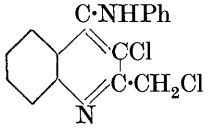
CCCXCI.—*The Constitution of the Bases formed by the Action of Phosphoryl Chloride on Acetanilide and on Phenacetin.*

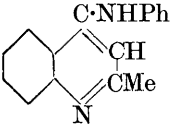
By Otto Guido Backeberg.

The action of phosphorus pentachloride on anilides of the type $Ph{\cdot}NH{\cdot}CO{\cdot}CH_2R$ (R = Cl, Me, or Ph) leads, as von Braun and his collaborators have shown (*Ber.*, 1930, **63**, 3191), to the formation of quinoline derivatives, except in the case of acetanilide itself (R = H), which yields an amidine only, and no quinoline derivative. In this connexion Silberstein (D.R.-P. 137121) found that when acetanilide and phenacetin were treated with phosphoryl chloride, in addition to the corresponding substituted acetamidines, the bases $C_{16}H_{14}N_2$ (A) and $C_{20}H_{22}O_2N_2$ (B) respectively were formed. The present investigation, primarily undertaken with the object of correlating Silberstein's observations with those of von Braun, establishes the constitution of these bases, which are of interest owing to the powerful local anæsthetic action ascribed to them by Silberstein.

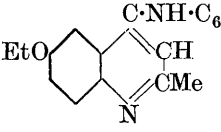
Von Braun (*loc. cit.*) has shown that ω-chloroacetanilide and phosphorus pentachloride form 3-chloro-4-anilino-2-chloromethylquinoline (I) and it therefore appeared probable that Silberstein's bases (A) and (B) could be formulated as 4-anilinoquinaldine (II) and 4-p-*phenetidino*-6-*ethoxyquinaldine* (III) respectively.



(I.)



(II.)

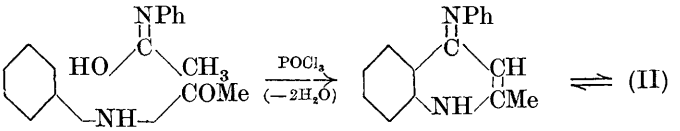


(III.)

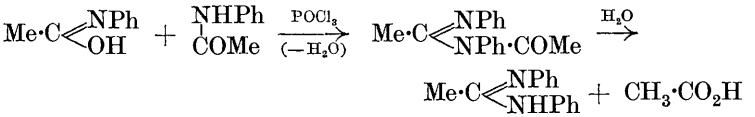
The compound (II) was synthesised by Conrad and Limpach (*Ber.*, 1887, **20**, 953), and a specimen prepared by their method was found to be identical with Silberstein's base (A); the compound (III) has not previously been described, but was similarly synthesised and found to be identical with the base (B).

The compound (II), heated in a sealed tube with fuming hydrochloric acid, lost the anilino-group and gave 4-hydroxyquinaldine and aniline; similar treatment of (III) removed the ethoxy-groups, but owing to considerable decomposition 4 : 6-dihydroxyquinaldine could not be isolated.

The following mechanism of the formation of these quinaldine derivatives is proposed :



The simultaneous formation of diphenylacetamidine would occur as follows :



Similar reactions would apply to the formation of (III) and of bis-(*p*-ethoxyphenyl)acetamidine.

Experimental.

4-Anilinoquinaldine (II) (base A) was obtained in 10% yield as the *hydrochloride* by heating acetanilide (50 g.) with phosphoryl chloride (55 g.) on the water-bath for 5 hours, pouring the product into water (100 c.c.), and heating the mixture to the boiling point. The bright yellow needles obtained on cooling were converted by repeated treatment with charcoal in dilute acetic acid solution into colourless needles, m. p. 266° after recrystallisation from aqueous-alcoholic hydrogen chloride (Found : Cl, 13·2. $C_{16}H_{14}N_2$,HCl requires Cl, 13·1%). Recrystallisation of the salt from either water or dilute hydrochloric acid alone gave a product which analysis indicated had undergone partial hydrolysis. The free base, precipitated from a dilute acetic acid solution of the hydrochloride by ammonia, crystallised from dilute alcohol in white needles, m. p. 156° (Conrad and Limpach, *loc. cit.*, give m. p. 151°). A specimen prepared by their method, after crystallisation from dilute alcohol, melted at 156°, alone or mixed with Silberstein's base (A).

Decomposition of 4-Anilinoquinaldine.—The base (1 g.) was heated in a sealed tube with fuming hydrochloric acid (10 g.) at 250° for 18 hours. The dark product was evaporated on the water-bath, neutralised, and distilled in a current of steam; the distillate gave the reactions for aniline. The residue was evaporated to dryness, extracted with alcohol, and after removal of the alcohol the product was dissolved in hot water (5 c.c.), and the solution decolourised with charcoal. On cooling, white needles (0·2 g.) were obtained; after being dried at 110°, they melted at 232°, and gave no depression in admixture with authentic 4-hydroxyquinaldine (Conrad and Limpach, *loc. cit.*; Limpach, *Ber.*, 1931, **64**, 969) (Found: N, by micro-Dumas, 9·0. Calc. for $C_{10}H_9ON$: N, 8·8%).

4-p-*Phenetidino-6-ethoxyquinaldine* (III) (base B) was obtained as the *hydrochloride* in 15% yield from phenacetin and phosphoryl chloride. The dark red, viscous product was dissolved in acetone, and ether added; the yellow precipitate, after purification as in the case of base (A), crystallised from alcoholic hydrogen chloride in pale lemon-yellow, silky needles, m. p. 264° (Found: Cl, 9·9. $C_{20}H_{22}O_2N_2$,HCl requires Cl, 9·9%). The free base crystallised from alcohol in white needles, m. p. 225° (Silberstein, *loc. cit.*, gives 220°), alone or mixed with the base, m. p. 225°, synthesised in quantitative yield by Conrad and Limpach's method (*loc. cit.*) by heating 4-chloro-6-ethoxyquinaldine with an equivalent of *p*-phenetidine at 190° for 3 hours (Found: N, by micro-Dumas, 8·55. $C_{20}H_{22}O_2N_2$ requires N, 8·7%).

The base (1 g.) was heated in a sealed tube with fuming hydrochloric acid (10 g.) for 18 hours at 220°. Ethyl chloride escaped when the tube was opened, but the product contained much carbonaceous matter, and 4 : 6-dihydroxyquinaldine could not be isolated from it.

4-*Chloro-6-ethoxyquinaldine*, obtained by refluxing 4-hydroxy-6-ethoxyquinaldine with excess of phosphoryl chloride for ½ hour, removing the excess of the latter under diminished pressure on the water-bath, and submitting the residue, made alkaline, to steam distillation, crystallised from dilute alcohol in white prismatic needles, m. p. 78° (Found: N, by micro-Dumas, 6·5. $C_{12}H_{12}ONCl$ requires N, 6·3%).

4-*Hydroxy-6-ethoxyquinaldine hydrochloride* crystallised, when a solution of the base in hot dilute hydrochloric acid was cooled, in white needles which became pale pink on drying; m. p. 241—243° (Found: Cl, 14·7. $C_{12}H_{13}O_2N$,HCl requires Cl, 14·8%).

4 : 6-*Dihydroxyquinaldine.*—4-Hydroxy-6-ethoxyquinaldine (2 g.) was heated in a sealed tube with fuming hydrochloric acid (10 g.) at 150° for 3 hours, ethyl chloride being formed. The product was

evaporated to dryness on the water-bath, the residue dissolved in hot water, and the solution decolourised with charcoal and, when cold, neutralised with ammonia. The *base* (1·7 g.) crystallised from water in white needles, m. p. 308° (decomp.), which became anhydrous at 110° (Found: loss of weight on heating, 9·5. $C_{10}H_9O_2N,H_2O$ requires H_2O, 9·3%. Found for the anhydrous base: N, by micro-Dumas, 8·1. $C_{10}H_9O_2N$ requires N, 8·0%). Aqueous and alkaline solutions of the base have a blue fluorescence, and the former give a red coloration with ferric chloride.

In view of the results obtained it is proposed to continue the investigation of similar compounds.

In conclusion the author records his appreciation of Prof. H. Stephen's interest in the investigation.

UNIVERSITY OF THE WITWATERSRAND,
JOHANNESBURG, SOUTH AFRICA. [*Received, September 7th,* 1931.]