416. *Some Derivatives of 1,2-Dihydro- and 1,2,3,4-Tetrahydroquinoline.*

By R. F. Collins.

1,2-Dihydro-1-toluene-*p*-sulphonylquinoline has been prepared by a new method from 1,2,3,4-tetrahydro-4-oxo-1-toluene-*p*-sulphonylquinoline, and a general method is described for the introduction of basic alkyl chains on to the weakly basic nitrogen atom of 1,2,3,4-tetrahydro-4-oxoquinoline and its derivatives.

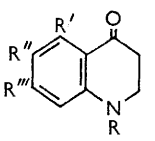
1,2-Dihydroquinoline was first prepared by Johnson and Buell [1] during an attempt to distil 1,2,3,4-tetrahydro-4-phenethylaminoquinoline and by Bohlmann [2] who reduced quinoline with lithium aluminium hydride. The dihydro-compound disproportionates within 24 hr. into quinoline and 1,2,3,4-tetrahydroquinoline, but the 1-toluene-*p*-sulphonyl [3] and the 1-benzoyl [4] derivative are stable. A new route to 1,2-dihydroquinolines from the readily prepared 1,2,3,4-tetrahydro-4-oxo-1-toluene-*p*-sulphonylquinoline (I; R = $SO_2 \cdot C_6H_4Me$-*p*, R′ = R″ = R‴ = H) is described which involves dehydrating the corresponding alcohol, with the toluene-*p*-sulphonate (II) as an intermediate.[5] An advantage is that the resultant 1,2-dihydro-1-toluene-*p*-sulphonylquinoline [3] is stable, and the method should be a general one.

Compounds of the type (I) containing a 1-(aminoalkyl) group were required for testing

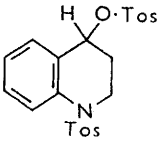
[1] Johnson and Buell, *J. Amer. Chem. Soc.*, 1952, **74**, 4517.
[2] Bohlmann, *Chem. Ber.*, 1952, **85**, 390.
[3] Rosenmund and Zymalkowski, *Chem. Ber.*, 1953, **86**, 37.
[4] Collins, *J.*, 1954, 3641.
[5] Cf. Collins, Ph.D. Thesis, London, 1956.

as agents against bilharzia. Methods [6] available for simple 1-alkyl derivatives were unsuitable or gave low yields. A new method involves reduction of a 1-acyl derivative and subsequent oxidation of the hydroxyl group thus formed from the 4-oxo-group.

1,2,3,4-Tetrahydro-4-oxoquinoline was prepared directly in almost quantitative yield by cyclisation of β-*N*-toluene-*p*-sulphonylanilinopropionic acid with polyphosphoric acid; the sulphonyl group was probably hydrolysed on dilution of the mixture after cyclisation.



(I)



(II)

(Tos = p-$C_6H_4Me{\cdot}SO_2$)

This is supported by the fact that β-anilinopropionic acid required a higher temperature for conversion into the tetrahydro-4-oxo-quiniline by means of polyphosphoric acid (and the yield was lower). Johnson *et al.*[7] obtained a good yield of the 1-toluene-*p*-sulphonyl derivative by cyclisation with stannic chloride in benzene and acid-hydrolysis was then quantitative. A sample of this toluene-*p*-sulphonyl derivative was prepared by their method and the 4-oxo-group was reduced by the Meerwein–Ponndorf reaction quantitatively to the alcohol, the toluene-*p*-sulphonate of which when heated with quinoline gave 1,2-dihydro-1-toluene-*p*-sulphonylquinoline [5] identical with that prepared by Rosenmund and Zymalkowsky.[3]

Direct *N*-alkylation of the tetrahydroquinolone (I; R = R′ = R″ = R‴ = H), which is a very weak base, with 2-diethylaminoethyl chloride proved difficult but in the presence of sodamide a poor yield (7·6%) of the ketone (I; R = $CH_2{\cdot}CH_2{\cdot}NEt_2$, R′ = R″ = R‴ = H) was isolated after careful fractionation of the reaction mixture. Another route to this compound was based on the fact that 1-acetyl-1,2,3,4-tetrahydro-4-oxoquinoline (I; R = Ac, R′ = R″ = R‴ = H) is reduced by lithium aluminium hydride to 1-ethyl-1,2,3,4-tetrahydro-4-hydroxyquinoline which is oxidised *in situ* under Oppenauer conditions to 1-ethyl-1,2,3,4-tetrahydro-4-oxoquinoline (I; R = Et, R′ = R″ = R‴ = H). 1-(2-Diethylaminoethyl)-1,2,3,4-tetrahydro-4-oxoquinoline (I; R = $CH_2{\cdot}CH_2{\cdot}NEt_2$, R′ = R″ = R‴ = H) was then prepared by the same method from the chloroacetyl derivative (I; R = $CO{\cdot}CH_2Cl$, R′ = R″ = R‴ = H) *via* 1-diethylaminoacetyl-1,2,3,4-tetrahydro-4-oxoquinoline (I; R = $CO{\cdot}CH_2{\cdot}NEt_2$, R′ = R″ = R‴ = H).

1,2,3,4-Tetrahydro-6-methyl-4-oxoquinoline [8] (I; R = R′ = R‴ = H, R″ = Me) obtained by the cyclisation of *N*-toluene-*p*-sulphonyl-β-*p*-toluidinopropionic acid in polyphosphoric acid was converted similarly into 1-(2-diethylaminoethyl)-1,2,3,4-tetrahydro-6-methyl-4-oxoquinoline (I; R = $CH_2{\cdot}CH_2{\cdot}NEt_2$, R′ = R‴ = H, R″ = Me). Both 5- and 7-chloro-1,2,3,4-tetrahydro-6-methyl-4-oxoquinoline (I; R = R‴ = H, R″ = Me, R′ = Cl; and R = R′ = H, R″ = Me, R‴ = Cl respectively) were isolated from the cyclisation of β-(3-chloro-4-methyl-*N*-toluene-*p*-sulphonylanilino)propionic acid with polyphosphoric acid. The structure of the 7-chloro-isomer (I; R = R′ = H, R″ = Me, R‴ = Cl) was confirmed by Wolff–Kishner reduction (as modified by Huang-Minlon [9]) to the known 7-chloro-1,2,3,4-tetrahydro-6-methylquinoline.[10] The 5-chloro-isomer (I; R = R‴ = H, R″ = Me, R′ = Cl) could not be obtained pure and was isolated as its *N*-chloroacetyl derivative [corresponding to 31% of 5-chloro-isomer in the mixture obtained after the cyclisation], whence acid-hydrolysis yielded the pure compound (I; R = R‴ = H, R″ = Me, R′ = Cl). Both 5- and 7-chloro-1,2,3,4-tetrahydro-6-methyl-4-oxoquinoline were converted *via* the chloroacetyl derivatives into the diethylaminoacetyl

[6] Allison, Braunholtz, and Mann, *J.*, 1954, 403.
[7] Johnson, Woroch, and Buell, *J. Amer. Chem. Soc.*, 1949, **71**, 1901.
[8] Clemo and Perkin, *J.*, 1925, 2297.
[9] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[10] Bayer, B.P. 758,570/1956.

derivatives (I; R = $CO{\cdot}CH_2{\cdot}NEt_2$, R′ = Cl, R″ = Me, R‴ = H; and R = $CO{\cdot}CH_2{\cdot}NEt_2$, R′ = H, R″ = Me, R‴ = Cl respectively), and the 7-chloro-isomer was converted by the above general method into 7-chloro-1-(2-diethylaminoethyl)-1,2,3,4-tetrahydro-6-methyl-4-oxoquinoline (I; R = $[CH_2]_2{\cdot}NEt_2$, R′ = H, R″ = Me, R‴ = Cl).*

Reduction of 5-chloro-1-diethylaminoacetyl-1,2,3,4-tetrahydro-6-methyl-4-oxoquinoline (I; R = $CO{\cdot}CH_2{\cdot}NEt_2$, R′ = Cl, R″ = Me, R‴ = H) with lithium aluminium hydride gave apparently a mixture of 5-chloro-1-(2-diethylaminoethyl)-1,2,3,4-tetrahydro-4-hydroxy-6-methylquinoline and 5-chloro-1,2,3,4-tetrahydro-4-hydroxy-6-methylquinoline which were separated by fractional distillation. (Lithium aluminium hydride converts certain *N*-acyl-1,2,3,4-tetrahydroquinolines into the corresponding alcohols and 1,2,3,4-tetrahydroquinoline.[11] This may have occurred partially in the earlier reductions, in which the low-boiling fractions were discarded, since the yields were not quantitative.) Neither of these alcohols was oxidised under Oppenauer conditions to a ketone, but activated manganese dioxide converted the lower-boiling 5-chloro-1,2,3,4-tetrahydro-4-hydroxy-6-methylquinoline into 5-chloro-6-methylquinoline. This unexpected product nevertheless confirmed the structure of the 5-chloro-6-methyl-4-oxoquinoline isomer isolated during the cyclisation of β-(3-chloro-4-methyl-*N*-toluene-*p*-sulphonylanilino)propionic acid. Unfortunately the high-boiling 5-chloro-1-(2-diethylaminoethyl)-1,2,3,4-tetrahydro-4-hydroxy-6-methylquinoline, obtained in the reduction, was not fully characterised. It was isolated after the distillation (which probably caused some decomposition) as a low-melting solid (which could not be recrystallised), giving a poor analysis, from which no crystalline derivative could be prepared.

The basic quinolines (I; R = $CH_2{\cdot}CH_2{\cdot}NEt_2$, R′ = R″ = R‴ = H; R′ = R‴ = H, R″ = Me; and R′ = H, R″ = Me, R‴ = Cl) were all yellow-fluorescent oils which did not form the usual crystalline derivatives, but eventually a crystalline (−)-di-*p*-toluoyl-base (+)-tartrate (suitable for identification and analysis) was prepared from each. Our colleague, Mr. J. Hill, reported that these compounds had no activity in bilharzia.

Experimental

1,2,3,4-*Tetrahydro*-4-*hydroxy*-1-*toluene*-p-*sulphonylquinoline*.—1,2,3,4-Tetrahydro-4-oxo-1-toluene-*p*-sulphonylquinoline [7] (5 g.) in dry propan-2-ol (200 ml.) was refluxed with aluminium isopropoxide (6·5 g.), and the resulting acetone was slowly distilled from the mixture. After 3 hr. no further acetone was detected, and the solvent was removed *in vacuo*. The residue was treated with an excess of dilute hydrochloric acid, and the product, which was isolated by means of chloroform, was crystallised from ethyl acetate–light petroleum (b. p. 60—80°). The pure *product* (5 g.) had m. p. 75—77° (shrinks at 70°) (Found: C, 63·5; H, 6·1; S, 10·55. $C_{16}H_{17}NO_3S$ requires C, 63·3; H, 5·6; S, 10·55%).

1,2-*Dihydro*-1-*toluene*-p-*sulphonylquinoline*.[3]—1,2,3,4-Tetrahydro-4-hydroxy-1-toluene-*p*-sulphonylquinoline (5 g.) in pyridine (100 ml.) was treated rapidly with toluene-*p*-sulphonyl chloride (5 g.), and the red solution was heated at 100° for 3 hr. The pyridine was removed by distillation and the residue taken up in chloroform, which was then washed with dilute hydrochloric acid and with water and dried. The solvent was evaporated and the residue, which did not solidify, was heated in quinoline (40 ml.) at 170—180° for 4 hr. The product was isolated as before and after removal of the solvent the residue partially solidified under light petroleum (b. p. 40—60°). Extraction of the semi-solid material with light petroleum (b. p. 80—100°) gave the dihydro-derivative (1 g.), m. p. 91° (Found: C, 67·3; H, 5·45; N, 4·7. Calc. for $C_{16}H_{15}NO_2S$: C, 67·3; H, 5·25; N, 4·9%) (Rosenmund and Zymalkowski [3] give m. p. 94°).

1,2,3,4-*Tetrahydro*-4-*oxoquinoline*.—(*A*) β-(*N*-Toluene-*p*-sulphonylanilino)propionic acid [7] (51 g.) was added, with stirring, to polyphosphoric acid (400 g.), and the mixture was heated on the

* This compound was reduced by the Wolff–Kishner method (as modified by Huang-Minlon [9]) to 7-chloro-1-(2-diethylaminoethyl)-1,2,3,4-tetrahydro-6-methylquinoline which formed a crystalline hydrochloride, and its m. p. was not depressed upon admixture with that of an authentic specimen [10] prepared independently.

[11] Mićovic and Mikailović, *J. Org. Chem.*, 1953, **18**, 1190.

steam-bath for 1·25 hr. The cooled orange melt was decomposed with water (the temperature reached 80°) and the solution was basified and extracted with ether. The ethereal extract afforded the product (23·4 g., 100%), b. p. 120—130°/0·02 mm., m. p. 38—40° (from light petroleum, b. p. 40—60°) (Johnson *et al.*[7] give m. p. 43—44·5°) [1-*acetyl* derivative, b. p. 206—210°/17 mm.; m. p. 92—93° (from ether) (Found: N, 7·4; Ac, 23·0. $C_{11}H_{11}NO_2$ requires N, 7·4; Ac, 23·3%)]. (*B*) β-Anilinopropionic acid (6·7 g.) was added with stirring to polyphosphoric acid (80 g.), and the mixture heated at 130—140° for 4 hr. The deep red melt was then worked up as in (*A*) to give the product (3·6 g., 60%), b. p. 120°/0·02 mm., m. p. 42—43°.

1-*Ethyl*-1,2,3,4-*tetrahydro*-4-*oxoquinoline*.—1-Acetyl-1,2,3,4-tetrahydro-4-oxoquinoline (5·2 g.) in dry tetrahydrofuran (40 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (2·2 g.) in ether (80 ml.). After being stirred and refluxed for 2 hr., the mixture was kept overnight. Ethyl acetate (about 5 ml.) was slowly added to decompose the excess of reagent, followed by aqueous sodium hydroxide. The ethereal layer afforded the crude 1-ethyl-1,2,3,4-tetrahydro-4-hydroxyquinoline as a colourless oil, which was heated in benzene (25 ml.) with cyclohexanone (25 ml.) and aluminium isopropoxide (3 g.) for 18 hr. on the steam-bath. Ether was added to the gelatinous yellow solution which was then extracted with 6N-hydrochloric acid (5 × 20 ml.). The extract was basified to give the *product* as a bright yellow oil (2·3 g., 48%), b. p. 185—190°/15 mm. (Found: C, 74·3; H, 7·5; N, 8·1. $C_{11}H_{13}NO$ requires C, 74·5; H, 7·4; N, 8·0%) [*semicarbazone*, m. p. 180—182° (from aqueous methanol) (Found: N, 24·0. $C_{12}H_{16}N_4O$ requires N, 24·2%)]. The infrared spectrum of this yellow fluorescent oil showed an intense absorption band at 1670 cm.$^{-1}$, indicative of an aromatic ketone rather than an alcohol. (An attempt to oxidise the intermediate 1-ethyl-1,2,3,4-tetrahydro-4-hydroxyquinoline with chromium trioxide failed to yield the ketone; Elderfield and Maggiolo [12] oxidised 1-benzoyl-6-chloro-1,2,3,4-tetrahydro-4-hydroxy-2-methylquinoline to the corresponding ketone by using this reagent.)

1-*Chloroacetyl*-1,2,3,4-*tetrahydro*-4-*oxoquinoline*.—1,2,3,4-Tetrahydro-4-oxoquinoline [7] (37 g.) was treated with chloroacetyl chloride (18·3 ml.) and heated on the steam-bath for 2 hr. Hydrogen chloride was evolved and a clear melt was obtained. After being triturated with ether the *product* (52 g., 93%) had m. p. 122—124° raised to 128—130° by recrystallisation from ethanol (Found: N, 6·15; Cl, 15·8. $C_{11}H_{10}ClNO_2$ requires N, 6·3; Cl, 15·9%).

1-*Diethylaminoacetyl*-1,2,3,4-*tetrahydro*-4-*oxoquinoline*.—1-Chloroacetyl-1,2,3,4-tetrahydro-4-oxoquinoline (52 g.) was treated with diethylamine (100 ml.), and the mixture refluxed for 1 hr. The cooled mixture was poured into excess of 2N-sodium hydroxide; the *product* (48 g., 79%) which was extracted by ether had b. p. 165—168°/0·02 mm. (Found: C, 69·3; H, 8·0; N, 10·85. $C_{15}H_{20}N_2O_2$ requires C, 69·2; H, 7·7; N, 10·8%).

1-(2-*Diethylaminoethyl*)-1,2,3,4-*tetrahydro*-4-*oxoquinoline*.—(*a*) 1-Diethylaminoacetyl-1,2,3,4-tetrahydro-4-oxoquinoline (24 g.) in tetrahydrofuran (100 ml.) was added dropwise to a suspension of lithium aluminium hydride (7·4 g.) in ether (250 ml.), and the reaction was carried out as described above. The crude 1-(2-diethylaminoethyl)-1,2,3,4-tetrahydro-4-oxoquinoline was dissolved in benzene (100 ml.) and heated with cyclohexanone (115 ml.) and aluminium isopropoxide (14 g.) on the steam-bath for 18 hr. The gelatinous yellow solution was worked up as before to give the *ketone*, a yellow oil (15 g., 66%), b. p. 145—150°/0·02 mm., n_D^{20} 1·572 (Found: C, 72·8; H, 9·2; N, 11·3. $C_{15}H_{22}N_2O$ requires C, 73·1; H, 8·9; N, 11·4%). The (−)-*di*-(p-*toluoyl*)-*base* (+)-*tartrate* formed bright yellow crystals (from ethanol), m. p. 166° (decomp.) (Found: N, 4·3. $C_{15}H_{22}N_2O,C_{20}H_{18}O_8$ requires N, 4·4%).

(*b*) 1,2,3,4-Tetrahydro-4-oxoquinoline (11·05 g.) in toluene (20 ml.) was added to a suspension of powdered sodamide (3·3 g.) in toluene (60 ml.), followed by 2-diethylaminoethyl chloride (10·2 g.) in toluene (105 ml.), and the mixture was stirred and heated at 80° for 1 hr. and then refluxed for 0·5 hr. It was kept overnight, excess of sodamide was destroyed by the careful addition of water, and the toluene layer was separated and then extracted with dilute acetic acid. This gave the crude product (3·5 g.), b. p. 145—155°/0·03 mm., whence refractionation afforded a pure sample (1·4 g., 7·6%), b. p. 145—150°/0·02 mm., n_D^{20} 1·577 (Found: C, 73·3; H, 9·0; N, 11·2%).

β-(N-*Toluene*-p-*sulphonyl*-p-*toluidino*)*propionic Acid*.[8]—Methyl β-*p*-toluidinopropionate [13] (110 g.) in pyridine (500 ml.) was treated with toluene-*p*-sulphonyl chloride (120 g.) at 0° (max. temp. was 30° during the addition). The mixture was heated at 100° for 15 min., cooled, and

[12] Elderfield and Maggiolo, *J. Amer. Chem. Soc.*, 1949, **71**, 1906.
[13] Crouch and Southwick, *J. Amer. Chem. Soc.*, 1953, **75**, 3413.

poured into dilute hydrochloric acid. The crude methyl β-(*N*-toluene-*p*-sulphonyltoluidino)-propionate (a gum) was dissolved in methanol (1 l.) and treated with potassium hydroxide (40 g.) in water (400 ml.). After 24 hr. the mixture was poured into water and acidified with acetic acid. The product (137 g., 72%), m. p. 109—111°, was recrystallised from benzene to yield the pure *acid*, m. p. 117—118° (Found: N, 4·2; S, 9·3. $C_{17}H_{19}NO_4S$ requires N, 4·2; S, 9·6%) (Clemo and Perkin [8] give m. p. 116—117° but no supporting analysis for this acid which was obtained from *N*-toluene-*p*-sulphonyl-*p*-toluidine and β-chloropropionic acid).

1,2,3,4-*Tetrahydro*-6-*methyl*-4-*oxoquinoline*.[8]—β-(*N*-Toluene-*p*-sulphonyl-*p*-toluidino)-propionic acid (134 g.) was cyclised in polyphosphoric acid (1 kg.) to the ketone [from light petroleum (b. p. 100—120°)] (34 g., 52%), m. p. 81—83° (Found: N, 8·45. Calc. for $C_{10}H_{11}NO$: N, 8·7%) (Clemo and Perkin [8] give m. p. 85—86° for this product obtained by acid hydrolysis of the *N*-toluene-*p*-sulphonyl derivative). The 1-*chloroacetyl* derivative (82%) had m. p. 123—124° (from ethanol) (Found: N, 5·8; Cl, 14·8. $C_{12}H_{12}ClNO_2$ requires N, 5·9; Cl, 14·9%).

1-*Diethylaminoacetyl*-1,2,3,4-*tetrahydro*-6-*methyl*-4-*oxoquinoline*.—1-Chloroacetyl-1,2,3,4-tetrahydro-6-methyl-4-oxoquinoline (40·2 g.) and diethylamine (100 ml.) were allowed to react as above, to give the *ketone* (yield 93%), b. p. 165—170°/0·03 mm. (Found: C, 69·9; H, 8·1; N, 10·0. $C_{16}H_{22}N_2O_2$ requires C, 70·0; H, 8·0; N, 10·2%).

1-(2-*Diethylaminoethyl*)-1,2,3,4-*tetrahydro*-6-*methyl*-4-*oxoquinoline*.—1-Diethylaminoacetyl-1,2,3,4-tetrahydro-6-methyl-4-oxoquinoline (42·0 g.) in ether (200 ml.) was reduced and oxidised as described above. The *ketone* was obtained as a yellow oil (30·2 g., 75%), b. p. 140°/0·02 mm. (Found: C, 73·6; H, 9·6; N, 11·0. $C_{16}H_{24}N_2O$ requires C, 73·8; H, 9·2; N, 10·8%). The (−)-*di*-(p-*toluoyl*)-*base* (+)-*tartrate* crystallised from ethanol as bright yellow crystals, m. p. 155° (decomp.) (Found: C, 66·8; H, 6·2; N, 4·5. $C_{16}H_{24}N_2O,C_{20}H_{18}O_8$ requires C, 66·8; H, 6·5; N, 4·3%).

Methyl β-(3-*Chloro*-4-*methylanilino*)*propionate*.—3-Chloro-4-methylaniline (154 g.), methyl acrylate (119 ml.), and acetic acid (19 ml.) were refluxed for 18 hr. The cooled mixture was mixed with ether and poured into cold aqueous potassium hydrogen carbonate. The ethereal layer was separated, washed with water, dried, and distilled. The *product* (196 g., 79%) had b. p. 135—140°/0·02 mm. (Found: N, 6·2; Cl, 15·1. $C_{11}H_{14}ClNO_2$ requires N, 6·15; Cl, 15·6%).

β-(3-*Chloro*-4-*methyl*-N-*toluene*-p-*sulphonylanilino*)*propionic Acid*.—Methyl β-(3-chloro-4-methylanilino)propionate (194 g.) in pyridine (700 ml.) was treated with toluene-*p*-sulphonyl chloride (197 g.) at below 30° as described above. The crude product, a gum, was dissolved in methanol (1·5 l.) and treated with potassium hydroxide (60 g.) in water (600 ml.). The mixture was shaken occasionally for 24 hr., and the resulting clear solution was poured into ice and excess of acetic acid. The product slowly solidified, and was then recrystallised from ether–light petroleum (b. p. 40—60°) to give the pure *acid* (170 g., 54%), m. p. 134—136° (Found: C, 55·6; H, 4·9; N, 3·8. $C_{17}H_{18}ClNO_4S$ requires C, 55·5; H, 4·9; N, 3·8%). A further crop (28·5 g., 9·4%), m. p. 127—135°, was isolated from the mother-liquors.

7-*Chloro*-1,2,3,4-*tetrahydro*-6-*methyl*-4-*oxoquinoline*.—β-(3-Chloro-4-methyl-*N*-toluene-*p*-sulphonylanilino)propionic acid (74·5 g.) was added with stirring to polyphosphoric acid (600 g.), and the mixture heated on the steam-bath for 5 hr. and finally at 120° for 1 hr. It was combined with another batch carried out with the same quantities of material and worked up as before, giving a crude crystalline mixture of the 5- and the 7-chloro-isomer (75 g., 95%), m. p. 95—120°, which was twice recrystallised from methanol to yield the pure 7-*chloro-isomer* (20·0 g., 25·4%), m. p. 153—154° (Found: N, 7·2; Cl, 18·3. $C_{10}H_{10}ClNO$ requires N, 7·2; Cl, 18·1%). A further crop (7·3 g., 9·2%), m. p. 154—155°, was obtained (*via* the 1-chloroacetyl derivative) from the mother-liquors during the isolation of the 5-chloro-isomer (see below). The structure of 7-chloro-1,2,3,4-tetrahydro-6-methyl-4-oxoquinoline was confirmed by a modified Wolff–Kishner [9] reduction to give 7-chloro-1,2,3,4-tetrahydro-6-methylquinoline (80%), m. p. 76—77° [from light petroleum (b. p. 60—80°)] not depressed on admixture with a specimen prepared independently by the reduction of 7-chloro-6-methylquinoline. The hydrochloride had m. p. 224—226° (Bayer [11] give m. p. 77—77·5° for the base, and 226—227° for the hydrochloride). The *chloroacetyl derivative* (90%), m. p. 123—124° [recrystallised from benzene–light petroleum (b. p. 60—80°)] (Found: N, 5·2; Cl, 25·75. $C_{12}H_{11}Cl_2NO_2$ requires N, 5·15; Cl, 26·1%), was prepared as before.

7-*Chloro*-1-*diethylaminoacetyl*-1,2,3,4-*tetrahydro*-6-*methyl*-4-*oxoquinoline*.—7-Chloro-1-chloroacetyl-1,2,3,4-tetrahydro-6-methyl-4-oxoquinoline (34·1 g.) reacted with diethylamine (100 ml.) as before, to give the *amino-compound* (34·8 g., 90%), m. p. 93—94° (from aqueous ethanol)

(Found: N, 8·7; Cl, 11·5. $C_{16}H_{21}ClN_2O_2$ requires N, 9·1; Cl, 11·5%). A further crop (1·8 g., 4·7%), m. p. 91—92°, was isolated from the filtrate.

7-*Chloro*-1-(2-*diethylaminoethyl*)-1,2,3,4-*tetrahydro*-6-*methyl*-4-*oxoquinoline*.—7-Chloro-1-diethylaminoacetyl-1,2,3,4-tetrahydro-6-methyl-4-oxoquinoline (36·6 g.) in tetrahydrofuran (200 ml.) was successively reduced and oxidised as before, to give a yellow oil (21·5 g., 62%) which was not distilled since it was thought that the presence of the 7-chloro-atom might lead to decomposition at the expected distillation temperature. The oil was converted into the (−)-*di*-(p-*toluoyl*)-*base*(+)-*tartrate*, bright yellow crystals, m. p. 169° (decomp.) (from ethanol) (Found: N, 4·2; Cl, 5·0. $C_{16}H_{23}ClN_2O,C_{20}H_{18}O_8$ required N, 4·1; Cl, 5·2%).

5-*Chloro*-1-*chloroacetyl*-1,2,3,4-*tetrahydro*-6-*methyl*-4-*oxoquinoline*.—Crude 5-chloro-1,2,3,4-tetrahydro-6-methyl-4-oxoquinoline (1·2 g.; m. p. 100—110°; recovered from residues after isolation of the 7-chloro-isomer) in benzene (10 ml.) was refluxed with chloroacetyl chloride (0·5 ml.) for 2 hr. Light petroleum was then added and the crystalline product was twice recrystallised from ethanol, to give the *chloroacetyl compound* (0·8 g., 48%), m. p. 166—168° (Found: N, 5·2; Cl, 25·95. $C_{12}H_{11}Cl_2NO_2$ requires N, 5·15; Cl, 26·1%). (The m. p. was depressed to 114° on admixture with the 7-chloro-isomer.) Use of this derivative of 5-chloro-1,2,3,4-tetrahydro-6-methyl-4-oxoquinoline was the best method for isolation of the 5-chloro-isomer from crude mixtures containing the 7-chloro-isomer (see below).

5-*Chloro*-1,2,3,4-*tetrahydro*-6-*methyl*-4-*oxoquinoline*.—5-Chloro-1-chloroacetyl-1,2,3,4-tetrahydro-6-methyl-4-oxoquinoline (0·7 g.) was refluxed for 15 min. in hydrochloric acid (10 ml.) and water (10 ml.) in the presence of " Lissapol N " wetting agent (1 drop). The solution was cooled and basified; the product (0·35 g., 70%) had m. p. 120—122°. Recrystallisation from aqueous methanol gave the pure 5-*chloro-isomer* (0·2 g.), m. p. 129—131° (Found: N, 7·1; Cl, 18·0. $C_{10}H_{10}ClNO$ requires N, 7·2; Cl, 18·1%). The m. p. was depressed to 105° by the 7-chloro-isomer.

5-*Chloro*-1-*diethylaminoacetyl*-1,2,3,4-*tetrahydro*-6-*methyl*-4-*oxoquinoline*.—5-Chloro-1-chloroacetyl-1,2,3,4-tetrahydro-6-methyl-4-oxoquinoline (34·0 g.) was refluxed with diethylamine (100 ml.), and the mixture worked up as for the 7-chloro-isomer. After being recrystallised from ether and light petroleum, the *product* (37 g., 96%) had m. p. 71—72° (Found: N, 8·9; Cl, 11·3. $C_{16}H_{21}ClN_2O_2$ requires N, 9·1; Cl, 11·5%).

Attempted Preparation of 5-*Chloro*-1-(2-*diethylaminoethyl*)-1,2,3,4-*tetrahydro*-6-*methyl*-4-*oxoquinoline*.—5-Chloro-1-diethylaminoacetyl-1,2,3,4-tetrahydro-6-methyl-4-oxoquinoline (37·0 g.) in tetrahydrofuran (80 ml.) was reduced and oxidised as before and, as a crystalline salt could not be isolated, the crude mixture was distilled. Two fractions were obtained: A (11 g., 46·5%), b. p. 140—150°/0·1 mm.; and B (8·3 g., 23%), b. p. 170—190°/0·1 mm. Fraction A solidified overnight and, after being crystallised from light petroleum (b. p. 40—60°), the product (6·8 g.) had m. p. 90—92° (Found: C, 61·0; H, 6·5; N, 7·1; Cl, 18·6. $C_{10}H_{12}ClNO$ requires C, 60·8; H, 6·1; N, 7·1; Cl, 18·0%). Thus the analysis agreed with its formulation as 5-*chloro*-1,2,3,4-*tetrahydro*-4-*hydroxy*-6-*methylquinoline*. A further independent treatment with cyclohexanone and aluminium isopropoxide gave unchanged material but oxidation with activated manganese dioxide under standard conditions yielded 5-chloro-6-methylquinoline (56%), m. p. 44—45° [from light petroleum (b. p. 40—60°)] (Found: C, 67·9; H, 5·1; N, 7·7. Calc. for $C_{10}H_8ClN$: C, 67·6; H, 4·5; N, 7·9%). The picrate, crystallised from ethanol, had m. p. 213—215° (Found: N, 13·7; Cl, 8·8. Calc. for $C_{10}H_8ClN,C_6H_3N_3O_7$: N, 13·8; Cl, 8·7%) (Bayer [11] give m. p. 45—46° for the base and 206—207° for the picrate. Marais and Backeberg [14] give m. p. 47° and 210°, respectively, for these compounds) (neither the base nor the picrate depressed the m. p. on admixture with authentic material prepared by Marais and Backeberg's method [14]). Fraction B (Found: C, 65·6; H, 8·3; N, 9·1; Cl, 11·9. $C_{16}H_{25}ClN_2O$ requires C, 64·9; H, 8·4; N, 9·4; Cl, 12·0%) did not possess the deep yellow fluorescence characteristic of the other ketones of this series, and it did not form a crystalline (−)-di-(*p*-toluoyl)-base (+)-tartrate. No crystalline derivative could be prepared from this crude base, by which to characterise the compound as a ketone or an alcohol, although the latter structure was favoured because of its general properties. Further attempts to purify fraction B were abortive owing to decomposition on storage, with loss of some of the halogen.

7-*Chloro*-1-(2-*diethylaminoethyl*)-1,2,3,4-*tetrahydro*-6-*methylquinoline*.—(*A*) A modified Wolff–Kishner [9] reduction of 7-chloro-1-(2-diethylaminoethyl)-1,2,3,4-tetrahydro-6-methyl-4-oxoquinoline (10·5 g.) in diethylene glycol (450 ml.) with 85% hydrazine hydrate (45 ml.) and

[14] Marais and Backeberg, *J.*, 1950, 2208.

potassium hydroxide (3·6 g.) at 195° for 2 hr. yielded material (1 g.), b. p. 145—148°/0·05 mm., which although not analytically pure gave a hydrochloride, m. p. 195—196° (from ethanol) which was not depressed by an authentic sample prepared independently by route (*B*). The *picrate*, m. p. 103—105° (decomp.) (Found: Cl, 7·5. $C_{16}H_{25}ClN_2,C_6H_3N_3O_7$ requires Cl, 7·0%), was also prepared.

(*B*) The compound was also formed as described in the Bayer patent [11] and isolated as the hydrochloride, m. p. 194—195° (from ethanol–ether) (Found: N, 8·9; Cl, 22·2. Calc. for $C_{16}H_{25}ClN_2,HCl$: N, 8·85; Cl, 22·4%) (Bayer [11] gives m. p. 190—191°).

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