Formation of 4-Phenacylideneflavene from 4-Phenacylflavene

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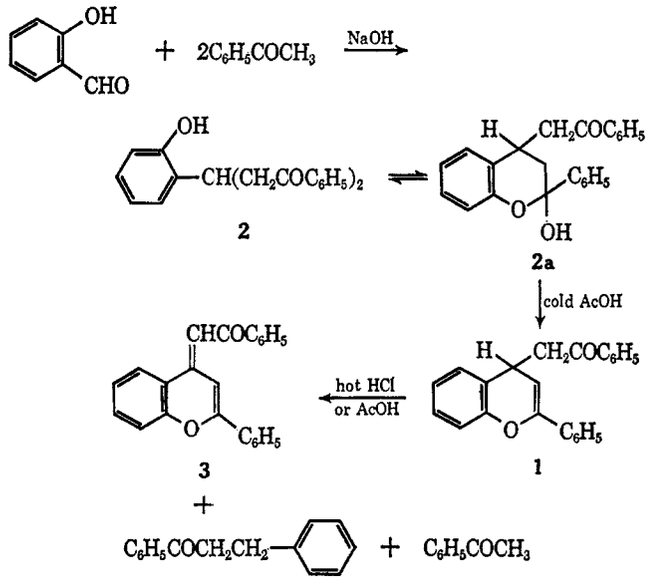
The conversion of 4-phenacylflavene to 4-phenacylideneflavene by means of acetic acid has been examined. It is postulated that flavylium acetate is an intermediate and acts as a hydride transfer agent. Nmr spectra are given for 4H-flavene (**4**), flavane (**7**), and 2-ethoxy-3-flavene (**9**). These spectra are consonant with the proposed structures.

In the course of preparing some flavylium salts, we had occasion to repeat the work of Hill[1] in which the preparation of 4-phenacylideneflavene was described. Our results and consequently our interpretation of the reaction differ from those reported by Hill.[1]

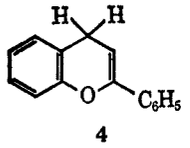
The reaction path proposed by Hill for the conversion of 4-phenacylflavene (**1**) to 4-phenacylideneflavene (**3**) is illustrated in Scheme I.

SCHEME I



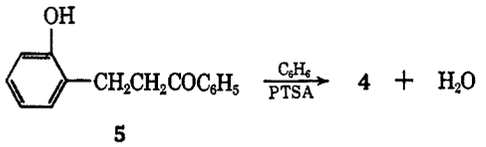
Hill definitely established that **1** was formed as an intermediate during the transformation of **2** (or **2a**)[2] to **3**, which disproved the mechanism of Feuerstein and Kostanecki.[3] These authors postulated that **2** reverted to 2-hydroxychalcone and acetophenone, and the chalcone dehydrogenated some of the unchanged **1** to give **3** and 2-hydroxydihydrochalcone. Hill also claimed to have isolated the dihydrochalcone and acetophenone from the reaction mixture, but he did not propose a mechanism whereby **1** could give these three products.

We have found that the refluxing of **1** in acetic acid yielded 43–46% **3**. Fractionation of the mother liquors gave acetophenone and a compound melting at 54°, which elemental analysis and nmr and infrared spectroscopy have shown to be the flavene **4**. No dihydrochalcone was isolated. It is probable that the dihydrochalcone obtained by Hill was formed by the hydrolysis of **4**, since he removed the acetophenone from the reaction mixture by steam distillation and then made the residue basic.



4

In order to establish firmly the identity of **4**, which has not been previously described, the chromene was prepared by an unambiguous method. For this purpose, the dihydrochalcone **5** was refluxed in benzene solution with a trace of *p*-toluenesulfonic acid and the water that was formed was separated by means of a Dean–Stark trap. The product obtained was identical



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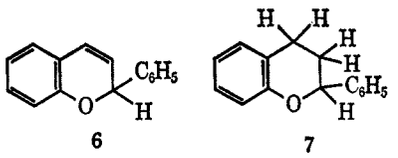
with the chromene isolated from the reaction of **1** with acetic acid. Incidentally, the compound, which was obtained by the lithium aluminum hydride reduction of flavylium perchlorate[4a] and was assigned structure **6**,[4b] has been shown by nmr spectroscopy to be the tautomer **4**. Another attempt to prepare **4** by fusion of **5** with zinc chloride gave the known flavane (**7**).[5] It is possible that the formation of **7** was a result of a disproportionation reaction. Compound **7** was conveniently prepared by cyclization of 2-(2-hydroxyphenyl)ethylphenylcarbinol with *p*-toluenesulfonic acid in refluxing benzene.



6 **7**

The determination of the structure of the by-product which was formed during the conversion of **1** to **3** leads us to propose Scheme II for the reaction. It is postulated that flavylium acetate (**8**) is an intermediate and acts as a hydride transfer agent which reacts with **1** to give **3** and **4**. This mechanism accounts for the reaction products and the fact that the yield of **3** never exceeds 50%.

As supplementary evidence, we have allowed equivalent amounts of **1** and the ether **9** to react in acetic

(1) D. W. Hill, *J. Chem. Soc.*, 1255 (1934).

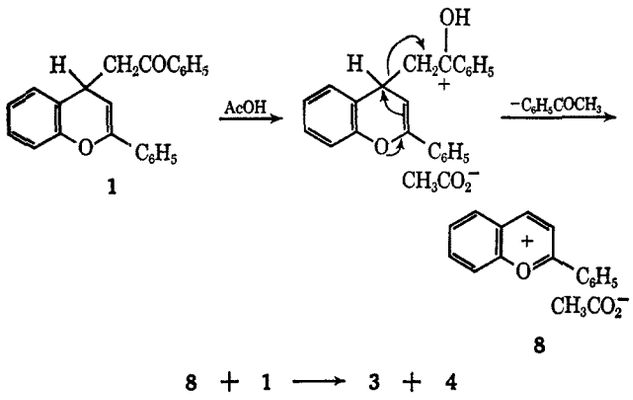
(2) Hill suggested the structure **2a** on the basis of its insolubility in alkali, but the nmr spectrum indicates that **2** is the correct structure. Details are given in the Experimental Section.

(3) W. Feuerstein and St. Kostanecki, *Ber.*, **31**, 710 (1898).

(4) (a) K. Freudenberg and K. Weinges, *Ann.*, **590**, 140 (1954). (b) NOTE ADDED IN PROOF.—K. G. Marathe, E. M. Philibin, and T. S. Wheeler [*Chem. Ind.* (London), 1793 (1962)] have shown the correct structure to be **4**.

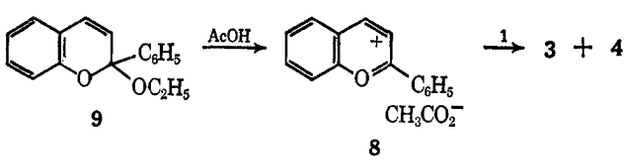
(5) W. Borsche and A. Geyer, *Ber.*, **47**, 1160 (1914).

SCHEME II



8 + 1 ⟶ 3 + 4

acid solution whereby **1** was converted in 94% yield to **3** and the by-product **4** was isolated from the reaction mixture. The structure of the ether, which was prepared from flavylium perchlorate and sodium hydroxide in aqueous ethanol, was shown to be **9** and not the 4-ethoxy isomer, as was reported in the literature.[6] The



ultraviolet spectrum of an acetic acid solution of the ether **9** was identical with the spectrum of flavylium perchlorate, which demonstrates the conversion of **9** to **8** by acetic acid.

Experimental Section[7]

4-Phenacylflavene (1).—Compound **1** (mp 95–96°) from petroleum ether (bp 30–60°) was prepared by the procedure of Hill.[1]

Treatment of 4-Phenacylflavene with Boiling Acetic Acid.—A mixture of 30 g of **2** and 200 ml of acetic acid was refluxed for 1 hr and then evaporated to dryness under reduced pressure. The residue was dissolved in boiling ethanol and, on chilling, 14.4 g of **3** (mp 127–128°) separated from solution. The alcohol filtrate was evaporated to dryness, the residue was extracted with benzene, and the benzene was distilled from the extract. The remaining oil was distilled *in vacuo* to give 4.6 g of acetophenone [bp 75° (10 mm)] and 8.8 g of 4H-flavene (**4**), which solidified on cooling and, after recrystallization from methanol, melted at 55°.

Anal. Calcd for $C_{15}H_{12}O$: C, 86.6; H, 5.8. Found: C, 86.5; H, 5.7.

The nmr spectra of **4** (in deuteriochloroform)[7] showed a doublet centered at δ 3.55 (J = 4 cps, two protons), a triplet centered at 5.68 (J = 4 cps, one proton), and a multiplet centered at 7.6 (nine aromatic protons). The mass spectrum of **4** showed a parent peak at m/e 208.

4H-Flavene (4).—A mixture of 10 g of 3-(2-hydroxyphenyl)-1-phenylpropanone-1 (**5**), 0.5 g of *p*-toluenesulfonic acid, and 100 ml of benzene was refluxed, and the water that separated was removed by means of a Dean–Stark water separator. The benzene solution was neutralized with aqueous sodium bicarbonate, the benzene phase was dried, and the solvent was removed. The residue solidified and after recrystallization, the product (7.2 g) melted at 54–55°. The flavene prepared by this procedure showed infrared and nmr spectra which were identical with those of **4** isolated from the reaction of **1** with acetic acid.

Flavane (7).—A mixture of 4 g of **5** and 8 g of zinc chloride was heated under vacuum, and the liquid that distilled at 185° (11 mm) was collected. The distillate which solidified was recrystallized from ligroin (bp 60–90°) to give 1.2 g of **7**, mp 42–43° (lit.[5] mp 44°). Nmr spectra (in deuterated acetone) showed a double doublet for the 2 H centered at δ 4.8 (J_1 = 9 cps, J_2 = 3 cps), a multiplet centered at 2.7 for the two 4 H atoms, a multiplet centered at 2.0 for the two 3 H atoms, and nine aromatic protons.

A superior procedure for the preparation of **7** consisted in refluxing a solution of 5 g of 2-(2-hydroxyphenyl)ethylphenylcarbinol[8] and 0.5 g of *p*-toluenesulfonic acid in 50 ml of benzene. The water that was formed was removed as an azeotrope. After cooling, the reaction mixture was neutralized with aqueous sodium bicarbonate, the benzene phase was dried, and the solvent was removed to yield 4 g of **7**, 42–43° (from ligroin, bp 60–90°).

2-Ethoxyflavene-3 (9).—This compound was prepared by the procedure of Hill[6] and melted at 76–77° (lit. mp 76°). The nmr spectra (in deuteriochloroform) showed a doublet for the 4 H at δ 6.54 (J = 9 cps one proton), a doublet for the 3 H at 5.68 (J = 9 cps, one proton), ten lines (of the possible 16 lines for the methylene group which is attached through oxygen to an asymmetric center) at 3.5 (two protons), a triplet at 1.1 for the methyl group (three protons), and nine aromatic protons. The ultraviolet spectrum in acetonitrile showed peaks at 248 mμ (ϵ 10 × 10^3), 257 (11.2 × 10^3), 266 (10 × 10^3), and 296 (4.1 × 10^3). The spectrum in acetic acid solution showed peaks at 258 mμ (ϵ 12 × 10^3) and 393 mμ (ϵ 28.3 × 10^3).

Compound 3 from 1 and 9.—A mixture of 1.4 g of **9** and 1.8 g of **1** in 7 ml of acetic acid was heated on the steam bath for 1 hr and then allowed to stand overnight. The solid was collected and crystallized from ethanol to give 1.2 g of **3**, mp 126–127°.

Nuclear Magnetic Analysis of 2.—The nmr spectrum of **2** in deuteriochloroform solution exhibits an 11 H multiplet from δ 6.7 to 7.6 and the characteristic 4 H multiplet standing separately at 7.9–8.2 for the orthohydrogens of the benzoyl moieties. A 1 H skewed pentuplet centered at δ 4.32, and a 4 H skewed doublet at 3.55 and 3.45, in which the high-field line is slightly split into a further doublet, together comprise the $(AB)_2M$ spectrum of the $CH(CH_2-)_2$ moiety. In deuteriochloroform solution δ_{AB} is nearly 0 and the very weak lines of the AB portion were not discernible. In benzene-d_6 solution, the pentuplet is centered at δ 4.51, and the $(AB)_2$ portion appears as a quadruplet of lines at 3.39, 3.35, 3.28, and 3.23. Again, because of limited solubility, the weak AB lines were not discernible above the background noise. A sharp singlet for the phenolic OH appears in benzene-d_6 at δ 8.27.

These spectra are exactly analogous to those for 1,3,5-triphenylpentane-1,5-dione which has no phenolic hydroxyl group and cannot form the fused heterocyclic ring. In deuteriochloroform the 4 H multiplet for the *ortho* protons of the benzoyl moiety falls at δ 7.8–8.1, the 11 H multiplet for the remaining aromatic protons being at 6.9–7.6. The methine hydrogen pentuplet is centered at 4.10 and the AB portion appears as a singlet at 3.47 and a doublet at 3.35 and 3.32. In benzene-d_6 solution the methine pentuplet falls at δ 4.25; the four strong lines of the AB portion fall at 3.28, 3.23, 3.17, and 3.10; the weak AB lines are visible, giving J_{AB} = 16.8 ± 0.3 cps averaged from the four equivalent peak separations.

The nonequivalence of the methylene protons arises from the lack of a symmetry plane along the methylene C-methine C bond; from the viewpoint of the methylene hydrogens the adjacent carbon is asymmetrically substituted even though the molecule as a whole has a symmetry plane.[9]

The Mass Spectrometric Analysis of 2.—This compound is thermally unstable in the heated inlet system of the mass spectrometer. One of the decomposition products gives a molecular ion at m/e 326 and a fragment ion at m/e 207 which is the mass of the flavylium ion. This fragmentation is supported by a metastable peak, and supports structure **1**.

The other thermal product detected from the mass spectrum gives a molecular ion at m/e 324. This corresponds to the phenacylidene derivative **3**. Both assignments have been confirmed by comparison with authentic samples.

The mass spectrum of 1,3,5-triphenylpentane-1,5-dione contains a molecular ion at m/e 328 and is thermally stable in the heated inlet.

(6) D. Hill and R. R. Melhuish, *J. Chem. Soc.*, 1161 (1935).

(7) Nmr spectra were measured at 60 Mc on a Varian A-60 spectrometer with tetramethylsilane as an internal standard.

(8) C. Harries and G. Basse, *Ber.*, **29**, 379 (1896).

(9) W. F. Reynolds and T. Schaeffer, *Can. J. Chem.*, **42**, 2119 (1964).

Registry No.—1, 10353-08-9; 2, 4728-00-1; 3, 10385-47-4; 4, 494-13-3; 7, 494-12-2; 9, 10353-10-3; acetophenone, 98-86-2.

Acknowledgments.—We are indebted to D. P. Maier and G. P. Happ, of these laboratories, for the mass spectrometric analysis and its interpretation.

The Reaction of Anthranil with N-Phenylmaleimide[1]

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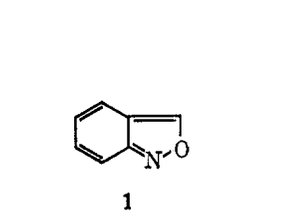
The reaction of anthranil with N-phenylmaleimide without solvent at 125° gives a low-melting (190°) adduct, while reaction in hot xylene solution gives a higher melting (231°) adduct. These products, previously claimed to be the *endo* and *exo* Diels–Alder adducts, have been shown to be the *exo* isomer (**3**) and (2-formylanilino)-N′-phenylmaleimide (**5**), respectively. Compound **3** is readily converted into **5** in hot xylene in 30 min, and into N-phenylacridinimide (**6**) in 20 hr; compounds **3** and **5** are also readily converted into **6** in ethanol solution containing a small amount of piperidine, or in dioxane containing hydrogen chloride.

In the course of our investigations of anthranil chemistry we had occasion to repeat a reaction described by Nenitzescu, *et al.*,[3] in which anthranil (**1**) was treated under Diels–Alder-type conditions with N-phenylmaleimide. These workers had reported that the products of this reaction were the *endo* adduct (**2**), mp 190°, and the *exo* adduct (**3**), mp 283°. Evidence cited in support of these structural assignments consisted of melting points,[4] microanalyses, and the conversion of these adducts to acridinic acid (**4**) upon treatment with base.



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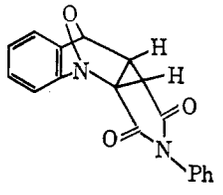

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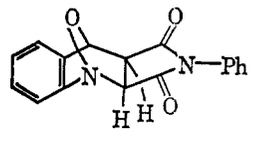

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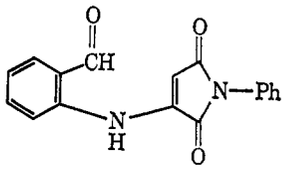

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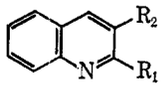

4, $R_1 = R_2 = COOH$
6, $R_1 = R_2 = CON(Ph)CO$
7, $R_1 = CONC_5H_{10}$; $R_2 = CONHPh$
8, $R_1 = COOH$; $R_2 = CONHPh$
9, $R_1 = H$; $R_2 = CONHPh$

Our results differ from those reported. The lower melting (190°) isomer we have shown to be the *exo*, not the *endo* adduct, while a higher melting (231°) product we have shown to be (2-formylanilino)-N′-phenylmaleimide (**5**). No product melting at 283° (described previously as the *exo* isomer) could be prepared in almost a score of attempts to repeat the given experimental conditions.[5] Our lower melting isomer (**3**) was readily converted to the aldehyde (**5**) in refluxing xylene in 30 min.[6] When the time of heating was extended to 20 hr, the product was N-phenylacridinimide (**6**), mp 322–323°; the same product was obtained directly when N-phenylmaleimide and anthranil were heated under these latter conditions.

The new structural assignments for the lower melting isomer (**3**) and the higher melting isomer (**5**) derive unequivocally from their nmr spectra. Thus, the spectrum of (**3**) exhibits a signal at δ 6.03, assigned to the H_4 proton, which is strongly shielded both by the aromatic ring and by the bridgehead oxygen. Two signals at δ 3.37 and 4.00, integrating to one proton each, are ascribed to the H_3 and H_2 protons, respectively, which are deshielded by the adjacent carbonyl groups of the imide function. The essential absence of spin–spin coupling between the H_3 and H_4 protons is in accord with the *exo* structure (**3**) rather than the *endo* structure (**2**). Examination of Drieding models indicates that the dihedral angle between the H_3 and H_4 protons is approximately 80° in the *exo* isomer (**3**) and near 25–30° for the *endo* isomer (**2**). The predicted vicinal coupling constants for these dihedral angles would be 0.0–0.3 cps for (**3**) (in good agreement with the experimentally observed value of approximately zero) and 5.3–7.0 cps for (**2**).[7] The spectrum of the ring-opened aldehyde (**5**) exhibits an aldehydic proton at δ 10.10 and a single vinyl proton at 5.88. Chemical substantiation of the structure of (**5**) consisted in its conversion to a 2,4-dinitrophenylhydrazone and the observation that it gave a positive Tollen's test.

Both the *exo* isomer (**3**) and the aldehyde (**5**) were readily converted in basic or acidic media to derivatives of acridinic acid.[8] Thus, when **3** or **5** was heated with

(1) This work was supported in part by a grant (CA-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service, which is gratefully acknowledged.

(2) National Institutes of Health Predoctoral Fellow, 1962–1965.

(3) C. D. Nenitzescu, E. Cioranescu, and L. Birladeanu, *Commun. Acad. Rep. Populare Romine*, **8**, 775 (1958).

(4) Without structural evidence, Nenitzescu, *et al.*,[3] apparently assumed that their low-melting (190°) product from the addition of N-phenylmaleimide to anthranil was the *endo* isomer because differences in thermodynamic stability dictate a higher melting point for the *exo* isomer. For a discussion of factors influencing *endo vs. exo* addition, see J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).

(5) The existence of Nenitzescu's higher melting isomer may have its origin in an error in transcription of an observed melting point of 238°.

(6) Nenitzescu, *et al.*,[3] reported the conversion of their lower melting isomer to their higher melting isomer under identical conditions.

(7) It must be noted that these predicted values for vicinal coupling constants of dihedral angles are only "zero order" approximations [M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963)] and that their magnitudes vary significantly with changes in the electronegativity of adjacent substituents [P. Laszlo and P. von R. Schleyer, *ibid.*, **85**, 2709 (1963)].

(8) As mentioned above, Nenitzescu, *et al.*,[3] reported that both their "*endo*" and "*exo*" isomers could be converted in potassium hydroxide solution to acridinic acid itself (**4**).