Synthesis and chemistry of 1-methyl-3-imino-4-hydroxy-4-phenyl-6-chloro-1,2,3,4-tetrahydroquinoline-2-one

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Reaction between 2-(*N*-methyl)dichloroacetamido-5-chlorobenzophenone and aqueous ammonia yields 1-methyl-3-amino-3,4-dihydroxy-4-phenyl-6-chloro-1,2,3,4-tetrahydroquinoline-2-one which dehydrates readily to give the title compound. Structural proof of this substance is reported and several of its transformation products are described.

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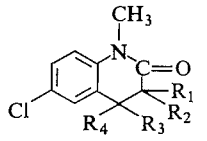
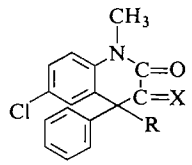
When a solution of 2-(*N*-methyl)-dichloroacetamido-5-chlorobenzophenone in dimethylformamide was allowed to stand overnight at room temperature in presence of concentrated aqueous ammonia, a crystalline precipitate formed which analyzed for $C_{16}H_{15}Cl\ N_2O_3$ and whose infrared spectra in Nujol exhibited peaks at 3430, 3360, 3280, 3185, 1660, and 1585 cm^{-1}. When stored at room temperature, this product lost after some time one molecule of water giving another crystalline substance, whose infrared spectra in Nujol contained a sharp peak at 3215 with an inflection at 3150, a strong peak at 1685, and a peak of medium intensity at 1670 cm^{-1} together with aromatic absorption at 1600 and 1580 cm^{-1}. This transformation was practically immediate when the first reaction product was heated in an inert solvent or even in suspension. On reduction with sodium borohydride the second product added one molecule of hydrogen while losing another molecule of water. The infrared spectra in Nujol of this last compound (3460, 3305, 1645, 1605, and 1595 cm^{-1}) suggested that a structure of aminoquinolone **3** should be considered. We have therefore undertaken an unambiguous synthesis of **3** in the following way: 2-(*N*-methyl)-chloroacetamido-5-chlorobenzophenone was allowed to react with sodium nitrite whereby nitroquinolone **4** was readily formed by spontaneous cyclization. Reduction of the nitro product with zinc in hydrochloric acid yielded the aminoquinolone **3**, which was found to be identical with the product obtained from the sodium borohydride reduction by comparing the physical properties and infrared spectra. On this basis the precursor of **3** has to be formulated as ketimine **2** and structure **1** has to be accepted for the precursor of **2**. The above mentioned infrared spectra are also in excellent agreement with both structures as are the reactions and transformations described below.

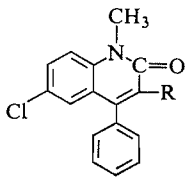
Acetylation of the ketimine **2** afforded two distinct products depending on the conditions used. When it was carried out at room temperature using acetic anhydride in pyridine, an *O*-acetate **5** (ν_{max} (KBr) 3205 (sharp), 1730, 1670, 1630, and 1580 cm^{-1}) was formed. Mild alkaline hydrolysis of the latter recovered the starting ketimine **2**, thus excluding any possibility of a rearrangement whereas controlled acid hydrolysis yielded the acetylated ketol **6** (ν_{max} (KBr) 1750 (inflection), 1740, 1680, and 1590 cm^{-1}), which in turn yielded the known ketol **7** (1) on heating with aqueous inorganic bases. When, however, the ketimine **2** was acetylated in boiling acetic anhydride in presence of anhydrous sodium acetate, the *N*-acetate **8** (ν_{max} (KBr) 3320, 1705, 1650, and 1600 cm^{-1}) was the reaction product. Its structure was established as follows: sodium borohydride reduction yielded the alcohol **9** (ν_{max} (KBr) 3340, 3160, 1680, 1630, and 1595 cm^{-1}) which in turn could be acetylated to give the *N,O*-diacetate **10** (ν_{max} (KBr) 3375, 1740, 1690, 1660, and 1595 cm^{-1}) thus proving the presence of a ketone conjugated with an aromatic ring in compound **8**. Furthermore, when the ultraviolet spectra of **8** were compared with those of the recently reported 1-methyl-3-acetoxy-3-phenyl-6-chloro-1,2,3,4-tetrahydroquinoline-2,4-dione (1), they were found to be superimposable exhibiting maxima at 239 mμ with a shoulder at 260 mμ. When **8** was refluxed overnight in aqueous–alcoholic hydrochloric acid, the α-aminoketone **11** was isolated as the reaction product (ν_{max} (KBr) 3365, 3285, 1700, 1665, 1655 (inflection), and 1600 cm^{-1}).



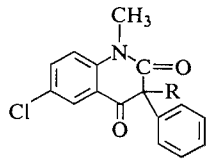
1 $R_1 = NH_2$, $R_2 = OH$, $R_3 = OH$, $R_4 = Ph$
9 $R_1 = NHAc$, $R_2 = Ph$, $R_3 = H$, $R_4 = OH$
10 $R_1 = NHAc$, $R_2 = Ph$, $R_3 = H$, $R_4 = OAc$
12 $R_1 = OH$, $R_2 = OH$, $R_3 = OH$, $R_4 = Ph$



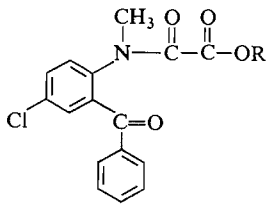
2 R = OH, X = NH
5 R = OAc, X = NH
6 R = OAc, X = O
15 R = OH, X = N—OH



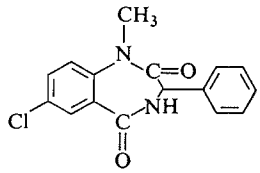
3 $R = NH_2$
4 $R = NO_2$
16 R = NO



7 R = OH
8 R = NHAc
11 $R = NH_2$



13 R = H
14 R = Et



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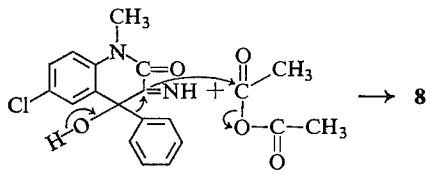
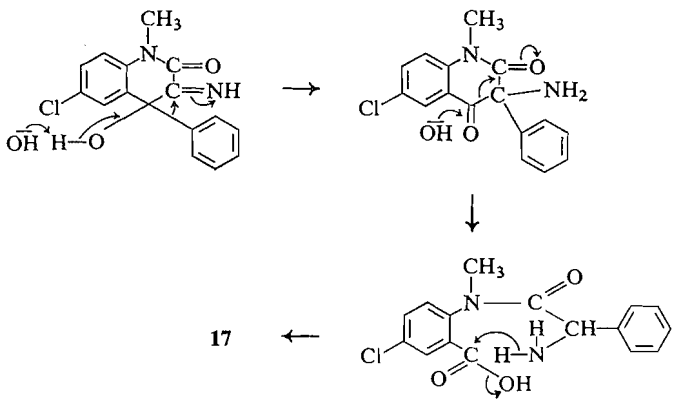
Mechanistically, the migration of the phenyl group during treatment of **2** with acetic anhydride is readily conceivable and can be represented as follows.



On contact with dilute acids **2** was transformed into the triol **12** (ν_{max} (KBr) 3440, 3415, 3365, 3305, 1670, and 1590 cm^{-1}) which in contrast to **1** was stable when heated in solvents and did not show any tendency to lose water on storage. Its reactions were typical for an α-hydroxy ketone. It was readily oxidized by periodic acid to the keto acid **13** (ν_{max} 1740, 1670, 1620, and 1590 cm^{-1}) which on treatment with ethanolic HCl yielded the keto ester **14** (ν_{max} (KBr) 1730, 1680, 1670, 1595, and 1585 cm^{-1}). We have also obtained the same ester by a direct condensation of 2-methylamino-5-chlorobenzophenone with ethyloxalylchloride whereby the structures of **12**, **13**, and **14** are rigorously established.

When the triol **12** was allowed to react with ammonia in methanolic solution containing catalytic amount of triethylamine, it afforded a mixture of the ketimine **2** and of the recently reported 1-methyl-3-hydroxy-3-phenyl-4-imino-6-chloro-1,2,3,4-tetrahydroquinoline-2-one (1), which clearly was formed by a ketol rearrangement of **12** preceding the reaction with ammonia. On acetylation of **12** the above mentioned ester **6** was obtained. It is noteworthy that in contrast to **12** this ester showed no tendency to exist as a geminal diol. A mixture of oxime **15** (ν_{max} (KBr) 3500 (sharp), 3090, 1640, 1590, and 1570 cm^{-1}) and its dehydration product **16** (ν_{max} (KBr) 3160, 1645, 1615 (short), and 1560



cm^{-1}) was isolated from the reaction mixture resulting from the condensation of the imine **2** with hydroxylamine. The same oxime **15** resulted also from a reaction between the triol **12** and hydroxylamine and it could be easily dehydrated to the nitroso product **16**. Attempted reduction of this last compound with zinc in hydrochloric acid yielded only trace quantities of the expected aminoquinolone **3** and most of the starting material was recovered unchanged. Aqueous inorganic bases transformed on heating both the imine **2** and the triol **12** into the recently reported 1-methyl-3-hydroxy-3-phenyl-6-chloro-1,2,3,4-tetrahydroquinoline-2,4-dione (**7**) thus confirming the correctness of the mechanism postulated for the formation of this compound (1). (The first step in this mechanism is also applicable for the explanation of the formation of the aminoalcohol **1**.)

An interesting rearrangement took place when the imine **2** was heated in anhydrous methanol in presence of a catalytic amount of trimethylbenzylammonium hydroxide (Triton B). The crystalline reaction product was shown by elemental analysis to be isomeric with the starting material but it lacked its basic character. Its infrared spectra in KBr exhibited maxima at 3165, 1680, 1665 (the last two peaks of equal intensity), and at 1610 cm^{-1}. On the basis of these data as well as on the basis of mechanistic considerations, structure **17** was tentatively assigned to this substance. This structure was proven to be correct by an independent synthesis consisting of (*a*) condensation of *N*-methyl-5-chloroanthranilic acid with D,L-phthalimidophenylacetyl chloride, (*b*) removing the phthaloyl group by means of hydrazine hydrate, (*c*) esterification of the carboxyl, and (*d*) cyclization of the resulting amino ester by refluxing in anhydrous methanol in presence of triethylamine.

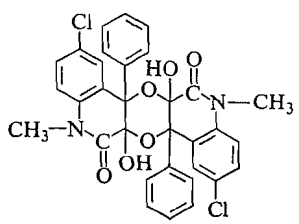
The following mechanism accounts fully for the transformation of **2** into **17**.

As the first intermediate postulated in the above mechanism is identical with the aminoketone **11**, we subjected this last compound to the same treatment as the imine **2**, whereby a fair yield of the cyclic diamide **17** was obtained.

When 2-(*N*-methyl)-dichloroacetamido-5-chlorobenzophenone was kept overnight in ethanol–dimethylformamide solution saturated with ammonia gas, a neutral crystalline substance was isolated whose elemental analysis corresponded to a formula of $C_{16}H_{12}ClNO_3$. The product was isolated in two crystalline modifications, one melting at 177–178°, the other at 212°, both having the same infrared spectra in chloroform solution (ν_{max} 3430, 1700, 1675, and 1600 cm^{-1}). The nuclear magnetic resonance (n.m.r.) spectrum in deuteriochloroform with tetramethylsilane as internal reference standard exhibited two *N*-methyl peaks at τ 6.42 and 6.89 and two one proton singlets at τ 4.00 and 5.22 plus a multiplet (16 protons) in the aromatic region with the strongest peak appearing at τ 2.80. Both spectra suggested that the product in question must be a dimer, which was confirmed by molecular weight determination. As the most obvious structure satisfying the elemental analysis, infrared, and n.m.r. spectra would correspond to formula **18**, we reasoned that it should be possible to prepare this compound by dehydration of the triol **12**. Refluxing of the latter in benzene solution with azeotropic removal of water yielded indeed the expected product thus

confirming the correctness of structure **18**. Subsequently we were able to obtain the same dimer by treatment of the ketimine **2** with glacial acetic acid. The chemical reactions of the dimer **18** resembled those of the triol **12**.

It is interesting to speculate about the stereochemistry of the dimer **18**. The four asymmetric centers present in the molecule would suggest eight possible stereoisomers due to the fact that identical substituents are present on both sides of the dioxane ring. Closer examination of the models, however, reveals that this is not the case. The quinolone moiety has to be flat due to the presence of the amide grouping and therefore one substituent on C-3 has to be in the same plane as one of the substituents on C-4, the same requirement being valid for the second pair of substituents. From that follows further, (and the study of models confirms it) that in a strain free molecule the dioxane moiety has to be in a boat conformation, with the oxygen atoms as flagpoles. Now, if the above reasoning is accepted, one is still left with three possible stereomers in which the quinolone moieties would be endo–endo, exo–exo, or endo–exo with respect to the dioxane ring. The fact, however, that the infrared spectra of this product exhibit two distinct amide absorptions and that in the n.m.r. spectra the chemical shift is different for the two hydroxyl protons as well as for the two *N*-methyls strongly suggests that these protons are situated in a different environment and therefore the endo–exo form would appear to be the most likely one. However, as the models built for this structure reveal a considerable degree of steric interference and as at the same time it is not possible to bring a chemical proof for the proposed conformation, the above suggestion based on spectral evidence has to be treated with extreme caution.



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Experimental

The infrared spectra were taken on Perkin–Elmer 237 and 237B instruments. The ultraviolet spectra were obtained with a Unicam SP 800 apparatus. The nuclear magnetic resonance (n.m.r.) spectra were recorded on Varian model HR-60 spectrometer. The melting points were determined in capillaries on a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by Organic Microanalysis, Dr. C. Daesslé, Montreal.

1-Methyl-3-amino-3,4-dihydroxy-4-phenyl-6-chloro-1,2,3,4-tetrahydroquinoline-2-one (1)

To a solution of 2-(*N*-methyl)-dichloroacetamido-5-chlorobenzophenone (1) (17 g, 0.478 mole) in dimethylformamide (120 ml) was added concentrated aqueous ammonia (80 ml) and the mixture stirred at room temperature overnight. The crystalline precipitate was collected by filtration (10 g, 65.9%), washed with water, then with acetone and dried for analysis at room temperature in high vacuum; m.p. 171–174°.

Anal. Calcd. for $C_{16}H_{15}ClN_2O_3$: C, 60.28; H, 4.74; Cl, 11.12; N, 8.79. Found: C, 60.53; H, 4.92; Cl, 11.39; N, 8.89.

1-Methyl-3-imino-4-hydroxy-4-phenyl-6-chloro-1,2,3,4-tetrahydroquinoline-2-one (2)

When **1** was kept in an oven at about 80° for approximately 2 h, a quantitative yield of **2** was obtained. The analytical sample was purified by crystallization from dimethylformamide–ether mixture, m.p. 182–183°.

Anal. Calcd. for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.35; Cl, 11.79; N, 9.32. Found: C, 63.86; H, 4.35; Cl, 11.44; N, 9.42.

The same product was obtained when **1** was heated in acetone suspension or when stored for several weeks at room temperature.

1-Methyl-3-nitro-4-phenyl-6-chloro-2(1H)-quinolone (4)

To a solution of 2-(*N*-methyl)-chloroacetamido-5-chlorobenzophenone (2) (6.44 g, 0.02 mole) in ethanol (50 ml) was added a solution of $NaNO_2$ (1.52 g, 0.022 mole) in water (15 ml) and the mixture was refluxed overnight. After cooling to room temperature the crystalline precipitate was collected by filtration (3 g, 47.7%) and recrystallized from ethyl acetate, m.p. 208–210°.

Anal. Calcd. for $C_{16}H_{11}ClN_2O_3$: C, 61.06; H, 3.52; Cl, 11.27; N, 8.90. Found: C, 61.02; H, 3.54; Cl, 11.23; N, 9.06.

1-Methyl-3-amino-4-phenyl-6-chloro-2(1H)-quinolone (3)

(*a*) To a solution of **2** (2 g, 0.00665 mole) in a mixture of methanol (100 ml) and dimethylformamide (20 ml) was added a solution of $NaBH_4$ (0.2 g, 0.00528 mole) in water (5 ml) and the mixture was left standing at room temperature overnight. After further dilution with water the crystalline precipitate was collected by filtration (1.22 g, 64.5%) and recrystallized from methanol, m.p. 134–136°.

Anal. Calcd. for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; Cl, 12.45; N, 9.84. Found: C, 67.32; H, 4.92; Cl, 12.50; N, 9.48.

(*b*) To a suspension of **4** (2 g, 0.00635 mole) in a mixture of ethanol (100 ml) and water (50 ml) was added zinc dust (2 g) and the pH was adjusted to about 3.0 by means of

5% HCl. After stirring at room temperature for 90 min the unchanged starting material (1 g) was filtered off, the filtrate was basified with aqueous sodium hydroxide, and the crystalline precipitate was collected by filtration (0.5 g, 27.7%). It was recrystallized from methanol to a m.p. of 134–135°. This product was found to be identical with the one obtained by the process (*a*) by mixture m.p. determination and by comparison of infrared spectra.

1-Methyl-3-imino-4-phenyl-4-acetoxy-6-chloro-1,2,3,4-tetrahydroquinoline-2-one (5)

A solution of **2** (2.5 g, 0.0083 mole) in dry pyridine (25 ml) containing acetic anhydride (3 ml) was left standing at room temperature overnight. After removal of the solvent *in vacuo* the residue was treated with ether and then collected by filtration (2 g, 70.1%). The product was purified by crystallization from benzene, m.p. 224–226°.

Anal. Calcd. for $C_{18}H_{15}ClN_2O_3$: C, 63.07; H, 4.41; Cl, 10.34; N, 8.18. Found: C, 63.42; H, 4.40; Cl, 10.21; N, 7.97.

A solution of this product in methanolic ammonia containing catalytic amount of sodium methoxide after standing at room temperature overnight yielded the starting **2**, identified by a mixture m.p. determination and comparison of infrared spectra.

1-Methyl-4-acetoxy-4-phenyl-6-chloro-1,2,3,4-tetrahydroquinoline-2,3-dione (6)

Into a solution of **5** (1.5 g, 0.0044 mole) in chloroform (15 ml) containing water (1 ml) HCl gas was introduced at room temperature. The organic phase was separated from the aqueous phase, the solvent distilled off *in vacuo*, and the residue was crystallized from ether, then from ethyl acetate. The yield was 1.35 g (90%), m.p. 210–212°.

Anal. Calcd. for $C_{18}H_{14}ClNO_4$: C, 62.88; H, 4.10; Cl, 10.32; N, 4.08. Found: C, 63.20; H, 4.34; Cl, 10.49; N, 4.12.

1-Methyl-3,3,4-trihydroxy-4-phenyl-6-chloro-1,2,3,4-tetrahydroquinoline-2-one (12)

A suspension of **2** (3 g, 0.00997 mole) in water (30 ml) acidified with glacial acetic acid (2 ml) was refluxed for 30 min. After cooling to room temperature the crystalline substance was collected by filtration and washed with water. The yield was 3 g (94.1%), m.p. 131–133 °C and the product was analyzed without further purification.

Anal. Calcd. for $C_{16}H_{14}ClNO_4$: C, 60.10; H, 4.41; Cl, 11.09; N, 4.38. Found: C, 60.04; H, 4.54; Cl, 11.11; N, 4.49.

When this product (2 g, 0.00625 mole) was allowed to stand at room temperature overnight in a mixture of pyridine (10 ml) and acetic anhydride (3 ml), 1.8 g (83.7%) of **6**, m.p. 210–212° was obtained after the work-up of the reaction mixture and purification by recrystallization from ethyl acetate. Its identity was established by m.p. and mixture m.p. as well as by comparison of the infrared spectra.

1-Methyl-3-hydroxy-3-phenyl-6-chloro-1,2,3,4-tetrahydroquinoline-2,4-dione (7)

A solution of **12** (0.15 g, 0.0005 mole) in methanol (5 ml) was basified with 35% aqueous NaOH and left standing for some time at room temperature. After dilution with water the reaction product was extracted into chloroform, the solvent distilled off *in vacuo*, and the residue recrystallized from ether. The yield was 0.1 g (71%), m.p. 170–172°, undepressed on admixture of an authentic sample (1). The infrared spectra of the two samples were superimposable. The same product was obtained when **5** was refluxed for 15 min in aqueous methanol in presence of some KOH (28% yield), when **6** was allowed to stand at room temperature for two days in aqueous–ethanolic solution containing some NaOH (50% yield) and when **2** was heated for 90 min in cellosolve–water mixture in presence of sodium acetate (45% yield).

1-Methyl-3-acetamido-3-phenyl-6-chloro-1,2,3,4-tetrahydroquinoline-2,4-dione (8)

A solution of **2** (15 g, 0.05 mole) in acetic anhydride (100 ml) containing some anhydrous sodium acetate was heated under reflux for 1 h. After cooling to room temperature the unreacted anhydride was decomposed by a careful addition of methanol, the reaction mixture was then further diluted with water and extracted with chloroform. Removal of the solvent *in vacuo* and treatment of the residue with methanol yielded 9 g (52.6%) of crystalline material, which was recrystallized from methanol – ethyl acetate mixture, m.p. 231–232°.

Anal. Calcd. for $C_{18}H_{15}ClN_2O_3$: C, 63.07; H, 4.41; Cl, 10.34; N, 8.18. Found: C, 63.41; H, 4.59; Cl, 10.49; N, 7.98.

1-Methyl-3-acetamido-3-phenyl-4-hydroxy-6-chloro-1,2,3,4-tetrahydroquinoline-2-one (9)

To a solution of **8** (3 g, 0.0087 mole) in methanol (100 ml) a solution of $NaBH_4$ (0.2 g, 0.00528 mole) in water (5 ml) was added and the mixture allowed to stand at room temperature for 3 h. After dilution with water the crystalline precipitate was collected by filtration and recrystallized from isopropanol. The yield was 2.8 g (93%), m.p. 191–193°.

Anal. Calcd. for $C_{18}H_{17}ClN_2O_3$: C, 62.70; H, 4.97; Cl, 10.28; N, 8.13. Found: C, 62.64; H, 4.93; Cl, 10.47; N, 7.98.

1-Methyl-3-acetamido-3-phenyl-4-acetoxy-6-chloro-1,2,3,4-tetrahydroquinoline-2-one (10)

A solution of **9** (2 g, 0.0058 mole) in acetic anhydride (10 ml) containing some anhydrous sodium acetate was heated under reflux for 1 h. After cooling to room temperature some methanol was added, the reaction mixture was then diluted with water and the crystalline precipitate collected by filtration (1.5 g, 67%). The analytical sample had a m.p. of 247–248° after recrystallization from isopropanol.

Anal. Calcd. for $C_{20}H_{19}ClN_2O_4$: C, 62.10; H, 4.95; Cl, 9.17; N, 7.24. Found: C, 61.96; H, 5.04; Cl, 8.91; N, 6.99.

1-Methyl-3-amino-3-phenyl-6-chloro-1,2,3,4-tetrahydroquinoline-2,4-dione (11)

A solution of **8** (2.5 g, 0.0073 mole) in ethanol (100 ml) containing 17% aqueous HCl (50 ml) was refluxed overnight. After cooling to room temperature the reaction mixture was diluted with water, basified to pH 8.0–9.0 with aqueous NaOH, and extracted with chloroform. The solvent was distilled off *in vacuo* and the residue recrystallized from ether, then from benzene. The yield was 1 g (45.6%), m.p. 154–156°.

Anal. Calcd. for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.35; Cl, 11.79; N, 9.32. Found: C, 64.13; H, 4.35; Cl, 11.55; N, 9.07.

*2-(N-Methyl)-oxalylamido-5-chlorobenzophenone (**13**)*

To a solution of **12** (1 g, 0.0031 mole) in ethanol (50 ml) a solution of periodic acid (0.76 g, 0.0033 mole) in water (5 ml) was added and the mixture allowed to stand for 2 h at room temperature. After dilution with water the reaction mixture was extracted with chloroform in order to remove the unchanged starting material (0.25 g). The aqueous layer was allowed to stand overnight at room temperature, whereby the reaction product separated in a crystalline form. It was collected by filtration (0.35 g, 35.3%) and recrystallized from ethyl acetate – hexane mixture, m.p. 122–124°.

Anal. Calcd. for $C_{16}H_{12}ClNO_4$: C, 60.48; H, 3.80; Cl, 11.16; N, 4.41. Found: C, 60.67; H, 3.59; Cl, 11.43; N, 4.64.

*2-(N-Methyl)-ethyloxalylamido-5-chlorobenzophenone (**14**)*

A solution of **13** (5 g, 0.0157 mole) in absolute ethanol (25 ml) was saturated with HCl gas and left standing overnight at room temperature. The reaction mixture was concentrated to a small volume, some ether was added and the crystalline precipitate collected by filtration (2.1 g, 38.6%). It was purified by recrystallization from methanol–water mixture, m.p. 80–81°.

Anal. Calcd. for $C_{18}H_{16}ClNO_4$: C, 62.52; H, 4.66; Cl, 10.26; N, 4.05. Found: C, 62.80; H, 4.70; Cl, 10.61; N, 4.11.

The same product was obtained in the following way: a solution of 2-methylamino-5-chlorobenzophenone (7.4 g, 0.03 mole) in dry chloroform (100 ml) was refluxed for 3 h in presence of ethyloxalyl chloride (4.1 g, 0.03 mole) (3). After removal of the solvent *in vacuo* the residue was crystallized first from ether–hexane, then from methanol–water mixture. The yield was 7 g (67.5%), m.p. 80–81°, unchanged on admixture of the product from the first experiment. Also the infrared spectra of both samples were superimposable.

*Reaction of **12** with Ammonia*

A solution of **12** (1 g, 0.00312 mole) in anhydrous methanol (40 ml) containing a few drops of triethylamine was saturated with NH_3 gas and left standing at room temperature for 3 days. 1-Methyl-3-hydroxy-3-phenyl-4-imino-6-chloro-1,2,3,4-tetrahydroquinoline-2-one (1) (identified by m.p., mixture m.p. with the authentic sample, and comparison of infrared spectra) was removed by filtration (0.15 g, 16%), the mother liquors were concentrated to a small volume, whereby 0.5 g (51.1%) of **2** identified by comparison with the authentic sample in the above described way separated.

*1-Methyl-3-isonitroso-4-hydroxy-4-phenyl-6-chloro-1,2,3,4-tetrahydroquinoline-2-one (**15**)*

A solution of **12** (2 g, 0.0063 mole), hydroxylamine hydrochloride (0.5 g, 0.0072 mole) and triethylamine (0.73 g, 0.0072 mole) in benzene (30 ml) was heated under reflux for 20 h, using water trap. After cooling to room temperature the triethylamine hydrochloride was removed by filtration, the filtrate evaporated to dryness *in vacuo* and the residue crystallized by treatment with ethyl acetate, then recrystallized from dimethylformamide–water mixture. The yield was 0.7 g, (35%), m.p. 195–197°.

Anal. Calcd. for $C_{16}H_{13}ClN_2O_3$: C, 60.68; H, 4.14; Cl, 11.19; N, 8.85. Found: C, 61.03; H, 4.18; Cl, 11.42; N, 8.80.

*1-Methyl-3-nitroso-4-phenyl-6-chloro-2(1H)-quinolone (**16**)*

A solution of **2** (4 g, 0.0133 mole), hydroxylamine hydrochloride (1 g, 0.0144 mole), and triethylamine (2.9 g, 0.028 mole) in a mixture of benzene (50 ml) and dimethylformamide (10 ml) was heated under reflux for 20 h. After cooling to room temperature the precipitated triethylamine hydrochloride was removed by filtration and the filtrate evaporated to dryness *in vacuo*. Treatment of the residue with ethyl acetate yielded 0.3 g (7.7%) of **16**, which was recrystallized for analysis from benzene, m.p. 225–227°.

Anal. Calcd. for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; Cl, 11.87; N, 9.38. Found: C, 64.58; H, 3.74; Cl, 12.06; N, 9.19.

The filtrate deposited on standing 2.2 g (52.4%) of the oxime **15**, identified by comparison with the authentic sample in the usual way.

When a solution of **15** (1 g, 0.0031 mole) in dry toluene (25 ml) was refluxed for 1 h in presence of a small amount of PCl_5, a crystalline precipitate of **16** separated on cooling of the reaction mixture (0.5 g, 53.2%).

*Reduction of **16***

To a suspension of **16** (0.15 g, 0.0005 mole) and zinc dust (0.15 g) in a mixture of ethanol (10 ml) and dimethylformamide (10 ml) 5% aqueous HCl was added dropwise until the pH of 3.0 was reached. After stirring at room temperature for 2 h the insolubles were removed by filtration, the filtrate was basified with aqueous NaOH, diluted with water, and extracted with chloroform. Evaporation of the chloroform *in vacuo* and dilution of the remaining dimethylformamide with water caused precipitation of a small amount of crystalline material, which was identified as **3** by m.p. and mixture m.p. determination and by comparison of the infrared spectra.

*1-Methyl-3-phenyl-7-chloro-3,4-dihydro-2H-1,4-benzodiazepine-2,5(1H)-dione (**17**)*

A solution of **2** (10 g, 0.033 mole) in a mixture of dimethylformamide (60 ml) and anhydrous methanol (120 ml) was refluxed for 3 h, in presence of 40% methanolic solution of Triton B (1 ml). After cooling to room temperature the reaction mixture was diluted with water and extracted with chloroform. Removal of the solvent *in vacuo* left a residue which crystallized on treatment with ether. It was collected by filtration and recrystallized from methanol. The yield was 5.1 g (51%), m.p. 234–235°.

Anal. Calcd. for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.35; Cl, 11.79; N, 9.32. Found: C, 63.73; H, 4.48; Cl, 11.82; N, 9.56.

The same product was obtained in 18% yield when a solution of **11** (0.55 g) in anhydrous methanol containing a few drops of a 40% methanolic solution of Triton B was refluxed for 3 h. It was isolated in the usual way and its identity was established by m.p. and mixture m.p. determination and by comparison of the infrared spectra.

*Synthesis of **17** from N-Methyl-5-chloroanthranilic Acid*

A solution of *N*-methyl-5-chloroanthranilic acid (1, 4) (3.1 g, 0.016 mole) and D,L-phthalimidophenylacetyl chloride (5) (5 g, 0.016 mole) in dry chloroform (70 ml)

was heated under reflux for overnight. The solvent was distilled off *in vacuo*, the residue dissolved in methanol (80 ml), and refluxed in presence of decolorizing carbon. The solution was filtered, the methanol was distilled off *in vacuo*, and the residue was crystallized from ethyl acetate. The yield of crystalline 2-(*N*-methyl)-phthalimidophenylacetamido-5-chlorobenzoic acid was 2.8 g (77%), m.p. 235–236°.

Anal. Calcd. for $C_{24}H_{17}ClN_2O_5$: C, 64.23; H, 3.82; Cl, 7.90; N, 6.24. Found: C, 64.09; H, 4.09; Cl, 8.01; N, 6.33.

The solution of the above product (2.64 g, 0.0058 mole) in ethanol (26 ml) containing hydrazine hydrate (0.6 g, 0.012 mole) was heated under reflux for 2½ h. After cooling in an ice bath the precipitate was collected on a Buchner filter funnel and put aside. The filtrate was evaporated to dryness, the crystalline residue was combined with the solid separated previously and suspended into 5% aqueous HCl (80 ml). After stirring at room temperature for 15 min the insolubles were removed by filtration and the filtrate was extracted with *n*-butanol. Removal of the solvent *in vacuo* left a residue which solidified on addition of ether (1.3 g). As we were unable to prepare an analytically pure sample of that product we proceeded with the preparation of the methyl ester: the above product (0.7 g, 0.0022 mole) was dissolved in anhydrous methanol (25 ml) and the solution saturated with HCl gas. After standing overnight at room temperature the methanol was distilled off *in vacuo* and the crystalline 2-(*N*-methyl)-phenylglycylamido-5-chlorobenzoic acid methyl ester hydrochloride was recrystallized from methanol – ethyl acetate mixture. The yield was 0.4 g (57.1%), m.p. 209–211°.

Anal. Calcd. for $C_{17}H_{18}Cl_2N_2O_3$: C, 55.30; H, 4.91; Cl, 19.21; N, 7.59. Found: C, 54.92; H, 4.83; Cl, 19.28; N, 7.73.

A solution of the above product (0.3 g, 0.00081 mole) in anhydrous methanol (5 ml) containing triethylamine (0.13 ml, 0.00094 mole) was refluxed for 2½ h. After cooling to room temperature the reaction mixture was diluted with water, extracted with chloroform, the solvent removed *in vacuo*, and the residue was treated with ether. The crystalline product was separated and recrystallized from methanol. It was found to be identical with **17** by m.p. and mixture m.p. determination and by comparison of the infrared spectra.

Dimer ***18***

A solution of 2-(*N*-methyl)-dichloroacetamido-5-chlorobenzophenone (10 g, 0.028 mole) in dimethylformamide (70 ml) was added to 95% ethanol (140 ml) previously saturated with NH_3 gas. After standing overnight at room temperature the solvent mixture was removed by distillation *in vacuo* and the semicrystalline residue was triturated with ether. The crystalline precipitate was collected on a Buchner filter funnel, suspended in ethyl acetate, the ammonium chloride was removed by filtration, and the filtrate was diluted with *n*-hexane. The crystalline precipitate (2.6 g, 30.7%) was collected by filtration and recrystallized from ethyl acetate – hexane mixture, m.p. 177–178°. Sometimes another crystalline modification m.p. 212° was obtained. The infrared spectra in chloroform solution of both polymorphs were superimposable.

Anal. Calcd. for $C_{32}H_{24}Cl_2N_2O_6$ (mol. wt., 603.44): C, 63.70; H, 4.01; Cl, 11.74; N, 4.64. Found (mol. wt., 632.9 Rast): C, 63.32; H, 4.12; Cl, 11.79; N, 5.01.

The same product was obtained in the following way: a solution of **12** (2.5 g, 0.0782 mole) in benzene (40 ml) was refluxed overnight with azeotropic removal of water. On concentration the solution deposited a crystalline product, which was identified as **18** by m.p. and mixture m.p. determination and by comparison of the infrared spectra (1.1 g, 46.5%).

Finally, when a suspension of **2** (2.5 g, 0.0083 mole) in glacial acetic acid (10 ml) was stirred at room temperature for 4 h, the work-up of the reaction mixture yielded 1.9 g (76%) of **18**, characterized by determination of m.p., mixture m.p., and by comparison of infrared spectra.

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