is cis to the cyclopropyl residue; *i.e.*, the oxygen atom is "above" the triangle. From the substances investigated by electron diffraction (cyclopropanecarboxylic acid chloride, cyclopropyl methyl ketone,[25] and cyclopropylcarboxaldehyde[26]) only average C–C distances were obtained, whereas the X-ray data for cyclopropanecarbohydrazide[27] and cyclopropanecarboxamide[28] yielded an asymmetry in the cyclopropyl residue; the C–C bond opposite the carbonyl group [*i.e.*, C(2)–C(3)] was found to be significantly (3.5 σ) smaller than the other two C–C bonds in the cyclopropyl ring which is also true (3 σ) for I, Figure 1. That the C(2)–C(3) bond distance in I is not so short as in the above two cyclopropane derivatives might be due to the steric hindrance between the C(4) and C(5) methyl groups discussed earlier.

Within the crystal structure the molecules are arranged such that the methyl groups come together in a region parallel to the *a,b* plane at $c = {}^1/_2$ and the phenyl rings are not stacked but alternately packed around the *a,b* plane in $c = 0$.

The intermolecular distances are all equal to or greater than the sums of the corresponding van der Waals radii. Relatively close contacts occur between the chlorine atoms, 3.378 Å, and between O(1) and HC(7), 2.506 Å.

The calculations were performed on a UNIVAC 1108 computer of the Gesellschaft für wissenschaftliche Datenverarbeitung mbH, Göttingen. The ORTEP plots were carried out at Deutsches Rechenzentrum, Darmstadt.

Registry No.—I, 31236-00-7.

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The Condensation of Succinic Anhydrides with Schiff Bases. Scope and Mechanism[1a]

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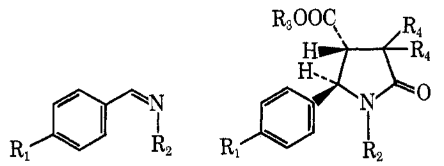
The condensation of a series of para-substituted benzylidenecyclohexylamines with succinic anhydride to yield the corresponding *trans*- and *cis*-1-cyclohexyl-4-carboxy-5-aryl-2-pyrrolidinones has been studied. The reactivities of the Schiff bases have been shown to increase with the increasing electron-donating ability of substituents, an order of reactivity opposite to that expected for a Perkin-type mechanism. Indirect evidence supporting a reaction sequence involving iminolysis of *gem*-dimethylsuccinic anhydride followed by rearrangement of the iminolysis adduct is also presented.

In a recent publication[2] we described the condensation of benzylidenemethylamine **1a** with succinic anhydride to yield *trans*- and *cis*-1-methyl-4-carboxy-5-phenyl-2-pyrrolidinone (**2a** and **3a**, respectively). In order to examine the mechanism of this reaction and concomitantly to extend its synthetic utility to the preparation of substituted 5-aryl-2-pyrrolidinones of interest as precursors to nicotine analogs,[3] we have studied the condensation of the para-substituted benzylidenecyclohexylamines **1b–f** with succinic anhydride. With the exception of the para nitro compound **1f**, which resisted reaction, each Schiff base yielded a diastereomeric mixture of pyrrolidinones which could be separated into the trans and cis isomers **2** and **3**, respectively. The cis acids **3b** and **3c** were characterized as their methyl esters **3b′** and **3c′**, respectively.



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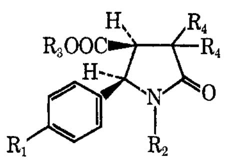

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Compd	R_1	R_2	R_3	R_4
a	H	CH_3	H	H
b	$(CH_3)_2N$	C_6H_{11}	H	H
b′	$(CH_3)_2N$	C_6H_{11}	CH_3	H
c	CH_3O	C_6H_{11}	H	H
c′	CH_3O	C_6H_{11}	CH_3	H
d	H	C_6H_{11}	H	H
e	Cl	C_6H_{11}	H	H
f	NO_2	C_6H_{11}	H	H
g	CH_3O	C_6H_{11}	H	CH_3
g′	CH_3O	C_6H_{11}	CH_3	CH_3

As previously shown,[2] stereochemical assignments in each case could be made on the basis of the magnitude of the coupling constant for the C-5 methine proton, which for the cis isomers is 9 Hz and for the trans isomers 2–5 Hz. Since the nmr signals for the methoxycarbonyl protons in the corresponding cis methyl esters appear about 0.4–0.5 ppm upfield from the trans esters,[2] it was possible to estimate the relative yields of the diastereomers by integration of the nmr spectra of the

(1) (a) Presented in part at the 158th National Meeting of the American Chemical Society, New York, N. Y., 1969; (b) NDEA Predoctoral Fellow and American Foundation for Pharmaceutical Education Fellow.

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mixture of esters obtained by diazomethane treatment of the crude carboxylic acid products. The pertinent analytical and physical data for these compounds are recorded in Table I.

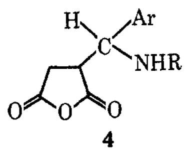
TABLE I
PHYSICAL AND ANALYTICAL DATA FOR 1-CYCLOHEXYL-4-CARBOXY-5-ARYL-2-PYRROLIDINONES[a]

Compd	Mp, °C	Reaction solvent (time, hr)	Crystn solvent	Yield,[b] %
2b	226–227		MeOH	37
		C_6H_6 (12)		
3b′	164–165		Me_2CO	3[c]
2c	217–218		MeOH	75
		C_6H_6 (12)		
3c′	127–128		Me_2CO–H_2O	10[c]
2d	167–168		50% EtOH	68
		C_6H_6 (24)		
3d	252–253		95% EtOH	7
2e	164–165		50% MeOH	63
		Xylene (24)		
3e	254–255		Me_2CO	8

[a] Satisfactory analytical data (±0.35% for C, H, and N) were reported for all compounds in the table: Ed. [b] Calculated from total yields of diastereomeric acids and per cent composition determined by nmr of methyl esters. [c] Refers to yield of cis acid.

Mechanistically this reaction can be viewed as proceeding in a manner analogous to the base-catalyzed Perkin condensation,[4] in which case product formation would be expected to proceed *via* the adduct **4**. An alternative proposal invokes rearrangement of the iminolysis adduct **5a** ⇄ **5b**, the formation of which finds analogy in the benzylideneaniline–acetic anhydride condensation product, **6**.[5] Ogata and Tsuchida[6] have demonstrated that the base-catalyzed Perkin condensation of acetic anhydride with substituted benzaldehydes proceeds more readily the greater the electronegativity of the aromatic substituent. In contrast to these effects, an electron-donating substituent would be expectd to facilitate the iminolysis reaction through the increased nucleophilicity of the Schiff base and increased ability to stabilize the positive charge developed during formation of **5a**. In dimethylacetamide the 60-MHz nmr signals for the methine protons of imines **1b–f** appear as singlets near 8.2 ppm and the doublets of the C-5 methine protons of the pyrrolidinones are centered near 5 ppm. Since no other signals for reactants or products occur in these regions, it was possible to follow the course of the reaction by nmr and to examine substituent effects on the reactivity of the imines.

Equimolar solutions (0.1 *M*) of the imines and succinic anhydride in dimethylacetamide were heated at 100° in sealed nmr tubes for specified time periods. After the reactions were quenched by cooling to 0°, the nmr spectra were recorded at ambient temperature. The per cent imine remaining *vs.* time was plotted and the 50% reaction time was determined. Based on these values, the relative reactivities of the imines are as follows: **1b**:**1c**:**1d**:**1e**:**1f** = 100:22:5:5:<1. The same order of reactivities in terms of product formation was also observed. Furthermore, the addition of triethylamine to the benzylidenecyclohexylamine reaction mixture in concentrations known to catalyze the Perkin condensation[6] had no effect on the reaction rate, indicating that the observed order of reactivity was not a consequence of the capability of the imine to deprotonate the anhydride. These data make untenable a Perkin-type mechanism but are consistent with a mechanism involving iminolysis of the anhydride.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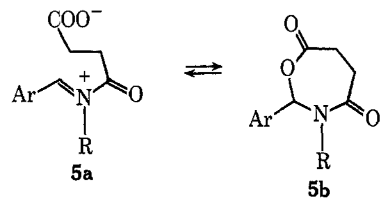
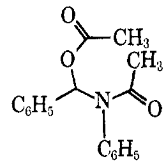

5a 5b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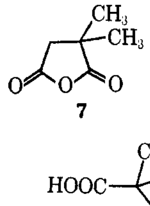
The condensation of *p*-methoxybenzylidenecyclohexylamine (**1c**) with *gem*-dimethylsuccinic anhydride (**7**) was studied in an effort to isolate the adduct **8**. When run in benzene the reaction yielded the succinamic acid **9**, which was also obtained in 98% yield by aminolysis of **7** with cyclohexylamine. The same reaction was attempted in refluxing xylene and the mixture was worked up by distillation. The distillation residue gave a low yield of the trans and cis pyrrolidinones **2g** and **3g**. The coupling constants of the C-5 methine proton doublets for these two diastereomers were too similar to allow stereochemical assignments. However, the nmr spectra of their corresponding methyl esters **2g′** and **3g′** displayed the anticipated[2] differences in shifts for the methoxycarbonyl proton signals. The distillate yielded two additional compounds which by glpc were shown to be present in equal quantities. The more volatile of these two compounds proved to be *p*-methoxybenzaldehyde, which was identified by glpc retention time and nmr after isolation *via* the bisulfite addition product. The second compound was shown to be 1-cyclohexyl-3,3-dimethylsuccinimide (**10**) by nmr and microanalysis. While these results can be rationalized in terms of the iminolysis mechanism, more definitive support for the postulated intermediate is being sought.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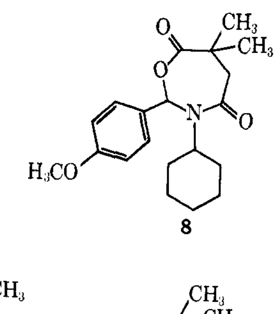
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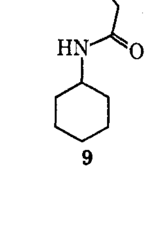
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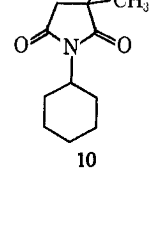
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Experimental Section[7]

General Procedure for the Synthesis of Schiff Bases.—The aldehyde (0.3 mol) and cyclohexylamine (0.3 mol) in 100 ml of C_6H_6 were heated under reflux for 2 hr, during which time 5.4 ml (0.3 mol) of H_2O was collected in the Dean–Stark trap. After removal of the solvent, the imines were obtained pure in about 90% yield by distillation or sublimation: **1b**, mp 81–82° (*Anal.* Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.28; H, 9.64; N, 12.12); **1c**, mp 32–33° (lit.[8] mp 12°); **1d**, bp 110–120° (2 mm) [lit.[9] bp 83–85° (0.08 mm)]; **1e**, mp 53–54° (lit.[10] mp 57–58°); **1f**, mp 84–85° (lit.[11] mp 85–86°).

***trans*- and *cis*-1-Cyclohexyl-4-carboxy-5-aryl-2-pyrrolidinones.**—The imines **1b–f** (0.1 mol) and succinic anhydride (0.1 mol) in 100 ml of anhydrous C_6H_6 or xylene were heated under reflux for the times given in Table I. After cooling to room temperature the solid which formed was collected. In the case of the para chloro system, **e**, the gel which formed was extracted with aqueous $NaHCO_3$ and the acids were precipitated at pH 2 with HCl. Separations of the diastereomers were achieved as follows. The trans acids **2b–d** were obtained by crystallization of the above solids from the solvents listed in Table I. In each case, elemental analyses, sharp melting points, and the appearance of a doublet in the nmr at $\delta \sim 5$ ppm with $J = 2–3$ Hz characteristic for the trans C-5 methine signal, established the purity of the product. The cis acid of the *p*-dimethylamino compound **3b** was isolated as its Me ester (**3b′**) by treating the residue obtained from the mother liquors after crystallization of the trans acid with 0.2 *M* methanolic sulfuric acid in the presence of molecular sieves at room temperature for 18 hr. After filtering, the resulting solution in $CHCl_3$ was washed with H_2O and twice with 5% aqueous $NaHCO_3$ and then dried ($MgSO_4$). The residue obtained after removing solvent was crystallized twice from Me_2CO to yield pure **3b′**. The cis acid of the para methoxy compound **3c** was also purified as its Me ester **3c′** by treating the residue obtained from the mother liquors after crystallization of the trans acid with an excess of diazomethane in EtOH–Et_2O. The reaction mixture in $CHCl_3$ was extracted twice with 5% aqueous $NaHCO_3$ and dried ($MgSO_4$), and the residue obtained after removing the solvent was crystallized from Me_2CO and then Me_2CO–H_2O. The cis acid of the unsubstituted system (**3d**) was obtained directly by concentrating the MeOH filtrate from crystallization of the trans acid. Recrystallization from EtOH provided the analytical sample. The cis acid of the para chloro system (**3e**) was obtained by treating the mother liquor residue from the trans acid crystallization with 50% aqueous Me_2CO and recrystallizing the resulting solid from Me_2CO. The purities of the above compounds were confirmed by elemental analyses, sharp melting points, and the appearance of a doublet at $\delta \sim 5$ ppm ($J = 9$ Hz) in the nmr spectrum characteristic for the cis C-5 methine proton.

Estimation of Relative Yields of Cis and Trans Acids.—Samples (0.5 g) of the diastereomeric mixtures were methylated by addition of an excess of diazomethane in EtOH–Et_2O. The nmr spectra in $CDCl_3$ of the oil obtained after removing the solvent displayed a singlet near 3.65 ppm for the methoxycarbonyl protons of the trans esters and a second singlet near 3.25 ppm for the methoxycarbonyl protons of the cis esters. Integration of these signals provided an estimation of the relative amounts of the trans and cis acids.

Reaction of *gem*-Dimethylsuccinic Anhydride with *p*-Methoxybenzylidenecyclohexylamine. A. In C_6H_6.—*p*-Methoxybenzylidenecyclohexylamine (**1c**, 10.86 g, 0.05 mol) and *gem*-dimethylsuccinic anhydride[12] (**7**, 6.40 g, 0.05 mol) in 100 ml of anhydrous C_6H_6 were heated under reflux for 48 hr in a flask equipped with a Dean–Stark trap and reflux condenser. No water was collected during the reaction. The solvent was then removed and the residue was dissolved in $CHCl_3$ and extracted with NH_4OH. The aqueous layer was separated and made acidic with HCl. The solid collected (2.2 g, 0.01 mol, 19%) was crystallized from Me_2CO to give pure ***N*-cyclohexyl-3,3-dimethylsuccinamic acid** (**9**): mp 193–194; nmr (pyridine-d_5) δ 1.52 (br, cyclohexylmethylenes), 1.55 (s, CH_3), 2.80 (s, CH_2), 4.02 (br, NCH).

Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.53; H, 9.42; N, 5.95.

The succinamic acid was also prepared by heating under reflux for 2 hr in C_6H_6 *gem*-dimethylsuccinic anhydride (**7**, 640 mg, 5 mmol) and cyclohexylamine (496 mg, 5 mmol). The solid obtained on cooling was precipitated from dilute NH_4OH with HCl to give pure **9** (1.10 g, 4.9 mmol, 98%) identical in all respects with the product from the imine condensation.

B. In Xylene.—*p*-Methoxybenzylidenecyclohexylamine (**1c**, 10.86 g, 0.05 mol) and *gem*-dimethylsuccinic anhydride (**7**, 6.40 g, 0.05 mol) in 50 ml of xylene were heated under reflux for 48 hr. After removal of the solvent, the oily residue was distilled at 72–135° (0.2 mm) to yield a yellow liquid (9.95 g, 58%). Glpc analysis of the distillate (5% Carbowax KOH on firebrick, 0.32 cm × 1.5 m) indicated two compounds with retention times of 4.5 min (identical with *p*-methoxybenzaldehyde) and 6.0 min. The distillate in $CHCl_3$ was stirred for 2 hr with aqueous $NaHSO_3$ (18 g in 85 ml) and, after separation, the aqueous layer was acidified with 5 ml of concentrated H_2SO_4 and then warmed on a steam bath until evolution of SO_2 ceased. The oily material which separated was extracted into $CHCl_3$, the latter was dried ($MgSO_4$), and the solvent was removed to yield *p*-methoxybenzaldehyde (1.38 g, 0.01 mol, 20%), which was identified by nmr.

The $CHCl_3$ layer obtained after the $NaHSO_3$ treatment was dried ($MgSO_4$) and the solvent was removed to yield a solid (3.02 g, 0.014 mol, 29%) mp 50–53°. Sublimation at 70° (2 mm) gave pure **1-cyclohexyl-3,3-dimethylsuccinimide** (**10**): mp 54–55°; nmr δ 1.33 (s, CH_3), 1.67 (br, cyclohexylmethylenes), 2.55 (s, O=CCH_2), 3.92 (br, NCH).

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 69.13; H, 8.94; N, 6.89.

The glpc tracing of the distillate was reproduced by an equimolar mixture of *p*-methoxybenzaldehyde and **10**.

The residue from the distillation of the reaction mixture was dissolved in 5% aqueous $NaHCO_3$ and filtered, and the filtrate was acidified with concentrated HCl to pH 1 to yield a mixture of the diastereomeric acids **2g** and **3g** (4.66 g, 27%), mp 161–205°. The trans acid **2g** was obtained from the above solid by crystallization twice from Me_2CO: mp 195–196°; nmr δ 1.10 (s, CCH_3), 1.40 (s, CCH_3), 2.85 (d, $J = 9$ Hz, C-4 H), 3.77 (s, OCH_3), 4.85 (d, $J = 9$ Hz, C-5 H).

Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.64; H, 7.72; N, 4.02.

Treatment of this acid with EtOH–Et_2O diazomethane gave the Me ester **2g′** in 72% yield, which was crystallized from hexane for analysis: mp 115–116; nmr δ 3.58 (s, O=$COCH_3$).

Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.23; H, 8.13; N, 3.86.

The cis acid **3g** was obtained by crystallization of the diastereomeric mixture twice from 95% EtOH: mp 186–187°; nmr δ 1.22 (s, CCH_3), 1.25 (s, CCH_3), 3.11 (d, $J = 8$ Hz, C-4 H), 3.78 (s, OCH_3), 4.89 (d, C-5 H).

Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.54; H, 7.78; N, 4.11.

Treatment of this acid with EtOH–Et_2O diazomethane gave the Me ester **3g′** in 91% yield, which was crystallized from hexane for analysis: mp 97–98°; nmr δ 3.34 (s, O=$COCH_3$).

Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.49; H, 7.70; N, 3.86.

Registry No.—**1b**, 31235-64-0; **2b**, 31281-10-4; **2c**, 31235-65-1; **2d**, 31235-66-2; **2e**, 31235-67-3; **2g**, 31235-68-4; **2g′**, 31235-69-5; **3b′**, 31235-70-8; **3c′**, 31235-71-9; **3d**, 31235-72-0; **3e**, 31235-73-1; **3g**, 31281-11-5; **3g′**, 31235-74-2; **9**, 31235-75-3; **10**, 31235-76-4.

(7) All reactions were performed under a nitrogen atmosphere and solvents were concentrated on a rotary evaporator under vacuum. Melting points were taken on a Thomas–Hoover apparatus and are uncorrected. Except where noted, nmr spectra were recorded in the Model A-60A Varian Associates spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal standard (TMS = 0.0 ppm). Glpc analyses were performed on a Varian Model 90-P. Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley.

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