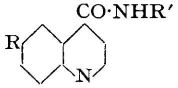
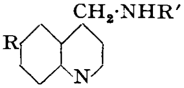
80. *The Synthesis of Amines from Amides through the Amidodichlorides.*

By Thomas S. Work.

The Sonn–Müller reaction for the preparation of aldehydes from anils, by reduction of the imidochlorides by stannous chloride and ethereal hydrogen chloride, is not applicable to quinoline-4-carboxyamides. The reaction of certain quinoline-4-carboxyamides with phosphorus pentachloride gives amidodichlorides which are reduced under the above conditions to secondary amines. The mechanism of both types of reaction is discussed. An analogous type of reaction is possible with *quinoline*-4-*aldehyde anil,* which gives with stannous chloride and ethereal hydrogen chloride N-*phenyl-lepidylamine.* Application of the Sonn–Müller conditions to *nicotinethylamide* gives pyridine-3-aldehyde and 3-N-*ethylaminomethylpyridine,* through the operation of both types of reaction.

It being desired (Work, preceding paper) to have a convenient method for the preparation of quinoline-4-aldehydes, an attempt was made to apply the reaction of Sonn and Müller (*Ber.*, 1919, **52**, 1927), *viz.*, $R{\cdot}CO{\cdot}NHR' \longrightarrow R{\cdot}CCl{:}NR' \longrightarrow R{\cdot}CH{:}NR' \longrightarrow R{\cdot}CHO + NH_2R'$. Accordingly *cinchoninanilide* (I; R = H, R′ = Ph) was allowed to react in toluene with phosphorus pentachloride (1 mol.) and the product (imidochloride?) was treated with stannous chloride in ethereal hydrogen chloride as recommended by Sonn and Müller. The product was, however, not quinoline-4-aldehyde, as might be expected, but *N*-phenyl-lepidylamine (II; R = H, R′ = Ph).


(I.)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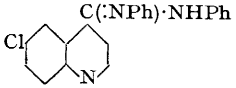

(III.)

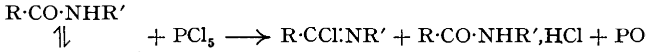
With phosphorus pentachloride (2 mols.) *N*-phenyl-lepidylamine was obtained in 68% yield. *Cinchonino-methylamide* (I; R = H, R′ = Me) and 6-*chlorocinchoninanilide* (I; R = Cl; R′ = Ph), treated in chloroform with phosphorus pentachloride, the products being reduced with stannous chloride, gave N-*methyl-lepidylamine dihydrochloride* (II + 2HCl; R = H, R′ = Me) and N-*phenyl*-6-*chlorolepidylamine* (II; R = Cl, R′ = Ph) respectively in good yield. 6-Methoxycinchoninamide (I; R = OMe, R′ = H) failed to furnish any amine. Cinchoninodiethylamide was recovered unchanged even after heating at 150° with phosphorus pentachloride. This result was not wholly unexpected in view of von Braun's work (*Ber.*, 1904, **37**, 2812, 2915) on the action of phosphorus pentachloride on the amides of secondary amines: $R\cdot CO\cdot NR'R'' \longrightarrow R\cdot CCl{:}NR' + R''Cl \longrightarrow R\cdot CO\cdot NHR'$.

Wallach (*Annalen*, 1877, **184**, 4) found that phosphorus pentachloride and acid amides gave in general amidodichlorides which lost hydrogen chloride spontaneously with formation of imidochlorides; from ethyl oxamate, however, he obtained an unstable crystalline amidodichloride.

Lander and Laws (J., 1904, **85**, 1695) found that hydrogen iodide combined with benzanilide imidochloride to give an amidochlorideiodide, Ph·CClI·NHPh, and Stephen and Bleloch (J., 1931, 888) showed that benzanilide imidochloride combined with hydrogen chloride in ethereal solution to give a crystalline amidodichloride hydrochloride. Hallmann (*Ber.*, 1876, **9**, 846) also isolated a crystalline amidodichloride, $Ph\cdot CCl_2\cdot NMe_2$, by the action of carbonyl chloride on benzodimethylamide.

It thus seemed probable that the production of secondary amines under the Sonn–Müller conditions in the quinoline series was dependent on the intermediate formation of amidodichlorides, which, under suitably controlled conditions, might be reduced to amines by stannous chloride. However, when the product of the reaction of benzanilide with phosphorus pentachloride at 0° was reduced with stannous chloride at 0°, only benzaldehyde and aniline were formed. Stephen and Bleloch's benzanilide amidodichloride hydrochloride, similarly reduced at 0°, also gave only benzaldehyde and aniline. The amidodichlorides of ethyl oxamate and ethyl ethyloxamate could not be reduced to the corresponding amines.

In view of these failures a more detailed study was undertaken of the reaction in the quinoline series and 6-chlorocinchoninanilide (I; R = Cl, R′ = Ph) was chosen as likely to provide the most readily crystallisable intermediates. When 6-chlorocinchonanilide in chloroform was treated with phosphorus pentachloride (2 mols.), 6-*chlorocinchoninanilide hydrochloride* corresponding to slightly more than one half the starting material separated almost immediately. The chloroform-soluble material was an unstable yellow oil, which gave on boiling with aniline NN-*diphenyl*-6-*chloro*-4-*quinolylamidine* (III) or with stannous chloride and hydrogen chloride *N*-phenyl-6-chlorolepidylamine (II; R = Cl, R′ = Ph). If the original mixture of anilide and pentachloride was refluxed for an hour, the only product was a yellow oil which could be reduced to *N*-phenyl-6-chlorolepidylamine. This oil, also obtained from solid 6-chlorocinchoninanilide hydrochloride in chloroform and phosphorus pentachloride, was eventually crystallised from carbon disulphide. It appears to have the formula $C_{16}H_{11}N_2Cl_3$. The solubility of this compound in chloroform, contrasted with the insolubility of cinchoninanilide hydrochloride, precluded the possibility that it was the imidochloride hydrochloride and it is justifiably formulated as 6-*chlorocinchoninanilide amidodichloride*, a structure consistent with the formation of the amidine and *N*-phenyl-6-chlorolepidylamine mentioned above. The formation of 6-chlorocinchoninanilide hydrochloride as one of the primary products of the reaction between the anilide and phosphorus pentachloride is consistent with the interpretation of the preliminary phase of the reaction as involving enolisation of the amide:



$$\begin{array}{c} R\cdot CO\cdot NHR' \\ \upharpoonleft\!\downharpoonright \\ R\cdot C(OH){:}NR' \end{array} + PCl_5 \longrightarrow R\cdot CCl{:}NR' + R\cdot CO\cdot NHR',HCl + POCl_3$$

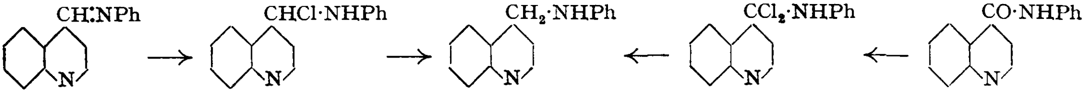
This interpretation is supported by the failure of disubstituted amides to undergo a similar reaction.

Since, however, iminochlorides add on hydrogen chloride under anhydrous conditions and since the Sonn–Müller reaction is carried out in the presence of excess of ethereal hydrogen chloride, it seems probable that the substance undergoing reduction with stannous chloride is always the amidodichloride. This being so, an explanation is required of why, in the case of amides derived from quinoline-4-carboxylic acids and primary amines, reduction to the secondary amine takes place, but in the case of benzanilide and of other anilides studied by Sonn and Müller reduction to an anil is the course followed, with subsequent hydrolysis to the aldehyde.

Hantzsch and Schwab (*Ber.*, 1901, **34**, 822) formulated the hydrogen chloride addition products of anils as true salts, $R\cdot CH{:}\overset{+}{N}HR']\overset{-}{Cl}$, although in certain cases sodium carbonate solution converted them into aldehydeanilines, R·CH(OH)·NHR′. Franzen and Henglein (*J. pr. Chem.*, 1915, **91**, 245), however, from observations on the addition of bromine to anils, formulated the hydrobromides of anils as R·CHBr·NHR′. This view was disputed by Hantzsch (*Ber.*, 1915, **48**, 1340). In accordance with modern theories the hydrogen chloride addition products of anils can probably be best regarded as mesomeric between the ionic and the covalent state. In the case of the amidodichlorides similar mesomerism is probable and in cases where secondary amines are produced by stannous chloride reduction, it is reasonable to assume that the electronic rearrangement due to the adjacent heterocyclic ring (R) is such that the halogen atoms become attached to carbon by covalent links, $R\cdot CCl_2\cdot NHR'$; on the other hand, in compounds where reduction to an anil takes place the linkage of halogen must approach the ionic state. The general scheme to cover both types of product can be formulated thus:

$$R\cdot CH_2\cdot NHR' \longleftarrow R\cdot CCl_2\cdot NHR' \rightleftarrows R\cdot CCl{:}NHR'^{+}Cl^{-} \longrightarrow R\cdot CH{:}NHR'^{+}Cl^{-} \longrightarrow R\cdot CHO + R'NH_3^{+}Cl^{-}$$

If this view is correct, it would seem to follow that an anil prepared from quinoline-4-aldehyde should combine with hydrogen chloride to give a covalent addition product reducible to a secondary amine. This proved to be so, for quinoline-4-aldehyde anil treated with stannous chloride in ethereal hydrogen chloride solution gave a secondary amine identical with that obtained from cinchoninanilide.



When, however the same reaction was applied to benzaldehyde-anil, benzaldehyde was isolated in quantitative yield.

An insufficient number of examples have been studied up to the present to determine what structural factors govern the direction of reduction of the amidodichlorides; it has been found, however, that when nicotinethylamide was treated with phosphorus pentachloride and the product submitted to the Sonn–Müller conditions, it gave, mainly, the anil which decomposed to yield pyridine-3-aldehyde, identified as its phenylhydrazone. 3-Ethylaminomethylpyridine was a minor product and was identified as the *picrate* and *platinichloride*. It is evident that in this case the behaviour is intermediate between that shown by 4-substituted quinolines and that shown by benzanilide in that both types of reaction have taken place, but in unequal proportion.

EXPERIMENTAL.

Cinchoninanilide.—Cinchoninic acid (20 g.) was converted by thionyl chloride into the acid chloride hydrochloride, which was added in small lots to a solution of aniline (40 g.) in chloroform (200 c.c.). Chloroform was removed, the residue suspended in water, and the *anilide* collected, twice precipitated from acetone solution by an equal volume of water, and crystallised from benzene; it formed stout needles (17 g.), m. p. 161—162° (Found: C, 76·9; H, 4·7. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·8%).

N-*Phenyl-lepidylamine.*—Cinchoninanilide (12·4 g.) was boiled in toluene with phosphorus pentachloride (11·0 g.) for 3 hours, the toluene distilled, and the solid residue added in small portions to a solution of anhydrous stannous chloride (40 g.) in dry ethereal hydrogen chloride (200 c.c. saturated with hydrogen chloride). After 24 hours' shaking with glass beads, the ether was decanted, the sludge washed with ether and boiled with 5N-hydrochloric acid (600 c.c.) until most of the solid dissolved, and the solution filtered hot. The tin salt (18 g.) that separated on cooling was suspended in water, and sodium hydroxide (50% solution) added in considerable excess. Ether extracted a crystalline substance, which was triturated with light petroleum (yield, 7·22 g.) and fractionally crystallised from methyl alcohol–water, giving cinchoninanilide (0·35 g.) and mainly *N*-phenyl-lepidylamine, m. p. 121°.

When 2 mols. of phosphorus pentachloride were used, cinchoninanilide (1·24 g.) gave N-*phenyl-lepidylamine* (0·8 g.) as the sole product (Found: C, 82·0; H, 6·0; N, 12·0. $C_{16}H_{14}N_2$ requires C, 82·0; H, 6·0; N, 12·0%).

Cinchoninomethylamide.—Methyl cinchoninate (2·0 g.) and 33% alcoholic methylamine (4·5 c.c.) were heated at 100° in a sealed tube for 6 hours, the alcohol removed, and the *amide* (1·7 g.) crystallised from ether; m. p. 111° (Found: C, 70·4; H, 5·4. $C_{11}H_{10}ON_2$ requires C, 70·9; H, 5·4%).

N-*Methyl-lepidylamine.*—Cinchoninomethylamide (1·5 g.) in dry chloroform (10 c.c.) was refluxed with phosphorus pentachloride (2·5 g.; 1½ mols.) for ½ hour, chloroform and phosphorus oxychloride removed in a vacuum, and the product dissolved in dry chloroform (10 c.c.) and added to a solution of stannous chloride (6·5 g.) in ethereal hydrogen chloride (65 c.c.). The mixture was shaken for 24 hours, diluted with water, and washed with ether, sodium hydroxide (50% solution) added in considerable excess, and the chloroform-soluble material extracted from the cooled solution. The extract was a reddish oil which gave a crystalline hydrochloride (1·51 g.) from alcohol, m. p. 215—220° (decomp.); recrystallised from methanol, it formed prisms or needles of N-*methyl-lepidylamine dihydrochloride* (Found for material dried at 100°: C, 53·4; H, 6·0. $C_{11}H_{12}N_2,2HCl$ requires C, 53·9; H, 5·7%). The base was a colourless oil soluble in water and in ether.

Cinchoninodiethylamide.—The acid chloride hydrochloride obtained from cinchoninic acid (3 g.) was suspended in dry benzene, excess of diethylamine added, and after 15 minutes the solution diluted with chloroform and water. The oil (5·5 g.) obtained from the chloroform–benzene was distilled, and the fraction (4·2 g.), b. p. 180°/2 mm., converted into the *picrate*, m. p. 189°, which was crystallised from alcohol (Found: C, 52·6; H, 4·4; N, 15·3. $C_{14}H_{16}ON_2,C_6H_3O_7N_3$ requires C, 52·5; H, 4·2; N, 15·3%).

6-*Chlorocinchoninanilide.*—This, prepared from 6-chlorocinchoninic acid (Work, *loc. cit.*) (10 g.) (for details, see cinchoninanilide) and crystallised from acetone–water and from acetone (yield, 10·8 g.), had m. p. 205° (Found: C, 68·0; H, 4·0. $C_{16}H_{11}ON_2Cl$ requires C, 67·9; H, 3·9%).

N-*Phenyl-*6-*chlorolepidylamine.*—6-Chlorocinchoninanilide (2 g.) in chloroform (50 c.c.) at 50° reacted vigorously with phosphorus pentachloride (2 mols.). The pale yellow solid that separated almost immediately (1·5 g.) was washed with chloroform, dried (Found: C, 59·8; H, 3·8; N, 8·5; Cl, 21·9. $C_{16}H_{11}ON_2Cl,HCl$ requires C, 60·2; H, 3·8; N, 8·8; Cl, 22·2%), and identified as 6-*chlorocinchoninanilide hydrochloride* by reconversion into the original material. The chloroform-soluble product was an unstable yellow oil, which crystallised and gave, on boiling with aniline, NN-*diphenyl-*6-*chloro-*4-*quinolylamidine* (0·6 g.), sparingly soluble in alcohol, which crystallised from acetone in prisms, m. p. 207° (Found: C, 73·4; H, 4·5; N, 11·9. $C_{22}H_{16}N_3Cl$ requires C, 73·8; H, 4·5; N, 11·9%).

A suspension of 6-chlorocinchoninanilide hydrochloride (0·5 g.) in chloroform (5 c.c.) and phosphorus pentachloride was refluxed for ½ hour, most of the chloroform removed from the clear orange solution, and dry carbon disulphide (15 c.c.) added; the unstable orange needles obtained (0·7 g.) were immediately transferred to a desiccator. (1) A sample, heated with aniline, gave *NN*-diphenyl-6-chloro-4-quinolylamidine. (2) A sample (0·38 g.) was reduced with stannous chloride in ethereal hydrogen chloride. The colourless crystalline product (180 mg.) was N-*phenyl-*6-*chlorolepidylamine*, m. p. 129°, sparingly soluble in petroleum (Found: C, 72·0; H, 5·0; N, 10·7. $C_{16}H_{13}N_2Cl$ requires C, 71·5; H, 4·8; N, 10·4%). The hydrochloride had m. p. 158—160° (decomp.). The *nitrosoamine* crystallised from ether in needles, m. p. 131° (Found: C, 65·2; H, 4·2; N, 14·1. $C_{16}H_{12}ON_3Cl$ requires C, 64·5; H, 4·0; N, 14·1%). (3) A sample was dissolved in dry chloroform containing a trace of phosphorus pentachloride, the solution evaporated almost to dryness, and carbon disulphide added. The orange-coloured crystals obtained were very unstable and analysis (Found: C, 54·2; H, 3·4; N, 7·6; Cl, 31·6. $C_{16}H_{11}N_2Cl_3$ requires C, 56·9; H, 3·2; N, 8·3; Cl, 31·5%) showed that they consisted mostly of 6-chlorocinchoninanilide amidodichloride.

*Quinoline-*4-*aldehyde Anil.*—Quinoline-4-aldehyde (0·3 g.) and aniline (0·18 g.) were heated at 100° for 15 minutes.

The *anil* was dried in a vacuum and crystallised from ether–ligroin, forming thin platelets (0·35 g.), m. p. 85° (Found : C, 82·4; H, 5·3. $C_{16}H_{12}N_2$ requires C, 82·8; H, 5·2%).

Reduction of Quinoline-4-aldehyde Anil.—The anil (0·35 g.) was shaken with stannous chloride (1·5 g.) in ethereal hydrogen chloride (15 c.c.) for 24 hours. The product, isolated by extraction with ether from alkaline solution and crystallised from ligroin, had m. p. 120—121°, not depressed by *N*-phenyl-lepidylamine.

Reaction of Ethyl Oxamate Amidodichloride and Stannous Chloride.—Ethyl oxamate (2·34 g.) was treated with phosphorus pentachloride as described by Wallach (*loc. cit.*); the amidodichloride, precipitated by petroleum, was washed, dried, and added to stannous chloride (10 g.) in ethereal hydrogen chloride (100 c.c.). After 24 hours the product was poured into water and washed with ether, and the acid solution evaporated to dryness. The residue was dissolved in water, tin removed as sulphide, and the solution evaporated, leaving ammonium chloride (0·7 g.).

A similar experiment with ethyl ethyloxamate gave oxalomonoethylamide.

Nicotinethylamide.—Methyl nicotinate (15 g.), heated with 33% alcoholic ethylamine (30 c.c.) in a sealed tube at 100° for 8 hours, gave an oil (13 g.) which distilled at 152°/12 mm., solidified, and could be crystallised from ether; m. p. 57° (Found : C, 63·7; H, 6·6. $C_8H_{10}ON_2$ requires C, 64·0; H, 6·7%).

Reaction of Nicotinethylamide with Phosphorus Pentachloride and Stannous Chloride.—The product of reaction between the ethylamide (3·3 g.) in chloroform (10 c.c.) and phosphorus pentachloride (9·5 g.; 2 mols.) was heated at 120° for $\frac{1}{2}$ hour, phosphorus oxychloride removed in a vacuum, and the residual oil shaken with stannous chloride (14 g.) in ethereal hydrogen chloride (140 c.c.) for 24 hours. Water was then added, the acid solution washed with ether and basified with sodium hydroxide (50% solution) in considerable excess, and ethylamine removed in a vacuum at room temperature. Continuous extraction with ether removed a pale brown oil, which was fractionally distilled, giving (*a*) b. p. 200—220°/760 mm. (0·8 g.), (*b*) b. p. 220—240°/760 mm. (0·22 g.), and (*c*) b. p. 150—180°/14 mm. (0·9 g.). Fraction (*c*) crystallised and was mainly unchanged amide. Fractions (*a*) and (*b*) gave with phenylhydrazine in dilute acetic acid a crystalline phenylhydrazone, m. p. 157° (Found : C, 72·7; H, 5·7. Calc. for $C_{12}H_{11}N_3$: C, 73·1; H, 5·6%). Harries and Lénárt (*Annalen*, 1915, **410**, 115) give m. p. 158° for pyridine-3-aldehyde phenylhydrazone. Fractions (*a*) and (*b*) also gave with platinic chloride and hydrochloric acid the crystalline *platinichloride* of 3-*ethylaminomethylpyridine*, sparingly soluble in cold water (Found : N, 4·8; Pt, 35·8. $C_8H_{12}N_2PtCl_6$ requires N, 5·1; Pt, 35·5%).

A sample of fraction (*b*) which appeared to contain a larger proportion of secondary amine than (*a*) was dissolved in methanol, and the aldehyde removed by oxidation with ammoniacal silver nitrate. The stable secondary amine was then isolated and converted into a *picrate*, m. p. 207°, sparingly soluble in ethanol (Found : C, 40·8; H, 3·2. $C_8H_{12}N_2,2C_6H_3O_7N_3$ requires C, 40·4; H, 3·0%).

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