C=N, C=C, NH); 757, 705 cm.$^{-1}$ (C_6H_5); $\lambda_{max.}$ (pH 13) 272; $\lambda_{max.}$ (pH 1) 276. TLC showed one spot.

Anal.—Calcd. for $C_{14}H_{18}N_4O$: C, 65.1; H, 7.02; N, 21.7. Found: C, 64.9; H, 6.83; N, 21.5.

2,6-Diamino-5-(3-phenylpropyl)-4-pyrimidinol (XI).—This compound was prepared from 3-phenylpropyl bromide as described for VIII; yield, 1.24 Gm. (48%) of analytically pure, white leaflets, m.p. 220–221°; $\nu_{max.}$ (Nujol) 3400, 3200–3050 (NH, OH); 1690, 1650, 1610, 1550 (NH, C=O, C=C, C=N); 740, 720, 695 cm.$^{-1}$ (C_6H_5). The ultraviolet spectrum was the same as that of VIII, and TLC showed one spot.

Anal.—Calcd. for $C_{13}H_{16}N_4O$: C, 63.9; H, 6.60; N, 22.9. Found: C, 63.9; H, 6.50; N, 22.9.

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Base-Catalyzed Addition and Solvolysis Reactions of *N*-Phenylmaleimide in Methanol

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The base-catalyzed reaction of methanol with *N*-phenylmaleimide provides mainly methyl α-methoxysuccinanilate (III), which is formed from the intermediate methyl maleanilate (II). The course of the reaction was followed gas chromatographically, and the role of various possible intermediates is discussed. Observations concerning the relative thermal stabilities of III and its β-methoxy isomer (IV) are also presented. Nuclear magnetic resonance spectra were recorded for III, *N*-phenyl-α-methoxysuccinimide (V), and dimethyl α-methoxysuccinate (VI), all of which exhibit *ABX*-type patterns. Calculations carried out on the spectrum of V indicated J_{ax}, J_{bx}, and J_{ab} to be 7.85, 4.5, and 18.4 c.p.s., respectively.

THE CONJUGATE addition of thiols (1–3) and amines (2) to the double bond of *N*-alkyl- and *N*-arylmaleimides is well established. Indeed, the reaction is used for both the qualitative and quantitative estimation of thiols (3–5). These addenda also react with *N*-carbamylmaleimides (6) but give rise to a complex mixture of products apparently derived by ring opening as well as addition to the activated double bond. The reaction of alcohols, however, with this latter type of acceptor leads exclusively to ring opened products (6). The authors had occasion to observe, during the course of another investigation, the reaction of methanol with *N*-phenylmaleimide (I) in the presence of a catalytic amount of aqueous sodium hydroxide, which led apparently to a single product in high yield. Microanalysis and molecular weight determinations indicated that this product was the result of the addition of 2 moles of methanol to 1 mole of I, and the infrared spectrum showed both ester and amide carbonyl bands as well as absorption due to a phenyl ring and an N—H group. These data are consistent either with the structure III, methyl α-methoxysuccinanilate or the β-methoxy isomer (IV), and the NMR spectrum of the product also accords with this conclusion. As will be shown, both isomers are actually formed in this reaction, although one is present in only a very minor amount. The authors envisioned three possible pathways by which III and IV could be formed from I. Path *A* involves first ring opening to give methyl maleanilate (II), followed by addition to the double bond. Path *B* consists of the reverse order of these events, that is: first, addition to

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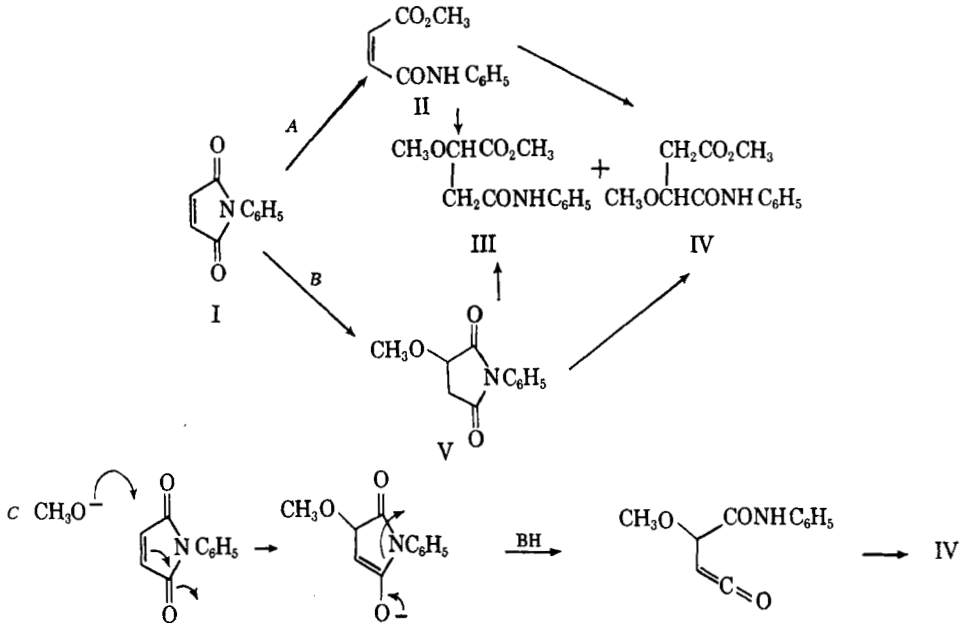

the double bond to provide *N*-phenyl-α-methoxysuccinimide (V), which subsequently undergoes ring opening. The third route (*C*) incorporates ring opening and addition in a semiconcerted fashion and suggests the possible intermediacy of a ketene. Path *C*, of course, can lead only to isomer IV. The authors sought, therefore, to assign a structure to the major product (and, by difference, to the minor one) and to examine its mode of formation.

DISCUSSION

The approach to this latter objective was simply to examine in separate experiments the behavior of the maleanilate (II) and succinimide (V) under the reaction conditions applied to I. Compound II was prepared in good yield by the acid-catalyzed methanolysis of I according to the procedure of Hoogewerff and Van Dorp (7). Compound V was formed from III (the product from I in basic methanol, see below) after it (III) had stood at room temperature for several months. The identity of this cyclization product, m.p. 117.5–118.5°, as V followed from the microanalytical and spectroscopic data. In particular, the NMR spectrum showed, in addition to the aromatic multiplet and the methoxyl singlet, a well-resolved *ABX* pattern arising from the mutual interactions of the remaining three protons attached to the five-membered ring. Calculations carried out in the prescribed (8) manner provided the chemical shift[1] for H_a, the proton *cis* to H_x, 3.11 p.p.m., and for H_b, 2.75 p.p.m. The coupling constants obtained, J_{ax} = 7.85 c.p.s., J_{bx} = 4.5 c.p.s., and J_{ab} = 18.4 c.p.s., are in accord (9) with this geometrical assignment.

With compounds II and V in hand, it was planned to compare them with compound I by following the progress of their reactions with methanol by gas chromatography. Since the major product derived from I, as has been noted above, undergoes cyclization to V even at room temperature, the authors determined the extent to which this thermal cyclization occurs during gas chromatographic analysis. When a partially purified sample of this product (ultimately given structure III) was analyzed, a significant quantity of compound V also appeared; however, by collection of pure III directly from the gas chromatograph followed by reanalysis, the actual extent of ring closure could be determined. Furthermore, by repetition of this cycle with the same sample, we were assured that the amount of reaction taking place as the sample passed from the detector cell to the collection tube was negligible. Under these conditions (190°, 17 min. retention time), it was determined that approximately 15% of III was transformed into V. At 208° (17 min.)[2] and at 222° (17 min.)[2] the extent of cyclization was about 26 and 37%, respectively. It was in the course of the initial studies with partially purified samples of III that the presence of a second product, assigned structure IV, was detected. Although this substance could not be obtained pure, its structure was assigned on the basis of its facile conversion to the succinimide (V). Under conditions (190°) which caused 15% of III to be converted to V, 80% of IV was similarly transformed. At 200°, the extent of ring closure was 85%. Finally, the thermal stability of compound II was investigated, and it was found that at 190°, 85% of II suffered ring closure to produce I; at 213°, all of II appeared as I.

When *N*-phenylmaleimide (I) was dissolved in methanol (0.33 *M*) with 1 mole per cent of added base, it was found to be about three-quarters con-

[1] Chemical shifts are reported in parts per million downfield from tetramethylsilane used as internal standard.

[2] The flow rate was adjusted to give the same retention time at the different temperatures.

verted to compound III *within 1 min.*[3] The conversion of I to a 95:5 mixture of III and IV was virtually complete in 20 min. In similar fashion, II was also converted to III, and significantly, at a comparable rate (95% conversion within 1 min.). However, when V was subjected to these reaction conditions, III was formed only very slowly in comparison to the former two cases (32% in 40 min.; 59% in 2.5 hr.). After 24 hr., a 95:5 mixture of III and IV was obtained. These data strongly indicate, therefore, that path *A* is of much greater importance than path *B* in the transformation of I to III. Path *C*, which can only provide compound IV, was eliminated as a significant process when the authors adopted structure III for the major product of the reaction.

The assignment of structure III was eventually made on the basis of a simple structural analogy. In contrast to the speed with which the base-catalyzed addition of methanol to II takes place, the addition to dimethyl maleate under the same conditions was extremely slow as judged by the observation that about 95% of the starting material could be recovered after 48 hr. If the reluctance of the unsaturated ester grouping to undergo addition is also operative in II, the high reactivity of II must indicate the fact that addition occurs to the unsaturated amide function, thereby resulting in the formation of III. That this direction of addition is preferred may be rationalized by pointing out that the intermediate anion formed α to the amide carbonyl would be less stable than the alternate anion α to the ester carbonyl. Accordingly, the equilibrium concentration of the latter would be sufficiently large to allow the reverse reaction (elimination of methoxide ion) to compete more effectively with the protonation step. The authors recall that a similar argument was advanced to explain the results obtained when hydroperoxides are added to unsaturated ketones, esters, and nitriles (10). It was hoped to place this structural assignment on more secure footing by a study of the NMR spectrum of III; however, the position of the *ABX* pattern differed only slightly from the position of the corresponding pattern in the spectrum of dimethyl α-methoxysuccinate.[4] (See *Experimental.*)

The direction of addition of methanol to II has been discussed above, and there remains only to comment on the observation that the solvolytic ring opening of V leads to a very similar product mixture,[5] that is, a predominance of III over IV. It would appear that the polar effect of the methoxyl substituent determines the direction of ring opening. This is in contrast to the relative ease of thermal cyclization of III and IV (IV faster than III), where the steric effect of the substituent apparently plays the major role. Finally, it may be pointed out that the reaction of ester-amides to form cyclic imides is of consequence in the peptide field and has been briefly reviewed by De Tar and his associates (11).

[3] In the absence of base, compound I in methanol was unchanged in 5 days (gas chromatographic analysis) and could be quantitatively recovered.

[4] In two attempts to carry out selective reductions of III using lithium borohydride, complex mixtures were obtained from which no pure products could be obtained by column chromatography. The infrared spectrum of the crude reduction product showed the presence of lactone, lactam, and imide carbonyl functions.

[5] It is possible that all species, I through V, are in equilibrium.

EXPERIMENTAL

The gas chromatographic analyses were carried out using an Aerograph model A-90-P instrument, with helium as carrier gas and equipped with a 5 ft. × 0.25 in. column packed with 20% silicone (SF-96) on 60–80 mesh fire brick. Infrared spectra were measured on Perkin-Elmer spectrophotometers, models 137B and 237. The NMR spectra were recorded on a Varian model A-60 spectrometer with samples prepared as 20% solutions in deuterochloroform. Melting points were determined on a Fisher-Johns block and are uncorrected as are the boiling points. Microanalyses were performed by Dr. A. Bernhardt, Mülheim, Germany. The methanol used was dried over calcium hydride and distilled.

Methyl α-Methoxysuccinanilate (III).—Ten grams of *N*-phenylmaleimide (I), prepared according to the method of Cava *et al.* (12), was dissolved in 120 ml. of methanol with 4 drops of 40% aqueous sodium hydroxide, and the solution was allowed to stand at room temperature for 20 hr. The methanol was then removed by distillation at low pressure, and the residual yellow oil was dissolved in chloroform, washed with water, and dried over magnesium sulfate. The residue (11.9 Gm.) remaining after removal of the solvent was distilled, 120°, 0.075 mm. (air bath, bulb to bulb) to yield 11.0 Gm. of product. This material was analyzed by gas chromatography (190°, flow rate, 125 ml./min.) and found to consist of 71% (88%) III, 28% (12%) V, 1% (5%) IV, and a trace of I.[6] The retention times for I, III, IV, and V were 3.5, 17, 19.5, and 10.5 min., respectively. Purification was effected by column chromatography on silica gel and redistillation provided a sample for analysis: $\nu_{max.}^{film}$ 3350, 2960, 1735, 1680, 1600, 1525, 1435, 1192, 1160, 1108, 807, and 680 cm.$^{-1}$.

Anal.—Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90; O, 26.98. Found: C, 60.70; H, 6.26; N, 6.08; O, 27.16.

This sample was also used for the NMR spectrum[1]: 2.88 p.p.m., center of H_aH_b octet; 4.26 p.p.m., center of H_x quartet; 3.55 p.p.m., methoxyl singlet (ether); 3.74 p.p.m., methoxyl singlet (ester); 7.50 p.p.m., center of aromatic multiplet; 8.26 p.p.m., NH proton, broad singlet.

Gas chromatographic analysis of a solution of I (1 Gm.) in methanol (15 ml.) which had stood for 5 days at room temperature in the absence of base showed the presence of I only. The starting material was quantitatively recovered on removal of the solvent.

When I (173 mg., 1 mole) was dissolved in methanol (3 ml.) and 1 μl. of 40% aqueous sodium hydroxide (0.01 *M* equivalent) was added, the mixture turned red instantly, fading only slowly to a faint yellow. The progress of the reaction was followed by gas chromatographic analysis (190°, flow rate, 125 ml./min.) and the results were as follows.[6] After 1 min.: I, 9%; III, 65% (76.5%); V, 26% (14.5%). After 20 min.: I, 1%; III, 84% (>94%); IV, <1% (<5%); V, 15% (0%). No further change occurred in the composition.

[6] The figures in parentheses are believed to represent the actual mixture since they are corrected for the extent of thermal reaction occurring on the column. (See the discussion in the text.)

N-Phenyl-α-methoxysuccinimide (V).—Compound III deposited crystals after having stood for several months at room temperature. These crystals were separated from III by centrifugation through a sintered disk while washing with ether. Purification of V was accomplished by recrystallization from acetone which afforded white crystals, m.p. 117.5–118.5°; $\nu_{max.}^{KBr}$ 3100, 2925, 2830, 1728, 1600, 1500, 1388, 1345, 1256, 1195, 1117, 994. 862. 801, 744, and 695 cm.$^{-1}$.

Anal.—Calcd. for $C_{10}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.39; H, 5.53; N,6.84.

The NMR spectrum showed signals at 2.93 p.p.m., center of H_aH_b octet; 3.6 p.p.m., methoxyl singlet; 4.31 p.p.m., center of H_x quartet; 7.38 p.p.m., center of aromatic multiplet.

When a sample of V (205 mg.) was dissolved in 6 ml. of methanol (saturated solution, 0.17 *M*) and 1 μl. of 40% aqueous sodium hydroxide (0.01 *M* equivalent) was added, the reaction mixture remained colorless. The progress of the reaction was followed by gas chromatographic analysis (212°, 100 ml./min.), and the results were as follows.[6] After 40 min.: III, 22% (32%); V, 78% (68%). After 2.5 hr.: III, 41% (59%), V, 59% (41%). After 24 hr.: III, 70% (>95%); IV, <1% (<5%); V, 30% (0%).

Methyl Maleanilate (II).—This material was prepared by the method of Hoogewerff and Van Dorp (7) and after recrystallization from an acetone–ether–hexane mixture had m.p. 77–78° [Lit. (9), m.p. 76–78.5°.] A sample (205 mg.) was dissolved in 3 ml. of methanol, and 1 μl. of 40% aqueous sodium hydroxide was added. A red color developed immediately, and the reaction was monitored by gas chromatographic analysis (213°, 100 ml./min.) with the following results.[6] After 1 min.: I, 5% (0%); II, 0% (5%); III, 69% (95%); V, 26% (0%). After 20 min.: I, trace (0%); II, 0% (trace); III, 75% (~100%); V, 25% (~0%). Under conditions of this analysis, compound II cyclyzes completely to I. At 190° (100 ml./min.), II appears as 85% of I and 15% of II (retention time, 13 min.). Compound II dissolved in acetone also gives rise to a red color when treated with aqueous alkali. Compound I, which gives the color in methanolic base as mentioned already, does not give it when an acetone solution is treated with base. The colored species is possibly the anion: $CH_3O_2CCH{=}CHCONC_6H_5$.

Dimethyl α-Methoxysuccinate.—To a solution of dimethyl maleate (2 Gm., 13.9 mmoles) in 10 ml. of methanol was added sodium methoxide (0.15 Gm., 3.3 mmoles) in small portions over a period of 20 min. After the mixture had stood at room temperature for 15 hr.,[7] the methanol was removed by distillation at reduced pressure and the residue dissolved in ether, washed with water until neutral, and dried over magnesium sulfate. Removal of the solvent left a faintly yellow oil which was distilled to provide a colorless liquid, b.p. 58–60° at 0.25 mm. or 130° at 40 mm. [Lit. (13) b.p. 135° at 42 mm.] Gas chromatographic analysis (190°, 200 ml./min., 15% diethylene glycol succinate on fire brick) showed 97% of the product, about 3% of dimethyl maleate, and less than 1% of an unidentified compound. A sample of the product was collected from the column and used for the NMR analysis and infrared spectrum: $\nu_{max.}^{film}$ 2980, 2860, 1745, 1440, 1372, 1280, 1205, 1170, 1128, 1040, 875, 857, and 785 cm.$^{-1}$; 2.69 p.p.m., center of H_aH_b octet; 3.39 p.p.m., methoxyl singlet (ether); 3.68 p.p.m., methoxyl singlet (ester, C_4); 3.73 p.p.m., methoxyl singlet (ester, C_1); 4.15 p.p.m., center of H_x quartet.

Dimethyl maleate (2 Gm., 13.9 mmoles) was dissolved in 10 ml. of methanol with 14 μl. (0.01 *M* equivalent) of aqueous sodium hydroxide and allowed to stand for 48 hr. at room temperature. After this time, the methanol was removed and the residue dissolved in ether, washed with 2 *N* sodium bicarbonate, water, and dried over magnesium sulfate. Removal of the solvent afforded 1.89 Gm. of colorless liquid whose infrared spectrum was *identical* with that of the starting material.

Thermal Cyclization of III and IV.—The once distilled, though still impure, sample of III which was described in the first experiment above was submitted to gas chromatography at 190° and with a flow rate of 125 ml./min. The collection of pure isomer III from the column presented no problems, and the sample was then analyzed at varying temperatures in order to assess the extent of cyclization to V. The following percentages of V were obtained: at 190° (flow rate, 166 ml./min.), 13.8, 16.6, and 14.4%; at 208° (flow rate, 85 ml./min.),[2] 24 and 27%; and at 222° (flow rate, 40 ml./min.),[2] 36 and 37%. Because of the small difference in retention times between the major (III) and the minor isomer (IV) (see above), the minor isomer could only be obtained as an enriched mixture with III. This mixture was analyzed at 190° and 200°, and taking into account the known production of V from III, the extent of cyclization of IV to V was estimated to be 80 and 85%.

[7] This is essentially the method of Purdie, T., *J. Chem. Soc.*, **47**, 855(1885).

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