(2,6-dimethylphenyl)hydrazine, 603-77-0; ethyl 2-thienylglyoxylate, 4075-58-5; *N*-(2,6-dimethylphenyl)-2-thienylglyoxylic acid hydrazide, 80387-75-3; ethyl 5-(4-amino-3,5-dimethylphenyl)-2-thienylglyoxylate, 80387-76-4; 5-(4-amino-3,5-dimethylphenyl)-2-thiophenecarboxylic acid, 80387-77-5; 3,5-dimethyliodobenzene, 22445-41-6; methyl levulinate, 624-45-3; 4-(4-acetamidophenyl)-2-(methoxycarbonyl)thiophene, 80387-78-6; oxalic acid ethyl ester chloride, 4755-77-5; 2-(4-nitrophenyl)thiophene, 59156-21-7; 5-(4-nitrophenyl)thiophene-2-carboxylic acid, 80387-79-7; 2-(methoxycarbonyl)-5-(4-nitrophenyl)thiophene, 61100-12-7; bis[2,6-dimethyl-4-(methylamino)phenyl]methane, 80387-80-0; 2,6-dimethylaniline, 87-62-7.

Azabutadiene Derivatives in the Synthesis of Five-Membered Heterocycles. Unequivocal Synthesis of 1*H*-Pyrrole-2-carboxylates

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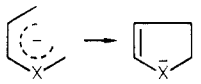
1,3-Diimines **1** react with glycine ethyl ester hydrochloride **2** as well as ethyl chloroacetate **9** in pyridine, giving rise to 1*H*-pyrrole-2-carboxylates **8** in both cases. The formation of heterocycles **8** can be explained in terms of an electrocyclic closure of the azapentadiene anion intermediate **6**.

The formation of aromatic and heteroaromatic compounds by electrocyclic ring closure with elimination is of high interest in organic synthesis.[1] This type of process is applied to form not only six-membered rings but also five-membered heterocycles.[2] In this last case, the electrocyclic reaction of the pentadienyl anion ⇌ cyclopentadienyl anion type is relatively unimportant. However, the presence of a heteroatom in the 2- or 4-position of the pentadiene favors the electrocyclic closure since the negative charge is supported by a heteroatom (N, O).



Azabutadiene derivatives **1** are easily obtained by reaction of Schiff bases with saturated nitriles in the presence of $AlCl_3$[3] and are useful precursors for the synthesis of six-membered heterocyclic rings. Usually the cyclization steps consist of a double condensation reaction[4] or an addition followed by the electrocyclic ring closure of the resulting intermediate.[5]

The azabutadienes **1** appeared to be potential precursors for the synthesis of five-membered heterocycles. With this in mind we have investigated the reaction of **1** with glycine ethyl ester hydrochloride and with ethyl chloroacetate. We report in this paper a new and unequivocal synthesis of 1*H*-pyrrole-2-carboxylates involving an azabutadiene anion (X = N).

Results and Discussion

Azabutadiene derivatives **1** react with glycine ester hydrochloride **2** at 80 °C in pyridine as solvent, giving, in high yields products whose structures from their elemental analyses and spectroscopic data are consistent with **7** or **8**.

The heterocyclization can be explained in terms of an exchange reaction between the amino group of the glycine and the imino group present in one of the tautomer forms of the azabutadiene.[6] Deprotonation of intermediates **3** and/or **4** leads to azapentadienyl anions **5** and/or **6**, which can undergo an electrocyclic closure, giving 1*H*-pyrrole-2-carboxylates (see Scheme I).

Table I. Pyrroles 8 from Diimines 1 and Glycine Ethyl Ester Hydrochloride 2

8	R^2	R^3	R^4	% yield	mp, °C
a	C_6H_5	CH_3	C_6H_5	88	135-137
b	C_6H_5	CH_3	p-$CH_3C_6H_4$	90	138-140
c	C_6H_5	CH_3	C_3H_7	80	111-113
d	C_6H_5	CH_3	c-C_6H_{11}	85	118-120
e	C_6H_5	CH_3	p-ClC_6H_4	85	178-180
f	C_6H_5	H	C_6H_5	81	137-139
g	C_6H_5	H	p-$CH_3C_6H_4$	87	168-170
h	p-ClC_6H_4	CH_3	C_6H_5	83	172-174
i	p-ClC_6H_4	CH_3	p-$CH_3C_6H_4$	85	173-175

In a previous paper on the reaction of **1** with heterocumulenes[5] we showed (by isolating the intermediate resulting from the addition of the imine NH to the heterocumulene) that the unsubstituted imine group is the main reactive center in the azabutadiene. Taking this into account, one can propose, that the reaction of **1** with **2** takes place through path b leading to pyrroles **8** (Scheme II). In addition, the same products are obtained from the reaction of **1** with either ethyl chloroacetate (**9**) or glycine ethyl ester hydrochloride (**2**).

Additional evidence to confirm this reaction mechanism lies in the isolation of the intermediate **4**. In this way diimine **1** (R^1 = c-C_6H_{11}, R^2 = C_6H_5, R^3 = CH_3, R^4 = p-$CH_3C_6H_4$) reacts with **2** at room temperature to afford **4b** (see Experimental Section). Moreover, ammonium chloride is identified. When **4b** is dissolved in pyridine and heated at 80 °C, the heterocycle **8b** is formed and isolated in quantitative yield.

Whereas the synthesis of alkylpyrroles has been widely developed,[7] this cannot be said of aryl pyrroles. By use of classical synthetic methods such as modified Knorr[8] and Hantzsch[9] procedures in order to prepare asymmetric

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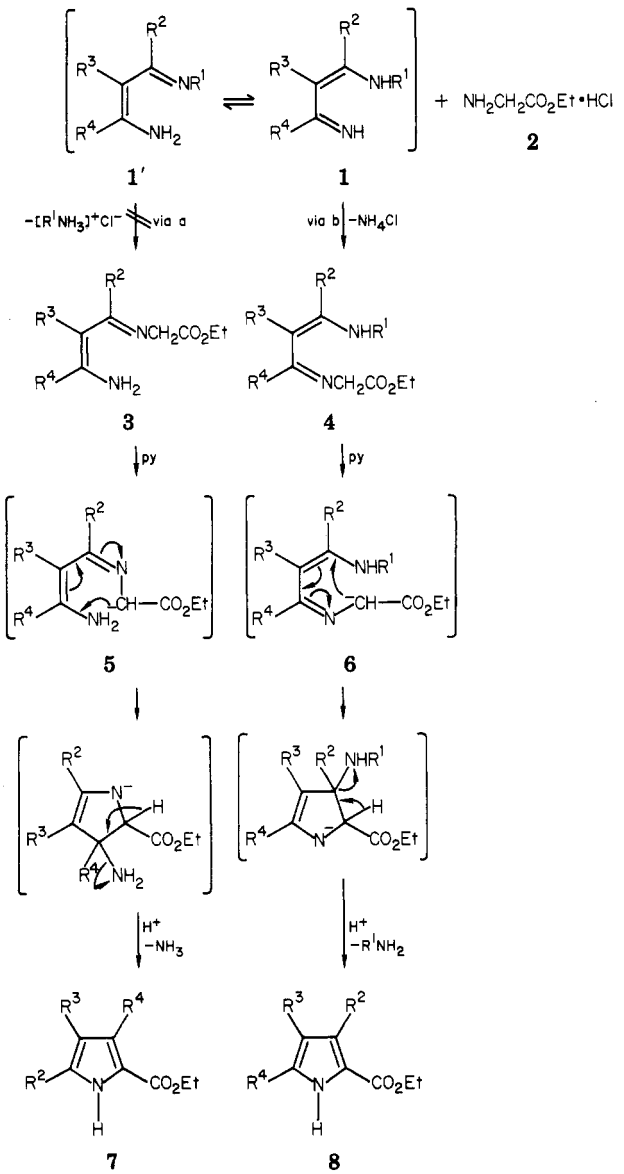
Table II. Spectral Data for Compounds 8

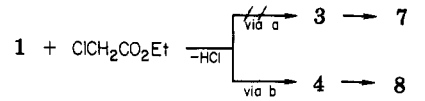
8	R^2	R^3	R^4	IR, cm^{-1}	^1H NMR, δ	MS (M^+), m/e
a	C_6H_5	CH_3	C_6H_5	3330, 1675	0.9 (t, CH_3), 1.9 (s, CH_3), 3.9 (q, CH_2), 7.1-7.5 (m, 10 H, arom), 9.7 (br, NH)	305
b	C_6H_5	CH_3	p-$CH_3C_6H_4$	3320, 1670	0.9 (t, CH_3), 1.9 (s, CH_3), 2.2 (s, CH_3), 3.9 (q, CH_2), 7.1-7.5 (m, 9 H, arom); 9.5 (br, NH)	
c	C_6H_5	CH_3	n-C_3H_7	3320, 1660	0.9 (t, CH_3), 1.0 (t, CH_3), 1.4-1.8 (m, CH_2), 1.8 (s, CH_3), 2.5 (t, CH_2), 4.0 (q, CH_2), 7.2-7.4 (m, 5 H, arom), 9.0 (br, NH)	
d	C_6H_5	CH_3	c-C_6H_{11}	3330, 1675	1.1 (t, CH_3), 1.1-2.1 (m, 10 H), 1.9 (s, CH_3), 2.5-2.8 (m, CH), 4.2 (q, CH_2), 7.3-7.5 (m, 5 H, arom), 9.2 (br, NH)	311
e	C_6H_5	CH_3	p-ClC_6H_4	3320, 1680	1.1 (t, CH_3), 2.1 (s, CH_3), 4.1 (q, CH_2), 7.3-7.5 (m, 9 H, arom), 9.3 (br, NH)	
f	C_6H_5	H	C_6H_5	3325, 1670	1.2 (t, CH_3), 4.2 (q, CH_2), 6.6 (d, CH, J = 3 Hz), 7.1-7.7 (m, 10 H, arom), 9.5 (br, NH)	
g	C_6H_5	H	p-$CH_3C_6H_4$	3320, 1675	1.2 (t, CH_3), 2.3 (s, CH_3), 4.2 (q, CH_2), 6.5 (d, CH, J = 3 Hz), 7.1-7.7 (m, 9 H, arom), 9.6 (br, NH)	
h	p-ClC_6H_4	CH_3	C_6H_5	3315, 1680	1.1 (t, CH_3), 2.0 (s, CH_3), 4.2 (q, CH_2), 7.0-7.5 (m, 9 H, arom), 9.4 (br, NH)	
i	p-ClC_6H_4	CH_3	p-$CH_3C_6H_4$	3320, 1680	1.1 (t, CH_3), 2.0 (s, CH_3), 2.4 (s, CH_3), 4.1 (q, CH_2), 7.1-7.5 (m, 8 H, arom), 9.2 (br, NH)	

Scheme I



arylpyrroles, mixtures of regioisomers are normally obtained in yields usually less than 60%.[10] Further, these syntheses are more useful for obtaining 3-carbonylpyrroles but less so for pyrrole-2-carboxylates.

Scheme II



The above-described method allows us to obtain in a regioselective manner 3,5-diarylpyrrole-2-carboxylates, whose difficult availability has already been reported,[11] as well as 3-arylpyrrole-2-carboxylates, which are one of the most important intermediates for the synthesis of pyrrolnitrin.[12] The high yields obtained in all instances (see Table I) and the availability of the starting materials make this synthesis one of the most convenient methods for the preparation of 1*H*-pyrrole-2-carboxylates.

Experimental Section

General Methods. Melting points are uncorrected. The NMR spectra were determined in deuterated chloroform by using a Varian FT-80 spectrometer (80 MHz) with internal tetramethyl silane as the reference. Infrared spectra were recorded in Nujol suspensions on a Pye Unicam SP-1000 spectrophotometer. Microanalyses were performed on a Perkin-Elmer Model 240.

Materials. 1,3-Diimines 1[3] and glycine ethyl ester hydrochloride[13] were obtained according to the literature procedures. All of the other reagents were commercially available (99%) and used as received.

1*H*-Pyrrole-2-carboxylates 8. General Procedures. Ethyl 3-(*p*-Chlorophenyl)-4-methyl-5-phenyl-2-pyrrolecarboxylate (8h). Glycine ethyl ester hydrochloride (1.4 g, 10 mmol) was added to a solution of 1-(*p*-chlorophenyl)-3-imino-2-methyl-*N*,3-diphenylprop-1-enamine (1h; 3.46 g, 10 mmol) in pyridine (60 mL) at room temperature, and the mixture was warmed to 80 °C. After being stirred 4 h, the solution was poured into ice-cooled 6 N H_2SO_4 (150 mL). The resulting mixture was extracted with ether, and the organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by recrystallization from hot hexane to afford 2.81 g (83%) of 8h: ^{13}C NMR

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($CDCl_3$, internal Me_4Si) δ 161.3 (s), 133.5, 133.3, 132.7, 132.2, 131.8, 131.4, 128.7, 127.7, 127.5, 118.5 (s), 117.6 (s), 60.2 (t), 14.0 (q), 10.8 (q). Anal. Calcd for $C_{20}H_{18}NO_2Cl$: C, 70.68; H, 5.34; N, 4.12. Found: C, 70.82; H, 5.19; N, 4.28.

Ethyl 5-(*p*-Chlorophenyl)-4-methyl-3-phenyl-2-pyrrolecarboxylate (8e). A mixture of 3-(*p*-chlorophenyl)-3-imino-2-methyl-*N*,1-diphenylprop-1-enamine (**1e**; 3.46 g, 10 mmol) and ethyl chloroacetate (1.22 g, 10 mmol) in pyridine was heated at 100 °C for 6 h and then slowly poured into ice-cooled 6 N H_2SO_4 (150 mL). The resulting mixture was extracted with ether, and the organic layer was dried over sodium sulfate, filtered, and evaporated. The residue was purified by recrystallization from hot hexane to afford **8e**: 2.50 g (74%); ^{13}C NMR ($CDCl_3$, internal Me_4Si) δ 161.7 (s), 134.7, 133.3, 132.6, 131.8, 129.8, 129.4, 128.7, 127.3, 127.1, 124.6, 118.7 (s), 117.8 (s), 60.1 (t), 13.9 (q), 10.8 (q). Anal. Calcd for $C_{20}H_{18}NO_2Cl$: C, 70.68; H, 5.34; N, 4.12. Found: C, 70.95, H, 5.07; N, 4.37.

Spectral data for the products **8** are given in Table II.

***N*-Cyclohexyl-3-[[(ethoxycarbonyl)methyl]imino]-2-methyl-1-phenyl-3-(*p*-tolyl)prop-1-enamine (4b, R^1 = c-C_6H_{11}).** A mixture of *N*-cyclohexyl-3-imino-2-methyl-1-phenyl-3-(*p*-tolyl)prop-1-enamine (**1b**, R^1 = c-C_6H_{11}; 3.32 g, 10 mmol) and glycine ethyl ester hydrochloride (1.4 g, 10 mmol) in pyridine (60 mL) was stirred at room temperature for 24 h. The solution was then acidified with 4 N H_2SO_4 (150 mL) and extracted with ether. The dry organic layer was evaporated and the residue recrystallized from hexane to afford 3.14 g (75%) of **4b** (R^1 = c-C_6H_{11}): mp 103–105 °C; IR (Nujol) ν_{max} 1745, 1195 cm^{-1}; ^1H NMR ($CDCl_3$, internal Me_4Si) δ 0.9-1.9 (16 H, m, CH_2CH_3, $=CCH_3$, $(CH_2)_5$), 2.2 (3 H, s, CH_3), 2.5–2.9 (1 H, m, NCH), 3.8 (2 H, s, NCH_2CO), 4.0–4.4 (2 H, q, $OCH2CH_3$), 6.9–7.6 (9 H, m, aromatic); ^{13}C NMR ($CDCl_3$, internal Me_4Si) δ 13.2 (q), 16.7 (q), 20.0 (q), 23.6 (t), 24.7 (t), 33.7 (t), 51.1 (d), 54.0 (t), 59.2 (t), 96.6 (s), 126.6, 127.0, 127.2, 127.6, 128.0, 134.5 (s), 136.4 (s), 137.3 (s), 170.5 (s); mass spectrum, m/e 418 (M^+). Anal. Calcd for $C_{27}H_{34}N_2O_2$: C, 77.48; H, 8.19, N, 6.69. Found: C, 77.72, H, 7.92, N, 6.78.

Conversion of 4b to 8b. A solution of **4b** (3 g, 7.1 mmol) in pyridine (50 mL) was heated at 80 °C for 4 h. The solution was poured into 150 mL of ice-cooled 4 N H_2SO_4, extracted with ether, dried over sodium sulfate, and concentrated. The residue was recrystallized from hexane to give 2.0 g (89%) of **8b**.

Registry No. 1b, 71115-26-9; **1e**, 71115-32-7; **1h**, 72923-06-9; **2**, 623-33-6; **4b**, 80765-52-2; **8a**, 80765-53-3; **8b**, 80765-54-4; **8c**, 80765-55-5; **8d**, 80765-56-6; **8e**, 80765-57-7; **8f**, 53778-26-0; **8g**, 80765-58-8; **8h**, 80765-59-9; **8i**, 80765-60-2; **9**, 105-39-5.

Retinoic Acid Metabolites. 1. Total Synthesis of 4-Hydroxy- and 4-Oxoretinoic Acid

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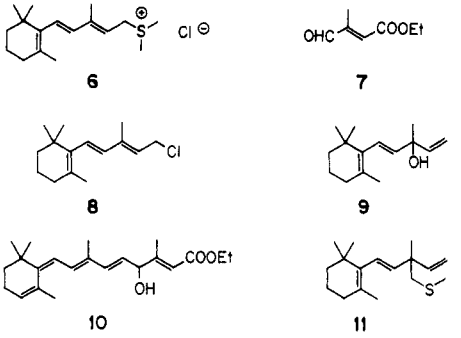
Two major metabolites of retinoic acid, 4-hydroxy- and 4-oxoretinoic acid, have been prepared by employing a polyene sulfonium salt and ethyl β-formylcrotonate.

Retinoic acid is a major metabolite of retinol, and like retinol it has several important functions in the body. It plays a key role in the maintenance and differentiation of epithelial tissue[1] and is essential for fetal development and growth promotion in general.[2]

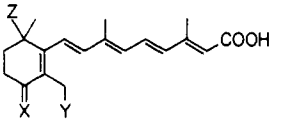
In animal tests, some striking effects have been demonstrated by retinoic acid and its derivatives in the inhibition and regression of precancerous[3] and cancerous conditions.[4] These exciting results coupled with the impressive effects demonstrated by 13-*cis*-retinoic acid in the treatment of cystic acne[5] have created a renewed interest in the area of retinoic acid and its metabolites.

The early literature[6] contains numerous reports of polar metabolites isolated from retinol which were inadequately characterized, possibly because of lack of material or suitable instrumentation. Some of the first well-characterized metabolites arising from retinoic acid were described by Rietz et al.,[7] who showed that the molecule

Chart I



underwent extensive oxidation to yield compounds such as **1–3**. Hänni et al.[8] continued in the footsteps of Rietz



1: Z = CH_3, Y = H, X = O
2: Z = CH_2OH, Y = H, X = O
3: Z = COOH, Y = H, X = O
4: Z = CH_3, Y = OH, X = H,H
5: Z = CH_3, Y = H, X = H,OH

and was able to isolate several new retinoic acid metabo-

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