The study of the spectroscopic properties of the olefins 2 shows that a good correlation exists between the chemical shift δ $^{13}C_\beta$ in NMR spectroscopy (Table III) and the Hammett constants σ (Y): δ $^{13}C_\beta = 107.18 + 0.436\sigma$ (Y) for the Z olefins ($|\delta_{calcd} - \delta_{obsd}| \leq 0.08$ ppm); δ $^{13}C_\beta = 108.08 + 0.436\sigma$ (Y) for the E olefins ($|\delta_{calcd} - \delta_{obsd}| \leq 0.15$ ppm). It is well known that in unsaturated systems, the contribution of the π electron density is an important component in the ^{13}C chemical shift, especially for analogous ring-substituted phenyl vinyl ethers.[7] Therefore the chemical shift of C_β seems to be a good criterion to evaluate the availability of the oxygen nonbonding electrons toward the benzene ring, whatever be the series.

In Figure 1, the percent of anti addition found when adding chlorine, bromine, and iodine monochloride is reported against the chemical shift of C_β. A rough linear relationship is found for chlorine: it appears that the same phenomenon occurs with the alcohol ether or the phenol ether, the six points falling on the same empirically derived straight line.

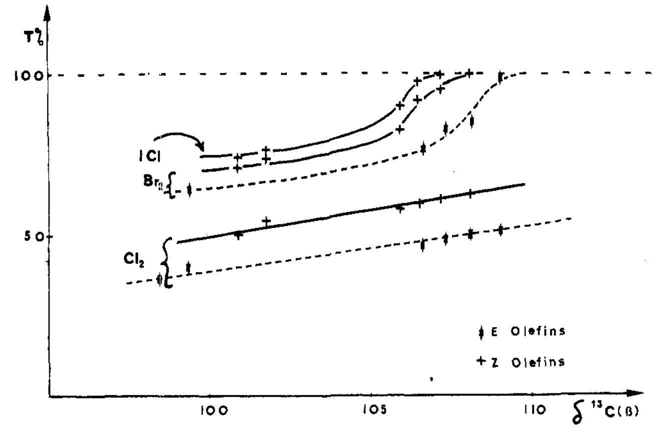

Figure 1. Correlation between the selectivity of electrophilic anti addition and the availability of π electron on C_β (evaluated by means of its chemical shift, see Hammett correlation in text).

When adding bromine or iodine monochloride, different curves tending towards the asymptotic value of 100% anti addition for electron-withdrawing groups are observed. In these cases, there is a stabilization of A due to the electrophilic reagent and a destabilization of B due to the electron-withdrawing groups. Since the concentration of B (at equilibrium) is an exponential function of $-\Delta G/RT$, its contribution to the reaction becomes negligible. In fact, the equilibrium conditions are not attained, as the Z and E isomeric enol ethers do not give the same erythro:threo ratio.

In conclusion, the electrophilic addition simultaneously involves the two intermediate species A and B, the bridged halonium ion and the classical carbonium ion.

Registry No.—(Z)-**1a**, 4696-25-7; (E)-**1a**, 4696-26-8; (Z)-**1b**, 32426-80-5; (E)-**1b**, 32426-79-2; (Z)-**2c**, 51896-37-8; (E)-**2c**, 51896-38-9; (Z)-**2d**, 51896-41-4; (E)-**2d**, 51896-42-5; (Z)-**2e**, 4696-23-5; (E)-**2e**, 4696-24-6; (Z)-**2f**, 51896-45-8; (E)-**2f**, 54912-31-1; Cl_2, 7782-50-5; Br_2, 7726-95-6; ClI, 7790-99-0.

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1-Phenylpiperidine-2,4,6-trione

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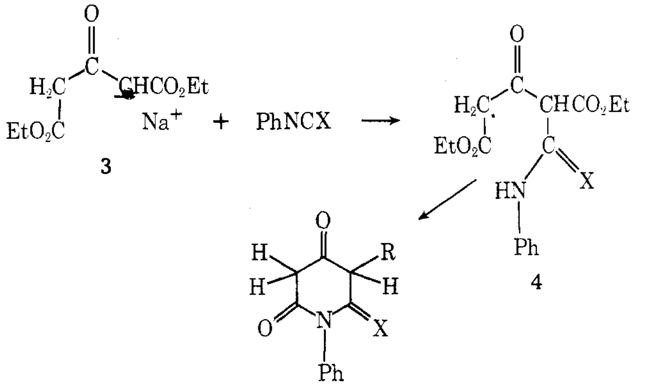
The synthesis of the title compound has been the subject of several papers that have appeared in the chemical literature. The compound identified by Kaushal[1] as **5c** was subsequently shown[2] to be an adduct of aniline and zinc chloride. Later, Nakhre and Deshapande[3] reported that **5c** may be obtained by the reaction of 3-oxoglutaric anhydride with aniline in anhydrous ether. Repetition of this reaction yielded the anilic acid **1**, which readily lost carbon dioxide upon heating, with the formation of acetoacetanilide (**2**).

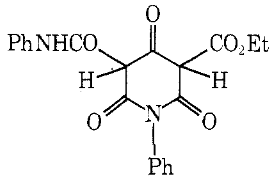
$$\underset{\textbf{1}}{PhNHCOCH_2COCH_2CO_2H} \xrightarrow{-CO_2} \underset{\textbf{2}}{PhNHCOCH_2COCH_3}$$

More recently, Junek, Metallidis, and Ziegler[4] described the reaction of the sodium salt of diethyl 3-oxoglutarate (**3**) with phenyl isothiocyanate[5] to give the ester **5a** via the intermediate formation of **4**.



5a, R = CO_2Et; X = S
b, R = CO_2Et; X = O
c, R = H; X = O

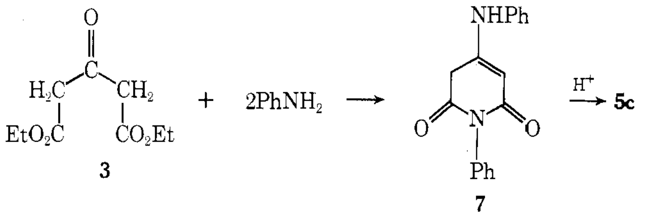
When the reaction was conducted using phenyl isocyanate, it was reported[4] that the product was not the expected ester **5b**, but **5c**, in which an ethoxycarbonyl group had been lost. We have re-examined this reaction, but have been unable to find any trace of **5c** among the products. The ester **5b** was obtained, accompanied by a small amount of a compound formed by reaction of **5b** with a second molecule of phenyl isocyanate, for which **6** is a probable structure.

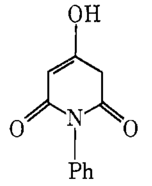


6

Finally, we have been able to synthesize the required trione **5c** by acidic hydrolysis of **7**, which is obtained by reaction of diethyl 3-oxoglutarate with aniline.[6]

The NMR spectrum of **5c** in DMSO-d_6 indicates three types of exchangeable protons, with singlets at δ 3.65 (2 H), 5.42 (1 H), and 17.1 (1 H, broad). Such a spectrum is consistent only with one of the two possible monoenol tautomers, **8** or **9**.





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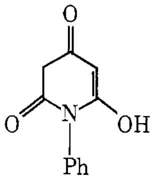

9

Experimental Section

3-Oxoglutaranilic Acid (1). A solution of 1.88 g (0.02 mol) of aniline in 20 ml of anhydrous ether was added at a slow drop rate to a stirred suspension of 2.56 g (0.02 mol) of 3-oxoglutaric anhydride in 20 ml of the same solvent. After the addition was complete, the mixture was stirred for a further 2 hr. The resulting solid was collected and washed with anhydrous ether to give 3.80 g (86%) of a white powder: mp 105–106°; ir (KBr) 3300, 1730, and 1660 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.7; H, 5.0; N, 6.4. Found: C, 59.9; H, 5.0; N, 6.5.

Decarboxylation of 1. Compound 1 (0.5 g, 0.0023 mol) was heated at 120° for 5 min, as CO_2 was evolved. On cooling, the reaction mixture solidified to give 0.40 g (100%) of 2: mp (benzene) 84–85°, undepressed on admixture with an authentic sample; ir (KBr) identical with that of an authentic sample.

Reaction of Phenyl Isocyanate with 3. Sodium (2.3 g, 0.1 mol) was added to a solution of 20.2 g (0.1 mol) of diethyl 3-oxoglutarate in 120 ml of anhydrous ether and the mixture was warmed gently until all the sodium had dissolved. The resulting solution was stirred at 0–5° as 11.9 g (0.1 mol) of phenyl isocyanate was added dropwise. The suspension thus obtained was heated at reflux temperature on a steam bath for 2 hr. After cooling, 500 ml of water was added and the mixture was stirred until all the solid had dissolved. The aqueous layer was separated and acidified with 5 *N* HCl, and the precipitated solid was collected and washed with water. Extraction of the solid with 300 ml of benzene, followed by evaporation of the solvent, yielded 0.75 g of 6. An analytical sample, obtained by recrystallization from ethanol, decomposed on heating, with no clearly defined melting point: mass spectrum *m/e* (rel intensity) 394 (29), 348 (27), 322 (4), 302 (11), 256 (38), 174 (5), 120 (12), 119 (5), 93 (100), 77 (8).

Anal. Calcd for $C_{21}H_{18}N_2O_6$: C, 64.0; H, 4.6; N, 7.1. Found: C, 63.7; H, 4.5; N, 6.8.

The undissolved material was again washed with benzene to give crude 5b, 10.8 g (39%): mp (EtOH) 198–200°, undepressed by admixture with an authentic sample;[7] ir (KBr) identical with that of an authentic sample.

4-Anilino-1-phenyl-2,6(1*H*,3*H*)-pyridinedione (7). This compound was prepared by the following modification of the method described by Emery.[6] A mixture of 40.1 g (0.2 mol) of diethyl 3-oxoglutarate and 37.2 g (0.4 mol) of aniline was heated at 120° for 4 hr in an open flask. After it had cooled, a vacuum distillation apparatus was attached and a pressure of about 50 mm was maintained as the bath temperature was raised to 180° over a 30-min period. The reaction was completed by heating for a further 1.5 hr at 180° under reduced pressure. After cooling, the reaction mixture was warmed with 100 ml of ethanol to obtain a suspension of yellow solid, which was filtered from the hot mixture. The solid was dissolved in a solution of 16 g of sodium hydroxide in 400 ml of 50% methanol. After filtration, the solution was acidified with acetic acid to obtain 6.7 g (12%) of 7: mp (DMF–methanol) 281–283° dec (lit.[6] mp 275° dec); NMR (DMSO-d_6) δ 9.20 (s, 1), 7.0–7.6 (m, 10), 5.45 (s, 1), 3.81 (s, 2).

1-Phenylpiperidine-2,4,6-trione (5c). Compound 7 (5 g, 0.018 mol) was added to a boiling mixture of 50 ml of 50% acetic acid and 5 ml of concentrated HCl. The mixture was heated at reflux temperature for 5 min and a small amount of undissolved solid was removed by filtration of the hot mixture. The filtrate was evaporated to dryness under reduced pressure, the residue was dissolved in 35 ml of water, and the solution was made basic by dropwise addition of 40% KOH. After extraction with ether (2 × 10 ml), the aqueous solution was acidified with acetic acid and the small amount of precipitated solid was removed by filtration. The solution was acidified to pH 3–4 with concentrated HCl and chilled, and the precipitated solid was collected. The yield of crude 5c was 2.0 g (55%): mp (CH_3CN) 183–184° dec; ir (KBr) 3110 (broad), 1711, 1670, 1640, 1370, 1255, 1208, 841, and 700 cm^{-1}; NMR (DMSO-d_6) δ 17.1 (broad s, 1), 7.0–7.6 (m, 5), 5.42 (s, 1), 3.65 (s, 2); mass spectrum *m/e* (rel intensity) 203 (55), 175 (18), 119 (100), 93 (38), 91 (37), 84 (55), 77 (9), 64 (19), 63 (10), 51 (11), 42 (21), 39 (12).

Anal. Calcd for $C_{11}H_9NO_3$: C, 65.0; H, 4.5; N, 6.9. Found: C, 64.6; H, 4.6; N, 7.2.

Registry No.—1, 55267-57-7; 2, 102-01-2; 3, 105-50-0; 5b, 55267-58-8; 5c, 55267-59-9; 6, 55267-60-2; 7, 55267-61-3; 3-oxoglutaric anhydride, 10521-08-1; phenyl isocyanate, 103-71-9.

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Bufadienolides. 30. Synthesis of the Ch'an Su Component 15β-Hydroxybufalin[1,2]

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Venom from the toad *Bufo bufo gargarizans* is generally employed to prepare the Chinese medicinal preparation, Ch'an Su.[4] The first bufadienolide component was isolated from Ch'an Su some 63 years ago,[5] and a number of later investigations produced most of the bufadienolides now considered representative of toad venoms. In a recent continuation of their very careful toad venom isolation studies the Meyer group[6] has succeeded in isolating 11 new bufadienolides from Ch'an Su. One of these new bufadienolides was found to be 15β-hydroxybufalin (**3d**). The structure of the substance was determined by instrumental methods and comparison with the higher melting cis diol obtained by osmium tetroxide hydroxylation of 14-dehydrobufalin acetate (**1a**). The mixture of diols **2** and **3a** obtained by this procedure amounted to a 10% yield. Interestingly, the β-cis glycol was obtained in about 2% yield.

Since 15β-hydroxybufalin may be a component of other toad venoms and possess potentially useful biological properties, we have developed a new synthesis of this substance based on our prior route to 15β-hydroxy digitoxigenin.[7] To begin with, we subjected 14-dehydrobufalin acetate to a modified osmium tetroxide hydroxylation procedure. By this means, α-cis diol **2** was obtained in up to 28% yield and β-cis diol **3a** was isolated in about 5% yield. The most efficient route to the β-cis diol was realized using a Woodward cis-hydroxylation procedure.[7] Treatment of 14-dehydrobufalin (**1b**) or its 3-acetate derivative **1a** with iodine and silver acetate led to 21% yields of 15β-acetate **3b** and **3c**. Next, an acid-catalyzed hydrolysis procedure was utilized to convert the acetate derivatives **3a–c** to 15β-hydroxybufalin (**3d**). By this approach yields of triol **3d** ranged from