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Kinetic Determinations. Iodine and all salts were reagent grade chemicals. The salts were dried at 120-140° overnight before use. The temperature of the kinetic runs was $30.00 \pm 0.05^{\circ}$, except for those used to determine the activation parameters, which varied from 15.0 to 50.0°. Complete stock solutions were made up at the appropriate temperatures. The procedure for the kinetic runs was that used before.² All rate constants were determined by leastsquares analysis, and the probable errors in individual rate constants averaged 0.5%. Duplicate runs were carried out for each set of conditions, except for runs used for the Hammett plot, for which triplicate determinations were made. Rate constants of the duplicate or triplicate runs usually agreed within 2%. Additional determinations were made if the error was greater. All reported rate constants are the observed rate constants. The true third-order rate constants, k_t (eq 1), can be obtained by dividing the observed rate constants by K (1.55 × 10⁻³ at 30°).²⁰ Activation energies had least-squares errors of 0.1-0.2 kcal and activation entropies of 0.1-0.4 eu.

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Registry No .--- m- Bromophenylpropiolic acid, 29835-28-7; pmethoxy- α,β,β -triiodostyrene, 53060-07-4; p-methyl- α,β,β -triiodostyrene, 53060-08-5; p-bromophenylpropiolic acid, 25294-65-9.

References and Notes

- (1) Taken in part from the Ph.D. Dissertation of V. L. Cunningham, Bryn
- Mawr College, May, 1973. M. H. Wilson and E. Berliner, *J. Amer. Chem. Soc.*, **93**, 208 (1971). (2)
- E. Mauger and E. Berliner, J. Amer. Chem. Soc., 94, 194 (1972)
- S. I. Miller and R. M. Noyes, J. Amer. Chem. Soc., 74, 3403 (1952).
- (5) From the filtrate of the styrene, there was obtained, after acidification, not only the expected unreacted p-methoxy- α,β -diiodocinnamic acid but also some *p*-methoxyphenylpropiolic acid, which indicates some reversibility of the iodination under these conditions. This nonacidic material melted at $49-52^{\circ}$ after one recrystallization from ethanol-water and contained halogen (Beilstein test). The amount
- (6) of material was not sufficient for further analysis. J. A. Pincock and K. Yates, *Can. J. Chem.*, **48**, 3332 (1970); *J. Amer.*
- (7)
- (1) G. A. I. House, and A. Hatsy, *Oct. Biol. Chem.*, **43**, 652 (1970), *B. Amer. Chem. Soc.*, **90**, 5643 (1968).
 (8) See also E. A. Shilov and I. V. Smirnov-Zamkov, *Izv. Akad. Nauk SSSR*, *Otd. Khim. Nauk*, 32 (1951); *Chem. Abstr.*, **45**, 7952 (1951).
- (9) R. C. Fahey and D. J. Lee, J. Amer. Chem. Soc., 90, 2124 (1968); 88, 5555 (1966).
- (10) K. Yates, G. H. Schmid, T. W. Regulski, D. G. Garratt, H. W. Leung, and R. McDonald, *J. Amer. Chem. Soc.*, **95**, 160 (1973). (11) R. C. Fahey, M. T. Payne, and D. J. Lee, *J. Org. Chem.*, **39**, 1124

- (11) R. C. Fahey, M. T. Payne, and D. J. Lee, J. Org. Chem., 39, 1124 (1974).
 (12) M. S. Newman and S. H. Merrill, J. Amer. Chem. Soc., 77, 5549 (1955).
 (13) F. G. Baddar, L. S. El-Assal, and N. A. Doss, J. Chem. Soc., 461 (1955).
 (14) J. I. Jones and T. C. James, J. Chem. Soc., 1600 (1935).
 (15) I. Benghiat and E. I. Becker, J. Org. Chem., 23, 885 (1958).
 (16) M. Reimer and E. Tobin, J. Amer. Chem. Soc., 63, 2490 (1941).
 (17) M. M. Otto, J. Amer. Chem. Soc., 56, 1393 (1934).
 (18) J. G. Kirchner, "Technique of Organic Chemistry," Vol. XII, E. S. Perry and A. Weissberger, Ed., Interscience, New York, N.Y., 1967, pp 151–176. 176.
- (19) L. F. Fieser, "Organic Experiments," D. C. Heath, Boston, Mass., 1964, pp 100 and 101.
- (20) E. N. Rengevich and E. A. Shilov, Ukr. Khim. Zh., 28, 1080 (1962); Chem. Abstr., 59, 4590f (1963).

Reactions of Benzaldehyde and Analogs with Ethyl Cyanoacetate in Ethanolic Ammonia¹

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Reactions of benzaldehyde and analogs with ethyl cyanoacetate in ethanolic ammonia produce α -cyanohydrocinnamamides, 2,6-dihydroxy-3,5-dicyano-4-phenylpyridines, and dimeric products. Similar reactions in aqueous ammonia or Cope-Knoevenagel condensations also produce some of these products. Those facts suggest that the reaction mechanisms are the same. The report elucidates the structures of dimeric products such as 3,5-dicyano-4,6-diphenyl-5-ethoxycarbonyl- α -piperidones.

LeMoal, et al.,² and Nagai, et al.,³ have reported the Cope-Knoevenagel condensation of para-substituted berizaldehydes with excess ethyl cyanoacetate to produce ethyl α -cyano-para-substituted cinnamates 1, but have not yet reported that the reaction products were always accompanied by trace amounts of high melting by-products. In the case of p-nitrobenzaldehyde, the above reaction gave a noticeable amount of a dimeric product (4d), which was assigned a cyclobutane structure (6) by LeMoal, $et \ al.^2$ From benzaldehyde and ethyl cyanoacetate, a similar dimeric product (4) was obtained by Carrick⁴ with sodium ethoxide in ethanol or by Issoglio⁵ and Guareschi⁶ with aqueous ammonia; however, these authors did not elucidate the structure of that product.

Table I shows the results of the reactions of para-substituted benzaldehydes with ethyl cyanoacetate in ethanolic ammonia at 0°. The formula for 3, the ammonium salt of 2,6-dihydroxy-3,5-dicyano-4-(para-substituted phenyl)pyridines,^{5,6} has been assigned on the basis of spectral data.

Table I Product Yield (mol %) for the Reactions of Para-Substituted Benzaldehydes and Ethyl Cyanoacetate in Saturated-Ethanolic Ammonia at 0°

		Product ^a	
Х	2	3 ^b	4
н		6.7	38.4
MeO	10.1	9.6^{c}	15.5
C1	23.2	38.7°	
\mathbf{NO}_2	21.2	34.6°	

^a At the similar reactions in concentrated aqueous ammonia, $X = H^6$ and $X = NO_2$,⁵ respectively, produced 2, 3, and 4. Ir data of 2a (Nujol) 3380 and 3195 cm⁻¹ (NH₂), 2250 cm⁻¹ (CN), 1660 and 1620 cm⁻¹ (amide C=O). ^b Yields of 3 of Cope-Knoevenagel condensation: X = H, 0.002%; X = MeO, 0.001%; X = Cl, 0.72%, $X = NO_2$, 1.18%. These compounds are not dehydrated. ^c Monohydrated.

			Nmr and	l Uv Spectral Data	of 2		
		δ	ppm in DMSO-d ₆				
	Benzene ring			Side chain			
	H _a H _b	OCH3	СН2	СН	NH2	λ_{max} (EtOH), m μ (log ϵ)	
Compound	(A ₂ B ₂)	(s)		(ABX)	(\$)	(in neutral medium)	
2a	7.26		$\begin{array}{c} J_{AB} \\ J_{AX} \\ J_{BX} \\ 3.10 \end{array}$	= 13 Hz = 3.5 Hz = 6.5 Hz 3.96	7.46	270 (3.89)	
2 b	6.85 7.18	3.72	3.03	3.88	7.75 7.70 7.38	203 (3.94), 227 (4.04), 276 (3.28), 283 (3.19)	
$2c^{\alpha}$	7.33		3.11	3.98	7.50	202 (3.70), 221 (3.93)	
2d	8.20 7.60		3.30	4.08	7.83	202 (4.10), 215 s (3.85), 268 (4.01)	

Table II Nmr and Uv Spectral Data of 2

^a Anal. data of 2c, mp 180–181°. Calcd: C, 57.55; H, 4.31; N, 13.43; Cl, 17.02. Found: C, 57.37; H, 4.07; N, 13.22; Cl, 17.06.

Table III Nmr and Uv Spectral Data of 3

		i	5 ppm in DMSC	^{D-d} 6		
	Pyridi	ne ring		Benzene ring		
	OH	NH4	Ha	нь	осн3	λ_{\max} (EtOH), m $_{\mu}$ (log ϵ)
Compd	(s)	(s) or (t)	(A ₂	^B ₂)	(s)	(in neutral medium)
3a	10.85	7.32	7.	55		206 (4.30), 259 (4.32), 345 (4.28)
3b	10.55	7.05	7.00	7.33		207 (4.29), 263 (4.37), 287 (3.67), 344 (4.30)
$\mathbf{3c}^{a}$	10.70	7.04	7.51	7.46	3.80	206 (4.33), 259 (4.34), 346 (4.24)
3d	10.90	7.23	8.45	7.83		203 (4.40), 266 (4.42), 310 (4.08), 345 (3.97)

^a Anal. (mp 320-325°). Calcd: C, 50.91; H, 3.59; N, 18.27; Cl, 11.58. Found: C, 51.66; H, 3.40; N, 18.05; Cl, 12.05.



The ir spectra of 3 have absorption bands at about 3200-3400 cm⁻¹, attributable to N-H of the ammonium salts, and a characteristic very strong band at about 2200 cm⁻¹ due to C=N. The nmr spectra of 3 in DMSO- d_6 (Table III) show a triplet signal at 7.50–6.0 ppm, corresponding to ${}^{14}N{-}^{1}H$ (J_{NH}) = 50 Hz) of the ammonium salts; furthermore, they show a signal at 10.65 ppm of the OH or NH group. The base peak (M - 17)⁺ of the mass spectra of 3, generally, corresponds to the 2,6-dihydroxy-3,5-dicyano-4-(para-substituted phenyl)pyridines. The second strongest peak is m/e (M - 60)⁺, the fragmentation of (M - 17)⁺-(M - 60)⁺ is supported by the following metastable peaks: 3a m^{*} = 159, 3b m^{*} = 188, 3c m^{*} = 192.

'The dimeric products (4) were assigned their structures on the basis of their similarity in nmr spectra to compound 5 (4. N-CH₃ for N-H)⁷ as shown in Table IV. We tried several chemical reactions on 4a to exclude the structures 6 and 7 that were proposed by Böhme.⁸ On hydrolysis in concentrated hydrochloric acid-acetic acid, 4a afforded β phenylglutaric acid and benzaldehyde, the latter being characterized as a 2,4-dinitrophenylhydrazone. 4a does not possess a primary amino group as shown in 7 because it could not be acetylated with acetic anhydride. When 4a was distilled at 160-170° (3 mm) (bath 225-230°), it afforded α -cyanocinnamamide and ethyl α -cyanocinnamate in the ratio of 1:1, and no other substances were found in the distillate. This fact also excludes the cyclopentane formula 7. Corresponding to this fact, the mass spectra of 4 show the peak which agrees with the molecular weight of α -cyano-para-substituted cinnamamide as the base peak and the peak which agrees with the molecular weight of Reactions of Benzaldehyde with Ethyl Cyanoacetate

ethyl α -cyano-para-substituted cinnamate in appropriate intensity (4a, 23%, 4b, 77%, 4d, 80%).

The reaction of 4a with p-nitrobenzyl bromide in the presence of sodium carbonate in 95% ethanol produced 8, as the main product, and 9. Compound 8, a mono-para-nitrobenzyl derivative of 4a, mp 256-267°, was assigned its structure from the nmr spectrum. The spectrum lost the signal of AB type at 4.51 ppm (H_a, d) and 4.75 ppm (H_b, d) of 4a and showed a new signal at 3.92 ppm and a new signal of AB type at 4.32 ppm (H_h, d) and 3.52 ppm (H_i, d), corresponding to the introduction of the p-nitrobenzyl group into H_b of 4a. The structure of compound 9, a di-p-nitrobenzyl derivative of 4a, mp 284-285°, was also assigned from its nmr spectrum. The nmr spectrum of 9 is similar to that of 8, but shows another signal of AB type at a lower magnetic field corresponding to a N-p-nitrobenzyl substitutent with disappearance of the N-H signal of 8.

Compound 10, mp 192–193°, is produced by the hydrolysis of 8 with concentrated hydrochloric acid-acetic acid. The ir spectrum of 10 has the bands $3100-3200 \text{ cm}^{-1}$ (NH), and the bands 1725 and 1685 cm^{-1} (C==O); these absorption bands, characteristic of glutarimide, indicate that structure 10 is correct.



The proposed reaction mechanisms for the formation of 2, 3, and 4 are considered as follows. First, the para-substituted benzaldehydes react with ethyl cyanoacetate to produce ethyl para-substituted benzylidene cyanoacetate (may be phenyl group vs. ester group are trans). For electron attracting substituents (NO₂, Cl), the esters undergo rapid ammonolysis to the amides, which in turn react with excess ethyl cyanoacetate to produce the intermediate 11. The ring closure of the intermediate 11 affords the 4-(para-substituted phenyl)dihydropyridines, which would give 3 by oxidation-reduction reactions with the para-substituted benzal cyanoacetamides, through the intermediate 12. The

					Nmr	(mqq ô)	and Uv S _F	ectral I)ata of 4,	5, 8, and 9				
			Benze	ne ring			Ĥ	etero ring		Benzyl	CH ₂	Ester		
Comp	d Solvent	I _d H _e (A ₂ B ₂)	H _f H _g (A ₂ B ₂)	$H_1 H_m$ (A ₂ B ₂)	H _n H _o (A2B2)	ocH ₃ (s)	$\begin{array}{c} H_{a} H_{b} \\ (AB) \\ J_{AB} = 13 \text{ Hz} \end{array}$	Н _с (s)	NH NCH ₃ (s) (s).	$\begin{array}{c} {\rm H_h} & {\rm H_i} \\ {\rm (AB)} \\ {\rm (AB)} \end{array} = {\rm 14 \ Hz} \end{array}$	$\begin{array}{ll} H_{j} & H_{k} \\ (AB) \\ J_{AB} = IS H_{z} \end{array}$	CH ₂ CH ₃ (q) (t)	λ _{max} (EtOH) in neutral medium	, mu (log e) in basic medium
4a	$DMSO-d_6$	7.40	7.40			7	4.514.73	5.51 7	. 83			3.86 0.83	215 (4.13), 230 (2.60),	218 (4.13), 257 (4.16)
4b ^a	DMSO- d_6 6.	96 7.39	6.96 7.42			3.72	4.44.4.84	5.30 8.	80			3.83 0.82	205 (2.70), 205 (3.78), 233 (3.84), 277 (2.80), 264 (5.77)	207 (3.82), 233 (3.99), 253 s (3.78)
4d	DMSO- d_6 8.	31 7.65	8.31 7.83			4	1.905.28	5.619.	20			3.95 0.88	281 (2.77) 210 (4.35), 265 (4.36)	210(3.47), 267 (4.49)
α α	DMSO- d_6	7.37	7.37	00 4 69 0		V. 6	4.53 5.20	5.35 5.00 £	2.67	1 23 2 53		3.38 (s)	919 (4 49)	
ი ი	coci, CDCI,	7 25	7 90-7 37	8 09 6 97	8 09 7 47	, c.	51	4 80 0	°.	3.95.3.19	5.064.31	3.62 0.56	265 (3.97) 208 (4.19).	210 (4.34), 270
							-						270 (3.80)	(3.82)
ر ⁴ ا	Anal. data of 4 .63. 8, mp 265-	b, mp 211-21 -267°. Calcd:	4°. Caled: C, 66. C, 68.50; H, 4.72	51; H, 5.31; N ; N, 11.02. Fo	1, 9.69. Found und: C, 68.26	I: C, 66.6 3; H, 4.86	0; H, 5.29; ; N, 10.98.	9, m nmr	p 284-285 data of m	°. Calcd: C, 67 ethyl ester of 5	7.18; H, 4.51; 1 5.	N, 10.88. Found:	C, 67.33; H, 4.65;	N, 1084. ^b Lit. ⁷ shows

Table IV



para-substituted benzal cyanoacetamides were reduced to 2 at this stage. Compound 3 may be partly formed by the air oxidation of the dihydropyridines. On the other hand, the ethyl α -cyanocinnamates with an electron donating group in the para position, owing to the slow formation of amides, as Dietz suggested,⁷ react with the para-substituted benzylidene cyanoacetamides, and then afford ring closing products (4). Compound 4 were obtained in a single stereoisomer. The formation of these compounds is apparently thermodynamically controlled; therefore, the conformation is the most stable one in 13, proposed by the inspection of the Dreiding model.

Experimental Section⁹

The Cope-Knoevenagel Condensation of p-Nitrobenzaldehyde with Ethyl Cyanoacetate. In a 200-ml round-bottomed flask with a continuous water separator, a mixture of 25 g $\left(0.17\right.$ mol) of p-nitrobenzaldehyde, 38 g (0.34 mol) of ethyl cyanoacetate, 13 g (0.17 mol) of ammonium acetate, and 32 g (0.53 mol) of acetic acid in 100 ml of benzene was refluxed in an oil bath at 140-150° for 5 hr, while 5.6 ml of an aqueous layer containing acetic acid and ammonium acetate separated. Yellow crystals separated out in the flask and were collected by vacuum filtration and recrystallized from 1.4 l. of 99% ethanol. The crystals that separated first contained 13.6 g of 1 and were identified by ir analysis. The mother liquor was concentrated to 250 ml, and the crystals that separated out were collected and recrystallized from 300 ml of 99% ethanol. These crystals contained 1.95 g of 1, and subsequently 0.9 g of 4 was separated and identified by ir analysis. On the other hand, the mother liquor (250 ml) that was concentrated and the crystals which separated already were again concentrated to 100 ml; 0.6 g of 3 was separated out from this solution.

The benzene layer, after it was washed with a saturated sodium carbonate solution and 10% sodium chloride solution, was dried on sodium sulfate, and then concentrated. The residual crystalline substance produced 5.1 g of 1 by recrystallization with 400 ml ethanol.

On the whole, three kinds of the following pure products were obtained in this experiment. **1d**, 20.7 g (yield 49.5%), mp 172–174°, light yellow needles. **3d**, 06. g (yield 1.11%), mp over 300°, yellow needles; ir (KBr) 2840–3540 cm⁻¹ (NH₄+), 2220 cm⁻¹ (CN), 1630 cm⁻¹ (2,2-dihydroxypyridine), 1525, and 1365 cm⁻¹ (NO₂). **4d**, 0.9 g (yield 2.36%), mp 202–204°, white scales or fine white needles; ir (Nujol) 3200 cm⁻¹ (NH), 2260 cm⁻¹ (CN), 1755 cm⁻¹ (ester C==O), 1690 cm⁻¹ (amide C==O), 1520, and 1350 cm⁻¹ (NO₂).

A similar procedure was used for the condensation of 25 g (0.18 mol) of *p*-chlorobenzaldehyde and 35 g (0.31 mol) of ethyl cyanoacetate. This procedure produced 24.84 g (yield 62.3%) of 1c (white plates, mp 91–92.5°) and 233 g (yield 0.72%) of 3c (pale yellow fine needles, mp 320-325°; ir (Nujol) 3440, 3200, and 3070 cm⁻¹ (NH₄⁺), 2210 cm⁻¹ (CN), 1610 cm⁻¹ (2,2-dihydroxypyridine), 830 cm⁻¹ (para-substituted benzene), 770 cm⁻¹ (C-Cl)).

Reaction of Benzaldehyde and Ethyl Cyanoacetate in Ethanolic Ammonia. To a solution of ammonia, 14 g (1.0 mol) in 200 ml of 95% ethanol, 53 g (0.5 mol) of benzaldehyde and 113 g (1.0 mol) of ethyl cyanoacetate were added; the mixture was kept in a refrigerator for 10 days with occasional stirring. Yellow crystals precipitated from the solution and were collected by vacuum filtration, washed twice with 100-ml portions of ethanol, and dried. The crude material, mp over 180°, weighed about 87 g. Further, the filtrate was allowed to stand in the refrigerator, to produce 1.51 g of the crystals (4a), mp 207-209°. The crude substance (87 g) having three kinds of CN bands was recrystallized several times from 95% ethanol (1000 ml in total) under continuous monitoring of the infrared spectra, to afford the following three kinds of pure compounds. Cyanoacetamide, 4.3 g, mp 118-121° (lit.¹⁰ 119.5°). 3a, 8.5 g (yield 6.7%), mp over 300°, white or pale yellow needles; ir (KBr) 3400 cm^{-1} (OH), $3200-2400 \text{ cm}^{-1}$ (NH₄⁺), 2200 cm^{-1} (CN), 1600 cm⁻¹ (2,2-dihydroxypyridine), 1510 and 1470 cm⁻¹ (hetero C-N), 1390 cm⁻¹ (pyridine ring C-N), 1250 and 1220 cm⁻¹ (C-O), 700-680 cm⁻¹ (monosubstituted benzene). **4a**, 35.8 g (38.4%), mp 208-210°, white needles; ir (Nujol) 3250 cm^{-1} (NH), 2255 cm^{-1} (CN), 1740 cm⁻¹ (ester C=O), 1679 cm⁻¹ (amide C=O), 1270, 1250 and 1005 cm⁻¹ (ester C-O-C). 2a was not afforded in any amount.

Similarly, 68 g (0.5 mol) of *p*-methoxybenzaldehyde afforded the following three pure compounds. **2b**, 10.3 g (yield 10.1%), mp 170–171°, white needles; ir (Nujol) 3400, 3320 and 3210 cm⁻¹ (NH₂), 2255 cm⁻¹ (CN), 1670 and 1620 cm⁻¹ (amide C==O), 1245 cm⁻¹ (aromatic ether). **3b**, 14.6 g (yield 9.7%), mp 302–305°, colorless fine needles, ir (Nujol) 3400–3200 cm⁻¹ (OH and NH₄⁺), 2215 cm⁻¹ (CN), 1600 cm⁻¹ (amide C==O), 1250 cm⁻¹ (arom. ether), 840 cm⁻¹ (para-substituted benzene), 1180 and 1030 cm⁻¹ (C–O–C). **4b**, 16.8 g (yield 15.5%), mp 211–214°, white needles; ir (Nujol) 3300 cm⁻¹ (MH), 2255 cm⁻¹ (CN), 1735 cm⁻¹ (ester C=O), 1690 cm⁻¹ (amide C==O), 1610 cm⁻¹ (C==C), 1250, 1180, and 1090 cm⁻¹ (ester C–O–C), 1020 cm⁻¹ (arom. ether), 850 and 830 cm⁻¹ (para-substituted benzene).

p-Chlorobenzaldehyde (25 g, 0.18 mol), under a similar procedure, afforded the following two pure compounds. **2c**, 8.2 g (yield 23.2%), mp 180–181°, colorless prisms; ir (Nujol) 3380 and 3180 cm^{-1} (NH₂), 2250 cm⁻¹ (CN), 1685 cm⁻¹ (amide C==0), 1095 and 1015 cm⁻¹ (C-H), 840 cm⁻¹ (para-substituted benzene), 790 cm⁻¹ (C-Cl). **3c**, 20.2 g (yield 38.7%), mp over 300°, fine long needles.

p-Nitrobenzaldehyde (25 g, 0.17 mol), under a similar procedure, afforded the following two pure compounds. **2d**, 7.7 g (yield 21.2%), mp 169–170°, pale yellow needles; ir (Nujol) 3440 and 3300 cm^{-1} (NH₂), 2240 cm^{-1} (CN), 1670 cm^{-1} (amide C=O), 1610 cm^{-1} (C=C), 1510 and 1340 cm^{-1} (NO₂), 850 cm^{-1} (para-substituted benzene). **3d**, 18.1 g (yield 34.6%), mp over 300°, deep yellow long needles.

Hydrolysis of 4a with Concentrated Hydrochloric Acid and Acetic Acid Solution. A mixture of 19 g (0.051 mol) of 4a, 200 ml of concentrated hydrochloric acid, and 100 ml of acetic acid was refluxed for 4 hr (bath temperature 130–140°). After cooling, the reaction mixture was diluted with 600 ml of water, then extracted with three 150-ml portions of ether. The ethereal solution was dried and evaporated. The residual oil was allowed to crystallize; the crystals were collected, and dried, weighing 6.83 g. Recrystalliz zation from water gave white crystals, 5.23 g (yield 49.3%), mp 141–142°. From elementary analysis, melting point, and nmr spectra, this substance was found to be β -phenylglutaric acid (lit.¹¹ mp 142°): nmr (acetone— d_6) δ 10.28 (s, 2, COOH), 7.25 (5, benzene), 3.63 (q, 1, H_c), 2.75 (d, 2, $J_{AC} = 6$ Hz, H_A), 2.73 (d, 2, $J_{BC} = 8$ Hz, H_B), J_{AB} , under investigation. Anal. Calcd for C₁₁H₁₂O₄: C, 63.45; H, 5.81. Found: C, 63.40; H, 5.64.

Hydrolysis of 4a with Ethanolic Hydrochloric Acid in Presence of 2,4-Dinitrophenylhydrazine. A mixture of 10.0 g (0.027 mol) of 4a, 5.5 g (0.028 mol) of 2,4-dinitrophenylhydrazine, 200 ml of concentrated hydrochloric acid, and 200 ml of 95% ethanol was refluxed for 7 hr at a bath temperature of $110-120^\circ$. The mixture was filtered while hot, to give orange-red crude crystals, mp 245–246°, which weighed 7.76 g (yield 99%), and recrystallization from 99% ethanol yielded the pure substance, mp 245–246°. Anal. Calcd for $C_{13}H_{10}N_4O_4$: C, 54.54; H, 3.52; N, 19.58. Found: C, 54.50; H, 3.68; N, 19.71.

Pyrolysis of 4a. Compound **4a**, 2.0 g (5.3 mmol), was distilled in a Hauben flask at 160–170° (3 mm) (bath temperature, 225–230°). The fore run (783 mg) crystallized upon standing. The nmr spec-

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trum showed this fraction to consist of 70.5% of α -cyanocinnamamide and 29.5% of ethyl α -cyanocinnamate. The after run (730 mg) is a pale yellow oil which crystallized gradually too. The nmr spectrum indicated this fraction to be composed of 27.7% of α -cyanocinnamamide and 72.3% of ethyl α -cyanocinnamate. Thus, α cvanocinnamamide and ethyl α -cvanocinnamate were obtained in 56.7 and 43.3% vield in total.

3.5-Dicyano-5-ethoxycarbonyl-3-p-nitrobenzyl-4,6-diphenyl-2-oxopiperidine (8) and 3,5-Dicyano-5-ethoxycarbonyl-1,3-di-p-nitrobenzyl-4,6-diphenyl-2-oxopiperidine (9).¹² mixture of 3.6 g (9.6 mmol) of 4a and 21 g of anhydrous sodium carbonate in 100 ml of 95% ethanol was refluxed to produce a clear vellow solution. To this solution was added a hot solution of 42 g (20 mmol) of p-nitrobenzyl bromide in 100 ml of 95% ethanol. The mixture was refluxed for 3 hr on a steam bath. Pale yellow crystals precipitated out. The organic layer containing the yellow crystals was separated by decantation from the insoluble sodium carbonate while hot. Pale yellow crystals were collected by vacuum filtration from the ethanol solution, washed with a small amount of water, and then dried. The crude white crystals, mp 275-279°, weighed 1.01 g (yield 16.3%); 1.0 g of the crude crystals were recrystallized from 60 ml of acetone to afford 255 mg of a pure substance (9), mp 284--285°. The filtrate from the crude crystals stood at room temperature and precipitated white crystals, 1.24 g (yield 25.4%), mp 247-249°. The crude white crystals, 1.2 g, were recrystallized from 200 ml of 99% ethanol to give 930 mg of a pure substance (8), mp 265-267°, as white crystals. 9, ir (Nujol) 2250 cm⁻¹ (CN), 1745 cm⁻¹ (ester C=O), 1655 cm⁻¹ (amide C=O), 1605 cm⁻¹ (C=C), 1520 and 1350 cm⁻¹ (NO₂), 1260 or 1220 and 1110 cm⁻¹ (ester C-O-C), 855 and 840 cm⁻¹ (para-substituted benzene), 700 cm⁻¹ (Data Substituted benzene), 100 cm⁻¹ (Data Substituted benzene), (monosubstituted benzene). 8, ir (Nujol) 2250 cm⁻¹ (CN), 1733 cm⁻¹ (ester C=O), 1695 cm⁻¹ (amide C=O), 1520 and 1340 cm⁻¹ (NO_2) , 1250 and 1110 cm⁻¹ (ester C–O–C), 850 cm⁻¹ (para-substituted benzene), 700 cm^{-1} (monosubstituted benzene).

3-p-Nitrobenzyl-4-phenyl-2,6-dioxopiperidine (10). Compound 8, 7.10 g (0.014 mol), was refluxed in a mixed solution of 50 ml of concentrated hydrochloric acid and 100 ml of acetic acid for 8 hr, to give a yellow solution which contained a small amount of insoluble substance 9. After cooling, the insoluble 9 was filtered off, 500 ml of water was added to the filtrate, and the mixture was extracted with three or four portions of 200 ml of ether. The ethereal solution was dried and distilled, to give 4.60 g of the residue. The residue was dissolved into 10 ml of hot 95% ethanol, and stood for several days at room temperature to precipitate considerable amounts of crystals. The crystals were collected, washed with 5 ml of cold ethanol, and then dried. The crude product, mp 155-160°,

1.86 g (yield 41.1%), was recrystallized from acetone to give pure 10: mp 191-192°; ir (Nujol) 3200 and 3100 cm⁻¹ (NH), 1725 and 1685 cm⁻¹ (imide C=O), 1959 cm⁻¹ (C=C), 1510 and 1350 cm⁻¹ (NO₂), 1320 cm⁻¹ (-CH₂-), 1240 cm⁻¹ (C--C-C), 1170 cm⁻¹ $(C-CH_2-C)$, 860 cm⁻¹ (para-substituted benzene); uv max (95%) C₂H₅OH), in neutral medium, 206 m μ (log ϵ 4.51), 275 (4.00); in alkaline medium, 206 mµ (4.67), 235 (4.14), 278 (4.05); in acidic medium, 205 m μ (4.43) and 276 (4.02); nmr (acetone- d_6) δ 9.61 (s, 2, NH), 8.01 and 7.25 (A $_2B_2$, 4, para-substituted benzene), 7.33 (s, 5, monosubstituted benzene), 3.45-3.73 (m, 6, CH2-CH-CH-CH- CH_2).

Registry No.-1c, 2286-35-3; 1d, 2286-33-1; 2a, 6731-58-4; 2b, 21739-28-6; 2c, 52906-62-4; 2d, 52906-63-5; 3a, 52906-64-6; 3b, 6327-92-0; 3c, 52906-65-7; 3d, 52906-66-8; 4a, 52906-67-9; 4b, 52906-68-0; 4d, 52906-69-1; 8, 52906-70-4; 9, 52906-71-5; 10, 52906-72-6; benzaldehyde, 100-52-7; p-methoxybenzaldehyde, 123-11-5; p-chlorobenzaldehyde, 104-88-1; p-nitrobenzaldehyde, 555-16-8; ethyl cyanoacetate, 105-56-6; β -phenyl
glutaric acid, 4165-96-2; benzaldehyde 2,4-DNPH, 1157-84-2.

References and Notes

- (1) Presented in part at the Third International Congress of Heterocyclic Chemistry, Sendai, Japan, 1971. (2) H. LeMoal, R. Carrie, A. Fougand, M. Bargain, and C. Sevellec, *Bull.*
- Soc. Chim. Fr., 1033 (1966).
- W. Nagai, T. Miwa, Nippon Kagaku Zasshi, 89, 958 (1968). (3) (4) J. T. Carrick, J. Prakt. Chem., [2], 45, 500 (1892); Chem. Zentralbl.,
- 41 (1892). (5) G. Issoglio, Atti Reale Accad. Sci. Torino, 39, 20 (1903); Chem. Zen-
- (a) Isosofficial Attractional Accas, Sci. Torino, 33, 20 (1903), Orient. 2214 tralbl., 876 (1904).
 (b) I. Guareschi, Atti Reale Accad. Sci. Torino, 37, 15, 16 (1901); Chem. Zentralbl., 118 (1899); 699 (1902).
 (7) G. Dietz, W. Fiedler, and G. Faust, Chem. Ber., 100, 3127 (1967).
 (8) H. Böhme and S. Ebel, Chem. Ber., 98, 1819 (1965).
 (9) Meinerschin, Attractional Accassion and Accassion and

- Mciroanalyses were performed by the Microanalytical Laboratories of Kyoto University; infrared spectra were determined by means of a Per-(9) kin Elmer 180 spectrometer, ultraviolet spectra by means of a Perkin Elmer 202 spectrometer, nmr spectra by means of a Hitachi R-20-B (60 MHz) and a JEOL PS-100 (100 MHz) spectrometer, and mass spectra "The Merck Index of Chemicals and Drugs," Merck, Rahway, N. J.,
- (10)1952, p 296.
- (11) E. H. Rodd, Chem. Carbon Compounds, B, 3, 946 (1956)
- In a run using 7.5 g of **4a**, 8.6 g of *p*-nitrobenzyl bromide, and 4.2 g of anhydrous sodium carbonate in 150 ml of 95% ethanol, 9.77 g of prod-uct was obtained. Recrystallization from ethanol, under monitoring with ir spectra, afforded 8, mp 264–265°, 6.514 g (yield 64.1%); and 9, mp 275–278°, 0.857 g (yield 6.6%).

Studies Directed toward a Mitomycin Synthesis

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Alkylations of heterocyclic anion 7 with chloromethyl ethers followed by photooxidation afforded products with the essential framework of the mitomycin antibiotics. A generalized scheme for attaching aziridines to this carbon framework was developed. It involved a photochemical ring contraction of triazolines in the presence of a triplet quencher so as to suppress subsequent photochemistry of the tetracyclic products which may serve as mitomycin models.

The mitomycins (1) are a class of antibiotics of wideranging activity. Since their structures were first elucidated in 1962,^{1,2} there have been a variety of synthetic approaches to their framework and that of the closely related aziridinomitosenes (2). The majority of published routes are concerned with the formation of the tricyclic pyrrolo[1,2-a]indole ring system A. The choice of the ultimate bond to be





mitomycin A, $X = CH_3O$; $Y = CH_3$; Z = Hmitomycin B, $X = CH_3O$; Y = H; $Z = CH_3$ mitomycin C, $X = NH_2$; $Y = CH_3$; Z = Hporfiromycin, $X = NH_2$; $Y = CH_3$; $Z = CH_3$