Heterocyclic N-Oxides as Synthetic Intermediates. III.[1] Conversion of 1,3,4-Oxadiazin-6-one 4-Oxides to Substituted Butenolides[2]

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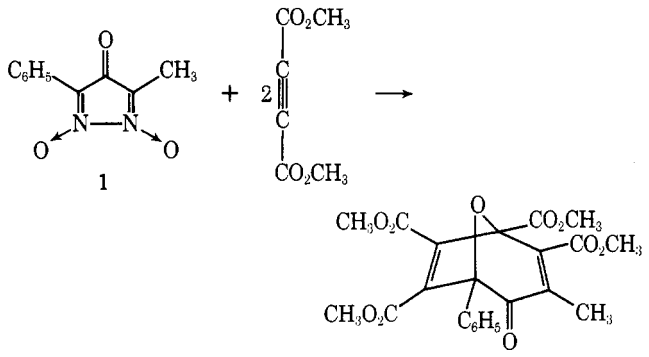
Received June 24, 1975

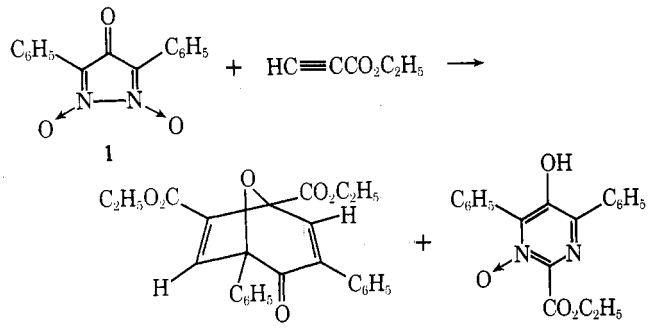
Cycloaddition of acetylenes and acetylenic esters to 1,3,4-oxadiazin-6-one 4-oxides (3) produces 3- and/or 5-acyl butenolides (4 and 5) in good yields. The degradation of these acyl lactones by bases to the parent lactones and succinic acid derivatives is described. A mechanism for the transformation involving a rearrangement of the primary cycloadduct, a fused Δ^4-isoxazoline, and subsequently a novel acyl migration step is proposed.

We have reported two reactions in which heterocyclic N-oxides undergo deep-seated transformations during cycloaddition with acetylenic dipolarophiles to produce new heterocycles. Treatment of 2-methyl-5-phenyl-3,4-diazacyclopentadienone 3,4-dioxide (1) with dimethyl acetylenedicarboxylate produced the bicyclic enone **2**.[1a]



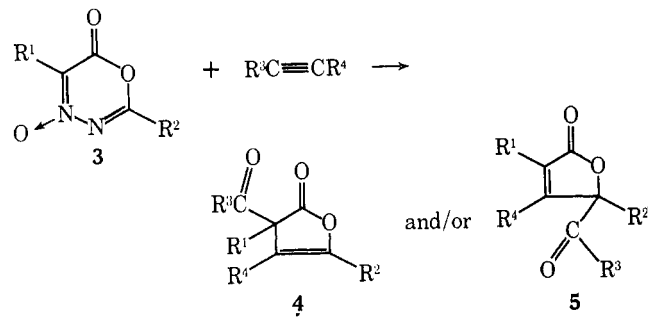
1 2

When the 2,5-diphenyl analog of 1 was treated with ethyl propiolate, an enone analogous to **2** was obtained, but in addition a pyrimidine derivative was also produced.[1b]



1

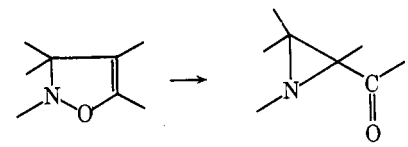
Synthesis of Butenolides. We have now found that 1,3,4-oxadiazin-6-one 4-oxides,[4] **3**, react with a variety of acetylenes to produce acyl butenolides, **4** and **5**, the exact



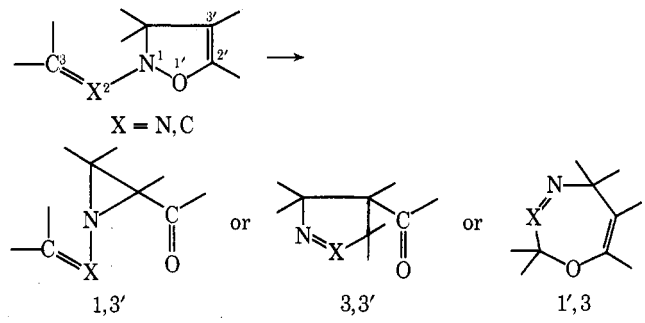
3 4 and/or 5

structure of which apparently is dependent upon the nature of the substituents in both the heterocycle and the acetylene (Table I). The structures of the butenolides are based on elemental analyses, spectral information (see Experimental Section), chemical degradation, and independent synthesis of degradation products. It should be noted that this reaction appears to be a general reaction of acetylenes and is not limited to those with electron-withdrawing groups.

Mechanism of Formation. The transformations previously reported[1] and the present conversion of the oxadiazinone oxides to acylbutenolides can be understood in terms of rearrangements of a first-formed Δ^4-isoxazoline. Baldwin and his coworkers[5] have shown that simple Δ^4-isoxazolines can isomerize to ketoaziridines. Recently there



have been reports of cycloaddition reactions of complex heterocyclic N-oxides which probably involve variations of this simple process.[6,7] Analogously N-unsaturated derivatives form heterologs of a Cope system.[8] Pyridine and quin-



X = N, C

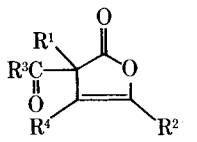
1,3′ 3,3′ 1′,3

oline N-oxides undergo reactions with acetylenes and benzyne that appear to involve a 1,5 shift after formation of a bicyclic Δ^4-isoxazoline.[9]

In the present case the Δ^4-isoxazoline intermediate **6** is thermally labile and rearranges in a fashion analogous to the Cope rearrangement of 1,5-dienes. The stereochemistry illustrated in **7** is that expected from a concerted 3,3-sigmatropic rearrangement. The products (**4** and/or **5**) can then result from the loss of nitrogen and the migration of the acyl group[10] to either of the two carbons formerly attached to nitrogen in **7**. The trends in this migration can be explained by assuming the intermediacy of a dipolar intermediate **8**.

First it should be noted that an acyl group always migrates in preference to carbalkoxy.[11] Then the nature of R^1 and R^3 play an important role in the migratory outcome. Migration of the acyl group (R^3CO) to the negative end of

Table I
Properties of Butenolides[f]



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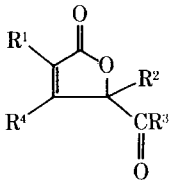
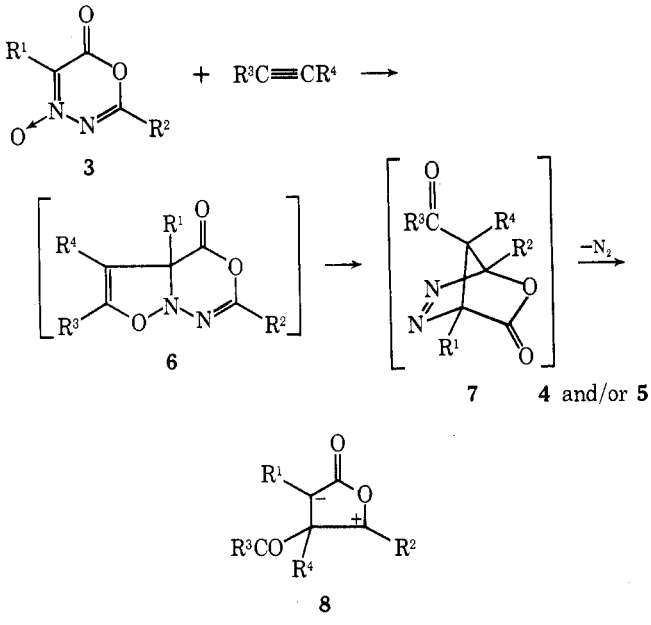


5

Compd	R^1	R^2	R^3	R^4	Mp, °C	Yield, %	Solvent	Procedure and reaction time, hr	Ir, cm^{-1} [a] Lactone C=O	Ir, cm^{-1} [a] Enol C=C	NMR, δ [b] Ester CH_3 (R^4)	NMR, δ [b] R^1	NMR, δ [b] Misc
4a	C_6H_5	C_6H_5	CO_2CH_3	CO_2CH_3	169–170 (CH_3OH)	75	Benzene	A-24	1810	1620	3.65		O=CCO_2CH_3, 3.85
4b	CH_3	C_6H_5	CO_2CH_3	CO_2CH_3	103–104 (hexane)	92	Heptane	A-24	1805	1625	3.66	1.7, s, 3	O=CCO_2CH_3, 3.81
4c	C_2H_5	C_6H_5	CO_2CH_3	CO_2CH_3	*c*	98	Heptane	B-24	1805	1625	3.65	2.22, q, 2 0.90, t, 3	O=CCO_2CH_3, 3.79
4e	CH_3	C_6H_5	C_6H_5	CO_2CH_3	100–103 (CCl_4)	90[d]	Heptane	B-60	1805	1600	3.58	1.90, s, 3	
5e	CH_3	C_6H_5	C_6H_5	CO_2CH_3	100–102 (CH_3OH)				1780		3.79	2.24, s, 3	
5d	C_6H_5	C_6H_5	C_6H_5	CO_2CH_3	146–148 (CH_3OH)	60	*p*-Xylene	A-60	1780		3.72		
5f	C_6H_5	C_6H_5	C_6H_5	$CO_2C_2H_5$	143–145 (CH_3OH)	55	*p*-Xylene	B-24	1780				
4g	CH_3	C_6H_5	C_2H_5	C_2H_5	*c*	34	Heptane	C-120	1805			1.58, s, 3	
5g	CH_3	C_6H_5	C_2H_5	C_2H_5	*c*	12			1775			1.86, s, 3	
4h	CH_3	C_6H_5	C_6H_5	H	65–67 (pentane)	32 13	Heptane	B-48	1805			1.76, s, 3	H(R^4) 6.03, s
5h	CH_3	C_6H_5	C_6H_5	H	*c*				1775			1.94, d (J = 1.5 Hz), 3; H (R^4) 7.63, q (J = 1.5 Hz)	
4i	CH_3	C_6H_5	CH_3	CH_3	*c*	33	Heptane	C-168	1805			1.53, s, 3	1.9, s, 3 2.2, s, 3
5i	CH_3	C_6H_5	CH_3	CH_3	*c*	*e*						1.83, s, 3	2.01, s, 3 2.25, s, 3
16[18]	H	H, H		CO_2CH_3	82				1785		3.88	6.65, t (J = 2 Hz), 1; ring CH_2, 4.99, d (J = 2 Hz), 2	
10	C_6H_5, H	C_6H_5		CO_2CH_3	105–106				1805	1635	3.56	4.85, s	

[a] Measured in KBr disks, except **4b** (Nujol mull) and **4c** (CCl_4). [b] Measured in $CDCl_3$, Me_4Si standard, 60 MHz. [c] Viscous oil purified by column chromatography. [d] Overall yield of mixture comprised of 86% **4e**, 14% **5e**. [e] **5i** was not isolated pure. [f] All compounds gave satisfactory elemental analyses.

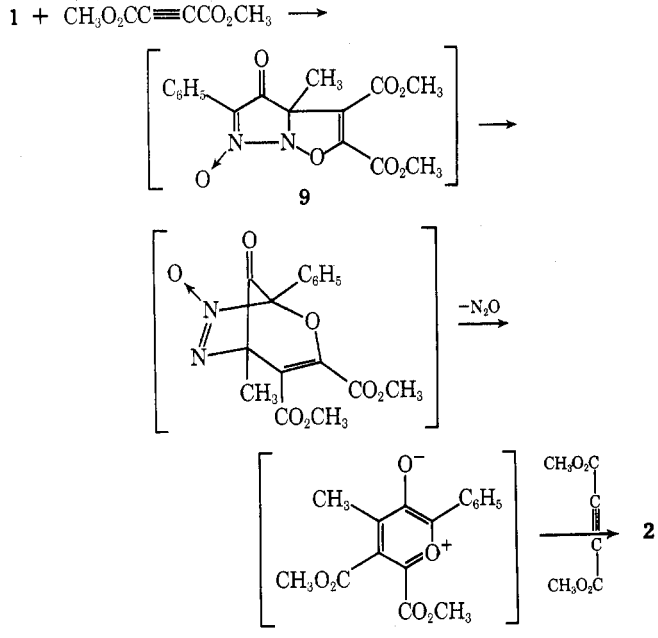


3 6 7 4 and/or 5

8

the dipole in 8 is dominant when the acyl group is highly electrophilic. Thus compounds with the electrophilic methoxalyl groups yield exclusively the β,γ-unsaturated butenolides **4a–c**. The less electrophilic benzoyl group migrated exclusively to the opposite center to yield **5d**. These results reflect a trend in the product formation as a function of the electrophilicity of the acyl group. This trend, however, is complicated by the ability of R^1 to accommodate negative charge in 8; there seems to be increased migration to that center when R^1 = methyl as contrasted to phenyl. Because of limitations on the synthesis of the oxadiazinones,[4] the effect of R^2 is more difficult to delineate.

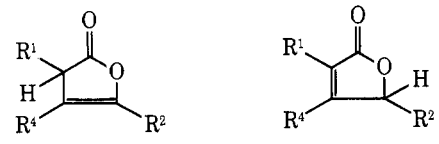
The thermal rearrangement of **6** is similar to that of the Δ^4-isoxazoline **9** presumed to be an intermediate in the diazacyclopentadienone reaction[1a] except that in that case a 1′,3 rearrangement must occur; a 3,3′ rearrangement would require formation of a strained, four-membered ring. These



9 2

reactions and others previously reported suggest that N-unsaturated Δ^4-isoxazolines should prove to be useful intermediates for the synthesis of a variety of heterocycles.

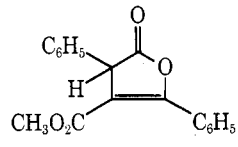
Reactions of the Acylbutenolides. Chemical Evidence. The butenolides **4** and **5** are labile to both acids and bases owing to retro-Claisen cleavage of the acyl group.



4′ 5′

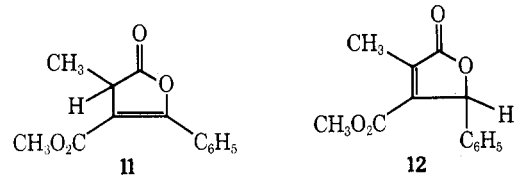
The product is either the β,γ-unsaturated lactone **4′** or the α,β-unsaturated lactone **5′**, the more stable isomer.[13,14] With bases, the retro-Claisen product reacts further to yield ring-opened products which will be discussed later.

The retro-Claisen products from "mild" acid treatment could be isolated in some cases; lactone **10** was isolated



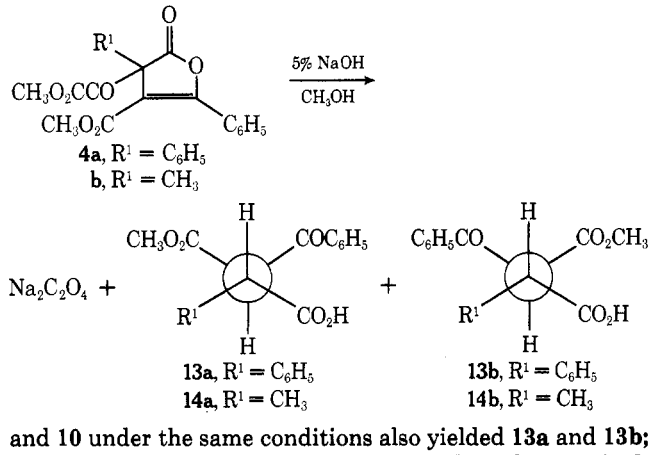
10

from the filtrate upon recrystallization of **4a** from wet (but not anhydrous) methanol. Partial deacylation of **4b** occurred on a silica gel column to yield principally lactone **11** and traces of **12** along with unaffected **4b.** These structures were assigned on the basis of their spectra and the isomerization of **11** to **12.**



11 12

Treatment of **4a, b** with base under mild conditions yielded the appropriate deacylated half-ester as a 1:1 mixture of diastereomers (NMR analysis). Treatment of **5d**

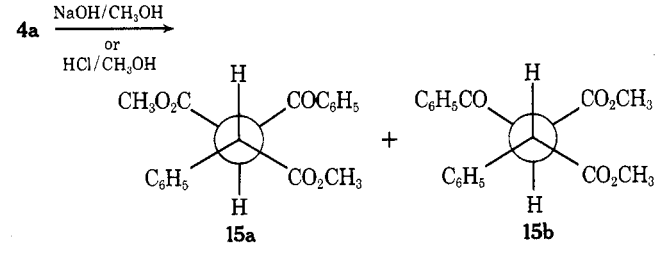


4a, $R^1 = C_6H_5$
b, $R^1 = CH_3$

13a, $R^1 = C_6H_5$ **13b**, $R^1 = C_6H_5$
14a, $R^1 = CH_3$ **14b**, $R^1 = CH_3$

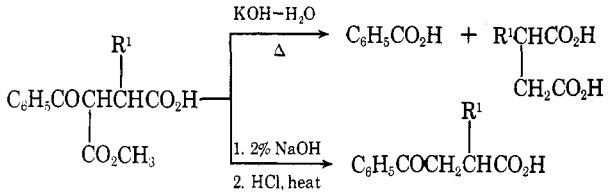
and **10** under the same conditions also yielded **13a** and **13b;** benzoic acid was also isolated from the degradation of **5d.** When R^1 was phenyl, one of the two diastereomers, **13a,** could be separated from the mixture. Treatment of pure **13a** with diazomethane yielded one diastereomer which was assigned as **15a** based upon the shielding effect on the methyl ester (see Experimental Section).

A mixture of the diesters **15a** and **15b** could also be obtained by the following reactions.



15a 15b

The structures of 13 and 14 were supported by their degradation to known compounds. These degradations involved the β-keto ester functional group as depicted below.



The structures of these degradation products were verified by comparison with known physical properties. (See Experimental Section.) The appropriate γ-keto acids were also isolated from the base hydrolysis of **4a** and **4c**. The deacylated succinate half-esters are probably intermediates in this transformation. These degradations therefore established the positions of R_1, R_2, and R_4 in **4** and **5**.

Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer Model 137-A Infracord. NMR spectra were measured on a Varian A-60A spectrometer. Mass spectra were measured with an A. E. I. MS 902 mass spectrometer at 70 eV. We are indebted to Mr. Donald Schifferl for these measurements. The elemental analyses were done by Midwest Microlab.

J. T. Baker silica gel (60–200 mesh) was dried at 135° for 4 hr before use and the column chromatography was monitored by TLC on Baker-flex sheets (silica gel 1B-F) using benzene as the developing solvent.

2,5-Diphenyl-1,3,4-oxadiazin-6-one 4-Oxide (3a).[4] To a stirred suspension of 23.4 g (92.9 mmol) of 1,4-dihydroxy-3,5-diphenylpyrazole[16] in 700 ml of CH_2Cl_2 and 40 ml of anhydrous CH_3OH at 0° was added 41 g of *m*-chloroperbenzoic acid. Stirring was continued for 4 days in a refrigerator. The mixture was filtered to remove a gold solid and the filtrate was concentrated to half its volume and an equal volume of CH_3OH was added. The solid that separated was filtered, combined with the first crop, and recrystallized from CH_2Cl_2–CH_3OH to give **3a** as yellow needles: mp 243–244°; yield 15.6–17.8 g (63–72%); ir (KBr) 1755, 1595, 1560 cm^{-1}; NMR ($CDCl_3$, Me_4Si) δ 8.12 (m, 4 H). 7.52 (m, 6); MS *m/e* (rel intensity) 266 (42), 105 (100), 77 (49), 51 (10).

Anal. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.79; N, 10.52. Found: C, 67.56; H, 3.81; N, 10.36.

5-Methyl-2-phenyl-1,3,4-oxadiazin-6-one 4-Oxide (3b).[4] To a stirred solution of 23.4 g (0.123 mol) of 1,4-dihydroxy-5-methyl-3-phenylpyrazole[16] in 130 ml of anhydrous ether and 35 ml of anhydrous CH_3OH at 0° was added 45 g of *m*-chloroperbenzoic acid in 240 ml of anhydrous ether. The dark red solution was stirred in a refrigerator for 1 day, 13.5 g of fresh peracid in 50 ml of ether was added, and stirring was continued in the cold for 2 days. The solid product was isolated as in **3a** above. The combined solid product was recrystallized from anhydrous C_2H_5OH to give **3b** as white flakes: mp 174–175°; yield 5.1–6.5 g (20–26%); ir (KBr) 1755, 1600 cm^{-1}; uv max (95% C_2H_5OH) 257 nm (ε 14700), 297 (12000); NMR ($CDCl_3$, Me_4Si) δ 2.38 (s, 3 H), 7.60 (m, 3 H), 8.20 (m, 2 H); MS *m/e* (rel intensity) 204 (29), 160 (15), 105 (100), 103 (41), 77 (43), 44 (26).

Anal. Calcd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 59.06; H. 4.10; N, 13.59.

5-Ethyl-2-phenyl-1,3,4-oxadiazin-6-one 4-Oxide (3c).[4] **3c** was prepared by the same procedure as **3b**: mp 177–178° (CH_2Cl_2–hexane); yield 30%; ir (Nujol) 1760, 1600, 1560 cm^{-1}; NMR ($CDCl_3$, Me_4Si) δ 1.21 (t, 3 H), 2.84 (q, 2 H), 7.61 (m, 3 H), 8.15 (m, 2 H); MS *m/e* (rel intensity) 218 (36), 105 (100), 77 (44), 57 (12), 51 (16), 39 (12).

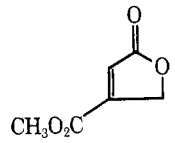
Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.80; H, 4.54; N, 12.59.

Cycloaddition Reactions. Procedure A. A suspension of 5–10 mmol of **3** in 50 ml of dry heptane containing 10–20 mmol of acetylene was stirred under reflux for 1 day. The residue from evaporation of the solvent[17] was recrystallized from hot CCl_4 or CH_3OH.

Procedure B. After the reflux period of procedure A, the oily residue was chromatographed on silica gel using benzene or CH_2Cl_2 as eluent. Fractions of similar R_f value was combined and crystallized from the appropriate solvent (Table I). Only **5h** could not be obtained crystalline by this procedure.

Procedure C. A suspension of 2 mmol of **3b** in 5 ml of dry heptane containing 1.5–2 ml of acetylene was heated in a Fischer-Porter sealed tube for 5–7 days at 100–120°. The tarry residue was washed from the tube with CH_2Cl_2 and concentrated to yield an oil that was chromatographed on silica gel using benzene as eluent. Fractions of similar R_f values were combined and concentrated to yield the two isomers.

Spectral Properties of Butenolides (Table I). Infrared. The position of the double bond in the butenolides is easily determined by the carbonyl band of the lactone and in some cases the presence or absence of the enol stretching band.[13] The β,γ-unsaturated lactones (**4**) showed carbonyl absorption at 1800–1795 cm^{-1} while the α,β isomers (**5**) usually absorbed around 1775 cm^{-1}. The infrared spectrum of methyl aconate[18] (**16**) was also used as a model for band assignments.



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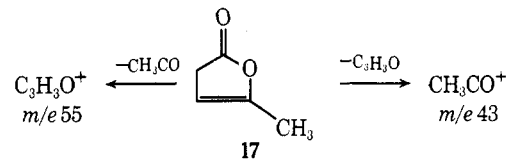
NMR. The spectra of **4** and **5** were consistent with the structure assignments, but the simplicity of the spectra limited their utility. Some points stand out, however. The chemical shifts of the ester methyl group of the 4-carbomethoxy substituents are rather different in the two ring systems (**4** and **5**). In the β,γ isomer the group is shielded (δ 3.57–3.66) as compared to the α,β isomer (δ 3.72–3.88), probably because the 4 position is enriched in electron density by the lactone oxygen in **4** and diminished by the lactone carbonyl group in **5**.

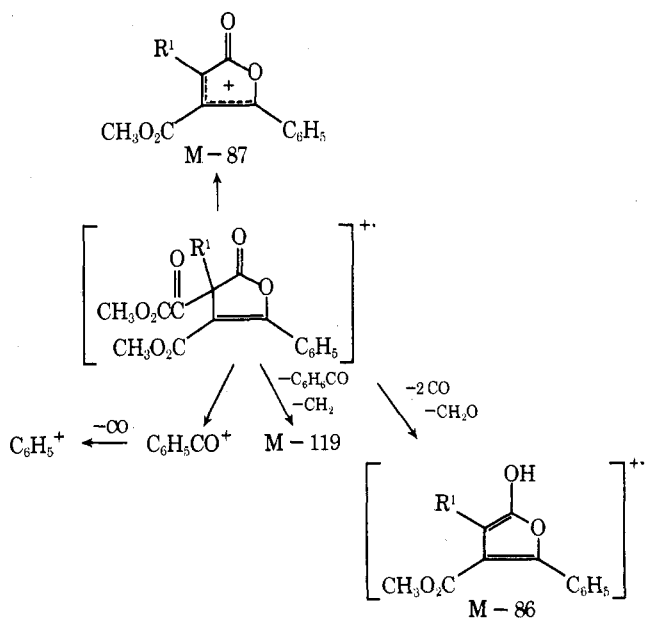
The chemical shifts of the pendant methyl group ($R^1 = CH_3$) in **4** and **5** reflect the differences in the hybridization at C-3 in the two isomers. The variations in shift of the methyl group in **4** can be attributed to the differential shielding effects of the acyl groups at C-3.

Mass Spectra. The cracking patterns of these butenolides bear a close resemblance to known spectra[19] in this series. In particular, the main fragmentation of α-angelica lactone[19b] (**17**) results from the cleavage

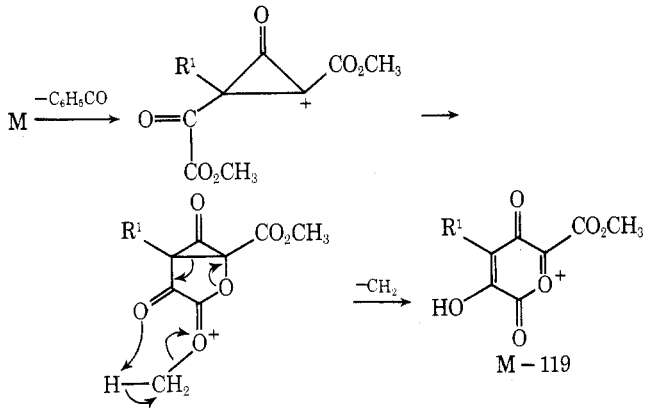


17

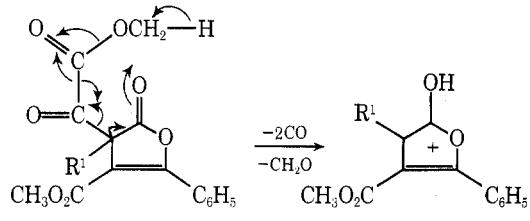
Extensive rearrangement was evident for the ion of mass 55 which was the base peak. In **4a–c, e, h, 5e, f,** and **10** the base ion was 105 ($C_6H_5C{\equiv}O^+$), which results from an analogous fragmentation. The molecular ions were also present; their cracking pattern is illustrated below for **4a–c**.



The M − 105 ion is not apparent but might have been expected by comparison with the cracking pattern of **17.** However, the M − 119 ion might result from this ion in the following manner.



The presence of methoxalyl group in the mass spectra of **4a–c** is also apparent in the formation of the M − 86 ion as shown below.

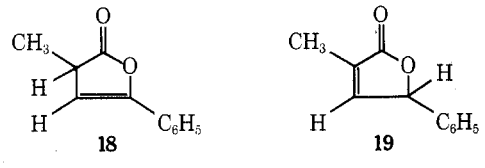


4-Carbomethoxy-3,5-diphenyl-2,3-dihydro-2-furanone (10). Lactone **4a** was prepared by procedure A. The filtrate from recrystallization of **4a** from technical grade methanol was evaporated in vacuo to yield a white solid.[20] Recrystallization of this solid from hexane gave white needles of **10:** mp 105–106°; ir and NMR, Table I; MS *m/e* (rel intensity) 294 (39), 265 (23), 235 (15), 206 (14), 189 (27), 178 (14), 129 (14), 105 (100), 77 (48).

The infrared spectrum of **10** is similar to its precursor except for the absence of the methoxalyl group. In its NMR spectrum the observed chemical shift of the methine proton (δ 4.85) agreed with the calculated value (δ 4.95)[21] and the chemical shift of the ester methyl protons is analogous to that expected from the spectra of the acyl butenolides (see Experimental Section). Its mass spectrum was similar to that of its precursor except the molecular ion was more prominent. The M − 119 ion was also absent but the M − 105 ion was very prominent which supports the mechanism suggested for the formation of the M − 119 ion.

4-Carbomethoxy-3-methyl-5-phenyl-2,5-dihydro-2-furanone (12). Lactone **4b** (0.156 g, 0.49 mmol) was washed through a silica gel column (10 g) with benzene. Evaporation of the solvent yielded 0.11 g (97%) of a yellow oil that was a mixture of **11** and **12:** ir (neat) 1810, 1775, 1725 cm^{-1}; NMR (CCl_4, Me_4Si) δ 1.45 (d, J = 7.5 Hz, 3 H), 2.2 (d, J = 2 Hz, 3 H).

This mixture was stirred in 6 ml of benzene containing 3 drops of $(C_2H_5)_3N$ at 25° for 1 day. The solution was washed with H_2O, dried, and concentrated to give an oil that was purified by chromatography on silica gel using $CHCl_3$ as eluent to give **12** as a yellow oil: ir (neat) 1775, 1725 cm^{-1}; NMR (CCl_4, Me_4Si) δ 2.21 (d, J = 2 Hz, 3 H), 3.68 (s, 3 H), 5.88 (q, J = 2 Hz, 1 H), 7.25 (s, 5 H). The spectra[22] of the model compounds **18** and **19** were used to assign the isomeric structures **11** and **12.**



18 **19**

Alkaline Hydrolysis of 4a. Formation of α-Phenyl-β-benzoyl-β-carbomethoxypropionic Acid (13a and 13b). A solution of 0.65 g (1.7 mmol) of **4a** and 6.5 ml of 5% NaOH in 25 ml of CH_3OH was stirred at 25° for 1 hr. The original bright yellow solution faded to a pale yellow. The solution was neutralized (5% HCl) and a white solid that had separated was removed by filtration and identified as sodium oxalate. The filtrate was acidified (5% HCl), diluted with 30 ml of H_2O, and extracted with 3 × 50 ml of ether. The ether extracts were washed, dried, and concentrated to yield 0.51 g (96%) of a yellow oil, a mixture of acids **13a** and **13b.** This oily mixture was dissolved in the minimal amount of hot benzene and hexane was added to turbidity. Upon cooling 0.13 g of ***RS(SR)*-β-benzoyl-β-carbomethoxy-α-phenylpropionic acid (13a)** separated as white needles: mp 156–157°; ir (Nujol) 2650, 1740, 1700, 1680 cm^{-1}; NMR ($CDCl_3$, Me_4Si) δ 3.33 (s, 3 H), 4.63 (d, J = 11.5 Hz, 1 H), 5.07 (d, J = 11.5 Hz, 1 H, 7.2–7.6 (m, 8 H), 7.95–8.15 (m, 2 H), 9.88 (br s, 1 H); MS *m/e* (rel intensity) 312 (1), 294 (24), 163 (25), 131 (34), 105 (100), 103 (28), 77 (54), 51 (37).

Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22, H, 5.16. Found: C, 69.63, H, 5.27.

The structure of **13a** is assigned on the basis of the selective chemical shift of the methyl group of the β-carbomethoxy group (δ 3.33) compared to that of **13b,** δ 3.65 (present in the original oily mixture). In the preferred and apparently predominant conformation of diastereomer **13a,** this methyl group is in the shielding cone of the α-phenyl group. The large coupling constant between the vicinal hydrogens (11.5 Hz) suggests a high population for this conformation. Similar shielding effects were seen in **14a** and **15a** as compared to **14b** and **15b.**

13a also appeared to be the more stable isomer as base equilibration of the two yielded a 2.6:1 mixture of **13a:13b.**

α-Phenyl-β-benzoylpropionic Acid. Treatment of the mixture of **13a** and **13b** with 2% aqueous NaOH for 1 day followed by acidification, heating on a steam bath, and cooling yielded a tan solid that gave white plates of α-phenyl-β-benzoylpropionic acid, mp 153–155°, which was not depressed upon admixture with an authentic sample.[23] Pure **13a** gave analogous results. **4a** could be converted directly to this acid by the same method.

α-Phenylsuccinic Acid. A mixture of **13a** and **13b** (261 mg) was heated under reflux with 10 g of KOH in 20 ml of H_2O. The product, isolated after acidification and extraction with ether, was purified by slurrying in benzene (to remove benzoic acid). The residue was recrystallized from ether–hexane to yield white needles of α-phenylsuccinic acid, mp 162–163°, which was not depressed upon admixture with an authentic sample,[24] yield 66 mg (41%).

Alkaline Hydrolysis of 5-Benzoyl-4-carbomethoxy-3,5-diphenyl-2,5-dihydro-2-furanone (5d). Using the same procedure as for **4a,** a crude solid residue was obtained. Benzoic acid (49% yield) was sublimed from this solid at 70° (2 Torr). The oily residue was identified as a mixture of **13a** and **13b** by NMR analysis.

***erythro*-Dimethyl α-Phenyl-β-benzoylsuccinate (15a).** To a solution of 0.1 g (3.16 mmol) of **13a** in 10 ml of ether was added dropwise an ethereal solution of diazomethane until the yellow color persisted. Evaporation of the ether yielded a clear oil that deposited white beads of **15a** from hexane: mp 86–87°; ir (KBr) 1740, 1680, 1290, 1230, 1190, 1175, 760, 708, 687 cm^{-1}; NMR (CCl_4, Me_4Si) δ 3.33 (s, 3 H), 3.58 (s, 3 H), 4.50 (d, J = 11.5 Hz, 1 H), 5.03 (d, J = 11.5 Hz, 1 H), 7.2–7.6 (m, 8 H), 8.0–8.2 (m, 2 H).

Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.94; H, 5.52. Found: C, 69.79, H, 5.61.

Acid-Catalyzed Methanolysis of 4a. To a suspension of 0.25 g (0.66 mmol) of **4a** in 30 ml of 1:1 v/v aqueous methanol was added 5 ml of concentrated HCl. This mixture was heated under reflux for 10 min and extracted with ether. The dried ether extracts were concentrated to an oil that was chromatographed on silica gel to yield a mixture of **15a** and **15b.** The NMR spectrum of this mixture showed the ester methyl hydrogens of **15b** as a six-proton singlet at δ 3.67 in addition to the singlets at δ 3.33 and 3.58 for **15a.**

Alkaline Hydrolysis of 4b. Formation of α-Methyl-β-benzoylpropionic Acid. Treatment of 1 g of **4b** with aqeuous methanolic NaOH at room temperature for 1 hr yielded 0.77 g of a yellow oil, a mixture of **14a** and **14b.** With no α-phenyl substituents the ester methyl groups of both diastereomers are at δ 3.64. However, the α-methyl group of one isomer is at higher field (δ 1.17) than the other (δ 1.33). Since the preferred conformation of **14b** has methyl and benzoyl groups syn to each other, it is suggested that **14b** is the isomer with the higher field methyl signal.

When this mixture was stirred in 2% aqueous NaOH at 25° for 1 day, then acidified with 5% HCl, heated on a steam bath for 30 min, and then cooled, long, white needles separated and were recrystallized from C_2H_5OH–H_2O to yield α-methyl-β-benzoylpropionic acid, mp 139–140° (lit.[25] mp 139–140°), NMR spectrum, ref 22.

α-Methylsuccinic Acid. Treatment of the mixture of **14a** and **14b** with a hot mixture of 10 g of KOH and 20 ml of H_2O for 4 hr gave, after the same work-up as for the formation of α-phenylsuccinic acid, a tan solid that yielded white needles (ether–benzene) of α-methylsuccinic acid, mp 109–111° (lit.[26] mp 110–111°), NMR spectrum, ref 27.

Alkaline Hydrolysis of 4c. Formation of α-Ethyl-β-benzoylpropionic Acid. A mixture of 4c (0.4 g) and 20 ml of 2% NaOH was stirred at 25° for 1 day. The mixture was acidified with 5% HCl, heated on a steam bath for 30 min, and cooled to yield a white solid. Recrystallization from petroleum ether produced white needles of α-ethyl-β-benzoylpropionic acid: mp 86–87° (lit.[28] mp 85°); ir (KBr) 2650, 1680, 757, 688 cm^{-1}; NMR ($CDCl_3$ Me_4Si) δ 1.00 (t, J = 7 Hz, 3 H), 1.68 (q, 2 H), 2.8–3.8 (m, 3 H), 7.3–7.7 (m, 3 H), 7.9–8.1 (m, 2 H), 10.7 (s, 1 H).

Registry No.—2 (R^3 = R^4 = CO_2CH_3), 762-42-5; 2 (R^3 = C_6H_5; R^4 = CO_2CH_3), 4891-38-7; 2 (R^3 = C_6H_5; R^4 = $CO_2C_2H_5$), 2216-94-6; 2 (R^3 = R^4 = C_2H_5), 928-49-4; 2 (R^3 = C_6H_5; R^4 = H), 536-74-3; 2 (R^3 = R^4 = CH_3), 503-17-3; **3a**, 28969-37-1; **3b**, 28969-38-2; **3c**, 28969-39-3; **4a**, 56615-23-7; **4b**, 56615-24-8; **4c**, 56615-25-9; **4e**, 56615-26-0; **4g**, 56615-27-1; **4h**, 56615-28-2; **4i**, 56615-29-3; **5d**, 56615-30-6; **5e**, 56615-31-7; **5f**, 56615-32-8; **5g**, 56615-33-9; **5h**, 56615-34-0; **5i**, 56615-35-1; **10**, 56615-36-2; **11**, 56615-37-3; **12**, 28970-27-6; **13a**, 56615-38-4; **13b**, 56615-39-5; **14a**, 56615-40-8; **14b**, 56615-41-9; **15a**, 56615-42-0; **15b**, 56615-43-1; 1,4-dihydroxy-3,5-diphenylpyrazole, 17953-00-3; *m*-chloroperbenzoic acid, 937-14-4; 1,4-dihydroxy-5-methyl-3-phenylpyrazole, 56615-44-2; α-phenyl-β-benzoylpropionic acid 4370-96-1; α-phenylsuccinic acid, 635-51-8; diazomethane, 334-88-3; α-methyl-β-benzoylpropionic acid, 1771-65-9; α-methylsuccinic acid, 498-21-5; α-ethyl-β-benzoylpropionic acid, 56615-45-3.

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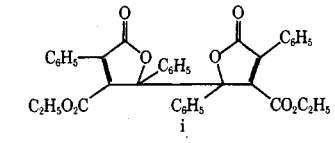

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Chemistry of *o*-Amino Aldehydes. Reactions of 2-Aminonicotinaldehyde and Cyclohexanediones

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Received April 25, 1975

1,3-Cyclohexanedione and 2-aminonicotinaldehyde form 6,7-dihydrodipyrido[2,3-*b*:2,3-*j*]-1,7-phenanthroline (**3**) or 6-oxo-6,7,8,9-tetrahydrobenzo[*b*]-1,8-naphthyridine (**4**) depending on the molar ratio of reagents. Excess 1,3-cyclohexanedione, on the other hand, results in a 2:1 addition product (**5**). Similar reactions with 1,4-cyclohexanedione were not successful; a series of addition–elimination steps in toluene results in the formation of 7-oxo-6,7,8,9-tetrahydrobenzo[*b*]-1,8-naphthyridine (**12**) and 6,7-dihydrodipyrido[3,2-*b*:2,3-*j*]-4,7-phenanthroline (**13**), demonstrating the feasibility of uncatalyzed Friedländer condensations. The isomeric pentacyclic systems are readily dehydrogenated to their fully aromatic analogs. 1,2-Cyclohexanedione gives the highly unreactive 6,7-dihydrodipyrido[2,3-*b*:2,3-*j*]-1,10-phenanthroline (**14**). The mechanism of the actual ring closing step in Friedländer condensation reactions of 2-aminonicotinaldehydes and ketomethylenes is discussed.

The incorporation of the 1,8-naphthyridine heterocyclic system into a polycyclic framework is of interest in view of the unusual stability and properties of "black orlon" obtained from poly(acrylonitrile) by controlled pyrolysis. A linearly annelated sequence of partially oxygenated 1,8-naphthyridine units has been proposed for this remarkable material.[1] The Friedländer condensation of *o*-amino aldehydes seemed a most promising synthetic sequence for the construction of such systems, since fully aromatic substrates without amino or oxo substituents are obtained and the direction of annelation is unequivocally determined by the location of the functional groups in the substrate. This paper deals with the reaction of 2-aminonicotinaldehyde and cyclohexanediones leading to three isomeric pentacyclic systems containing two 1,8-naphthyridine units.

The reaction of 1,3-cyclohexanedione (**1**) and excess 2-