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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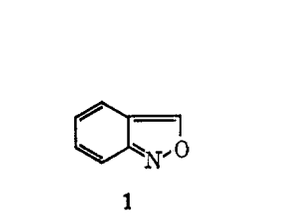
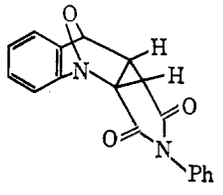
The reaction of anthranil with N-phenylmaleimide without solvent at 125° gives a low-melting (190°) adduct, while reaction in hot xylene solution gives a higher melting (231°) adduct. These products, previously claimed to be the *endo* and *exo* Diels–Alder adducts, have been shown to be the *exo* isomer (**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.



1



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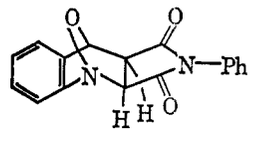

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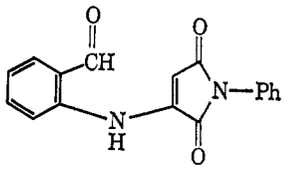
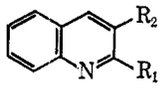


5



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°.

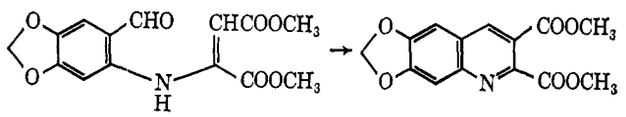
(6) Nenitzescu, *et al.*,[3] reported the conversion of their lower melting isomer to their higher melting isomer under identical conditions.

(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**).

a catalytic amount of piperidine in ethanol, dehydration resulted with the formation of N-phenylacridinimide (**6**). Treatment of either **3**, **5**, or **6** with an excess of piperidine gave the diamide (**7**). Mild basic hydrolysis of **7**, **6**, **5**, or **3** yielded the 3-anilide of acridinic acid (**8**). The position of the anilide grouping in this latter compound was established by thermal decarboxylation to the known quinoline-3-carboxanilide (**9**).

Similar conversions could be carried out in acidic solution. Thus, both the *exo* isomer (**3**) and the aldehyde (**5**) could be converted to **6** by heating in dioxane containing hydrochloric acid. This acid-catalyzed dehydration resembles the conversion of **10** to **11** reported by Hendrickson, *et al.*,[9] which was carried out under similar conditions.



10 11

Experimental Section[10]

***exo*-(1,4-Epoxy-1,2,3,4-tetrahydroquinoline)-2,3-dicarboxylic Acid N-Phenylimide (3).**—A mixture of 2.38 g of anthranil[11] and 3.46 g of N-phenylmaleimide was heated for 1 hr in an oil bath maintained at 125–130°. The mixture was cooled to room temperature and extracted with anhydrous ether, and the remaining solid material was recrystallized from a mixture of dimethylformamide and anhydrous ethanol to give 1.0 g (17%) of the *exo* isomer: mp 190°; λ_{max}^{EtOH} 230, 267, 273, 388 mμ (ε 29,000, 10,000, 11,000, and 8000); ν_{max} (Nujol) 3055, 1790, 1720, 1500, 1400, 1200, 850, 745 cm^{-1}.

Anal. Calcd for $C_{17}H_{12}N_2O_5$: C, 69.85; H, 4.14; N, 9.59. Found: C, 69.53; H, 4.14; N, 9.47.

(2-Formylanilino)-N′-phenylmaleimide (5).—A solution of 2.38 g of anthranil and 3.46 g of N-phenylmaleimide in 10 ml of dry xylene was refluxed for 1 hr and cooled, and the yellow crystals which separated were collected by filtration to give 4.6 g (79%): mp 231°; λ_{max}^{EtOH} 203, 207, 240, 258 mμ (ε 33,780, 34,190, 36,560 and 20,430); ν_{max} (Nujol) 3440, 2750, 1760, 1710, 1665, 1640, 1600, 1400 cm^{-1}.

Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.85; H, 4.14; N, 9.59. Found: C, 69.75; H, 4.20; N, 9.55.

This compound could be formed from the *exo* adduct (**3**, 1.8 g) by refluxing for 30 min in 20 ml of dry xylene, cooling, and recrystallizing the product from a mixture of dimethylformamide and anhydrous ethanol, yielding 0.8 g of yellow needles, mp 231°. This compound was identical in all respects with the product obtained from anthranil and N-phenylmaleimide as described above.

The 2,4-dinitrophenylhydrazone of **5** was prepared in hot dioxane, mp 279°.

Anal. Calcd for $C_{23}H_{16}N_6O_6$: C, 58.47; H, 3.41; N, 17.79. Found: C, 58.75; H, 3.58; N, 17.68.

N-Phenylacridinimide (6).—A solution of 0.5 g of (2-formylanilino)-N′-phenylmaleimide (**5**) in 20 ml of anhydrous ethanol containing 3 drops of piperidine was heated under reflux for 5 min. The initially deep yellow solution became colorless and a white solid separated from the refluxing solution. Cooling and filtering gave 0.25 g (50%) of white crystals: mp 322–323° (lit.[12] mp 319–320°); λ_{max}^{EtOH} 221, 261 mμ (ε 10,600, 17,900).

Anal. Calcd for $C_{17}H_{10}N_2O_2$: C, 74.44; H, 3.68; N, 10.21. Found: C, 74.15; H, 3.82; N, 10.16.

The same compound was obtained when the *exo* isomer (**3**) was treated under the same conditions.

Quinoline-2-carboxypiperidide-3-carboxanilide (7).—A solution of 0.4 g of (2-formylanilino)-N′-phenylmaleimide (**5**), 20 ml of ethanol, and 1 ml of piperidine was heated under reflux for 5 min and cooled. The crystalline product which was collected by filtration was recrystallized from aqueous ethanol to give 0.3 g (61%): mp 171–172°; λ_{max}^{EtOH} 238, 312, 326 mμ (ε 46,470, 6840, 4980).

Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.51; H, 5.89; N, 11.69. Found: C, 73.29; H, 6.09; N, 11.69.

This compound was obtained in 95% yield upon heating 2.0 g of N-phenylacridinimide for 15 min in a solution containing 20 ml of ethanol and 1 ml of piperidine.

Quinoline-3-carboxanilide-2-carboxylic Acid (8).—A solution of 0.2 g of (2-formylanilino)-N′-phenylmaleimide in 10 ml of 10% potassium hydroxide in methanol was heated under reflux for 2 min, cooled, diluted with 20 ml of water, and acidified with dilute hydrochloric acid. The yellow crystals which separated were collected by filtration and recrystallized from aqueous methanol to give 0.15 g (68%): mp 212° (the yellow crystals turned white at 170°); λ_{max}^{EtOH} 338 mμ (ε 46,430).

Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.85; H, 4.14; N, 9.59. Found: C, 69.88; H, 4.10; N, 9.45.

Compound **8** was similarly obtained by alkaline hydrolysis of **3** or **7**.

Quinoline-3-carboxanilide (9).—One gram of quinoline-3-carboxanilide-2-carboxylic acid was heated in an oil bath for 2 hr. at 130–140°, and the resulting solid was recrystallized from aqueous ethanol to give 0.5 g (59%) of white crystals, mp 212° (lit.[12] mp 212°).

Registry No.—**1**, 271-58-9; N-phenylmaleimide, 941-69-5; **3**, 10351-58-3; **5**, 10351-59-4; 2,4-dinitrophenylhydrazone of **5**, 10351-60-7; **6**, 10351-61-8; **7**, 10351-62-9; **8**, 10351-63-0; **9**, 10414-79-6.

(9) J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Am. Chem. Soc.*, **86**, 107 (1964).

(10) All melting points are uncorrected. We are indebted for the microanalyses to Dr. George Robertson, Florham Park, N. J.

(11) P. Friedländer and R. Henriques, *Ber.*, **15**, 2105 (1882).

(12) L. Hozer and St. v. Niementowski, *J. Prakt. Chem.*, **116**, 43 (1927).