## 191. *The Synthesis of Some 3-Aminohydrocarbostyrils.*

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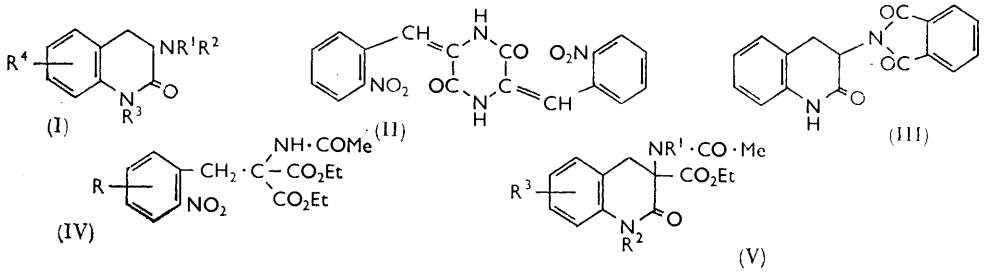
Synthetic routes to 3-aminohydrocarbostyrils and their various *N*-alkyl derivatives are described.

There have been several reports [1-4] of the preparation of 3-aminohydrocarbostyril (3-amino-3,4-dihydro-2(1*H*)-quinolone) derivatives. Some have been shown to be amyostatic poisons [4] whilst local anaesthetic [5] and antipyretic [6] behaviour have also been noted. We wished to prepare some 1-alkyl-3-alkylaminohydrocarbostyrils (I) for pharmacological testing. This Paper describes the synthetic routes used and some other reactions encountered in the course of the work.



Ueda [1] prepared 3-aminohydrocarbostyril (I; $R^1 = R^2 = R^3 = R^4 = H$) as the hydriodide by condensation of *o*-nitrobenzaldehyde with piperazine-2,5-dione in the presence of sodium acetate and acetic anhydride, followed by treatment of the condensation product of probable structure (II) with phosphorus and hydriodic acid. In our experience, the initial condensation gave poor yields as the scale of the reaction was increased. In large-scale experiments the yield and purity of the product were much improved by condensing *NN'*-diacetylpiperazine-2,5-dione with *o*-nitrobenzaldehyde. The identity of the product with that obtained by Ueda's method [1] confirmed his suggestion [2] that the condensation involved an initial formation of a diacetyl derivative; the presence of an NH band ($\nu_{max.}$ 3210 cm.$^{-1}$) in the infrared spectrum of the product indicated that at least partial deacetylation subsequently took place. Furthermore, methylation of the intermediate (II) gave a mixture of *N*-methylated and *O*-methylated products. Subsequent reduction of the former with phosphorus–hydriodic acid afforded 3-methylaminohydrocarbostyril (I; $R^1 = Me$; $R^2 = R^3 = R^4 = H$).

Substituents $R^1$, $R^2$, $R^3$ (formula I) were readily introduced into 3-aminohydrocarbostyril. 3-Dimethylaminohydrocarbostyril (I; $R^1 = R^2 = Me$, $R^3 = R^4 = H$) was prepared by hydrogenation of the primary amino-compound (I; $R^1 = R^2 = R^3 = R^4 = H$) in the presence of formaldehyde. Methylation of 3-phthalimidohydrocarbostyril (III), followed by removal of the phthaloyl group, gave 3-amino-1-methylhydrocarbostyril (I; $R^1 = R^2 = R^4 = H$, $R^3 = Me$) which was itself methylated to give 3-dimethylamino-1-methylhydrocarbostyril (I; $R^1 = R^2 = R^3 = Me$, $R^4 = H$). Conversion of 3-acetamidohydrocarbostyril [7] into a dimethyl derivative (I; $R^1 = Ac$, $R^2 = R^3 = Me$, $R^4 = H$) with sodium hydride (2 moles) and an excess of methyl iodide in dimethylformamide solution,

[1] Ueda, *Ber.*, 1928, **61**, 146.
[2] Ueda, *J. Chem. Soc. Japan*, 1929, **50**, 502 (*Chem. Abs.*, 1932, **26**, 91).
[3] Sasaki and Hasimoto, *Proc. Imp. Acad.* (*Tokyo*), 1939, **15**, 233; Sasaki and Ueda, *ibid.*, p. 239.
[4] Hashimoto, *J. Pharm. Soc. Japan*, 1955, **75**, 340.
[5] Sasaki and Otsuka, *J. Biochem.* (*Japan*), 1930, **12**, 429.
[6] Watanabe, *J. Biochem.* (*Japan*), 1930, **12**, 71.
[7] Ueda, *Proc. Imp. Acad.* (*Tokyo*), 1939, **15**, 148.

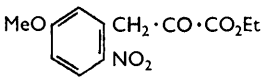
followed by acid hydrolysis, afforded 1-methyl-3-methylaminohydrocarbostyril (I; $R^1$ = $R^4$ = H, $R^2$ = $R^3$ = Me).

3-Ethylamino-1,2,3,4-tetrahydroquinoline and the 3-ethylmethylamino-1-methyl-analogue were prepared by lithium aluminium hydride reduction of 3-acetamidohydrocarbostyril and 1-methyl-3-(*N*-methylacetamido)hydrocarbostyril, respectively.

An alternative method, which was particularly suited to the synthesis of 3-aminohydrocarbostyrils having hydroxyl or methoxyl substituents in the benzene ring, was as follows. 5-Methoxy-2-nitrobenzylchloride was treated with diethyl sodioacetamidomalonate. Hydrogenation of the condensation product (IV; R = 5-MeO) yielded ethyl 3-acetamido-6-methoxyhydrocarbostyril-3-carboxylate (V; $R^1$ = $R^2$ = H, $R^3$ = 6-MeO) which was converted by alkali into 3-acetamido-6-methoxyhydrocarbostyril (I; $R^1$ = Ac, $R^2$ = $R^3$ = H, $R^4$ = 6-MeO). Subsequent conversion into *N*-alkyl-substituted 3-aminohydrocarbostyrils was readily achieved by methods described above.

Methylation of diethyl acetamido-(2-nitrobenzyl)malonate (IV; R = H) gave a product which cyclised on hydrogenation to form ethyl 3-(*N*-methylacetamido)hydrocarbostyril-3-carboxylate (V; $R^1$ = Me, $R^2$ = $R^3$ = H). Methylation of the ester (V; $R^1$ = $R^2$ = $R^3$ = H) and subsequent hydrolysis of the dimethyl derivative (V; $R^1$ = $R^2$ = Me, $R^3$ = H) afforded another route to 1-methyl-3-methylaminohydrocarbostyril (I; $R^1$ = $R^4$ = H, $R^2$ = $R^3$ = Me).

Other approaches to aminohydrocarbostyrils have been investigated. It was hoped that hydrogenation of ethyl 5-methoxy-2-nitrophenylpyruvate (VI) in the presence of a large excess (~30-fold) of ethylamine might afford 3-ethylamino-6-methoxyhydrocarbostyril but, in fact, a good yield of the indole derivative (VII) was obtained.



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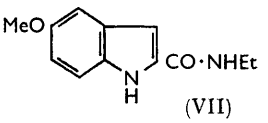

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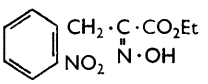
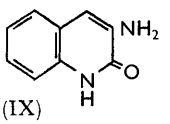


(VIII)

In other cases, formation of the carbostyril system frequently occurred. For example, when ethyl 2-nitrophenylpyruvate oxime (VIII) was hydrogenated under neutral conditions, a mixture of 3-aminocarbostyril (IX) and the indole ester (X) was obtained, whilst under acid conditions, a mixture of the indole (X) and hydroxylamine was produced. Conversion of the phenylpyruvate ester (VI) into the ketal (XI), followed by hydrogenation, afforded the hydrocarbostyril (XII; R = H). Treatment with sodium hydride and methyl iodide gave the methyl derivative (XII; R = Me) which, on acid hydrolysis, afforded a mixture of the two carbostyrils (XIII) and (XIV).



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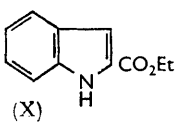

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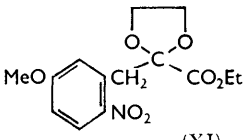

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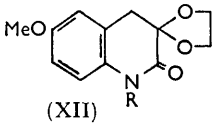
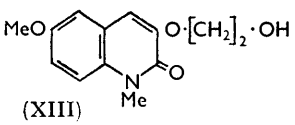
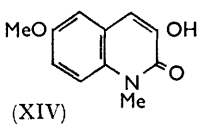


(XII)



(XIII)



(XIV)

The ultraviolet spectra of the 3-aminohydrocarbostyrils in 0·1N-hydrochloric acid or ethanol were characterised by a single band near 250 mμ (ε ~10,000). In contrast, 3-aminocarbostyrils, *e.g.*, (IX), had complicated ultraviolet spectra which were pH-dependent. In 0·1N-hydrochloric acid, three principal bands were normally found, near 230 mμ (ε ~30,000), near 280 mμ (ε ~7000), and near 340 mμ (ε ~6000). In 0·1N-sodium hydroxide,

bands occurred near 220 mμ (ε ~40,000) and centred around 330 mμ (ε ~11,000). Those near 330 mμ had a characteristic shape and showed some fine structure. The ultraviolet spectra of carbostyrils such as (XIII) and (XIV) conformed to the same general picture.

## Experimental

Anhydrous dimethylformamide–benzene used in this work was obtained by refluxing dimethylformamide (500 ml.) with benzene (500 ml.). Water was removed in a Dean–Stark apparatus. The mixture was distilled and after 330 ml. of distillate had been collected, the residual dimethylformamide–benzene was used.

*3,6-Bis-o-nitrobenzylidenepiperazine-2,5-dione* (II).—Piperazine-2,5-dione (13·6 g.) and acetic anhydride (50 ml.) were refluxed for 3—6 hr., after which the excess of acetic anhydride was removed by distillation. *o*-Nitrobenzaldehyde (40 g.), anhydrous sodium acetate (35 g.), and xylene (100 ml.) were added to the diacetylpiperazinedione and the mixture refluxed with vigorous stirring for 4 hr. After cooling to about 70°, the mixture was filtered and the dark residue pulverised and washed successively with acetone, water, dimethylformamide, acetone, and ether to give the piperazine (II) (26 g.), as a buff powder m. p. 330° (decomp.) [lit.,[1] 334—336° (decomp.)], $\nu_{max.}$ (Nujol) 3210 cm.$^{-1}$ (NH).

*3-Aminohydrocarbostyril* (I; $R^1 = R^2 = R^3 = R^4 = H$) *Hydriodide.*—The above piperazine (II) was converted into 3-aminohydrocarbostyril hydriodide by treatment with red phosphorus and hydriodic acid as described by Ueda.[1]

*Methylation of 3,6-Bis-o-nitrobenzylidenepiperazine-2,5-dione.*—The dione (24 g.) was added to a suspension of sodium hydride (7 g.; 50%) in benzene–dimethylformamide (300 ml.). The suspension was stirred for 1 hr. at 110°, cooled, methyl iodide (10 ml.) added, and the mixture stirred at 60—70° for 30 min. On cooling, the yellow solid which separated was filtered off and washed successively with dimethylformamide, water, and acetone. Recrystallisation from dimethylformamide gave *2,5-dihydro-3,6-dimethoxy-2,5-bis-o-nitrobenzylidenepyrazine* (3·5 g.) as needles, m. p. 296° (Found: C, 59·1; H, 3·7; N, 13·5; OMe, 14·6. $C_{20}H_{16}N_4O_6$ requires C, 58·8; H, 3·95; N, 13·7; OMe, 15·2%). The filtrate after removal of the *O*-methylated product was evaporated to dryness *in vacuo* and the residue triturated with light petroleum (b. p. 80—100°). The crystalline solid was filtered off, washed with light petroleum and water, and boiled with methanol (3 l.). The insoluble solid was filtered off and recrystallised from 2-methoxyethanol giving fine yellow needles of *1,4-dimethyl-3,6-bis-o-nitrobenzylidenepiperazine-2,5-dione* (6·8 g.), m. p. 235° (Found: C, 59·0; H, 3·7; N, 13·5. $C_{20}H_{16}N_4O_6$ requires C, 58·8; H, 3·95; N, 13·7%), $\nu_{max.}$ (Nujol) 1682 cm.$^{-1}$ (C:O).

*3-Methylaminohydrocarbostyril* (I; $R^1 = Me$, $R^2 = R^3 = R^4 = H$) *Hydrochloride.*—The foregoing dione (6·8 g.) was refluxed with red phosphorus (0·3 g.) in 55% hydriodic acid (70 ml.) for 6 hr. The filtered solution was evaporated, the residue extracted with boiling water (100 ml. and 50 ml.), and the extracts made alkaline with solid potassium carbonate. The aqueous solution was extracted with chloroform (2 × 75 ml.), the organic phase washed with water (2 × 20 ml.), and extracted successively with 2N-hydrochloric acid (20 ml. and 10 ml.) and water (4 × 10 ml.). The bulked aqueous acidic extracts were evaporated to dryness under reduced pressure. Recrystallisation of the residue from ethanol gave *3-methylaminohydrocarbostyril hydrochloride*, (2·7 g.) as needles, m. p. 253—254° (Found: C, 56·0; H, 5·8; N, 12·9. $C_{10}H_{13}ClN_2O$ requires C, 55·5; H, 6·2; N, 13·2%).

*3-Dimethylaminohydrocarbostyril* (I; $R^1 = R^2 = Me$, $R^3 = R^4 = H$).—3-Aminohydrocarbostyril [1] (2·8 g.) in 50% aqueous ethanol (100 ml.) and 36% aqueous formaldehyde (4·5 ml.) was hydrogenated at 60—65° in the presence of 10% palladised charcoal (1 g.) and acetic acid (20 ml.) The filtered solution was evaporated, the residue (0·8 g.) dissolved in warm ether (100 ml.), the solution filtered, and the filtrate evaporated. Crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave *3-dimethylaminohydrocarbostyril* (0·6 g.) as prisms, m. p. 115—116° (Found: C, 69·7; H, 7·6. $C_{11}H_{14}N_2O$ requires C, 69·4; H, 7·4%). The *hydrochloride* separated from propan-2-ol, containing concentrated hydrochloric acid, as prisms, m. p. 225—226° (Found: C, 58·7; H, 7·1; N, 12·8. $C_{11}H_{15}ClN_2O$ requires C, 58·3; H, 6·7; N, 12·4%).

*o-Nitrobenzyl Chloride.*—*o*-Nitrobenzyl alcohol (100 g.) suspended in benzene (660 ml.) and pyridine (3·0 ml.) was treated with thionyl chloride (96 ml.). After 1 hr. at 30°, the mixture was refluxed for 4 hr. and left overnight. After removal of solvent, the residue was extracted repeatedly with boiling light petroleum (b. p. 40—60°). The oil which separated from the

extracts was crystallised from light petroleum (b. p. 60—80°) to give *o*-nitrobenzyl chloride (75 g.) as rods, m. p. 46—47° (lit.,[8] 48—49°).

*5-Methoxy-2-nitrobenzyl Chloride.*—Reduction of 5-methoxy-2-nitrobenzaldehyde [9] with potassium borohydride [10] gave *5-methoxy-2-nitrobenzyl alcohol* as yellow prisms, m. p. 119—122° (from methanol) (Found: C, 52·0; H, 5·2; N, 7·8. $C_8H_9NO_4$ requires C, 52·5; H, 4·95; N, 7·7%). The alcohol (39·5 g.) was treated with thionyl chloride and gave a dark oil (26 g.) which failed to crystallise and was not characterised.

*4,5-Dimethoxy-2-nitrobenzyl Chloride.*—4,5-Dimethoxy-2-nitrobenzaldehyde [11] (15·1 g.) was reduced with potassium borohydride giving *4,5-dimethoxy-2-nitrobenzyl alcohol* (11·5 g.) as yellow prisms, m. p. 142—145° (from ethanol) (Found: C, 51·2; H, 4·9; N, 6·15. $C_9H_{11}NO_5$ requires C, 50·7; H, 5·2; N, 6·6%). Treatment of the alcohol (11·0 g.) with thionyl chloride gave 4,5-dimethoxy-2-nitrobenzyl chloride (9·3 g.) as yellow prisms, m. p. 89—91° (lit.,[12] 87—88°).

*Diethyl Acetamido-(2-nitrobenzyl)malonate* (IV; R = H).—*o*-Nitrobenzyl chloride (49·7 g.) was added to a solution of diethyl sodioacetamidomalonate [from sodium (6·3 g.) and diethyl acetamidomalonate (65·1 g.)] in dry ethanol (500 ml.). The mixture was refluxed for 3 hr., and poured into water (2 l.). The solid was collected and recrystallised from benzene–light petroleum (b. p. 60—80°) to give the ester (61·0 g.) as needles, m. p. 103—104° (lit.,[13] 106°).

The *5-methoxy-derivative*, prepared similarly, in good yield as needles from crude 5-methoxy-2-nitrobenzyl chloride, had m. p. 126—128° (Found: C, 53·8; H, 5·5; N, 7·3. $C_{17}H_{22}N_2O_8$ requires C, 53·4; H, 5·8; N, 7·3%), and the *4,5-dimethoxy-derivative* was similarly obtained as needles, m. p. 171—173° (from ethanol) (charcoal) (Found: C, 52·7; H, 5·6; N, 6·9. $C_{18}H_{24}N_2O_9$ requires C, 52·4; H, 5·9; N, 6·8%).

*Ethyl 3-Acetamidohydrocarbostyril-3-carboxylate* (V; $R^1 = R^2 = R^3 = H$).—This compound was prepared by hydrogenation of diethyl acetamido-(2-nitrobenzyl)malonate as described by Connors *et al.*[13] The *6-methoxy-derivative* (V; $R_1 = R^2 = H$, $R^3$ = 6-OMe), where it was necessary to heat the residue from the hydrogenation at 120—130° for 5 min. to effect cyclisation, formed prisms, m. p. 195—197° (from methanol) (Found: C, 58·9; H, 5·8; N, 9·1. $C_{15}H_{18}N_2O_5$ requires C, 58·8; H, 5·9; N, 9·15%). The *6,7-dimethoxy-derivative* was readily prepared by hydrogenation as prisms, m. p. 212—215° (from ethanol) (Found: C, 56·7; H, 5·6. $C_{16}H_{20}N_2O_6$ requires C, 57·1; H, 6·0%).

*3-Acetamidohydrocarbostyril.—From 3-aminohydrocarbostyril hydriodide.* The hydriodide (57 g.), anhydrous sodium acetate (45·6 g.), and glacial acetic acid (400 ml.) were heated on a steam-bath with stirring for 0·5 hr. Acetic anhydride (86 ml.) was added to the stirred suspension and heating was continued for a further 2 hr. About 200 ml. of solvent was removed by distillation and the suspension was poured into ice–water (500 ml.). The small amount of yellow solid which separated was removed by filtration and the filtrate was set aside overnight; the crystals which separated were removed, washed with water, ethanol, and ether, and dried. Concentration of the mother-liquors gave a further crop of crystals. Recrystallisation from ethanol gave the acetamido-compound (26·8 g.) as needles, m. p. 238—239° (Found: C, 64·3; H, 5·95; N, 14·2. Calc. for $C_{11}H_{12}N_2O_2$: C, 64·7; H, 5·9; N, 13·7%).

*From ethyl 3-acetamidohydrocarbostyril-3-carboxylate.* The ester (2·27 g.) and sodium hydroxide (1·63 g.) were refluxed in water (16·3 ml.) for 2 hr. The cooled solution was acidified with concentrated hydrochloric acid (5·0 ml.); carbon dioxide was immediately evolved. The mixture was heated for 10 min., cooled, and the solid collected (0·8 g.), m. p. 238—240°, identical with the sample prepared previously.

Other 3-acetamido-compounds prepared by this latter route were 3-acetamido-6-methoxyhydrocarbostyril, needles, m. p. 263—266° (Found: N, 12·1. Calc. for $C_{12}H_{14}N_2O_3$: N, 12·0%) and *3-acetamido-6,7-dimethoxyhydrocarbostyril*, prisms, m. p. 261—263° (from ethanol) (Found: C, 59·0; H, 5·7; N, 10·6. $C_{13}H_{16}N_2O_4$ requires C, 59·1; H, 6·1; N, 10·6%).

*3-Aminomethoxyhydrocarbostyril Hydrochlorides.*—3-Amino-6-methoxyhydrocarbostyril hydrochloride was prepared by acid hydrolysis of 3-acetamido-6-methoxyhydrocarbostyril, as prisms, m. p. 273—275° (from ethanol) (lit.,[14] 270—271°).

[8] Gabriel and Borgmann, *Ber.*, 1883, **16**, 2064.
[9] Hornig, *J. Amer. Chem. Soc.*, 1952, **74**, 4572.
[10] Vogel, "A Text-book of Practical Organic Chemistry," Longmans, London, 3rd edn., 1956, p. 881.
[11] Fletscher, *Org. Synth.*, 1953, **33**, 65.
[12] Kulka and Van Stryk, *Canad. J. Chem.*, 1955, **33**, 1130.
[13] Connors, Ross, and Wilson, *J.*, 1960, 2994.
[14] Hashimoto, *Proc. Japan. Acad.*, 1948, **24**, No. 10, 15.

3-Acetamido-6,7-dimethoxyhydrocarbostyril (0·5 g.) was refluxed with 6N-hydrochloric acid (15 ml.) for 1 hr. The solution was evaporated to dryness and the residue recrystallised from methanol–water in the presence of 2N-hydrochloric acid to give *3-amino-6,7-dimethoxyhydrocarbostyril hydrochloride* (0·1 g.) as needles, m. p. 289—291° (Found: C, 51·5; H, 5·9; N, 10·8. $C_{11}H_{15}ClN_2O_3$ requires C, 51·1; H, 5·85; N, 10·8%).

*1-Methyl-3-(N-methylacetamido)hydrocarbostyril* (I; $R^1$ = Ac, $R^2$ = $R^3$ = Me, $R^4$ = H).—Sodium hydride (4·7 g.) was suspended in dry dimethylformamide–benzene (250 ml.). 3-Acetamidohydrocarbostyril (15 g.) was added with stirring and after about 15 min., the exothermic reaction subsided. The mixture was heated at 50—60° and methyl iodide (35 ml.) was added during 4 hr. The mixture was cooled and filtered, and the residue washed with dimethylformamide. The combined filtrates were evaporated and the residue was treated with water (50 ml.). The *product*, isolated with methylene chloride, separated from benzene–light petroleum (b. p. 60—80°) then carbon tetrachloride as prisms, m. p. 108—109° (Found: C, 66·8; H, 7·0; N, 11·8; OMe, 0·0. $C_{13}H_{16}N_2O_2$ requires C, 67·2; H, 6·9; N, 12·1; OMe, 0·0%).

Similarly prepared were *1-methyl-3-(N-methylacetamido)-6-methoxyhydrocarbostyril*, plates, m. p. 145—147° (from benzene) (Found: C, 64·1; H, 6·7; N, 11·1. $C_{14}H_{18}N_2O_3$ requires C, 64·1; H, 6·9; N, 10·7%) and *1-methyl-3-(N-methylacetamido)-6,7-dimethoxyhydrocarbostyril*, prisms, m. p. 160—163° (from carbon tetrachloride) (Found: C, 61·3; H, 6·6; N, 9·4. $C_{15}H_{20}N_2O_4$ requires C, 61·6; H, 6·9; N, 9·6%).

*3-Ethylmethylamino-1-methyltetrahydroquinoline Hydrochloride.**—1-Methyl-3-(*N*-methylacetamido)hydrocarbostyril (10 g.) in benzene (300 ml.) was added to a refluxing suspension of lithium aluminium hydride (5·6 g.) in anhydrous ether (150 ml.) and refluxing was continued for 5 hr. After cooling, wet ether (50 ml.), water (90 ml.), and 5N-sodium hydroxide solution (30 ml.) were successively added, and the suspension was refluxed for 2 hr. and filtered. Isolation of the basic material from the filtrate with ethyl acetate afforded an oil (6·8 g.), which was converted into the *hydrochloride* (5 g.), prisms, m. p. 175—176° (from methanol–ethyl acetate) (Found: C, 64·4; H, 9·0; N, 11·6. $C_{13}H_{21}ClN_2$ requires C, 64·7; H, 8·8; N, 11·6%).

*1-Methyl-3-methylaminohydrocarbostyril* (I; $R^1$ = $R^4$ = H, $R^2$ = $R^3$ = Me) *Hydrochloride.*—*From 1-methyl-3-(N-methylacetamido)hydrocarbostyril.* The acetamido-compound (7·0 g.) in 6N-hydrochloric acid (210 ml.) was refluxed for 2 hr. The solution was evaporated to dryness and the residue recrystallised from hot ethanol (*ca.* 100 ml.) to which a few drops of water were added to effect solution, to give the *amine hydrochloride* (5·3 g.) as needles, m. p. 270° (Found: C, 58·1; H, 6·7; N, 12·1. $C_{11}H_{15}ClN_2O$ requires C, 58·3; H, 6·7; N, 12·4%).

Similarly prepared were *6-methoxy-1-methyl-3-methylaminohydrocarbostyril hydrochloride*, prisms, m. p. 227—229° (from ethanol) (Found: C, 52·6; H, 7·2; N, 10·6. $C_{12}H_{17}ClN_2O_2,H_2O$ requires C, 52·4; H, 7·0; N, 10·2%), and *6,7-dimethoxy-1-methyl-3-methylaminohydrocarbostyril hydrochloride*, prisms, m. p. 238—240° (from ethanol) (Found: C, 54·85; H, 6·7; N, 9·4. $C_{13}H_{19}ClN_2O_3$ requires C, 54·4; H, 6·7; N, 9·8%).

*From ethyl 3-acetamidohydrocarbostyril-3-carboxylate.* The ester (16·1 g.) was added to a stirred suspension of sodium hydride (7·0 g.; 50%) in dimethylformamide at 20°. After 15 min., methyl iodide (31·5 g.) was added, and the mixture stirred for ½ hr. at room temperature, then for 3 hr. at 60°, and finally left overnight. The filtered solution was evaporated, and the residue, in ethyl acetate, was washed with water, dried ($Na_2SO_4$), and evaporated to give the crude methylated product (V; $R^1$ = $R^2$ = Me, $R^3$ = H) which was refluxed with 6N-hydrochloric acid (200 ml.) for 11 hr. The cooled mixture was extracted with ethyl acetate and the aqueous solution evaporated to dryness. Crystallisation of the residue from aqueous ethanol gave the amine hydrochloride as needles (5·7 g.), m. p. 267—268°, indistinguishable from the sample previously prepared.

*6-Hydroxy-1-methyl-3-methylaminohydrocarbostyril Hydrobromide.*—6-Methoxy-1-methyl-3-methylaminohydrocarbostyril hydrochloride (2·1 g.) was refluxed with 48% hydrobromic acid (15 ml.) for 1¼ hr. Evaporation of the solution to dryness and crystallisation of the residue from methanol (charcoal) gave the *hydrobromide* (1·7 g.) as prisms, m. p. 250—251° (Found: C, 46·35; H, 5·6; N, 10·2. $C_{11}H_{15}BrN_2O_2$ requires C, 46·1; H, 5·3; N, 9·8%).

*6,7-Dihydroxy-1-methyl-3-methylaminohydrocarbostyril Hydrobromide.*—The corresponding dimethoxy-compound (3·0 g.) was refluxed with 48% hydrobromic acid for 1½ hr. The *dihydroxyhydrobromide* (2·65 g.) separated as prisms on cooling. After washing with water, drying, and

* The authors thank Mr. D. Huckle for the preparation of this compound.

recrystallising from methanol, the product had m. p. 276° (Found: C, 43·2; H, 4·9; N, 9·3. $C_{11}H_{15}BrN_2O_3$ requires C, 43·6; H, 5·0; N, 9·2%).

*Ethyl* 3-(N-*methylacetamido*)*hydrocarbostyril*-3-*carboxylate* (V; $R^1$ = Me, $R^2$ = $R^3$ = H).—Diethyl acetamido-(2-nitrobenzyl)malonate (36·0 g.) was added to a stirred suspension of sodium hydride (6·12 g.; 50%) in dimethylformamide (180 ml.) at 20°. After 15 min., methyl iodide (11·9 ml.) was added, and the mixture stirred at 20° for 30 min., at 60° for 2 hr., and then left overnight. The filtered solution was evaporated, and the residue dissolved in ethyl acetate, washed with water, dried ($Na_2SO_4$), and evaporated. The residue (41·0 g.) in ethanol (150 ml.) was hydrogenated over 10% palladised charcoal (2·0 g.). The filtered solution was evaporated and the oily residue triturated with ether. The solid was recrystallised from 50% aqueous ethanol giving the *amide* as prisms, m. p. 143—145° (Found: C, 61·7; H, 6·2; N, 9·7. $C_{15}H_{18}N_2O_4$ requires C, 62·1; H, 6·3; N, 9·7%).

3-*Phthalimidohydrocarbostyril* (III).—3-Aminohydrocarbostyril hydriodide (2·0 g.) and anhydrous sodium acetate (0·6 g.) in glacial acetic acid (12 ml.) were refluxed with phthalic anhydride (1·1 g.) in glacial acetic acid (7 ml.) for 1 hr. The mixture was filtered hot and, on cooling, 3-*phthalimidohydrocarbostyril* (1·4 g.) crystallised, pale yellow prisms, m. p. 288—290° (from glacial acetic acid) (Found: C, 69·7; H, 4·3. $C_{17}H_{12}N_2O_3$ requires C, 69·85; H, 4·1%).

1-*Methyl*-3-*phthalimidohydrocarbostyril*.—3-Phthalimidohydrocarbostyril (12·6 g.) was methylated as described for the preparation of 1-methyl-3-(*N*-methylacetamido)hydrocarbostyril. The *product* (10 g.) formed prisms, m. p. 200—204° (from ethanol) (Found: C, 70·3; H, 4·8; N, 9·2. $C_{18}H_{14}N_2O_3$ requires C, 70·6; H, 4·6; N, 9·15%).

3-*Amino*-1-*methylhydrocarbostyril* (I; $R^1$ = $R^2$ = $R^4$ = H, $R^3$ = Me) *Hydrochloride*.—1-Methyl-3-phthalimidohydrocarbostyril (7·0 g.) in ethanol (140 ml.) was refluxed with hydrazine hydrate (1·4 ml.) for 2 hr., and the mixture left overnight. Ethanol was removed by distillation and the residue thoroughly stirred with a mixture of chloroform (70 ml.), 2N-ammonium hydroxide solution (30 ml.), and water (40 ml.) for 2½ hr. The organic phase was separated and the aqueous solution washed with chloroform. Isolation of the basic material from the combined chloroform extracts with 2N-hydrochloric acid afforded the *hydrochloride* (3·3 g.) as prisms, m. p. 269—273° (from ethanol) (charcoal) (Found: C, 52·3; H, 6·7; N, 11·65. $C_{10}H_{13}ClN_2O,H_2O$ requires C, 52·1; H, 6·6; N, 12·1%).

1-*Methyl*-3-*dimethylaminohydrocarbostyril* (I; $R^1$ = $R^2$ = $R^3$ = Me, $R^4$ = H) *Hydrochloride*.—3-Amino-1-methylhydrocarbostyril hydrochloride (2·0 g.) and sodium hydrogen carbonate (0·8 g.) were mixed with 98% formic acid (10 ml.) with cooling, followed by addition of 36% formaldehyde (1·4 ml.). The mixture was refluxed (bath 120°) for 6½ hr. The excess of formic acid was removed by distillation *in vacuo*. The residue was dissolved in N-sodium hydroxide solution (40 ml.) and the alkaline solution was extracted with chloroform (2 × 25 ml.). The combined chloroform solutions were extracted with N-hydrochloric acid (2 × 25 ml.). The product obtained on evaporation of the aqueous extracts was recrystallised from ethanol (charcoal) to give the *trimethyl compound* (1·3 g.), as prisms, m. p. 214—215° (Found: C, 59·4; H, 7·0; N, 11·2. $C_{12}H_{17}ClN_2O$ requires C, 59·9; H, 7·1; N, 11·6%).

3-*Ethylamino*-1,2,3,4-*tetrahydroquinoline*.—3-Acetamidohydrocarbostyril (4·0 g.) was extracted (Soxhlet) into a refluxing suspension of lithium aluminium hydride (3·0 g.) in dioxan (200 ml.). The mixture was refluxed for 7 hr., decomposed by addition of water, and evaporated. Distillation of the basic material afforded the quinoline, b. p. 104°/0·15 mm., which set to colourless needles, m. p. 46—50° (Found: C, 74·4; H, 8·7; N, 15·9. Calc. for $C_{11}H_{16}N_2$: C, 74·9; H, 9·1; N, 15·9%).

*Ethyl* 5-*Methoxy*-2-*nitro*-*phenylpyruvate* (VI).—The sodium salt [15] of ethyl 5-methoxy-2-nitrophenylpyruvate was suspended in acid solution and extracted with ethyl acetate. Removal of the ethyl acetate by distillation gave the ester as needles, m. p. 87—91° (from ethanol) (lit.,[16] 81—82°) (Found: C, 54·1; H, 5·1. Calc. for $C_{12}H_{13}NO_6$: C, 53·9; H, 4·9%). To a solution of the ester (10·7 g.) in hot ethanol (50 ml.) was added a hot aqueous solution of hydroxylamine hydrochloride (3·5 g.). The resulting solution was neutralised with N-sodium hydroxide solution (Bromophenol Blue indicator) and, on cooling, the *oxime* (8·7 g.) separated as needles, m. p. 156—157° (from ethanol) (Found: C, 51·1; H, 5·0; N, 9·5. $C_{12}H_{14}N_2O_6$ requires C, 51·1; H, 5·0; N, 9·9%).

[15] Blaikie and Perkin, *J.*, 1924, **125**, 296.
[16] Faltis, Wagner, and Adler, *Ber.*, 1944, **77**, 686.

2-(*Ethylcarbamoyl*)-5-*methoxyindole* (VII).—A mixture of ethyl 5-methoxy-2-nitrophenylpyruvate (10·0 g.) and 33% (w/w) alcoholic ethylamine solution (150 ml.) in absolute ethanol (120 ml.) was hydrogenated in the presence of 10% palladised charcoal (1·0 g.). The catalyst was removed by filtration and the filtrate evaporated to dryness *in vacuo*. The residue was treated with N-hydrochloric acid (300 ml.), the suspension filtered, and the residue washed with ether and dried. The *indole* (5·85 g.) thus obtained was recrystallised from methanol–water to give plates, m. p. 201—203° (Found: C, 66·0; H, 6·5; N, 12·5. $C_{12}H_{14}N_2O_2$ requires C, 66·0; H, 6·5; N, 12·8%).

*Ethyl* 2-*Nitrophenylpyruvate Oxime* (VIII).—The sodium salt[17] of ethyl 2-nitrophenylpyruvate was converted into the ester and thence to the oxime as described for the 5-methoxy-compounds. The oxime crystallised as needles, m. p. 118—122° from methanol (lit.,[18] 121—122°).

*Hydrogenation of Ethyl* 2-*Nitrophenylpyruvate Oxime.—Neutral conditions.* The oxime (6·7 g.) in absolute ethanol (100 ml.) was hydrogenated in the presence of 10% palladised charcoal (1·0 g.). Filtration and evaporation of the filtrate gave a solid (3·5 g.) which was treated with N-hydrochloric acid (70 ml.) and the mixture filtered. Neutralisation of the filtrate with N-sodium hydroxide solution afforded 3-aminocarbostyril (IX) (2·3 g.), m. p. 209—211° (from ethanol) (lit.,[19] 211—213°) (Found: C, 67·1; H, 5·2; N, 17·5. Calc. for $C_9H_8N_2O$: C, 67·5; H, 5·0; N, 17·5%), whilst washing of the residue with water and drying gave ethyl indole-2-carboxylate (0·5 g.) as needles, m. p. 119—120° (from ethanol) (lit.,[20] 121—122°) (Found: C, 69·9; H, 5·9; N, 7·4. Calc. for $C_{11}H_{11}NO_2$: C, 69·8; H, 5·9; N, 7·4%).

*Acidic conditions.* Ethanolic hydrogen chloride (18 ml.; 0·075N) was added to a suspension of the oxime (5·0 g.) and 10% palladised charcoal (1·0 g.) in absolute ethanol (100 ml.) *in vacuo*. The mixture was hydrogenated, the catalyst removed by filtration, and the filtrate evaporated to dryness *in vacuo* to give a gummy residue (4·5 g.). A sample of the residue (1·0 g.) was treated with N-hydrochloric acid, the suspension was filtered, and the solid (0·6 g.) recrystallised from ethanol as needles, m. p. 121—122°, of the ester (X). A further portion of the gummy residue was repeatedly recrystallised from propan-2-ol to give hydroxylamine hydrochloride, m. p. and mixed m. p. 149—152°.

3-*Amino*-1-*methylcarbostyril Hydrochloride.*—A mixture of 3-aminocarbostyril (10·3 g.) in glacial acetic acid (60 ml.) and phthalic anhydride (10·3 g.) in glacial acetic acid (60 ml.) was refluxed for 30 min., cooled, and the product recrystallised from dimethylformamide to give 3-*phthalimidocarbostyril* (10·2 g.) as pale yellow prisms which did not melt below 360° (Found: C, 70·1; H, 3·8; N, 9·65. $C_{17}H_{10}N_2O_3$ requires C, 70·3; H, 3·5; N, 9·65%). The product (12·6 g.) was methylated as already described to give 1-*methyl*-3-*phthalimidocarbostyril* (11·6 g.) which crystallised from benzene as pale yellow prisms, m. p. 238—242° (Found: C, 71·4; H, 4·1; N, 9·6. $C_{18}H_{12}N_2O_3$ requires C, 71·0; H, 4·0; N, 9·2%). 1-Methyl-3-phthalimidocarbostyril (8·2 g.) was suspended in ethanol (180 ml.). Hydrazine hydrate (1·4 ml.) was added, the mixture heated under reflux for 4 hr., and ethanol removed by distillation *in vacuo*. Chloroform (100 ml.), 6N-ammonia (30 ml.), and water (70 ml.) were added, and the mixture was vigorously stirred for 2 hr. Isolation of the basic material from the separated organic layer with 2N-hydrochloric acid furnished 3-*amino*-1-*methylcarbostyril hydrochloride* (2·9 g.) as needles, m. p. 240—243° (Found: C, 56·5; H, 5·35; N, 13·5. $C_{10}H_{11}ClN_2O$ requires C, 57·0; H, 5·3; N, 13·3%).

1-*Methyl*-3-*methylaminocarbostyril Hydrochloride.*—Acetic anhydride (21 ml.) was added to a suspension of 3-aminohydrocarbostyril (12·0 g.) in pyridine (45 ml.). The mixture was heated on a steam-bath for 15 min., and poured on to crushed ice. The solid which separated was removed by filtration, washed with water, and dried. 3-Acetamidocarbostyril (8·85 g.) crystallised from ethanol with m. p. 262—264° (Found: C, 65·4; H, 5·15; N, 13·9. Calc. for $C_{11}H_{10}N_2O_2$: C, 65·3; H, 5·0; N, 13·9%). The acetyl derivative was methylated in the usual way to give 1-*methyl*-3-(N-*methylacetamido*)*carbostyril* as needles m. p. 149—151° (from propan-2-ol) (Found: C, 67·6; H, 6·2; N, 11·9. $C_{13}H_{14}N_2O_2$ requires C, 67·8; H, 6·1; N, 12·2%). Hydrolysis of the methylated product (2·9 g.) with 6N-hydrochloric acid under reflux for 1 hr. gave 1-*methyl*-3-*methylaminocarbostyril hydrochloride* (2·65 g.) as prisms, m. p. 195—197° (from ethanol) (Found: C, 58·7; H, 6·0; N, 13·1. $C_{11}H_{13}ClN_2O$ requires C, 58·8; H, 5·8; N, 12·5%).

[17] Di Carlo, *J. Amer. Chem. Soc.*, 1944, **66**, 1420.
[18] Wislicenus and Thoma, *Annalen*, 1924, **436**, 42.
[19] Hashimoto and Nagase, *J. Pharm. Soc. Japan*, 1960, **80**, 1806.
[20] Taylor, *Helv. Chim. Acta*, 1950, **33**, 164.

3,3-*Ethylenedioxy*-6-*methoxy*-1-*methylhydrocarbostyril* (XII; R = Me).—Ethyl 5-methoxy-2-nitrophenylpyruvate (30·0 g.), ethylene glycol (17·4 g.) and toluene-*p*-sulphonic acid (0·5 g.) in benzene (300 ml.; AnalaR) were refluxed in a Dean–Stark apparatus until elimination of water was complete. The cooled solution was washed with dilute sodium hydrogen carbonate solution and water, and dried. Removal of the solvent gave a gum (31·0 g.) which was not purified but the infrared spectrum [$\nu_{max}$ (Nujol) 1087, 1058 cm.$^{-1}$ (strong twin ether peaks)] was consistent with its being the required ketal (XI). The crude ketal (67·5 g.), in methanol, was hydrogenated (uptake 3 mol.) in the presence of Raney nickel (W.7) at atmospheric pressure. The catalyst was removed by filtration and the solution concentrated by distillation. Solid which separated during concentration was filtered off and dried to give 3,3-*ethylenedioxy*-6-*methoxyhydrocarbostyril* (XII; R = H) (11·5 g.) as prisms, m. p. 198—200° (from methanol) (Found: C, 61·1; H, 5·7; N, 5·9. $C_{12}H_{13}NO_4$ requires C, 61·3; H, 5·6; N, 6·0%). Final evaporation of the methanol solution gave a black intractable tar (29 g.). Methylation of the ethylenedioxyhydrocarbostyril using the procedure described above gave the *ketal* (XII; R = Me) as needles, m. p. 105—107° (from propan-2-ol) (Found: C, 62·5; H, 6·1; N, 5·2. $C_{13}H_{15}NO_4$ requires C, 62·6; H, 6·1; N, 5·6%).

*Hydrolysis of* 3,3-*Ethylenedioxy*-6-*methoxy*-1-*methylhydrocarbostyril*.—The methylated ketal (6·5 g.) was dissolved in ethanol (90 ml.), concentrated hydrochloric acid (90 ml.) was added, and the mixture heated on a water-bath (70—80°) for 2¼ hr. The crystalline solid (2·4 g.) which separated on cooling recrystallised from benzene to give 3-(2-*hydroxyethoxy*)-6-*methoxy*-1-*methylcarbostyril* (XIII) *monohydrate*, needles, m. p. 85—87° (Found: C, 58·8; H, 6·3; N, 5·2. $C_{13}H_{15}NO_4,H_2O$ requires C, 58·4; H, 6·4; N, 5·2%). The infrared [$\nu_{max.}$ (Nujol), 3350, 3145 (OH), and 1624 cm.$^{-1}$ (amide)] and ultraviolet spectra [$\lambda_{max.}$ (0·1N-NaOH) 223, 281, 337 mμ (ε 42,600, 7700, 8900)] confirmed the assigned structure. The filtrate was concentrated and the aqueous solution thus obtained extracted with chloroform. The extracts were dried and evaporated to dryness *in vacuo*, and the residue (3·7 g.) was recrystallised from ethanol to give 3-*hydroxy*-6-*methoxy*-1-*methylcarbostyril* (XIV) (0·5 g.), prisms, m. p. 171—172° (Found: C, 64·1; H, 5·2; N, 6·7. $C_{11}H_{11}NO_3$ requires C, 64·4; H, 5·4; N, 6·8%). The infrared [$\nu_{max.}$ (Nujol) 3210 (OH) and 1616 cm.$^{-1}$ (amide)] and ultraviolet spectra [$\lambda_{max.}$ (0·1N-NaOH) 219, 230, 338, 352 mμ (ε 34,700, 31,200, 14,800, 13,600)], and the green coloration with ferric chloride, all confirmed that the product was in the enolic form. It did not form a 2:4-dinitrophenylhydrazone. Evaporation of the mother-liquors from the recrystallisation gave a solid residue, m. p. 78—83°, indicating that the ether was the predominant product of hydrolysis.

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