The acid hydrolysis (reaction 3) was repeated in deuterium oxide, using 6 *N* deuterium chloride. Mass spectrometric examination of the methyl chloride confirmed the complete absence of deuteration. The mass spectrum of the diphenylpyrazolone was consistent with deuteration in the 2 and 4 positions of the ring. Therefore, the methyl groups are not eliminated as carbene. They are expelled intact, either as methyl cations or through a concerted attack by the chloride ion with elimination of the nitrogen function. It seems likely that the first step in the hydrolysis is formation of the amine imide hydrochloride salt. This is suggested by dissolution of the water-insoluble amine imide (II) upon acidification, as well as by deuteration in the ring. The hydrochloride might be expected to split out one methyl group as methyl chloride, much the same as tetramethylammonium chloride decomposes thermally to trimethylamine and methyl chloride. Loss of the second methyl group would be thermodynamically favored by formation of the aromatic pyrazolone ring.

Experimental Section

Dimethylphenylhydrazonium Chloride.—Anhydrous, gaseous chloramine, generated in an apparatus similar to that described by Sisler,[12] was bubbled through pure anhydrous dimethylaniline at 25° to yield a thick slurry of the hydrazonium salt in unreacted dimethylaniline. The crystals were separated by vacuum filtration and washed with benzene, then with ether. To remove ammonium chloride from the product, the solids were extracted in a Soxhlet apparatus with an anhydrous mixture of ethyl acetate–methanol (90:10), in which ammonium chloride is practically insoluble. Dimethylphenylhydrazonium chloride precipitated from the extract upon cooling. Recrystallization from methanol with ether yielded a pure product, mp 188–189° (lit.[13] mp 187–188°).

Anal. Calcd for $C_8H_{13}ClN_2$: Cl, 20.5. Found: Cl (Volhard), 20.8.

N-Dimethylanilinophenylpropiolimide (II).—Dimethylphenylhydrazonium chloride (12.6 g, 0.073 mole) was added to a stirred suspension of freshly prepared sodium ethylate (4.9 g, 0.072 mole) in 150 ml of anhydrous tetrahydrofuran and maintained for several hours at −20° under a nitrogen atmosphere. Ethyl phenylpropiolate (6.3 g, 0.036 mole) was then added and the mixture was allowed to warm to room temperature. After stirring for 48 hr at room temperature, most of the solvent was removed by distillation under reduced pressure; the solid residue was collected by suction filtration and washed with ether and then with cold water. There was obtained 8.1 g (86%) of a white solid, mp 157–158° dec.

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60; mol wt, 264.3. Found: C, 76.92; H, 6.01; N, 10.90; mol wt (cryoscopic in nitrobenzene), 259.

Infrared bands (KBr disk) were found at 4.5 (C≡C) and 6.35 (C=N) μ. The nmr spectrum ($CDCl_3$, against tetramethylsilane) showed the usual peaks for aromatic protons in the region of τ 2.5, and also a single peak at 6.4 for methyl protons. The ratio of aromatic to methyl protons was the expected 10:6.

1,5-Diphenylpyrazolone-3.—A solution of N-dimethylanilinophenylpropiolimide (4.7 g, 0.018 mole) in 30 ml of 6 *N* hydrochloric acid was subjected to reflux for 2 hr in a helium atmosphere. The evolved gas was found by mass spectrometric analysis to be methyl chloride. The precipitate formed during reaction was collected by suction filtration, washed with acetone, and recrystallized from ethanol to give 3.2 g (76%) of a white solid which sublimed at 254°. An analytically pure sample was obtained by vacuum sublimation, mp 257° (closed capillary lit.[14] mp 256°).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.35; H, 5.14; N, 12.09.

The infrared spectrum was identical with that of an authentic sample of 1,5-diphenylpyrazolone-3 prepared by the method of Willert.[4] A mixture melting point determination with the authentic sample showed no depression.

When the above hydrolysis was carried out with 6 *N* deuterium chloride in deuterium oxide, no deuterated methyl chloride was formed. The deuterium appeared, instead, in the diphenylpyrazolone.

(12) H. H. Sisler, F. T. Neth, R. S. Drago, and D. Yaney, *J. Am. Chem. Soc.*, **76**, 3906 (1954).

(13) G. M. Omietanski (Ohio State University), German Patent 1,056,140 (April 30, 1959).

(14) S. Veibel, K. Eggersen, and S. C. Linholt, *Acta Chem. Scand.*, **8**, 770 (1954).

Friedländer Syntheses with *o*-Aminoaryl Ketones. II. Structure of the Product Formed in the Condensation of *o*-Aminobenzophenone with Acetylacetone[1]

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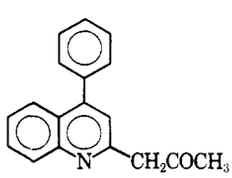
In 1939 Borsche and Sinn[2] described a compound, $C_{18}H_{15}NO$, which they obtained as the product of a Friedländer-type condensation between *o*-aminobenzophenone and acetylacetone and to which they assigned structure **1**. No evidence was offered to support the proposed structure, and no consideration seems to have been given to the possibility that an alternative (and more likely) course of reaction would lead to structure **2**. Since their observations on the behavior of other



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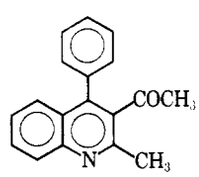

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ketones had led Borsche and Sinn to conclude that only methyl ketones are capable of undergoing normal Friedländer-type condensations with *o*-aminobenzophenone, their assignment of structure **1** to this product seems to have been based on the tacit assumption that the α-methyl group of the ketone must be directly involved in ring formation and must consequently provide C-3 in the resultant 4-phenylquinoline. In view of the results described in the preceding paper in this series,[3] however, it seemed to us most unlikely that acetylacetone would undergo this type of condensation at a methyl group rather than at the much more reactive methylene group,[4] and we have therefore reinvestigated the Friedländer condensation of this β-diketone with *o*-aminobenzophenone. We are now able to report that the product of this reaction is indeed 3-acetyl-4-phenylquinaldine (**2**) and not, as originally assumed, 2-acetonyl-4-phenylquinoline (**1**).

(1) This investigation was supported in part by Public Health Service Research Grant CY-2726(C3) from the National Cancer Institute of the National Institutes of Health.

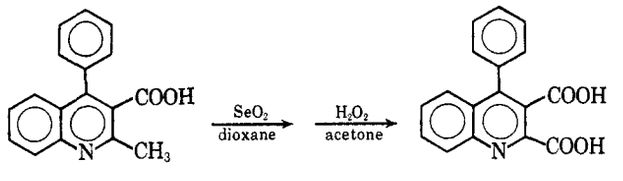
(2) W. Borsche and F. Sinn, *Ann.*, **538**, 283 (1939).

(3) E. A. Fehnel, *J. Org. Chem.*, **31**, 2899 (1966).

(4) The condensation of acetylacetone with *o*-aminobenzaldehyde yields the expected 3-acetylquinaldine: J. Eliasberg and P. Friedländer, *Ber.*, **25**, 1752 (1892).

The condensation of *o*-aminobenzophenone with acetylacetone was carried out both by the original method of Borshe and Sinn (150°, no solvent, no catalyst) and also by the recently described procedure[3] involving acid catalysis. The same compound, mp 113–114°, was obtained under both sets of conditions, although the yield was significantly higher in the acid-catalyzed reaction. The nmr spectrum of the product shows two sharp equal-intensity singlets at τ 8.00 and 7.30 and a group of complex multiplets between τ 1.7 and 2.7 (relative areas 1:1:3). This result clearly indicates the presence of two methyl groups[5] and nine aromatic protons and is thus compatible with structure **2** but not with structure **1**.

Oxidation of the condensation product with a limited amount of chromic acid provided a monocarboxylic acid, $(C_{16}H_{12}N)COOH$, which underwent decarboxylation when heated in mineral oil at 265–275° to give 4-phenylquinaldine. Further oxidation of the acid with selenium dioxide in dioxane followed by hydrogen peroxide in acetone, a procedure which converts quinaldine derivatives to quinaldic acids,[6] yielded a product which was identified as 4-phenylacridinic acid (**4**) by conversion to the anhydride and comparison of this derivative with an authentic sample of 4-phenylacridinic anhydride. It follows from these results that the carboxylic acid derived from the Friedländer condensation product by chromic acid oxidation must be 4-phenyl-3-quinaldinecarboxylic acid (**3**) and that the Friedländer condensation product itself must have structure **2**.



3 **4**

Experimental Section[7]

Friedländer Condensation of *o*-Aminobenzophenone with Acetylacetone. A. Method of Borsche and Sinn.[2]—A mixture of 1.97 g (0.010 mole) of *o*-aminobenzophenone and 2.00 g (0.020 mole) of acetylacetone was heated under reflux on a metal bath at 150° for 4 hr. The reaction mixture was then cooled, 100 ml of water was added, and the resultant suspension was stirred until the oil phase solidified.[8] The precipitate was collected, washed with water, and recrystallized from aqueous ethanol to provide 1.82 g (70%) of pale yellow needles melting at 110–113°. Treatment with decolorizing carbon and further recrystallization from aqueous ethanol gave almost colorless needles: mp 113–114°;[9] λ_{max}^{EtOH} 237 mμ (log ε 4.50), 285 (3.78), sh 320 (3.54); λ_{max}^{Nujol} 5.91 μ (C=O), other prominent peaks at 6.41, 8.25, 8.65, 13.1, 13.3, 14.0, 14.2 μ; nmr ($CDCl_3$) singlet τ 8.00 (3 H), singlet 7.30 (3 H), complex multiplets 1.7–2.7 (9 H).

The **picrate**, prepared in the usual way[10], was obtained as silky yellow needles, mp 181–182°, after recrystallization from ethanol.

Anal. Calcd for $C_{24}H_{18}N_4O_8$: C, 58.78; H, 3.70; N, 11.43. Found: C, 58.90; H, 3.86; N, 11.15.

B. Improved Procedure Using Acid Catalysis.—A solution of 1.97 g (0.010 mole) of *o*-aminobenzophenone and 1.00 g (0.010 mole) of acetylacetone in 10 ml of glacial acetic acid containing 0.1 ml of concentrated sulfuric acid was refluxed for 2 hr. The reaction mixture was then cooled and poured slowly into an ice-cold solution of 15 ml of concentrated ammonium hydroxide in 40 ml of water. The resultant suspension was stirred and then allowed to stand in an ice bath until the gummy precipitate had hardened, after which the crude product was collected, washed with water, and recrystallized from aqueous ethanol to give 2.19 g (84%) of almost colorless needles, mp 110–112°. Further recrystallization from aqueous ethanol raised the melting point to 113–114°. No melting-point depression was observed when this product was mixed with the compound prepared by the method of Borsche and Sinn. The infrared spectra of the products obtained by both methods were identical.

Chromic Acid Oxidation of the Friedländer Condensation Product.—A mixture consisting of 1.28 g of the Friedländer condensation product, 2.2 ml of concentrated sulfuric acid, 1.31 g of chromium trioxide, and 10 ml of water was heated on a steam bath until the orange precipitate had completely dissolved and carbon dioxide was no longer being evolved (*ca.* 4 hr). The solution was then cooled, made basic with an excess of ammonium hydroxide, and diluted with water to a total volume of *ca.* 75 ml. The gelatinous precipitate was removed by gravity filtration and washed with water, after which the combined filtrates were evaporated to a small volume (*ca.* 10 ml) on a steam bath. The residue was cooled, acidified with acetic acid, and filtered to provide 0.58 g of almost colorless powder, mp 261–264° dec, after washing with water and drying at 110°. Treatment of this product with decolorizing carbon and recrystallization from ethanol gave colorless crystals of **4-phenyl-3-quinaldinecarboxylic acid** melting at 267–268° dec.

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32; neut equiv, 263. Found: C, 77.02; H, 4.73; N, 5.36; neut equiv, 264.

Decarboxylation of Chromic Acid Oxidation Product.—A slurry of 0.20 g of the above oxidation product and 2 ml of purified mineral oil was heated on a metal bath at 265–275° for 1 hr. The mixture was then cooled and dissolved in several times its own volume of benzene, and the solution was extracted successively with 10-ml portions of 5% sodium hydroxide, water, and 5% hydrochloric acid. The hydrochloric acid extract was made basic by the addition of excess ammonium hydroxide, and the resultant suspension was allowed to stand in an ice bath until the oily precipitate had solidified. The precipitate was then collected, washed with water, and dried to give 0.12 g of pale straw-colored powder, mp 89–96°. Recrystallization from aqueous ethanol provided colorless crystals melting at 98–99°; λ_{max}^{EtOH} 231 mμ (log ε 4.55), 292 (3.88), sh 306 (3.78), sh ~318 (3.61); picrate derivative mp 204–205° dec. This compound showed no melting-point depression when mixed with authentic 4-phenylquinaldine (lit. mp 98–99°,[11] picrate mp 205–206°[12]) and its

(5) The lower-field singlet may be provisionally assigned to the 2-methyl protons (*cf.* the 2-methyl resonances in 2,4-dimethylquinoline, τ 7.30, and 2,6-dimethylquinoline, τ 7.28 [N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution NMR Spectra of Organic Compounds," Varian Associates, Palo Alto, Calif., 1963, Spectra No. 578 and 579]) and the higher-field singlet to the acetyl methyl protons. Although the latter absorption occurs at somewhat higher field than is usually observed for similar protons in simple aryl methyl ketones (*e.g.*, acetophenone, τ 7.41), an upfield shift would be expected in this crowded molecule as a result of steric influences. Inspection of a scale model of 3-acetyl-4-phenylquinaldine shows that the only stable conformations of this molecule are those in which both the acetyl group and the 4-phenyl group lie in planes more or less perpendicular to the plane of the heterocyclic ring. This has the effect of placing the acetyl methyl protons in a region where they are subjected to the shielding influence of the π electrons of both ring systems, and a higher τ value should therefore be observed for these protons than for the corresponding protons in the relatively unhindered acetyl group of a simple aryl methyl ketone. *Cf.* the discussions of steric effects on nmr spectra of aromatic compounds by C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958), and H. A. P. De Jongh and H. Wynberg, *Tetrahedron*, **21**, 515 (1965). *Cf.* also the similar upfield displacement of acetyl methyl absorptions in the nmr spectra of 2-acetylbiphenyl (τ 8.13) and 4,6-dimethyl-2-acetylbiphenyl (τ 8.26) reported by J. Wiemann, N. Ronzani, and J. J. Godfroid, *Compt. Rend.*, **256**, 4677 (1963).

(6) E. A. Fehnel, *J. Org. Chem.*, **33**, 432 (1958).

(7) Microanalyses were performed by Clark Microanalytical Laboratory, Urbana, Ill.

(8) In the original preparation of this compound by Borsche and Sinn,[2] isolation of the crude product was accomplished by extraction of an ether solution of the reaction mixture with dilute acid, followed by precipitation from the aqueous extract with base. The procedure employed here is more convenient and gives approximately the same yield.

(9) Borsche and Sinn[2] described their product as yellow needles, mp 113–115°, after recrystallization from ligroin.

(10) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, John Wiley and Sons, Inc., New York, N. Y., 1964, p 263, method a.

(11) R. Geigy and W. Koenigs, *Ber.*, **18**, 2400 (1885).

(12) W. Koenigs and F. Meimberg, *ibid.*, **28**, 1038 (1895).

infrared spectrum was identical with that of the latter compound (prominent peaks at λ_{max}^{Nujol} 6.27, 6.70, 7.11, 11.2, 12.9, 13.1, 13.5, 14.2 μ).

Oxidation of Chromic Acid Oxidation Product to 4-Phenylacridinic Acid.—A mixture of 1.00 g (3.8 mmoles) of the above chromic acid oxidation product, 0.63 g (5.7 mmoles) of freshly resublimed selenium dioxide, 5 ml of purified dioxane,[13] and 0.3 ml of water was refluxed for 2 hr, after which the hot reaction mixture was filtered to remove the precipitated selenium. The filtrate was diluted with *ca.* 100 ml of water and the resultant suspension was allowed to stand for 30 min. The supernatant liquid was then decanted and the precipitate was collected, washed with water, and dried to give 0.42 g of pale yellow powder, mp 125–135° dec. This product was added to a solution of 1.5 ml of 30% hydrogen peroxide in 15 ml of acetone, and the mixture was refluxed for 1 hr and was then evaporated to a small volume (*ca.* 3 ml) on a steam bath. The residue was diluted with 50 ml of water, and the resultant waxy precipitate was collected, washed with water, and dried. Treatment of this product with acetic anhydride at 120–150° as previously described for the conversion of 4-phenylacridinic acid to 4-phenylacridinic anhydride[14] provided almost colorless crystals, mp 263–265°, after recrystallization from benzene; no melting-point depression was observed when this compound was mixed with an authentic sample of 4-phenylacridinic anhydride (mp 264–266°).

(13) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 285, method a.

(14) E. A. Fehnel, J. A. Deyrup, and M. B. Davidson, *J. Org. Chem.*, **23**, 1996 (1958).

Synthesis and Cyclization Reactions of 3-(2-Hydroxybenzylidene)-2(3H)-coumaranones

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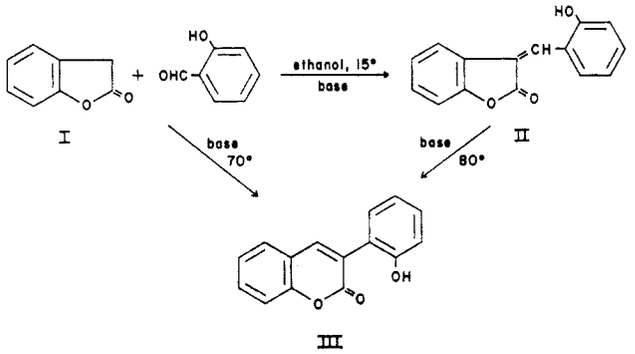
That aromatic aldehydes condense in the presence of an organic base with the α-methylene group of 2,3-dihydrofuran-2-ones is well established.[1] However, in spite of previous attempts[1b,2] the base-catalyzed preparation of 3-(2-hydroxybenzylidene)-2,3-dihydrofuran-2-ones, in which the phenolic hydroxyl remains free, has yet to be documented.

In the present study the effect of temperature on the aldol condensation of the lactone 2(3H)-coumaranone (I) with 2-hydroxybenzaldehydes was investigated. The results revealed that 3-(2-hydroxybenzylidene)-2(3H)-coumaranones (II) are indeed isolated in high yields (Table I) as long as the condensation is carried out below room temperature. The reaction proceeded most favorably in ethanol at 15° with dropwise addition of triethylamine. From the corresponding coumarin isomers the type II compounds, characterized by their superior solubility in ethanol, ultraviolet absorption at longer wavelengths, and higher lactone carbonyl stretching frequency (1750–1765 cm^{-1}),[1d] are readily distinguishable.

Preliminary experiments revealed that an increase in temperature (25–40°) during the condensation of I with 2-hydroxybenzaldehyde diminished the yield of II while giving rise to an additional product, 3-(2-hydroxyphenyl)coumarin[3] (III, Scheme I). At a

SCHEME I



still higher temperature (70°) III represented the sole product. Under these rigorous reaction conditions the primary condensation product II evidently underwent intramolecular cyclization *in situ* to the coumarin isomer. Similar results were recorded during the condensation of the lactone with substituted 2-hydroxybenzaldehydes (Table II). These findings recall the isolation of coumarins from the cyclodehydration of 2-hydroxybenzaldehydes with 5-methyl-2,3-dihydrofuran-2-ones[4] and, similarly, with β-aroylpropionic acids and acylglycines.[5,6]

An unequivocal structure proof in favor of the coumaranone skeleton for the condensation product was advanced by treatment of 3-(2-hydroxy-3,5-dibromobenzylidene)-2(3H)-coumaranone with diazomethane and by subsequent oxidation of the resulting methyl ether with potassium permanganate. The ensuing isolation of 2-hydroxybenzoic acid and 2-methoxy-3,5-dibromobenzoic acid[7] from this reaction mixture can be explained only if a coumaranone, rather than a coumarin, was the original product.

Treatment of II at 80° with an organic base resulted in the expected formation of III in high yields. That these coumaranones also underwent thermocyclization to coumarins at temperatures near their melting point was indicated by decolorization and resolidification of the melt of several type II compounds (see footnotes in Table I).[8] The phenolic coumarins were likewise formed upon irradiation of an ethanolic solution of the corresponding coumaranones with a tungsten lamp. These light-catalyzed cyclizations were accompanied by a hypsochromic shift of the absorption maxima in the ultraviolet region, and the final curve for each compunod was superimposable with the ul-

(1) (a) J. Thiele, R. Tischbein, and E. Lossow, *Ann.*, **319**, 180 (1910); (b) W. F. von Oettingen, *J. Am. Chem. Soc.*, **52**, 2024 (1930); (c) E. Erlenmeyer and E. Braun, *Ann.*, **333**, 254 (1904); (d) R. Walter and H. Zimmer, *J. Heterocyclic Chem.*, **1**, 205 (1964).

(2) E. Baltazzi and E. A. Davis, *Chem. Ind.* (London), 1653 (1962).

(3) See the reference in Table II.

(4) D. H. Marrian and P. B. Russel, *J. Chem. Soc.*, 753 (1946).

(5) Y. S. Rao, *Chem. Rev.*, **64**, 353 (1964).

(6) E. Baltazzi, *Quart. Rev.* (London), **9**, 150 (1955).

(7) N. W. Hiwe and B. V. Patil, *Proc. Indian Acad. Sci.*, **5A**, 321 (1937).

(8) The infrared spectra from melts of coumaranones revealed the presence of the corresponding coumarins.