, 18·8%).

3-Nitro-2- and -4-pyridylcyanoacetates.—The cyanoacetic acid ester (0·022 mol.) was added to a solution of potassium (0·02 mol.) in anhydrous t-butanol (25 ml.). To the resultant suspension was added a hot solution of 2- or 4-chloro-3-nitropyridine (0·01 mol.) in t-butyl alcohol (25 ml.). The red mixture was heated under reflux protected from moisture, for 5—12 hr. at 120—130°. The cooled mixture was acidified with N-hydrochloric acid (15 ml.), and most of the alcohol removed *in vacuo*. The residues crystallised from aqueous ethanol as bright orange needles. Analytical samples were recrystallised from methanol or aqueous ethanol.

				Analysis					
				Found (%)			Required (%)		
Ester	Position	M. p.	Yield (%)	C	H	N	C	H	N
Methyl.....	2	186—188°	82	48·7	3·5	18·5	48·9	3·2	19·0
Ethyl	2	136—137	87	51·2	3·9	17·7	51·1	3·9	17·9
Ethyl	4	177—178	52	51·2	4·2	17·4	51·1	3·9	17·9
Benzyl.....	2	141—142	77	60·6	3·4	13·8	60·6	3·7	14·1
Benzyl.....	4	**204** (decomp.)	60	60·4	3·7	13·9	60·6	3·7	14·1

[9] S. J. Holt, "General Cytochemical Methods," Academic Press, New York, 1958, vol. 1, p. 389.
[10] R. Blank, *Ber.*, 1898, **31**, 1812.
[11] M. Bellas and H. Suschitzky, *J.*, 1963, 4007.

Benzyl 3-Amino-2-pyridylcyanoacetate.—The nitro-ester (2·0 g.) was suspended in ethyl acetate (150 ml.) and shaken with 10% palladium–charcoal (1·0 g.) at 80—90° under 3·2 atm. of hydrogen for 2½ hr. The cooled suspension was filtered, and the catalyst washed with ethyl acetate. The filtrate was evaporated *in vacuo* and the residue, crystallised from dilute ethanol, gave the *amino-ester* (0·4 g., 21%) as fine yellow needles, m. p. 128—130°. Recrystallisation from ethanol and drying at 70°/1 mm. raised the m. p. to 139—140° (Found: C, 67·2; H, 4·75; N, 15·8. $C_{15}H_{13}N_3O_2$ requires C, 67·4; H, 4·9; N, 15·7%).

Benzyl 3-Amino-4-pyridylcyanoacetate.—The nitro-ester (1·4 g.) was reduced in the same way as the 2-isomer to give the *amino-ester* (0·65 g., 50%), m. p. 129—131° (decomp. at 140°) after two recrystallisations from water (Found, for material dried at 70°/1 mm.: C, 65·2; H, 5·1; N, 15·3. $C_{15}H_{13}N_3O_2,0{\cdot}5H_2O$ requires C, 65·2; H, 5·1; N, 15·2%).

3-Nitro-2-picoline 1-Oxide.—To 3-nitro-2-picoline (from 1·76 g. of its hydrochloride), dissolved in glacial acetic acid (6 ml.), was added 30% hydrogen peroxide (2 ml.), and the solution heated on a steam-bath for 3 hr. Additional peroxide (1 ml.) was added, and heating continued overnight (19 hr.). Addition of water and evaporation *in vacuo* afforded, [after drying in chloroform (Na_2CO_3) and recrystallisation from methanol] fine yellow needles of the *N-oxide* (0·3 g., 20%), m. p. 158—159° (Found: C, 47·2; H, 4·1; N, 18·1. $C_6H_6N_2O_3$ requires C, 46·8; H, 3·9; N, 18·2%).

3-Acetoxy-1-acetyl-1,4-diazaindene.—A mixture of 3-(carboxymethyl)aminopicolinic acid [12] (2·2 g.), freshly fused potassium acetate (2·7 g.), and acetic anhydride (15 ml.) was heated with stirring (120—130°) for 40 min. The dark mixture was cooled. The potassium acetate was filtered off, and washed with a little acetic anhydride. The filtrate was concentrated to small volume *in vacuo*, and the residue treated with water. This solution was evaporated to dryness and the residue, recrystallised from aqueous ethanol, gave *3-acetoxy-1-acetyl-1,4-diazaindene* (1·55 g., 63%), m. p. 122—126°. Recrystallisation from absolute ethanol gave colourless needles, m. p. 125—127° (Found: C, 60·8; H, 4·8; N, 12·9. $C_{11}H_{10}N_2O_3$ requires C, 60·5; H, 4·6; N, 12·8%). Its infrared (i.r.) spectrum (Nujol) showed carbonyl absorption at 1790sh, 1765, and 1710 $cm.^{-1}$.

3-(Carboxymethyl)aminoisonicotinic Acid.—A solution of 3-aminoisonicotinic acid (1·2 g.), chloroacetic acid (0·9 g.), and anhydrous potassium carbonate (1·87 g.) in water (30 ml.) was heated on a steam-bath overnight. The solution was filtered, cooled in ice, and acidified with acetic acid. Refrigeration afforded the *diacid* (0·9 g., 52%) as a yellow, crystalline powder, m. p. 155—160°. Repeated recrystallisation from ethanol gave fine yellow needles, m. p. 160—163° (Found: C, 44·2; H, 4·7; N, 12·9. $C_8H_8N_2O_4,H_2O$ requires C, 44·9; H, 4·7; N, 13·1%).

1-Acetyl-3-oxo-1,7-diazaindene-2-carboxylic Acid.—A mixture of 2-(carboxymethyl)aminonicotinic acid [13] (0·95 g.), freshly fused sodium acetate (1·24 g.), and acetic anhydride (6·2 ml.) was heated in an oil-bath (130°), with stirring, for 1 hr. The red suspension was cooled slightly, and water (10 ml.) added dropwise. Acetic acid was removed *in vacuo*, and the residue suspended in water. The *acid* (0·85 g., 80%), filtered off and recrystallised from aqueous ethanol, had m. p. 155—157° (Found: C, 54·4; H, 3·7; N, 12·6. $C_{10}H_8N_2O_4$ requires C, 54·55; H, 3·7; N, 12·7%). The sodium salt, obtained from an attempted hydrolysis with sodium sulphite, was recrystallised from ethanol as fine, colourless needles, which did not melt below 320° (Found: C, 49·2; H, 3·1; N, 11·4. $C_{10}H_7N_2NaO_4$ requires C, 49·6; H, 2·9; N, 11·6%).

Ethyl (3-Pyridyl)aminohydroxymalonate 1-Oxide.—A mixture of 3-aminopyridine 1-oxide (2·2 g.) and ethyl mesoxalate (3·8 g.) was warmed on a steam-bath for 30 min., and the hot solution diluted with hot acetone (10 ml.). Cooling afforded the *hydroxy-ester* (3·8 g., 67%), m. p. 135—139°. Repeated crystallisation from acetone gave fine, colourless needles, m. p. 139—141° (Found: C, 50·4; H, 5·65; N, 9·5. $C_{12}H_{16}N_2O_6$ requires C, 50·7; H, 5·7; N, 9·9%). The i.r. spectrum (Nujol) showed strong absorption at 3280 $cm.^{-1}$.

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Department of Medical Chemistry, John Curtin School of Medical Research,
Australian National University, Canberra,
A.C.T., Australia. [*Received, July 7th,* 1964.]

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