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THE STRUCTURE OF THE DIMER OF 2,2,4-TRIMETHYL-1,2-DIHYDROQUINOLINE

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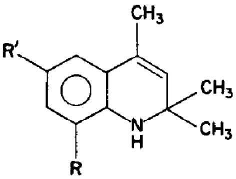
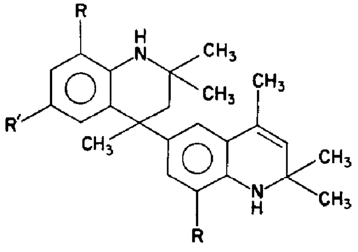
Abstract—The acid-catalyzed dimerization of 2,2,4-trimethyl-1,2-dihydroquinoline ("acetone anil") is shown to occur between the 4,6′-positions of the two dihydroquinoline ring systems. The mode of formation of the dimer is in accord with observed substituent effects in the benzene ring of "acetone anil" derivatives and with dueterium exchange studies on the monomer.

THE product of the condensation of aniline with two molar equivalents of acetone is a dihydroquinoline the structure of which has been established as 2,2,4-trimethyl-1,2-dihydroquinoline.[1] This compound, known by the trivial and somewhat misleading name "acetone anil", undergoes several extraordinary reactions catalyzed by acid and base. When 2,2,4-trimethyl-1,2-dihydroquinoline(I) is heated with a trace of acid at 120°, a mixture of monomeric, dimeric and polymeric(I) results. The pure dimer from this reaction reverts to the monomer when distilled with a trace of acid at 180°.[2] Heating acid salts of I above 200° yields methane, ethane, 2,4-dimethylquinoline and 2,3,4-trimethylquinoline in a complex mixture of other products.[2,3] On the other hand, I refluxed with a strong base gives methane and 2,4-dimethylquinoline in high yield.[4]

We have studied the dimerization of acetone anil and have determined the structure of the dimer as part of a general investigation of the chemistry of dihydroquinolines.[5,6]



I, R = R′ = H
V, R = CH_3, R′ = H
VII, R = H, R′ = OEt



IV, R = R′ = H
VI, R = CH_3, R′ = H
VIII, R = H, R′ = OEt

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[1] I. W. Elliot and P. Yates, *J. Org. Chem.* **26**, 1287 (1961).

[2] D. Craig, *J. Amer. Chem. Soc.* **60**, 1458 (1938).

[3] The mechanism of this reaction is under investigation by H. C. D.

[4] W. R. Vaughan, *Org. Synth.* Coll. Vol. III, 329 (1955).

[5] H. C. Dunathan, I. W. Elliot and P. Yates, *Tetrahedron Letters* **21**, 781 (1961).

[6] H. C. Dunathan and I. W. Elliot, *139th Meeting, American Chemical Society*, St. Louis, 1961, abstract p. 5–0. The abstract for this talk gave an incorrect structure for the dimer proposed before the N.M.R. results were available. The correct structure was presented at the meeting.

Acetone anil dimer, previously reported as a yellow glass,[2] crystallized from ethanol as white prisms, m.p. 95·5–97°. Examination of the I.R. and U.V. spectra of the dimer indicates that one monomer unit is present in the dimer as a 1,2,3,4-tetrahydroquinoline while the other is still in the form of a 1,2-dihydroquinoline. Absorptions at 2·95 μ and 6·03 μ are assigned to N—H and C═C stretching vibrations. Absorption in the near U.V. is that of an equal molar mixture of I and the 3,4-dihydro derivative of I (Fig. 1). Both the N,N′-dimethyl and the N,N′-diacetyl derivatives of the dimer are known. The latter absorbs one mole of hydrogen on catalytic hydrogenation and the dihydro product shows U.V. absorption expected for N-acetyl-1,2,3,4-tetrahydroquinoline with nearly twice the intensity. Further confirmation of the presence of 1,2-dihydro and 1,2,3,4-tetrahydroquinoline units in the dimer is found in the base strengths of the two basic nitrogen groups in the dimer. Potentiometric titration by the method of Fritz[7] gave values of pK_B of 9·1 and 10·2 for the dimer compared with pK_B 9·8 for I and pK_B 9·0 for the dihydro derivative of I.

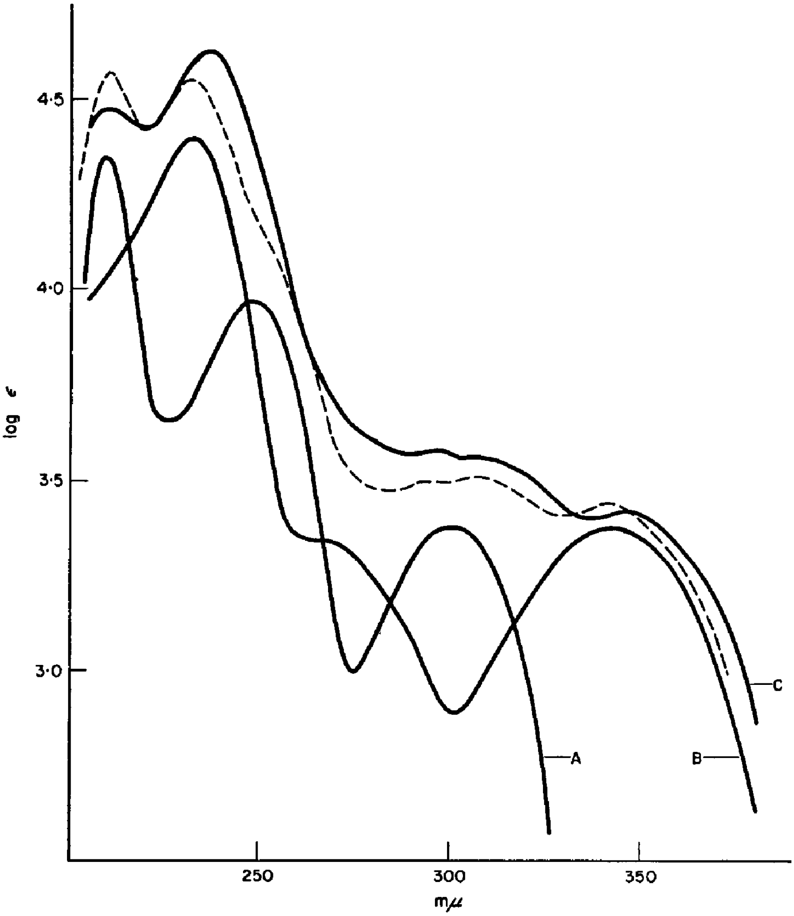

FIG. 1. Ultraviolet absorption spectra of: 2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline(A), 2,2,4-trimethyl-1,2-dihydroquinoline(B), 2,2,4-trimethyl-1,2-dihydroquinoline dimer(C), the line (- - - - -) represents the sum of the absorptions of (A) and (B).

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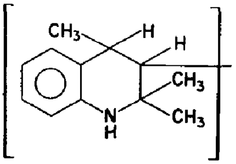
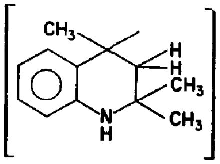
[7] J. S. Fritz, *Analyt. Chem.* **25**, 407 (1953).

The above evidence indicates a tetracyclic structure in which the two monomer units are joined by a single bond. The position of this bond can be largely defined by examination of the N.M.R. spectrum of the dimer. The chief features of this spectrum are the low field aromatic proton multiplet corresponding to seven protons; a single olefinic proton seen as poorly resolved quartet at $\tau = 4{\cdot}75$ with $J = 0{\cdot}7$ c/s; two N–H protons at $\tau = 6{\cdot}47$; a doublet at $\tau = 8{\cdot}12$, $J = 0{\cdot}7$ c/s corresponding to three protons; an AB quartet centered at $\tau = 7{\cdot}79$ and $8{\cdot}09$ with $J_{AB} = 13{\cdot}0$ c/s and single resonances at $\tau = 8{\cdot}33$, $8{\cdot}78$, $8{\cdot}81$ and $9{\cdot}19$ corresponding to 3, 6, 3 and 3 protons. This spectrum immediately places one terminus of the bond joining the monomers in the aromatic ring of one of the units since the dimer spectrum shows seven, not eight aromatic protons. Since the resonances at 8·12, 8·33, 8·81 and 9·19 correspond to six methyl groups, the three methyl groups of each monomer must be intact in the dimer. The dimer preserves another structural feature of the monomer in a $CH_3C{=}C{-}H$ grouping seen in the single proton quartet centered at $\tau = 4{\cdot}75$ and the methyl doublet centered at $\tau = 8{\cdot}12$, for both $J = 0{\cdot}7$ c/s. These occur at $\tau = 4{\cdot}78$ and $8{\cdot}06$ in I.[8] One combination must still have an intact "acetone anil" structure in the hetero ring, and the other unit is bonded to it through its aromatic ring. It follows that the bond to the tetrahydroquinoline unit must terminate at either C_3 or C_4 if the aromatic protons and the methyl groups of that ring are to be preserved. If the bond is at C_3, the partial structure II results; if at C_4, the structure III. These two possibilities are readily distinguished via the N.M.R. spectrum. The single methyl resonances and the simple AB quartet can only be consistent with III. A structure proposed by Craig[2] embodies the structural features of II and must be rejected as incompatible with the N.M.R. spectrum.



II



III

Although a dimer structure IV in which the bond to the aromatic ring is placed para to the activating nitrogen is perhaps the most likely of the four possibilities, this assumption was tested by dimerization of substituted "acetone anils."

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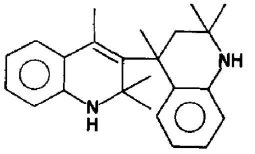
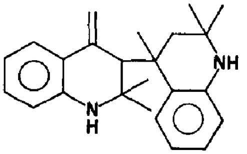
[8] This combination of factors eliminates from consideration such structures as (i) or (ii) for the dimer that might be proposed on the basis of analogy with certain alkoxyphenylalkene (or styrene) dimers:



i



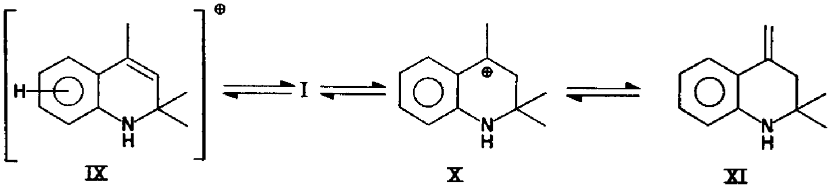
ii

Cf. A. Muller, *J. Org. Chem.* 17, 1077 (1952); C. W. Roberts and N. E. Nuenke, *J. Org. Chem.* 24, 1907 (1959).

When 2,2,4,8-tetramethyl-1,2-dihydroquinoline (V) was treated with a trace of acid at 120°, a dimer, m.p. 140–141°, was formed the properties of which were in all ways consistent with its formulation as VI. The two new single methyl resonances appeared in the N.M.R. at 7·92 and 8·05. However, when 6-ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (VII) was treated in the same way, monomeric VII was recovered in high yield[9]. A mixture of VII and I, under these conditions, yielded both dimeric I and a new dimer the properties of which were those expected for the mixed dimer VIII. The absence in this dimer of a long wavelength absorption band at $\lambda_{max} = 355$ mμ that is present in the monomer VII indicates that VII exists in the dimer as the tetrahydroquinoline unit. The new ethyl group is seen in the N.M.R. spectrum as the expected multiplets centered at $\tau = 6{\cdot}17$ and 8·70.

Ready dimerization of V, in which the position *ortho* to nitrogen is blocked, the failure of VII, blocked in the 6 position, to dimerize and the participation of this 6-substituted compound in dimer formation as the unit bonded through the 4-position, all confirm the dimer structures IV, VI and VIII formed by *para* substitution.

Formation of such dimers might result from the attack of a cation X at the 6-position of the dihydroquinoline. Equilibria potentially involved in the formation of X are shown in IX–XI. The reality of these reactions was tested by examining the extent of the incorporation of deuterium in I when it was treated with D_2O under dimerizing conditions. The recovered I was treated with aqueous ethanol to remove nitrogen-bond deuterium and the N.M.R. spectrum determined. (The N.M.R. spectrum of I has been reported by Elliott and Yates.[1]) The vinyl hydrogen at C_3, the methyl group at C_4 and the aromatic ring hydrogen showed respectively 78, 73 and 40% deuterium incorporation. No deuterium incorporation in the *gem*-dimethyl groups at C_2 was detectable. These results would be predicted from any equilibration between I, IX, X and XI. This facile exchange reaction confirms the ease of formation of X and the high reactivity of the aromatic ring of I towards electrophilic attack. The coincidence of these properties in one molecule leads to the observed dimerization which can be described as an electrophilic aromatic substitution reaction forming a carbon–carbon bond at moderate temperatures in an essentially basic medium.



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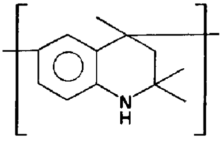
[9] Failure to isolate appreciable quantities of polymeric materials from this reaction suggests that the polymer formed during the dimerization of I is formed via successive aromatic substitution reactions and thus contains the repeating unit:



EXPERIMENTAL

Acetone anil dimer (IV). Acetone anil monomer[4] was heated with acid according to the procedure of Craig.[3] The crude dimer was distilled at 0·5 mm and the fraction boiling at 200–250° collected. The dimer was purified by repeated evaporative distillation at 150° and 0·5 mm. Attempted crystallizations from alcohol finally yielded white crystals, m.p. 95·5–97°. U.V. spectrum λ_{max}(log e): 345 mμ (3·42), 305 (3·56), 295 (3·57), 235 (4·61). I.R. spectrum shows double bond absorption at 6·03 μ.

The dimer (IV) when distilled at 180° (bath temp) and 10 mm with a trace of phosphoric acid decomposed to yield 65% monomeric acetone anil.

The diacetyl derivative reported by Craig[3] (m.p. 185–186°) was purified by column chromatography on alumina yielding white crystals m.p. 194–195°; λ_{max} 248 (log e 4·63).

Dihydrodiacetyl acetone anil dimer. An ethanolic solution of dimer diacetate (2·15 g, 5 mmoles) was hydrogenated at atm. press. in the presence of platinic oxide catalyst. The mixture absorbed the equivalent of 1·04 moles of hydrogen per mole of dimer. The filtered solution was concentrated to yield 1·8 g of pale yellow crystals, m.p. 183–187° which after repeated recrystallization from ethanol gave colorless crystals, m.p. 196–197°; λ_{max}253 mμ(log e 4·49). (Found: C, 77·93; H, 8·32; N, 6·52. $C_{28}H_{36}N_2O_2$ requires: C, 77·74; H, 8·39; N, 6·48%).

N,N′-*Dimethyl acetone anil dimer.* A solution of acetone-anil dimer (3 g) in excess methyl iodide at room temp slowly deposited a granular yellow solid, m.p. 185°. Attempts to recrystallize the methiodide resulted in extensive hydrolysis; therefore the salt (1·0 g) was treated with 10% sodium hydroxide solution to give an oil. The base was dissolved in hot ethanol, and the solution deposited a crystalline solid, m.p. 139–142°. Recrystallization from ethanol gave 0·5 g of colorless needles, m.p. 148–149°. I.R. spectrum: 6·03, 6·24 and 6·30 μ; there was no band in the 3 μ region; λ_{max} (log e): 237 (4·70) and 351 mμ (3·43). (Found: C, 83·34; H, 9·17; N, 7·48. $C_{26}H_{34}N_2$ requires: C, 83·37; H, 9·15; N, 7·52%).

Potentiometric titration of acetone anil and its dimer. The method of Fritz[7] was used with perchloric acid in acetic acid as the titrant. The titrations were carried out with a constant speed burette and a Beckman zeromatic pH meter attached to a Leeds and Northrup recorder. The millivolt potentials at the midpoints and the corresponding pK_B values from Fritz's plot are shown below.

Acetone anil dimer	360(9·1) and 460(10·2)
Acetone anil	410(9·8)
Dihydro acetone anil	350(9·0)
N-Methylaniline	360(9·1)

2,2,4-*Trimethyl*-8-*methoxy*-1,2-*dihydroquinoline.* By the method[4] used to prepare acetone anil *o*-anisidine, (216 g), iodine (9 g) and acetone (600 ml) were allowed to react, and 400 ml of acetone-distillate was collected during the reaction. The mixture was distilled under red. press. (13 mm) and the following fractions were collected: A (b.p. 27–145°), B (b.p. 145–175°) and C (175–210°). Fractions B and C on long standing in a solution of benzene and ligroin deposited large colorless prismatic crystals, (12 g), m.p. 56–58°. The crude product was distilled at 147–150°/11 mm and recrystallized from ligroin (b.p. 66–75°) as colorless prisms, m.p. 57–58°; I.R. bands at 2·95, 6·04, 6·20, 6·30 μ. (Found: C, 77·08; H, 8·47; N, 6·98. $C_{13}H_{17}NO$ requires: C, 76·82; H, 8·44; N, 6·89%).

Attempted dimerization of 6-*ethoxy*-2,2,4-*trimethyl*-1, 2-*dihydroquinoline* (VII). 6-Ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline* (23·0 g 0·11 moles), b.p. 193–192° (26·0 mm) was treated with conc hydrochloric acid (0·8 ml, 0·01 moles) and kept at 120° under nitrogen for 21 hr. The product was taken up in ether and extracted with 10% sodium hydroxide (2 × 20 ml) and water (2 × 50 ml). The combined aqueous layers were extracted with ether (50 ml) and this ether layer was extracted with water. The combined ether layers were dried ($NaSO_4$) and reduced to 22·7 g of a mobile yellow oil. Evaporative distillation of 18·9 g of this oil at 125° (0·5 mm) yielded 18·0 g of a yellow oil shown by V.P.C. to be pure VII. The recovery of unchanged VII was 95%.

Crossed dimerization of VII *and* I. 6-Ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (VII; 22·0 g, 0·10 moles) and 2,2,4-trimethyl-1,2-dihydroquinoline (I; 4·3 g, 0·025 moles) were heated with conc hydrochloric acid (1·0 ml, 0·025 moles) under nitrogen at 120° for 21 hr. The product was worked up as above, yielding 24·7 g of a viscous dark oil. Distillation of 23·7 g of this oil at 0·5 mm yielded 18·7 g

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* We are indebted to Dr. J. O. Harris of the Monsanto Company for a supply of this compound.

of a fraction, b.p. 110–145° and 4·8 g, b.p. 145–235°. The first fraction was found to consist of 90% VII and 10% I by V.P.C. analysis. Chromatography of the high boiling fraction on aluminum oxide (100 g) and analysis of the fractions by the technique of thin layer chromatography[10] showed the presence of I, VII, dimeric I and a new compound eluated in 30% ether-in-hexane. A second chromatography of the fractions containing this compound yielded 2·1 g of a viscous yellow oil that crystallized from petroleum ether in white prisms, m.p. 121–122°. (Found: C, 80·02; 80·25; H, 8·94; 8·74; N, 7·06. $C_{26}H_{34}N_2O$ (mixed dimer) requires: C, 79·94; H, 8·78; N, 7·17%).

Preparation and dimerization of 2,2,4,8-*tetramethyl*-1,2-*dihydroquinoline* (V). The procedure of Vaughan[4] for the synthesis of acetone-anil was followed with slight modification. In the apparatus described by Vaughan *o*-toluidine (170 g, 1·58 moles) was heated at 180–190° with iodine (4·5 g), and acetone (525 ml, 7·1 moles) was passed through the rapidly stirred solution. The addition was complete in 2·5 hr, when 490 ml of a mixture of acetone, water and traces of toluidine had distilled. The reaction mixture was crudely fractionated by distillation through a Widmer column. The fraction b.p. 120–165° (30 mm), 63 g, was carefully fractionated through a four-foot glass helices column. A forerun of *o*-toluidine (8 g) was followed by an intermediate fraction of a yellow liquid before the main fraction, b.p. 136–138° (12·1 mm), 40 g, of 2,2,4,8-tetramethyl-1,2-dihydroquinoline distilled.

The monomer (V; 19·7 g, 0·105 moles) was heated with conc hydrochloric acid (0·8 ml, 0·01 moles) at 120° for 17 hr. The mixture was taken up in ether and washed with 10% sodium hydroxide (25 ml). The dried ether layer was reduced to an oil and distilled to yield a fraction b.p. 100–115° (5 mm) which was more than 90% V. The material remaining in the pot was distilled from an evaporative still at 225° and 2–3 mm. A glassy orange solid (6·45 g) distilled leaving a polymeric residue (2·7 g). Column chromatography of the 6·45 g fraction on alumina yielded in the 10% ether-in-hexane fraction the dimer VI (4·9 g). Recrystallization from petroleum ether (b.p. 60–70°) gave an analytical sample, m.p. 140–141°. (Found: C, 83·18, 83·31; H, 9·09, 8·97; N, 7·73. $C_{13}H_{17}N$ requires: C, 83·36; H, 9·16; N, 7·48%).

Deuterium exchange experiment. 2,2,4-Trimethyl-1,2-dihydroquinoline (I; 15·5 g, 0·09 moles) was dissolved in 26 ml of 99% deuterium oxide containing 0·066 moles of hydrochloric acid, and 40 ml of purified dioxane was added. The solution was heated at 100–101° for 60 hr. Sodium carbonate (16 g, 0·15 moles) was added to the solution and the two-phase system was extracted with ether. The ether-dioxane layer was dried and concentrated at the water pump. Fractional distillation yielded only 1·4 g of monomeric I. Slow distillation with a trace of phosphoric acid afforded an additional 9·5 g of I. Both of these were dissolved in aqueous ethanol, allowed to equilibrate for 6 hr and recovered by dilution with water and extraction with ether. Fractional distillation yielded a fraction b.p. 67·5–68·0° (0·5 mm). The I.R. spectrum of this fraction showed no absorption due to N–D stretching vibration. The N.M.R. spectrum showed a diminution in the area of the peaks at $\tau = 8·06$, 4·78 and 3·0–3·7 (aromatic multiplet) corresponding to the incorporation of 73, 78 and 40% respectively of deuterium in these positions. The resonance absorption at 8·81 was unchanged. (All peaks measured relative to N–H.)

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[10] E. Stahl, *Angew Chem.* 73, 646 (1961).