(6) D. Bilovic, Z. Stojanac, and V. Hahn, *Tetrahedron Lett.*, 2071 (1964).
(7) Z. Stojanac and V. Hahn, *Croat. Chem. Acta*, **34**, 237 (1962).
(8) N. Finch, L. Blanchard, R. T. Puckett, and L. H. Werner, *J. Org. Chem.*, **39**, 1118 (1974).
(9) S. Seltzer, *Adv. Alicyclic Chem.*, **2**, 17–32 (1968).
(10) For analogous reactions see G. Schwenker, J. Meyer, and S. Stauss, *Arch. Pharm. (Weinheim, Ger.)*, **305**, 839 (1972).
(11) (a) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957); A. C. Darby, H. B. Henbest, and I. McClenaghan, *Chem. Ind. (London)*, 462 (1962); (b) H. Kwart and T. Takeshita, *J. Org. Chem.*, **28**, 670 (1963).
(12) G. Kotowycz and R. U. Lemieux, *Chem. Rev.*, **73**, 669 (1973).
(13) C. F. Huebner, U.S. Patent 3,031,459 (April 24, 1962) (we gratefully acknowledge a sample of the hydrogenated Diels–Alder adduct **28** provided by Dr. C. F. Huebner).
(14) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, *J. Am. Chem. Soc.*, **79**, 6562 (1957).
(15) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

2-(3-Aryl-5-pyrazolyl)benzoic Acid Chemistry

Alexander L. Johnson* and Philip B. Sweetser

Contribution No. 2281 from the Central Research and Development Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

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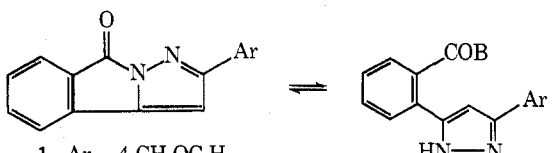
The nucleophilic ring-cleavage reactions of 2-(4-methoxyphenyl)-8*H*-pyrazolo[5,1-*a*]isoindol-8-one (1) and its analogues with aqueous base, alcohols, and primary and secondary amines are convenient syntheses of 2-[3-(4-methoxyphenyl)-5-pyrazolyl]benzoic acid (4), its esters (5), and amides (6), and their analogues. These reactions may be reversed by heat and by dehydrating agents such as $SOCl_2$, $POCl_3$, and Ac_2O. The derivative chemistry of 4 is discussed.

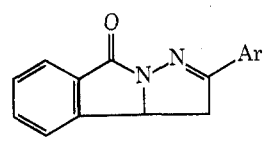
We have described[1] the synthesis of 2-(4-methoxyphenyl)-8*H*-pyrazolo[5,1-*a*]isoindol-8-one (1) from its 3,3a-dihydro derivative (9), which was prepared from phthalaldehydic acid, 4-methoxyacetophenone, and hydrazine. We now wish to report the further chemistry of these interesting plant growth regulants,[2-9] which concerns their conversion to 2-[3-(4-methoxyphenyl)-5-pyrazolyl]benzoic acid (4), its esters (5), and amides (6) by reaction with aqueous base, alcohols, and amines. These new compounds are also plant growth regulants.[10,11] In solution at 25°, the pyrazoloisoindolone 1 and its analogues are very susceptible to nucleophilic attack at the γ-lactam function to form 4–6 and their analogues. The progress of these reactions is readily followed by the rapid disappearance of the bright yellow color of 1, an observation which appears to have escaped Leclerc,[12] who reported the uv spectrum of the phenyl analogue 2 in ethanol as λ_{max} 248 nm (ε 36000) and 335 (1480). The true spectrum of 2, obtained in an unreactive solvent such as THF, has λ_{max} 337 nm (ε 10960), 323 (10880), 290 (13890), and 254 (35950), showing clearly that Leclerc's sample had partly decayed in solution to ester 7 after preparation. The ring-opened ester 7 has λ_{max} (EtOH) 252 nm (ε 25140), a value which is typical of this class of compounds.



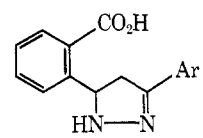
1, Ar = 4-$CH_3OC_6H_4$
2, Ar = C_6H_5
3, Ar = 4-HOC_6H_4

4, Ar = 4-$CH_3OC_6H_4$; B = OH
5, Ar = 4-$CH_3OC_6H_4$; B = OR
6, Ar = 4-$CH_3OC_6H_4$; B = NR_1R_2
7, Ar = C_6H_5; B = OC_2H_5
8, Ar = 4-HOC_6H_4; B = OH

The 3,3a-dihydro derivative 9 behaves similarly to 1 toward nucleophiles, but the resulting 2,3-dihydropyrazole derivatives (e.g., 11) are oxidatively unstable, and the usual product after atmospheric isolation is a mixture of 11 and 4. An exception is the phenol 12, which can be isolated pure in good yield by treating the phenol 10 with aqueous base.



9, Ar = 4-$CH_3OC_6H_4$
10, Ar = 4-HOC_6H_4



11, Ar = 4-$CH_3OC_6H_4$
12, Ar = 4-HOC_6H_4

Although dihydropyrazole 10 may be prepared most conveniently by the demethylation of 9 with 48% HI, the corresponding pyrazole 1 is converted to the ring-opened phenol 8 by this treatment.[13] Table I lists the compounds prepared by these methods, using the general procedures described in the Experimental Section.

Spectra. The fused γ-lactam structure of 1 and 2 gives their spectra characteristic ir bands at 1780 and 1760 (1), 1790 and 1760 cm^{-1} (2), and a pair of intense uv bands at 346 and 331 (1) and 337 and 323 nm (2). The compounds in Table I have entirely different spectra, with the ir carbonyl frequencies expected for aromatic acids (1670–1690 cm^{-1}), their esters (1705–1720 cm^{-1}), and amides (1610–1670 cm^{-1}), and uv absorptions near 260 nm with slight variations in extinction coefficient for the acids (30000–36000), esters (26000–29000), and amides (31000–33000). The position of the singlet pyrazole proton signal (δ 6.60–7.00 ppm) in the proton NMR spectra of the ring-opened compounds does not distinguish them from the cyclic forms where the signal is at 6.63 ppm in 1 and 6.68 ppm in 2. The spectral differences between the cyclic dihydro form 9 [1690 cm^{-1}, 323 nm (ε 18070), 277 (9080), and 268 (9150)] and its cleavage product 12 [1700 cm^{-1}, 282 nm (ε 17400)] are less pronounced, but do reflect the differences between these structures.

Table I
2-(3-Aryl-5-pyrazolyl)benzoic Acids and Their Derivatives[a]

Entry	Structure	Yield, %	Recrystn solvent	Mp, °C	Ir ν_{max} (KBr), cm^{-1}	Uv λ_{max} (EtOH) (ϵ_{max})	NMR, δppm[b] ($CDCl_3$–Me_4Si)	Formula
				2-(3-Aryl-5-pyrazolyl)benzoic Acids				
1	4	85	60% EtOH	223–225 dec	1690	266 (35700)[c]	6.80[d]	$C_{17}H_{14}N_2O_3$
2	8	76	3:1:1 EtOH–Me_2SO–H_2O	260–264 dec	1690	261 (30000)	6.75[d]	$C_{16}H_{12}N_2O_3$
				2-(3-Aryl-5-pyrazolyl)benzoic Acid Esters				
3	5, R = CH_3	59	Hexane–EtOAc	92–93	1720[e]	261 (28200)	6.65	$C_{18}H_{16}N_2O_3$
4	5, R = CH_3, HCl salt	55	Me_2CO	181–191 dec	1710	261 (28100)	6.85[d]	$C_{18}H_{17}N_2O_3Cl$
5	5, R = C_2H_5	23	Hexane–EtOAc	99.5–101	1710[e]	260 (28400)	[f]	$C_{19}H_{18}N_2O_3$
6	5, R = C_2H_5, HCl salt	66	Me_2CO	164–167.5	1720	262 (28000)	6.95[d]	$C_{19}H_{19}N_2O_3Cl$
7	7	50	Hexane–EtOAc	66–70	1710[e]	252 (25140)	6.68	$C_{18}H_{16}N_2O_2$
8	5, R = n-C_3H_7	58	Hexane–EtOAc	107–109	1710[e]	261 (28800)	7.00	$C_{20}H_{20}N_2O_3$
9	5, R = n-C_4H_9	47	Hexane–EtOAc	92–94	1710[e]	260 (29000)	[f]	$C_{21}H_{22}N_2O_3$
10	5, R = n-C_5H_{11}	23	Hexane–EtOAc	82–83.5	1705[e]	261 (28200)	6.63	$C_{22}H_{24}N_2O_3$
11	5, R = n-C_6H_{13}	73	[g]	[g]	1710[e]	262 (26600)	6.60	$C_{23}H_{26}N_2O_3$
12	5, R = $HOCH_2CH_2$	79	50% EtOH	148–150	1710	261 (28400)	6.62	$C_{19}H_{18}N_2O_4$
				2-(3-Aryl-5-pyrazolyl)benzoic Acid Amides				
13	6, $R_1 = R_2 = H$	89–96	1:1 EtOH–Me_2SO	205–207 dec	1660, 1610	261 (31600)	6.86[d]	$C_{17}H_{15}N_3O_2$
14	6, $R_1R_2 = (CH_2)_4$	81	EtOAc–$CHCl_3$	199–201 dec	1660, 1630, 1610	261 (32300)	6.77[d]	$C_{21}H_{21}N_3O_2$
15	6, $R_1R_2 = CH_2CH_2$-OCH_2CH_2	84	EtOAc–MeOH	221–223 dec	1610, 1500	262 (32600)	6.73[h]	$C_{21}H_{21}N_3O_3$
16	6, $R_1 = C_6H_5CH_2O$ $R_2 = H$	61	3:1:1 EtOH–Me_2SO–H_2O	180–181.5	1650	261 (31800)	6.93[d]	$C_{24}H_{21}N_3O_3$
				2-[3-Aryl-(2-acetyl-5-pyrazolyl)]benzoic Acid Esters				
17	13	92	1:1 petroleum ether–EtOAc	119–121	1730, 1610	300 (14500) 282 (21100) 233 (21200)	6.57	$C_{20}H_{18}N_2O_4$
18	14	37	1:1 petroleum ether–EtOAc	71–73.5	1730, 1610	305 (12600) 288 (21500) 235 (22900)	6.60	$C_{22}H_{22}N_2O_4$
19	15	77	1:1 petroleum ether–EtOAc	65–69	1730, 1610	305 (12300) 288 (20800) 235 (21300)	6.50	$C_{23}H_{24}N_2O_4$

[a] Analytical data (C, H, N) agree with theoretical values (±0.3%). [b] Chemical shift of singlet pyrazole proton signal. [c] Measured in DMF. [d] Measured in Me_2SO-d_6. [e] Measured in $CHCl_3$. [f] Signal obscured by other aromatic protons. [g] Not obtained crystalline. [h] Measured in CF_3CO_2H.

Cyclization of Pyrazolylbenzoic Acids to Pyrazoloisoindolones. The reverse process, the cyclization of 4 to 1, requires a chemically active dehydrating agent such as $SOCl_2$, $POCl_3$, or Ac_2O. Strong acids such as H_2SO_4, *p*-TsOH, or CF_3CO_2H are ineffective cyclization reagents for this reaction. The cyclization is rapid, proceeds in good yield, and is signaled by the return of the yellow color of 1. Thermal cyclization of structures 4–6 to 1 occurs at 200°, but the yields are low, and the isolation procedures are less satisfactory than for the chemical methods. Visually, this thermal reversion is seen in a melting point capillary with those compounds in the series which melt above 200° with decomposition. Thermal cyclization is the only known method with the esters 5 and amides 6. The phenol 3 must be prepared by the circuitous route 9 → 1 → 8 → 3, using $SOCl_2$ as the cyclization reagent, because 10 cannot be dehydrogenated to 3 with DDQ.[13]

Kinetics of Ester Formation and Hydrolysis. Qualitatively, the disappearance of the yellow color of 1 is a useful indication of the progress of its conversion to 4–6. In alcoholic solvents, the reaction becomes visually slower as the chain length or bulk of the nucleophile increases, there being essentially no reaction with *t*-BuOH. These reactions are accelerated by a trace of base, and in MeOH or EtOH containing a chip of sodium, the conversion to 5 (B = OCH_3 or OC_2H_5) is complete within a few minutes. The solubility of 1 in the solvent containing the nucleophile is important; structure 1 is insoluble in, and is not attacked by, dilute aqueous alkali, but the addition of MeOH or EtOH to such mixtures causes rapid conversion to the anion of 4.

The rate of alcoholysis of 1 in neutral solution can be easily followed by the disappearance of its 346- and 331-nm bands in a uv spectrophotometer. Table II lists the first-order pseudounimolecular rate constants determined this way at 25°, methanolysis being approximately 100 times faster than ethanolysis. The arylpyrazolyl substituent was found to enhance the rate of base-catalyzed hydrolysis of benzoate esters approximately sixfold when the methyl and *n*-butyl esters 5 (B = OCH_3, B = O-*n*-C_4H_9) were compared with methyl and *n*-butyl benzoates in aqueous EtOH. Table II lists the second-order bimolecular rate constants for these compounds.

***N*-Alkyl and *N*-Acyl Derivatives.** Because 4 is rapidly

Table II
Kinetics of Ester Formation and Hydrolysis

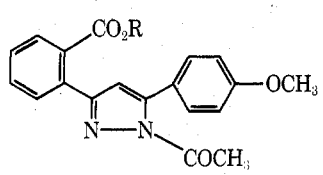
A. Alcoholysis of 1 at 25 ± 1°

Solvent	k_1, sec^{-1}	Relative rate
CH_3OH	$(4.94 \pm 0.19) \times 10^{-4}$	99.5
C_2H_5OH	$(4.96 \pm 0.20) \times 10^{-6}$	1.0

B. Hydrolysis of Esters at 26 ± 0.1°

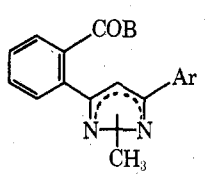
Compd	k_2, l.$^{-1}$ mol^{-1} sec^{-1}	Relative rate
5, B = OCH_3	$(3.26 \pm 0.15) \times 10^{-3}$	6.65
5, B = O*n*-C_4H_9	$(3.04 \pm 0.27) \times 10^{-3}$	6.45
$C_6H_5CO_2CH_3$	$(6.54 \pm 0.47) \times 10^{-4}$	1.33
$C_6H_5CO_2$*n*-C_4H_9	$(4.79 \pm 0.16) \times 10^{-4}$	1.00

cyclized to 1 in the presence of acid anhydrides, *N*-acyl derivatives of the ring-opened forms must be prepared from the esters 5. Treatment of 5 (B = OCH_3, O-*n*-C_3H_7, or O-*n*-C_4H_9) with Ac_2O in pyridine gave only one of the two possible *N*-acetyl derivatives as determined by spectra of the crude and purified materials.[14] Mass spectral fragmentation data favor the 2-acetyl derivatives (13–15) rather



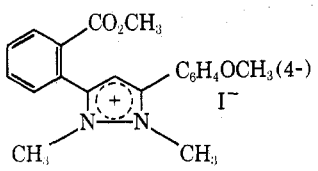
13, R = CH_3
14, R = *n*-C_3H_7
15, R = *n*-C_4H_9

than the isomeric 1-acetyl derivatives with *m/e* 350 $(M)^+$, 308 $(M - CH_2CO)^+$ base peak, and 176 $(C_{10}H_{10}NO_2)^+$ corresponding to the fragment $[4\text{-}CH_3OC_6H_4CNCOCH_3]^+$ in 13. The alkylation of 4 with CH_3I in DMF in the presence of Na_2CO_3 gives a mixture of the isomeric *N*-methyl esters 16 and 17 and the quaternary iodide 22. After separation,



16, 1-CH_3; B = OCH_3; Ar = 4-$CH_3OC_6H_4$
17, 2-CH_3; B = OCH_3; Ar = 4-$CH_3OC_6H_4$
18, 1-CH_3; B = OH; Ar = C_6H_5
19, 2-CH_3; B = OH; Ar = C_6H_5
20, B = Cl; Ar = C_6H_5
21, B = OC_2H_5; Ar = C_6H_5; HCl salt

the mixture of 16 and 17 is readily quaternized to 22, and 22 is readily demethylated to the mixture of 16 and 17. The *N*-methyl derivatives of the parent acid (18, 19) may be prepared by treating the disodium salt (23)[15] with meth-



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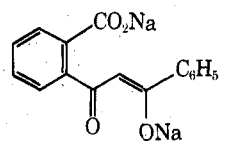

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ylhydrazine hydrochloride. The product of this reaction is a 5:1 isomer mixture from which the major isomer may be separated by recrystallization. Mass spectra did not distinguish between the isomers. The major isomer was converted to its acid chloride (20) and its ethyl ester hydrochloride (21) by the usual procedures. These experiments demonstrate that blocking (a) the pyrazole nitrogen by alkyl substitution prevents cyclization to the pyrazoloisoindolone structure, and (b) the carboxyl group by esterification increases the difficulty of cyclization.

Experimental Section[16]

2-[3-(4-Methoxyphenyl)-5-pyrazolyl]benzoic Acid (4). A mixture of 1 (46.7 g, 0.169 mol), H_2O (750 ml), MeOH (750 ml), and NaOH (8.0 g, 0.20 mol) was stirred mechanically at 25° for 6 hr, then acidified with 25 ml of concentrated HCl, and cooled to 0°. The colorless precipitate of 4 was filtered and recrystallized from a mixture of EtOH (1400 ml) and H_2O (1000 ml), yield 42.1 g (0.143 mol, 85%) of colorless, crystalline solid, mp 223–225° dec.

2-[3-(4-Hydroxyphenyl)-5-pyrazolyl]benzoic Acid (8). A mixture of 1 (5.0 g, 18.1 mmol) and constant boiling point HI (50 ml) was stirred at reflux for 6 hr, then poured into 250 ml of H_2O, cooled, and filtered. The crude phenol 8 was rinsed with aqueous $Na_2S_2O_3$ and H_2O, and recrystallized from a mixture of EtOH (30 ml), Me_2SO (10 ml), and H_2O (10 ml), yield 3.85 g (13.7 mmol, 76%) of colorless, crystalline solid, mp 260–264° dec.

Preparation of Esters of 2-[3-(4-Methoxyphenyl)-5-pyrazolyl]benzoic Acid (5). A. A mixture of 1 (5.0 g, 18.0 mmol) and the appropriate alcohol (100 ml) containing 0.1 g (4 mg-atom) of Na was stirred at 25° until the yellow color had disappeared (1–2 hr). The alcohol was evaporated or removed by steam distillation (*n*-$C_5H_{11}OH$, *n*-$C_6H_{13}OH$), and the residue was dissolved in C_6H_6 (100 ml) and stirred overnight with a few grams of Florisil. Filtration and evaporation left a colorless, gummy residue of crude ester which was recrystallized from EtOAc–hexane mixtures. The ethylene glycol monoester (Table I, entry 12) was directly filtered from the reaction mixture and recrystallized from 50% EtOH.

B. Ester 7 was similarly prepared from 2[1] and EtOH.

C. The hydrochlorides of the methyl and ethyl esters 5 (B = OCH_3, OC_2H_5) were prepared by dissolving the crude esters in Et_2O and treating this solution at 0° with HCl gas. The crude hydrochlorides were recrystallized from Me_2CO containing a drop of HCl.

D. Acid 4 (5.0 g) was directly converted to ester 5 (B = OCH_3) in 26% yield by 4 hr reflux in a mixture of MeOH (50 ml) and H_2SO_4 (1.0 ml).

Preparation of Amides of 2-[3-(4-Methoxyphenyl)-5-pyrazolyl]benzoic Acid (6). A mixture of 1 (5.0 g, 18.0 mmol) and excess amine was stirred for several hours until the yellow color had disappeared. With liquid NH_3, the reaction temperature was −33°, and with other amines it was 25°. Low-boiling amines were evaporated to leave the crude amide as a solid. The reaction product with morpholine was isolated by pouring the reaction mixture into H_2O. The reaction with benzyloxyamine was done in C_6H_6 solution from which the crude product precipitated. The crude amides were recrystallized from suitable solvents (Table I).

2-[3-(4-Hydroxyphenyl)-4,5-dihydro-5-pyrazolyl]benzoic Acid (12). A. A mixture of 9 (5.0 g, 18.0 mmol) and constant boiling point HI (50 ml) was heated at reflux for 5 hr, poured into 250 ml of H_2O, and filtered. The crude phenol 10 was recrystallized from a mixture of MeOH (200 ml) and DMF (50 ml), yield 3.34 g (12.65 mmol, 70%) of colorless, crystalline solid: mp 283–285° dec; ν_{max} (Nujol) 3295 and 1670 cm^{-1}; λ_{max} (DMF) 324 nm (ϵ 17800); ^1H NMR (Me_2SO-d_6) δ 7.70–6.81 (m) 8 H (aromatic), 5.55 (X part) 1 H and 3.60–3.07 ppm (AB part) 2 H ($CHCH_2$). Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.61; H, 4.56; N, 10.52.

B. A mixture of 10 (5.0 g, 18.9 mmol) and 10% NaOH (50 ml) was stirred at 25° for 2 hr; then it was acidified with concentrated HCl, cooled, and filtered to give crude 12 (4.93 g, 17.5 mmol, 92%) which could be purified either by reprecipitation from NaOH solution with HCl, or by recrystallization from 30% DMF. Pure 12 formed colorless crystals: mp 248–250° dec; ν_{max} (KBr) 3440, 1610, and 1570 cm^{-1}; λ_{max} (DMF) 282 nm (ϵ 17400); ^1H NMR (D_2O + KOH) δ 7.61–6.81 (A_2B_2 + m) 8 H (aromatic), 5.30 (X part) 1 H, and 3.73–2.82 ppm (AB part) 2 H (CH_2CH). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.89; H, 4.90; N, 9.98.

2-(4-Hydroxyphenyl)-8*H*-pyrazolo[5,1-*a*]isoindol-8-one (3). A mixture of 8[1] (1.0 g, 3.6 mmol) and $SOCl_2$ (10 ml) was allowed to

evaporate at 25°. The yellow residue was recrystallized from 25% Me_2CO: yield 0.69 g (71%) of yellow needles of **3**; mp 220–223° dec; ν_{max} (KBr) 3400, 1780, and 1740 cm^{-1}; λ_{max} (THF) 390 nm (ϵ 2040), 347 (11000), 332 (11100), 297 (15500), 286 (20000), 265 (28700), 240 (25100), and 235 (24200); ^1H NMR (Me_2SO-d_6) δ 7.78–6.91 (A_2B_2 + m) 8 H (aromatic) and 7.03 ppm (s) 1 H (pyrazole proton). Anal. Calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.25; H, 4.18; N, 10.30.

2-(4-Methoxyphenyl)-8*H*-pyrazolo[5,1-*a*]isoindol-8-one (1) from 4–6. A. $SOCl_2$. Treatment of **4** with $SOCl_2$ as described above for **8** gave a 90% yield of **1**, identified by mixture melting point and spectra.

B. Ac_2O–C_5H_5N. Treatment of **4** (5.0 g, 17.0 mmol) with a mixture of Ac_2O (30 ml) and pyridine (20 ml) at 25° produced a copious yellow precipitate of **1** after 1 hr. The product was isolated by pouring the reaction mixture into 400 ml of H_2O and filtration, and was identified as in A.

C. $POCl_3$–C_5H_5N. Treatment of **4** (1.0 g, 3.4 mmol) with a mixture of $POCl_3$ (0.54 g, 3.4 mmol) and pyridine (25 ml) at 25° for 3 hr, followed by isolation as in B, gave an 88% yield of **1**.

D. Heat. One-gram samples of **4**, **5** (B = OCH_3), and **6** (B = NH_2) were each held at 200–220° (0.1 mm) in a sublimer for 2–4 hr. The yellow sublimate from **4** was rinsed with 5% $NaHCO_3$ to remove unreacted **4**, and the insoluble residue was recrystallized from Me_2CO to give 0.37 g (1.34 mmol, 39%) of **1**. NMR and ir examination of the yellow sublimate from **5** (B = OCH_3) showed that it was an 85:15 mixture of **5**:**1**. The yellow sublimate from **6** (B = NH_2) was rinsed with $CHCl_3$ to remove **1** (0.77 g, 2.78 mmol, 82%) and leave unreacted **6** on the filter.

Kinetics of Alcoholysis of 1. The glassware was rinsed with dilute acid and distilled water before use to remove basic impurities. Approximately 10^{-4} *M* solutions of **1** were prepared at time zero by diluting more concentrated THF solutions of **1** with MeOH and EtOH; the reaction solutions were 95:5 alcohol–THF by volume. The disappearance of the 346- and 331-nm bands of **1** in the uv was followed by recording the optical densities at regular intervals (3 min for MeOH, 3 hr for EtOH), the spectrum in pure THF being used for the zero-time and blank readings. The rate constants were calculated in the usual way from $k_1 = 2.303/t\ [\log a/(a - x)]$.

Kinetics of Ester Hydrolysis. The hydrolysis medium[17] was 0.03 *N* base prepared by the addition of Na(0.7 g $l.^{-1}$) to degassed 87.8% w/w EtOH–H_2O, and standardized by adding a 10-ml aliquot to 20 ml of standard H_2SO_4, followed by back-titration with standard NaOH to phenolphthalein end point. Three volumetric flasks were partly filled with the hydrolysis medium and allowed to equilibrate at 26 ± 0.1° before the hydrolysis was started by adding the ester under study to two of the flasks, and using the contents of the third flask to bring the solution up to the mark and serve as a blank control. At selected times (0.5–1.0-hr intervals) 10-ml aliquots of the hydrolysis medium were titrated as described above. The second-order rate constants were calculated in the usual way from $k_2 = 2.303/t(a - b)\ [\log b(a - x)/a(b - x)]$.

2-[2-Acetyl-3-(4-methoxyphenyl)-5-pyrazolyl]benzoate Esters (13–15). A mixture of ester **5** (B = OCH_3, O-*n*-C_3H_7, or O-*n*-C_4H_9) (1–3 g), pyridine (10–25 ml), and Ac_2O (5–12 ml) was left overnight at 25°, then poured into H_2O and extracted with C_6H_6. The crude products were recrystallized from 1:1 petroleum ether–EtOAc; the details are given in Table I. The NMR spectra showed the presence of only one isomer (singlet peaks for pyrazole and *N*-acetyl signals).

Reaction of 4 with CH_3I. A. A mixture of DMF (100 ml), **4** (13.0 g, 44.1 mmol), Na_2CO_3 (9.36 g, 88.2 mmol), and CH_3I (25 ml) was stirred at reflux for 6 hr, poured into 100 ml of H_2O, acidified to pH 3, and extracted with $CHCl_3$. The yellow syrup obtained from the extracts was chromatographed on 100 g of SilicAR CC-4, taking 200-ml fractions. Fractions 1–6 (2:1 cyclohexane–EtOAc) gave 6.04 g (19.6 mmol, 44%) of a mixture of **16** and **17** in approximately equal proportions, and fractions 7 and 8 (MeOH) gave 8.47 g (18.3 mmol, 41%) of **22**. The ester mixture (**16**, **17**) has ν_{max} ($CHCl_3$) 1720 cm^{-1}; ^1H NMR ($CDCl_3$–Me_4Si) δ 8.12–6.85 (A_2B_2 + m) 8 H (aromatic), 6.44 (s) 1 H (pyrazole proton), 3.76 (s) and 3.68 (s) 3 H (OCH_3 isomers), and 3.64 ppm (s) 3 H (NCH_3); *m/e* 322 (M^+), 291 ($M - OCH_3$)$^+$, 176 ($C_{10}H_{10}NO_2$)$^+$, and 133 (C_8H_7NO)$^+$ from **16**, 161 ($C_9H_7NO_2$)$^+$ and 148 ($C_9H_{10}NO$)$^+$ from **17**. The quaternary iodide **22** was recrystallized twice from EtOH (35 ml) as a colorless, crystalline solid: mp 153–155°; ν_{max} ($CHCl_3$) 1720 cm^{-1}; λ_{max} (EtOH) 277 nm (ϵ 19500) and 218 (37400); ^1H NMR ($CDCl_3$–Me_4Si) δ 8.20–7.00 (m) 8 H (aromatic), 6.56 (s) 1 H (pyrazole), 4.35 (s) 3 H and 4.21 (s) 3 H (NCH_3), and 3.88 ppm (s) 3 H (OCH_3). Anal. Calcd for $C_{20}H_{21}N_2O_3I$: C, 51.73; H, 4.56; N, 6.03. Found: C, 51.57; H, 4.65; N, 5.95.

B. The same experiment done in refluxing Me_2CO with K_2CO_3 as the base gave a 98% yield of the ester mixture (**16**, **17**).

C. The ester mixture from A or B was converted to methiodide **22** in 20–60% yield by stirring at reflux in a mixture of DMF and CH_3I.

D. Treatment of methiodide **22** (1.0 g, 2.16 mmol) with a mixture of Ag_2O (from 2.0 g of $AgNO_3$), MeOH (25 ml), H_2O (25 ml), and NaOH (1.0g) at 25° for 1 hr gave, after filtration and evaporation, a residue which reverted to the ester mixture (**16**, **17**) (0.21 g, 30%) on heating at 180° (0.1 mm).

2-[3-Phenyl-5-(*N*-methylpyrazolyl]benzoic Acids (18, 19). A. A mixture of **23**[15] (12.0 g, 40 mmol), EtOH (80 ml), 1 *N* HCl (40 ml, 40 mmol), and methylhydrazine (8.0 g, 0.17 mol) was stirred at reflux for 1 hr, cooled, acidified to pH 3 with HCl, and filtered. The crude solid precipitate (6.46 g, 23 mmol, 58%) was a 5:1 isomer mixture by NMR [*N*-methyl signals at δ 3.88 (major) and δ 3.63 ppm (minor)]. Recrystallization of 2.90 g of this material from 85% EtOH (17 ml) gave 0.59 g of the pure major isomer as a colorless, crystalline solid: mp 163–165°; ν_{max} (KBr) 1680 cm^{-1}; λ_{max} (EtOH) 248 nm (ϵ 23200); ^1H NMR ($CDCl_3$–Me_4Si) δ 9.03 (s) 1 H (CO_2H), 8.29–7.25 (m) 8 H (aromatic), 6.57 (s) 1 H (pyrazole), and 3.88 ppm (s) 3 H (OCH_3). Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07; *m/e* 278.1055. Found: C, 73.35; H, 5.27; N, 10.06; *m/e* 278.1029.

B. The pure major isomer (0.10 g) was converted to its acid chloride **20** with $SOCl_2$ (2 ml). Evaporation gave crude **20**, ν_{max} ($CHCl_3$) 1790 and 1750 cm^{-1}, which was treated with warm EtOH (2 ml). Evaporation of this mixture left the colorless ethyl ester hydrochloride **21** as a solid: mp 139–148° dec; ν_{max} (KBr) 3420, 1710 cm^{-1}; λ_{max} (EtOH) 244 nm (ϵ 22200); ^1H NMR (Me_2SO-d_6) δ 12.83 (s) 1 H (NH), 8.10–7.33 (m) 8 H (aromatic), 6.63 (s) 1 H (pyrazole proton), 4.35 (q, J = 7 Hz) 2 H (OCH_2), 4.26 (s) 3 H (NCH_3), and 1.32 ppm (t, J = 7 Hz) 3 H (CH_3). Anal. Calcd for $C_{19}H_{19}N_2O_2Cl$: C, 66.56; H, 5.59; N, 8.17. Found: C, 66.21; H, 5.57; N, 8.07.

Registry No.—**1**, 37564-17-3; **3**, 54665-99-5; **4**, 56978-19-9; **5** (R = Me), 56978-20-2; **5** (R = Me) HCl, 56978-21-3; **5** (R = Et), 56978-22-4; **5** (R = Et) HCl, 56978-23-5; **5** (R = Pr), 56978-24-6; **5** (R = Bu), 56978-25-7; **5** (R = C_5H_{11}), 56978-26-8; **5** (R = C_6H_{13}), 56978-27-9; **5** (R = CH_2CH_2OH), 56978-28-0; **6** (R_1 = R_2 = H), 56978-29-1; **6** (R_1R_2 = $(CH_2)_4$), 56978-30-4; **6** (R_1R_2 = $CH_2CH_2OCH_2CH_2$), 56978-31-5; **6** (R_1 = $C_6H_5CH_2O$; R_2 = H), 56978-32-6; **7**, 56978-33-7; **8**, 56978-34-8; **9**, 21138-13-6; **10**, 56978-35-9; **12**, 56978-36-0; **13**, 39785-21-2; **14**, 56978-37-1; **15**, 56978-38-2; **16**, 39785-18-7; **17**, 39785-19-8; **18**, 39785-20-1; **19**, 56978-39-3; **21** isomer A, 56978-40-6; **21** isomer B, 56978-41-7; **22**, 57014-90-1; **23**, 56978-42-8; methanol, 67-56-1; ethanol, 2348-46-1; propanol, 71-23-8; butanol, 71-36-3; pentanol, 71-41-0; hexanol, 111-27-3; 1,2-ethanediol, 107-21-1; iodomethane, 74-88-4.

References and Notes

(1) E. W. Bousquet, M. D. Moran, J. Harmon, A. L. Johnson, and J. C. Summers, *J. Org. Chem.*, **40**, 2208 (1975).
(2) E. W. Bousquet, U.S. Patent 3,407,206 (Oct 22, 1968).
(3) E. W. Bousquet, U.S. Patent 3,409,425 (Nov 5, 1968).
(4) "Experimental Growth Regulant DPX-1840", Du Pont Information Bulletin, E. I. du Pont de Nemours and Co., Wilmington, Del., March 1971.
(5) B. C. McKusick, U.S. Patent 3,700,689 (Oct 24, 1972).
(6) E. M. Beyer, Jr., *Plant Physiol.*, **50**, 322 (1972).
(7) B. Quebedeaux and E. M. Beyer, Jr., *HortScience*, **7**, 474 (1972).
(8) P. W. Morgan, "Regulation of Ethylene as an Agricultural Practice", Bulletin MP-1018, Texas A & M University, College Station, Texas, Jan 1972.
(9) B. T. Brown, O. Johansen, and W. H. F. Sasse, *Experientia*, **28**, 1290 (1972).
(10) A. L. Johnson, U.S. Patent 3,849,436 (Nov 19, 1974).
(11) E. M. Beyer, Jr., A. L. Johnson, and P. B. Sweetser, in preparation.
(12) G. Leclerc, *C. R. Acad. Sci., Ser. C*, **276**, 1033 (1973).
(13) A referee has commented that 48% HI converts **1** to **8** and **9** to **10** (rather than **12**). Some possible reasons for this difference are (a) the dihydro system **9** is less strained than the pyrazole **1**, as indicated by ir and uv, (b) more importantly, **1** is an *N*-acylpyrazole, whereas **9** is more like a tertiary amide or hydrazide. The former readily undergo cleavage (ref 14, p 96) whereas the latter should be more stable to hydrolysis.
(14) T. L. Jacobs in "Heterocyclic Compounds", Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1957, p 95, states that generally, in the acylation of pyrazoles, only the more stable isomer is obtained, and the less stable isomer (obtained by another method) rearranges readily to the more stable isomer.

(15) Kindly supplied by Dr. R. M. Forbis, Biochemicals Department, E. I. du Pont de Nemours and Co., Experimental Station, Wilmington, Del.
(16) All melting points are uncorrected; ir spectra were determined on Perkin-Elmer 21, 221, and 621 instruments, uv spectra on a Carey 14 instrument, NMR spectra on a Varian Associates A-60 instrument, and mass spectra on Consolidated 103 and 110B (high-resolution) instruments.
(17) K. Kindler, *Justus Liebigs Ann. Chem.*, **450**, 1 (1926).

Conjugate Addition Reactions of Alkali Diphenylmethides to Acrylic Esters

William G. Kofron* and Jacob Mathew

Chemistry Department, The University of Akron, Akron, Ohio 44325

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In contrast to previous failure to obtain conjugate addition products from the reaction of alkali diphenylmethides to acrylic esters, reaction conditions can be selected to afford adducts even from methyl acrylate. Yields of addition products are increased as alkyl substituents are introduced into the acrylate. Certain highly substituted cinnamates do not undergo conjugate addition but instead undergo carbonyl addition to give low yields of ketones.

The addition of anions to conjugated carbonyl compounds has been the object of much study and ranks among the most useful of organic synthetic reactions. The mechanism for the reversible addition of weaker bases (conjugate bases of carbon acids strong enough to be deprotonated by Grignard reagents[1]) to conjugated systems is generally accepted as involving direct addition to the β carbon to produce an enolate (eq 1).[2] Recently the importance of a second mechanism, an electron transfer from the nucleophile to the enone, has been demonstrated (eq 2).[3]

$$N:^- + C{=}C{-}C{=}O \longrightarrow N{-}C{-}C{=}C{-}O:^- \quad (1)$$

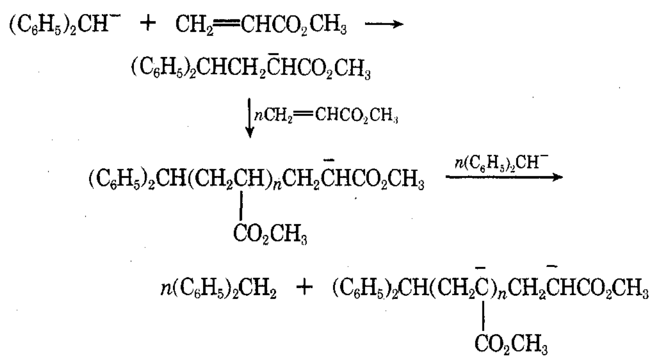
$$N:^- + C{=}C{-}C{=}O \longrightarrow N\cdot + \overbrace{C{\cdots}C{\cdots}C{\cdots}O^-}^{5e} \longrightarrow N{-}C{-}C{=}C{-}O^- \quad (2)$$

Strongly basic nucleophiles, for example, diphenylmethide ion, are less commonly encountered as Michael donors. The reaction with ethyl cinnamate to give ethyl 3,4,4-triphenylbutyrate[4] and with ethyl α-phenylacrylate to give ethyl 2,4,4-triphenylbutyrate[5] and addition to several 1,1-diarylethylenes[6] have been reported, but an attempt to synthesize ethyl 4,4-diphenylbutyrate from potassium diphenylmethide and ethyl acrylate gave no adduct, although the color of the anion was discharged. Instead, polymerization of the ethyl acrylate apparently took place, and diphenylmethane was recovered.

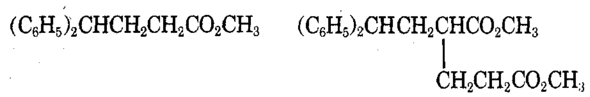
We now find that sodium or potassium diphenylmethide will react with acrylates and substituted acrylates, and that the ease of reaction is remarkably affected by the structure of the acrylate, in a manner not predicted by a consideration of the usual addition mechanism of eq 1.

When sodium diphenylmethide in liquid ammonia was treated with 1 molar equiv of methyl acrylate, 80% of the diphenylmethane was recovered, 8% of a high-boiling ester was obtained along with a large amount of nonvolatile residue, and none of the Michael adduct, methyl 4,4-diphenylbutyrate, was detected. The reaction was interpreted as a polymerization of the methyl acrylate initiated by diphenylmethide ion, and neutralization of the unreacted diphenylmethide ion by the relatively acidic α hydrogens of the polyester (Scheme I). The small amount of distillable ester

Scheme I



presumably corresponded to short chains of self-addition. Since the anionic polymerization of methyl acrylate is itself a series of conjugate additions reactions, it seemed possible to manipulate conditions so that mono adduct **1** could be



1 **2**

obtained. Accordingly, a very dilute ethereal solution of methyl acrylate was added very slowly (2 hr) to sodium diphenylmethide. Work-up of this reaction afforded the mono adduct **1** in 10% yield, 60% of the diphenylmethane, and much nonvolatile material. Polymerization was further minimized by an increase in the mole ratio of sodium diphenylmethide to methyl acrylate to four. From this reaction the mono adduct **1** was obtained in 40% yield, the diadduct dimethyl 2-(2′,2′-diphenylethyl)glutarate **2** was isolated in 10% yield, and 83% (3.3 molar equiv) of the diphenylmethane was recovered. These results can be interpreted as indicating that the affinity of methyl acrylate for