[CONTRIBUTIONS FROM THE DIVISION OF ANALYTICAL CHEMISTRY, NATIONAL PHYSICAL LABORATORY OF INDIA, NEW DELHI]

Structures of the Products Obtained by the Condensation of Phenylbenzimino Chloride and Ethyl Sodioacetoacetate and Subsequent Cyclization[1]

BY GURBAKHSH SINGH AND G. V. NAIR

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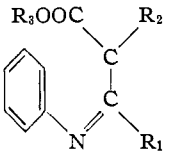
The condensation of phenylbenzimino chloride with ethyl sodioacetoacetate has been found to yield a mixture of the C-alkylation and O-alkylation products II and XII. These on cyclization have produced 2-phenyl-3-acetyl-4-hydroxyquinoline (VIII) and 2-methyl-3-benzoyl-4-hydroxyquinoline (IX), respectively. A mechanism for the formation of 2-methyl-3-benzoyl-4-hydroxyquinoline (IX) from XII is discussed. Several old formulations have been revised.

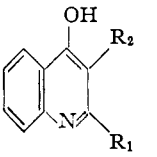
An excellent method for the syntheses of various 2-aryl-4-hydroxyquinolines, originally described by Just[2] and later by Seka and Feuchs[3] and also by Shah and Heeramaneck,[4] consists in the condensation of an aryl benziminochloride with ethyl sodiomalonate followed by the cyclization of the intermediate I to 2-aryl-4-hydroxy-3-carbethoxyquinoline (VII). Further hydrolysis and decarboxylation results in the formation of the desired 2-aryl-4-hydroxyquinoline. An obvious variation of this synthesis was the use of ethyl acetoacetate in place of ethyl malonate. This was attempted by Desai and Shah,[5] who isolated the intermediate condensation product only as an oil. This on cyclization was reported to yield a crystalline compound $C_{17}H_{13}NO_2$, m.p. 289°. By analogy with the ethyl malonate condensation product, the oily intermediate and the cyclization product were formulated as II and 2-phenyl-3-acetyl-4-hydroxyquinoline (VIII), respectively.

We have now found that this particular variation is not as simple as claimed by Desai and Shah.[5] Whereas these authors considered the oily intermediate to arise exclusively through the C-alkylation of ethyl acetoacetate by phenylbenzimino chloride, it actually has been found to be a mixture of almost equal amounts of C-alkylation and O-alkylation products. Thus on chromatographic separation over activated alumina, the oily mixture was resolved into a crystalline material XII, m.p. 82°, and a colorless viscous oil II which could not be obtained in a crystalline form.

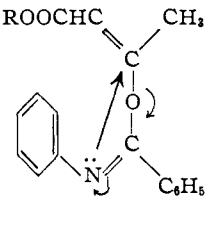
The methyl esters XIII and III corresponding to the above two condensation intermediates were both obtained as solids (m.p. 102° and 83°) when methyl acetoacetate was used in place of ethyl acetoacetate. The 82° ethyl ester XII was shown to have the composition $C_{19}H_{19}NO_3$, while the two methyl esters III and XIII were found to be isomeric and analyzed correctly for $C_{18}H_{17}NO_3$. The 82° ethyl ester XII and the 102° methyl ester XIII lost the elements of ethyl alcohol and methyl alcohol, respectively, on cyclization in boiling diphenyl ether and gave rise to the $C_{17}H_{13}NO_2$ product of m.p. 289° reported by Shah, *et al.*[4] This product has now been shown to have the structure 2-methyl-3-benzoyl-4-hydroxyquinoline (IX) and not 2-phenyl-3-acetyl-4-hydroxyquinoline (VIII) as assumed by Shah, *et al.*[4]



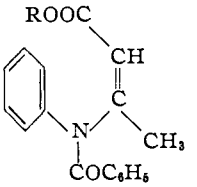
I, R_1 = Ar; R_2 = $COOC_2H_5$; R_3 = C_2H_5
II, R_1 = C_6H_5; R_2 = $COCH_3$; R_3 = C_2H_5
III, R_1 = C_6H_5; R_2 = $COCH_3$; R_3 = CH_3
IV, R_1 = CH_3; R_2 = COC_6H_5; R_3 = C_2H_5
V, R_1 = CH_3; R_2 = COC_6H_5; R_3 = CH_3
VI, R_1 = CH_3; R_2 = $CH_2C_6H_5$; R_3 = C_2H_5



VII, R_1 = Ar; R_2 = $COOC_2H_5$
VIII, R_1 = C_6H_5; R_2 = $COCH_3$
IX, R_1 = CH_3; R_2 = COC_6H_5
X, R_1 = CH_3; R_2 = $CH_2C_6H_5$
XI, R_1 = C_6H_5; R_2 = COCHO



XII, R = C_2H_5
XIII, R = CH_3



XIV, R = C_2H_5
XV, R = CH_3

The residual oily fraction (ethyl ester) II or the 83° methyl ester III on similar cyclization gave rise to a new isomeric quinoline, m.p. 248°, in a quantitative yield. As expected, a mixture of the two quinolines was obtained when the original oily intermediate was cyclized without any previous separation. It was, however, possible to separate the two quinolines VIII and IX almost quantitatively by separation of the potassium salt of the former from a concentrated solution of potassium hydroxide.

In the following, it is further proved that the structure 2-phenyl-3-acetyl-4-hydroxyquinoline (VIII) should now be assigned to the product melting at 248°. It gave a positive test with an alcoholic solution of ferric chloride and yielded a crystalline dinitrophenylhydrazone and oxime. It was found to be soluble in dilute potassium hydroxide and could be precipitated unchanged on the addition of hydrochloric acid. On treatment with phos-

(1) A preliminary account of this work has been published in *Chemistry & Industry*, 253 (1954).

(2) F. Just, *Ber.*, **18**, 2632 (1885); **19**, 1462, 1541 (1886).

(3) R. Seka and W. Feuchs, *Monatsh.*, **57**, 52 (1931).

(4) R. C. Shah and V. R. Heeramaneck, *J. Chem. Soc.*, 428 (1936).

(5) T. B. Desai and R. C. Shah, *J. Indian Chem. Soc.*, **26**, 121 (1949).

phoryl chloride, it yielded 2-phenyl-3-acetyl-4-chloroquinoline, m.p. 136°. The chloroquinoline could be hydrolyzed by refluxing with a mixture of hydrochloric acid and acetic acid to the parent 2-phenyl-3-acetyl-4-hydroxyquinoline (VIII). When the chloroquinoline was treated with sodium methoxide in methanol, the halogen was replaced by elements of methoxyl group.

On oxidation with neutral potassium permanganate or chromic acid in glacial acetic acid, both the chloroquinoline or the parent 2-phenyl-3-acetyl-4-hydroxyquinoline VIII yielded benzoylanthranilic acid in good yield. On hydrolysis, with concentrated hydrochloric acid, VIII yielded quantitatively 2-phenyl-4-hydroxyquinoline. When an alcoholic solution of VIII was treated with selenium dioxide, the corresponding α-ketoaldehyde XI was obtained in high yield. This on oxidation with hot alkaline hydrogen peroxide gave a quantitative yield of 2-phenyl-3-carboxy-4-hydroxyquinoline. This on decarboxylation by heating above its melting point yielded 2-phenyl-4-hydroxyquinoline. These experiments, in our opinion, conclusively show that the compound, m.p. 248°, is correctly represented as 2-phenyl-3-acetyl-4-hydroxyquinoline (VIII). The results of the infrared analysis are also in accord with this structure. Thus it shows the expected bands due to the hydroxyl group, conjugated carbonyl and the C=N function at 2.92, 5.90 and 6.15μ, respectively.

These results also indicate that the intermediates (oily ethyl ester and 83° methyl ester) leading to 2-phenyl-3-acetyl-4-hydroxyquinoline (VIII) must be represented by II and III, respectively. This formulation also is supported by the infrared analysis of III which shows bands at 5.81μ (-CO-OCH_3 and -$COCH_3$) and 6.21μ (C=N).

The structural assignment of XII and XIII as substituted vinyl ethers is based on the observation that on treatment with warm dilute hydrochloric acid, these two intermediates yield benzanilide and ethyl (or methyl) acetoacetate in a quantitative yield. In contrast the products II and III corresponding to a C-alkylation of ethyl or methyl acetoacetate with phenylbenzimino chloride yield only benzoic acid and aniline after long refluxing with dilute hydrochloric acid. The infrared spectrum also lends further support to the formulation of XII and XIII. Both these compounds exhibit three strong bands at 5.82, 6.0 and 6.04μ which we attribute to the conjugated ester, C=N and the vinyl ether, respectively.

The evidence for the formulation of 2-methyl-3-benzoyl-4-hydroxyquinoline (IX) is as follows: On oxidation with neutral potassium permanganate, it gave a mixture of acetylanthranilic acid and benzoic acid in small yield. On treatment with phosphoryl chloride, 2-methyl-3-benzoyl-4-chloroquinoline was obtained. The chlorine atom in the chloroquinoline was labile and could be replaced by the methoxyl group on treatment with sodium methoxide in methanol. Further support for the formulation of 2-methyl-3-benzoyl-4-hydroxyquinoline (IX) was forthcoming from the following three syntheses.

(1) Methyl β-anilinocrotonate[6] (which already had been obtained by the condensation of methyl acetoacetate and aniline in the presence of hydrochloric acid) was treated with one equivalent of powdered sodium metal in anhydrous toluene. After the evolution of hydrogen had ceased, it was further allowed to react with one equivalent of benzoyl chloride. The crystalline intermediate thus obtained on cyclization yielded 2-methyl-3-benzoyl-4-hydroxyquinoline IX. The intermediate could be represented by either structures V or XV. Infrared analysis showed that the former structure is preferable. The spectrum (bands at 5.82 and 6.22μ) was quite similar to the spectrum of III in the double bond region.

(2) 2-Methyl 4-quinolinobenzoate on treatment with anhydrous aluminum chloride at about 200° underwent the Fries migration to give IX.

(3) Ethyl benzylacetoacetate was condensed with aniline and the intermediate VI on cyclization yielded 2-methyl-3-benzyl-4-hydroxyquinoline (X). This was oxidized with chromic acid in acetic acid to yield 2-methyl-3-benzoyl-4-hydroxyquinoline (IX). In all these cases the identity of these products was confirmed through melting points and mixed melting points of the final products as well as several of the derivatives.

The imino ethers XII and XIII on heating would be expected to undergo the imino ether–amide rearrangement[7] to yield XIV and XV, respectively. This change may be considered as a nucleophilic displacement brought about by the pair of electrons on the nitrogen atom, as indicated in arrows on the structures XII and XIII. XIV and XV, which are vinylogously N-substituted diacylanilines, could be expected to result in the formation of 2-methyl-3-benzoyl-4-hydroxyquinoline (IX) after loss of elements of ethyl alcohol and methyl alcohol, respectively, and migration of the benzoyl group. This latter part of the rearrangement is quite analogous to the well known[8] conversion of dibenzanilide to *p*-benzamidobenzophenone by heating in the presence of an acid catalyst.

Kulkarni, Thakor and Shah[9] claimed confirmation of their views regarding the structure of the quinoline, m.p. 289°, through its synthesis, along with another isomeric product, m.p. 284°, by the cyclization of the oily intermediate resulting from the condensation of aniline and ethyl benzoylacetoacetate. These authors assigned structures II and IV to the intermediates and considered that they were formed *via* the interaction of aniline and the carbonyl function of the benzoyl and acetyl groups of the ethyl benzoylacetoacetate molecule, respectively. Subsequent cyclization was claimed to yield VIII and IX and these structures were assigned, respectively, to the products of m.p. 289° and 284°. Further support for their conclusions regarding the separate entity and structure of the product of m.p. 284° was claimed because of its formation by Friedel–Crafts benzoylation of 2-methyl-4-hydroxyquinoline. Careful repetition of their

(6) M. Conrad and L. Limpach, *Ber.*, **21**, 1968 (1888).
(7) A. W. Chapman, *J. Chem. Soc.*, 569 (1929).
(8) F. D. Chattway, *Proc. Chem. Soc. (London)*, **19**, 57 (1904).
(9) S. A. Kulkarni, V. M. Thakor and R. C. Shah, *J. Indian Chem. Soc.*, **28**, 688 (1951).

work, however, revealed the presence of only one product of m.p. 289° and no trace of the reported isomeric compound of m.p. 284° could be detected in either experiment. Obviously the 284° product of Shah and co-workers was only a slightly impure sample of their higher melting (289°) product. This is also borne out by the close melting points of the oxime and the dinitrophenylhydrazone which they prepared from the 284 and 289° products. Exclusive reaction of the carbonyl function of the acetyl group of ethyl benzoylacetoacetate with aniline is understandable when one considers the decreased activity of the carbonyl function of the benzoyl group due to conjugation with a phenyl ring.

A similar condensation was attempted with methyl benzoylacetoacetate in the hope of isolating a crystalline intermediate. In this case, however, the only isolable product was methyl β-phenyl-β-anilinoacrylate, m.p. 89°. It gave correct analytical values and also yielded 2-phenyl-4-hydroxyquinoline on cyclization. Apparently the acetyl function of the methyl benzoylacetoacetate was hydrolyzed before the condensation with aniline could take place.

Experimental[9a]

Condensation of Ethyl Acetoacetate and Phenylbenzimino Chloride and Isolation of the Intermediates XII and II.—The maximum total yield was obtained when sodium metal, ethyl acetoacetate and phenylbenzimino chloride were used in the molar proportions of 2:4:1, respectively. The relative preponderance of the two isomers was dependent on the solvent used as the reaction medium. A typical experiment is described. To a solution of 11.5 g. (0.5 g. atom) of sodium metal in 160 cc. of absolute ethyl alcohol in a flask protected from moisture, 130 g. (1 mole) of ethyl acetoacetate was slowly added with stirring and this was followed by the addition of 53.8 g. (0.25 mole) of phenylbenzimino chloride dissolved in 50 cc. of toluene over a period of 30–40 minutes. The reaction mixture was kept refluxing during the course of addition and for an additional five hours. It was then cooled and decomposed with ice-cold water. The toluene layer was separated and the residual aqueous layer was twice extracted with 200 cc. of toluene. The combined toluene layers were washed with water, until the washings were free of alkali. The washings were dried over anhydrous magnesium sulfate and toluene was then removed on a water-pump. The unreacted ethyl acetoacetate was further removed by heating on a steam-bath under a vacuum of about 2 mm. The residue, 76 g., represented a yield of 98%. It was triturated with petroleum ether and on cooling and seeding, 18 g. of the O-alkylation product XII separated. It melted between 73° to 79°. After two crystallizations from petroleum ether (60–80°), as large white crystals, the m.p. rose to 82°.

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.15; N, 4.53. Found: C, 73.41; H, 6.19; N, 4.45.

The residue was chromatographed over activated alumina. The column was developed with petroleum ether (60–80°) and about twenty 30-cc. fractions were collected. The first eight fractions yielded about 35 g. of the C-alkylation product II as a clear viscous oil. The remainder yielded another 7 g. of the O-alkylation product XII. When the reaction was run in petroleum ether (60–80°) and sodium hydride was used in place of sodium metal, a total of 40 g. of the crystalline O-alkylation product XII was obtained in place of the 25 g. isolated in the above experiment.

The corresponding **methyl esters XIII and III** were obtained similarly by using methyl acetoacetate. O-Alkylation product XIII which separated out from the oily mixture by cooling, etc., after crystallization from a mixture of benzene and petroleum ether as white needles had m.p. 102°.

Anal. Calcd. for $C_{18}H_{17}NO_3$; C, 73.22; H, 5.79; N, 4.74. Found: C, 72.76; H, 5.68; N, 4.96.

The residual oil was chromatographed as above and the C-alkylation product III, the faster moving component, was obtained as a solid, which after crystallization from petroleum ether as stout prismatic crystals had m.p. 83°.

Anal. Calcd. for $C_{18}H_{17}NO_3$; C, 73.22; H, 5.79; N, 4.74. Found: C, 72.98; H, 5.81; N, 4.70.

Hydrolysis of the O-Alkylation Product (XII).—Two grams of O-alkylation product XII was warmed with about 30 cc. of 4–5% hydrochloric acid on a steam-bath. After about 15 minutes, the oily product suddenly deposited a solid. The reaction mixture was cooled and the solid filtered off. This was crystallized from ethyl alcohol and had a m.p. 161° alone or in admixture with an authentic sample of benzanilide. The filtrate from the reaction mixture was extracted with ether. After drying over anhydrous magnesium sulfate, ether was distilled off and the residual oil was shown to be ethyl acetoacetate by the formation of its semicarbazone, which after crystallization from ether had a m.p. 132° and was not depressed on mixing with an authentic sample of the semicarbazone.

Cyclization of the Intermediates XII and II and the Isolation of 2-Phenyl-3-acetyl-4-hydroxyquinoline (VIII) and 2-Methyl-3-benzoyl-4-hydroxyquinoline (IX).—The cyclization was carried out according to conditions described by Desai and Shah.[3] Twenty-five grams of the oily intermediate mixture obtained as above was added slowly to about 200 cc. of boiling diphenyl ether. The mixture was refluxed for about 30 minutes. After cooling, it was poured into about 300 cc. of petroleum ether. The solid mass (17 g.) was filtered and washed thoroughly with petroleum ether. The mixture was dissolved by warming in about 200 cc. of 5% potassium hydroxide and the solution was filtered from any suspended material. Solid potassium hydroxide was added, until the potassium salt of 2-phenyl-3-acetyl-4-hydroxyquinoline (VIII) started separating out. The mixture was cooled and then filtered. The solid mass was dissolved in water and then acidified with hydrochloric acid. The precipitate was filtered and washed with water. After two crystallizations from methanol, it was obtained as plates, m.p. 246–248°, yield 5.5 g. This quinoline was obtained in a quantitative yield when the methyl ester III or the oily ethyl ester II (after separation) was cyclized as above.

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.56; H, 4.94; N, 5.32. Found: C, 77.09; H, 4.87; N, 5.30.

The dinitrophenylhydrazone prepared in the usual manner after crystallization from a mixture of benzene and ethanol had m.p. 294° dec.

Anal. Calcd. for $C_{23}H_{17}N_5O_5$: N, 15.80. Found: N, 15.40.

The **oxime** was crystallized from ethanol and had m.p. 285° dec.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: N, 10.10. Found: N, 10.20.

The alkaline mother liquor after the separation of the solid potassium salt was acidified with hydrochloric acid. The precipitated 2-methyl-3-benzoyl-4-hydroxyquinoline (IX) was filtered and washed with water. It was twice crystallized from glacial acetic acid as white needles, m.p. 287–289°. The same quinoline was obtained in quantitative yield when the O-alkylation intermediates XII and XIII were cyclized as described above. The solubility of the higher melting quinoline IX was less in solvents like methanol and acetic acid and it was possible to separate it from the mixtures of the two quinolines by two crystallizations from acetic acid. The dinitrophenylhydrazone after crystallization from benzene–ethanol mixture into orange needles did not melt up to 300°. The oxime was crystallized from ethanol and had m.p. 262°. Both melting points compare well with those given by Desai and Shah.[5]

2-Phenyl-3-acetyl-4-chloroquinoline.—The corresponding hydroxyquinoline (VIII) (5 g.) was refluxed with about 50 cc. of phosphoryl chloride for one hour. Excess of phosphoryl chloride was removed under vacuum and the residue was decomposed with ice-cold water and then made slightly alkaline by the addition of aqueous ammonia. The solid product was filtered and crystallized from dilute alcohol as white needles, m.p. 136°, yield quantitative.

(9a) Analyses were performed by Weiler and Strauss, Oxford, England. All melting points are uncorrected.

Anal. Calcd. for $C_{17}H_{12}ClNO$: C, 72.46; H, 4.26; Cl, 12.59; N, 4.97. Found: C, 72.36; H, 4.32; Cl, 12.45; N, 4.95.

The replacement of the chlorine atom by elements of methoxyl was carried by treating 2 g. of the chloro compound with a solution of sodium methoxide prepared by dissolving 1 g. of sodium metal in 25 cc. of methanol. The mixture was refluxed for about an hour. Excess methanol was removed under vacuum and the residue treated with water. The solid material thus obtained was filtered and recrystallized from dilute alcohol as white needles, m.p. 200°.

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.98; H, 5.42; N, 5.04. Found: C, 78.58; H, 5.43; N, 4.80.

It is not known with certainty whether the methylation took place on the nitrogen atom or it yielded the corresponding methoxyquinoline.

2-Methyl-3-benzoyl-4-chloroquinoline.—This was prepared from the corresponding hydroxyquinoline IX by treatment with phosphoryl chloride as described above. It was crystallized from ethanol as white needles, m.p. 121°.

Anal. Calcd. for $C_{17}H_{12}ClNO$: C, 72.46; H, 4.26; Cl, 12.45; N, 4.95. Found: C, 72.36; H, 4.94; Cl, 12.50; N, 4.80.

This chloroquinoline on treatment with sodium methoxide as described gave a compound which was crystallized from ethanol as white needles, m.p. 219–220°.

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.98; H, 5.42; N, 5.04. Found: C, 77.93; H, 5.20; N, 4.82.

Oxidation of 2-Phenyl-3-acetyl-4-hydroxyquinoline (VIII).—Five grams of VIII was suspended in about 100 cc. of water. The mixture was brought to reflux and treated with a slight excess of a 10% solution of potassium permanganate (until the color was not discharged on further refluxing). The precipitated manganese dioxide was filtered and washed with a small quantity of hot water. The filtrate was concentrated to about 50 cc. and after cooling was decomposed with concentrated hydrochloric acid. The precipitated mass was redissolved in dilute sodium bicarbonate solution, filtered and decomposed with concentrated hydrochloric acid. The white precipitate after drying was recrystallized from benzene as a white powder, m.p. 181°, yield 1.5 g. The mixed melting point with an authentic sample of benzoylanthranilic acid was undepressed. 2-Phenyl-3-acetyl-4-chloroquinoline on similar oxidation also gave benzoylanthranilic acid.

Oxidation of 2-Methyl-3-benzoyl-4-hydroxyquinoline (IX).—The oxidation was carried out with potassium permanganate as described above. In this way a total yield of about 100 mg. of a mixture of benzoic acid and acetylanthranilic acid was obtained. Repeated crystallizations from benzene gave pure acetylanthranilic acid, m.p. 185°, which was not depressed on admixture with an authentic sample. The mother liquor was concentrated and the solid after repeated crystallization from hot water gave a small amount of benzoic acid, m.p. 121°, undepressed on mixing with an authentic sample.

Acid Hydrolysis of 2-Phenyl-3-acetyl-4-hydroxyquinoline (VIII).—Five grams of the quinoline VIII was heated with 100 cc. of concentrated hydrochloric acid in a sealed tube at 200° for about six hours. At first a clear solution was obtained and this later deposited the solid hydrochloride of 2-phenyl-4-hydroxyquinoline. The reaction mixture after cooling was diluted with 250 cc. of ice-cold water. The precipitate was filtered off and crystallized as a white crystalline mass from alcohol, m.p. 255–257°, undepressed on admixture with an authentic[4] sample, yield quantitative.

Oxidation of 2-Phenyl-3-acetyl-4-hydroxyquinoline (VIII) to 2-Phenyl-3-carboxy-4-hydroxyquinoline *via* the Corresponding α-Ketoaldehyde XI.—A solution of 5 g. of the quinoline VIII and 3.5 g. of selenium dioxide in 40 cc. of ethanol was boiled under reflux for about three hours and the precipitated selenium was filtered from the hot solution. The filtrate was concentrated, and the α-ketoaldehyde XI was collected as pale yellow solid, yield 3.2 g. This was sufficiently pure for use in the next step. A portion was dissolved in benzene and passed over a column of activated alumina to remove all the colloidal selenium. It was finally crystallized from ethanol as pale needles, m.p. 206°. For oxidation 3 g. of the aldehyde was dissolved in 20 cc. of 5% sodium hydroxide solution. The mixture was warmed on a water-bath and treated with about 15 cc. of 30% hydrogen peroxide with stirring and heating. The yellow color was slowly discharged. After about 30 minutes, the reaction mixture was cooled and acidified with hydrochloric acid. The acid was filtered, redissolved in warm bicarbonate and reprecipitated by the addition of hydrochloric acid; yield 2.5 g. It was crystallized from ethanol and had a m.p. 230–232° dec. The melting point showed no depression after admixture with an authentic sample.[3]

Fries Migration of 2-Methyl-4-quinolinobenzoate.—Five grams of 2-methyl 4-quinolinobenzoate, prepared by the action of benzoyl chloride on the sodium salt of 2-methyl-4-hydroxyquinoline according to the directions of Conrad and Limpach,[10] was mixed with 10 g. of anhydrous aluminum chloride and the mixture was heated in an oil-bath. There was a vigorous reaction while the temperature was being slowly raised and the reaction was finally completed by heating for another two hours at 200°. After cooling, it was cautiously decomposed with ice-cold hydrochloric acid. The solid mass thus obtained was filtered and washed with dilute hydrochloric acid and water. It was dissolved in 5% sodium hydroxide solution and reprecipitated by addition of acid. Finally it was crystallized from acetic acid as needles, m.p. 287–289°, undepressed on admixture with the sample obtained by cyclization.

Benzoylation of Methyl β-Anilinocrotonate and Isolation of V.—Eleven and a half grams (0.5 gram atom) of finely powdered sodium was suspended in about 350 cc. of dry toluene. The mixture was ice-cooled and treated with 95.5 g. (0.5 mole) of methyl β-anilinocrotonate prepared according to the directions given for the corresponding ethyl ester,[11] with stirring. The reaction mixture was left overnight, and practically all of the sodium metal reacted. It was then treated slowly with 70 g. (0.5 mole) of benzoyl chloride. The reaction mixture was heated on a steam-bath for about two hours and allowed to stand overnight. Ice-cold hydrochloric acid was added and the toluene layer was washed with aqueous sodium hydroxide solution and dried over anhydrous magnesium sulfate. The solvent was distilled off and the oily residue was triturated with petroleum ether. At this stage about 25 g. of a solid material separated out, and was filtered. This proved to be a mixture consisting mostly of benzanilide along with another product, which was separated by taking advantage of its greater solubility in boiling benzene. The latter was recrystallized from benzene as white glistening needles, m.p. 160–163°.

Anal. Found: C, 79.48; H, 5.70; N, 5.43.

It did not give any quinoline on cyclization. At this stage it is not possible to assign any structure to this compound. The residual oil after removal of benzanilide and petroleum ether weighed 105 g. Twenty grams of this oil was chromatographed over Brockman activated alumina and the column was developed with petroleum ether (40–60°). The entire eluate was found to consist only of the desired condensation intermediate V which after recrystallization from petroleum ether was obtained as white glistening plates, m.p. 101°.

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.22; H, 5.79; N, 4.74. Found: C, 73.11; H, 5.65; N, 4.85.

On cyclization, it gave 2-methyl-3-benzoyl-4-hydroxyquinoline (IX).

2-Methyl-3-benzyl-4-hydroxyquinoline (X).—A mixture of 22 g. (0.1 mole) of ethyl benzylacetoacetate[12] and 9.3 g. (0.1 mole) of aniline, 0.1 cc. of concentrated hydrochloric acid and 200 cc. of benzene was heated under reflux (water separator) until no more water separated out. This took about three hours. The benzene solution was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue was cyclized by pouring into 200 cc. of boiling diphenyl ether. The desired quinoline X separated out after about 10 minutes. The reaction mixture was diluted with petroleum ether to give 10 g. of the solid quinoline. This was crystallized from a large volume of ethanol into glistening platelets, m.p. 282–284°. It is only sparingly soluble in sodium hydroxide solution.

(10) M. Conrad and L. Limpach, *Ber.*, **21**, 1970 (1888).

(11) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., pp. 374–375.

(12) M. Conrad, *Ann.*, **204**, 179 (1880).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 81.92; H, 6.02; N, 5.62. Found: C, 81.64; H, 5.89; N, 5.55.

Oxidation of 2-Methyl-3-benzyl-4-hydroxyquinoline (X) to 2-Methyl-3-benzoyl-4-hydroxyquinoline (IX).—Five grams of the benzylquinoline (X) was dissolved in 50 cc. of glacial acetic acid and the mixture was treated with 7 g. of chromic acid in small amounts at a time. The reaction mixture was warmed at 70° for about 20 minutes. It was cooled and then decomposed with ice-cold water and left in the refrigerator overnight. The solid that had separated was filtered off. It was digested with 5% solution of warm sodium hydroxide and filtered free from the unreacted quinoline. The filtrate was acidified with hydrochloric acid and the precipitate after crystallization from glacial acetic acid proved to be 2-methyl-3-benzoyl-4-hydroxyquinoline (IX) as shown by the mixed melting point determination; yield 1.8 g.

Methyl (or Ethyl) Benzoylacetoacetate.—The following procedure for the benzoylation of methyl (or ethyl) acetoacetate which is completed in a much shorter period of time, is to be preferred to that given in reference 13. Eleven and one-half grams (0.5 g. atom) of sodium metal was dissolved in 200 cc. of absolute ethanol. To 100 cc. of this solution was added 32.5 g. (0.25 mole) of ethyl acetoacetate with stirring and keeping the temperature below 5°. To this mixture was added dropwise 14 g. of benzoyl chloride dissolved in 50 cc. of toluene, maintaining the temperature below 5°. An additional 50 cc. of the sodium ethoxide solution was added and this was again followed by the addition of 7 g. of benzoyl chloride dissolved in 25 cc. of toluene. These additions were repeated once more in a similar fashion. After standing overnight, the reaction mixture was decomposed with ice-cold hydrochloric acid. The toluene layer was removed and the aqueous solution was further extracted with ether. The combined extracts were dried and after removal of the solvent yielded 35 g. (75%) of a colorless oil, b.p. 145–148° (6 mm.). The methyl ester, b.p. 142–145° (6 mm.), was also prepared similarly in 75–80% yield.

Condensation of Ethyl Benzoylacetoacetate and Aniline and Subsequent Cyclization to 2-Methyl-3-benzoyl-4-hydroxyquinoline (IX).—The condensation was carried out as described under methyl β-anilinocrotonate. After removal of benzene, the reaction mixture was diluted with petroleum ether. A small amount of a white crystalline solid separated out at this stage. This, after crystallization from ethanol as white needles, had m.p. 109–112°. The product was soluble in hydrochloric acid and could be recovered on neutralization or dilution. It could be distilled at atmospheric pressure completely unchanged and failed to undergo cyclization.

Anal. Found: C, 71.74; H, 6.90; N, 9.90.

The structure is unknown. The filtrate after removal of the solid was heated under vacuum to remove all the petroleum ether. The residual oil was cyclized in boiling diphenyl ether to give a 35–40% yield of 2-methyl-3-benzoyl-4-hydroxyquinoline.

When methyl benzoylacetoacetate was condensed with aniline and the oily condensation product was chromatographed over activated alumina and the column was eluted with petroleum ether, there was obtained a 20–25% yield of methyl β-phenyl-β-anilinoacrylate which after crystallization from petroleum ether into large stout cubic crystals had m.p. 89–90°.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.90; H, 5.90; N, 5.50. Found: C, 75.68; H, 5.68; N, 5.93.

On cyclization in boiling diphenyl ether, it gave 2-phenyl-4-hydroxyquinoline, m.p. 255–257°, undepressed on admixture with an authentic sample.[4]

NEW DELHI, INDIA

(13) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., pp. 266–267.

[CONTRIBUTIONS FROM THE DIVISION OF ANALYTICAL CHEMISTRY, NATIONAL PHYSICAL LABORATORY OF INDIA, NEW DELHI, AND CONVERSE MEMORIAL LABORATORIES, HARVARD UNIVERSITY]

Condensation of 1-Vinyl-6-methoxy-3,4-dihydronaphthalene and 3-Methyl-3-cyclopentene-1,2-dione. Structure of Dane's Adduct

BY GURBAKHSH SINGH

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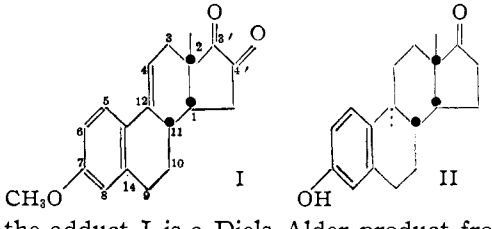
Dane and Schmitt's work on the condensation of 1-vinyl-6-methoxy-3,4-dihydronaphthalene and 3-methyl-3-cyclopentene-1,2-dione has been carefully repeated. The conclusions drawn by these authors as to the structure of the adduct thus obtained have been shown to be erroneous. This diene condensation has been found to give a mixture of two adducts, whose structures have been definitely established through degradative and synthetic experiments as 1-methyl-7-methoxy-1,2-cyclopenteno-1,2,3,4,9,10-hexahydrophenanthrene-4',5'-dione (V) and 2-methyl-7-methoxy-1,2-cyclopenteno-1,2,3,4,9,-10-hexahydrophenanthrene-3',4'-dione (VI). Their synthetic stereoisomer of estrone has been shown to be only a structural isomer of estrone.

One of the earliest attempts toward a total synthesis of estrone was that made by the German investigators Dane and Schmitt.[1] This consisted in the condensation of 1-vinyl-6-methoxy-3,4-dihydronaphthalene and 3-methyl-3-cyclopentene-1,2-dione. The adduct, which was assigned structure 2-methyl-7-methoxy-1,2-cyclopenteno-1,2,3,9,10,-11-hexahydrophenanthrene-3,4-dione (I), was converted through a series of steps (hydrogenation of the C_4–C_{12}-double bond and the $C_{4'}$-carbonyl group to the ketol, followed by the demethylation and dehydration to a $\Delta^{4'-5'}$-dehydroestrone by treatment with hydrogen bromide and acetic acid mixture and subsequent hydrogenation of the $C_{4'}$–$C_{5'}$-double bond) to what was claimed to be a stereoisomer of estrone, m.p. 210°. Dane and Schmitt's estrone appeared to be identical with the estrone "a" of Anner and Miescher[2] (m.p. 214–216°), to which the latter authors assigned the configuration II. It is easy to rationalise that Dane and Schmitt's estrone also had the same configuration (II). This follows from the considerations



that the adduct I is a Diels–Alder product from a *cis*-dienophile and, further, due to maximum accumulation of the unsaturation in the transition

(1) E. Dane and J. Schmitt, *Ann.*, **537**, 246 (1939).

(2) G. Anner and K. Miescher, *Helv. Chim. Acta*, **32**, 1957 (1949); **33**, 1379 (1950).