Reactions of Ethyl Diazoacetate with Thianaphthene, Indoles, and Benzofuran

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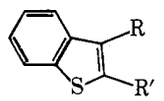
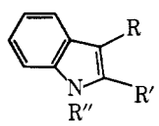
The thermolysis of ethyl diazoacetate in thianaphthene leads in low yield to the heterocycle's 3-acetic ester and 2,3-cyclopropanation products. Copper catalysis furnishes the same products along with triethyl 1,2,3-cyclopropanetricarboxylate. Copper-induced thermolysis of the diazo ester in 1,3-dimethylindole produces in low yield ethyl 1,3-dimethyl-2-indolylacetate, whereas the reaction on *N*-acylindoles leads to the trapping of the enamine double bond in the form of cyclopropane esters. A similar reaction of benzofuran yields cyclopropane carboxylates, whose acid-catalyzed ring opening yields 2- and 3-benzofuranacetic esters. In aqueous acid a major product is *o*-(β-carboxypropionyl)phenol. Acid-induced opening of carbinol reduction products of the cyclopropane esters give 2- and 3-vinylbenzofurans.

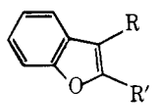
As part of a study of the cyclopropanation of enol ethers and esters with acyldiazomethanes and the exploitation of the products in natural product synthesis,[4] an investigation of the reaction of ethyl diazoacetate with thianaphthene (**1a**), indole (**2a**) and its derivatives, and benzofuran (**3a**) was undertaken.



1a, R = R′ = H
b, R = CH_2CO_2Et; R′ = H
c, R = H; R′ = CH_2CO_2Et

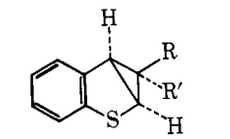


2a, R = R′ = R″ = H
b, R = R′ = H; R″ = Me
c, R = CH_2CO_2Et; R′ = H; R″ = Me
d, R = R″ = Me; R′ = H
e, R = CH_2CO_2Et; R′ = R″ = Me
f, R = R″ = Me; R′ = CH_2CO_2Et
g, R = R′ = R″ = Me
h, R = R′ = H; R″ = Ac
i, R = R′ = H; R″ = CO_2Me
j, R = Me; R′ = H; R″ = CO_2Me

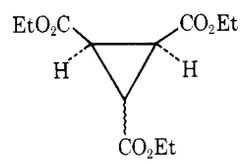


3a, R = R′ = H
b, R = CH_2CO_2Me; R′ = H
c, R = H; R′ = CH_2CO_2Me
d, R = C_2H_3; R′ = H
e, R = H; R′ = C_2H_3

It has been reported that thermolysis of ethyl diazoacetate in liquid thianaphthene (**1a**) leads to products of cyclopropanation of the unsubstituted thiophene double bond, **4a** and **4b** (of unsubstantiated stereochemistry),[5a,b] and of the benzene moiety.[5a,b,c] Repetition of this experiment afforded now a mixture of esters in 8% yield from which there could be isolated and characterized cyclopropanes **4a** and **4b** (in ca. 1:13 ratio) and acetic ester **1b** and in which benzocyclopropanated products and another acetic ester, conceivably **1c**, appeared to be present. Ester **1b**, a previously unobserved product of the reaction,[5] seemed to be a primary product instead of one of isomerization of the cyclopropanes **4**, as illustrated by the thermal stability and workup inertness of at least **4a**. When the reaction was carried out under traditional cyclopropanation conditions,[6] i.e., with copper catalysis, the aforementioned products were observed, but the major product (30% yield) proved to be a stereoisomer mixture of triethyl 1,2,3-cyclopropanetricarboxylate (**5**). The formation of the latter solely



4a, R = H; R′ = CO_2Et
b, R = CO_2Et; R′ = H
c, R = H; R′ = CO_2H



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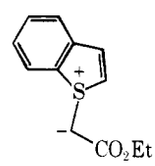

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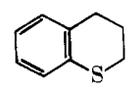

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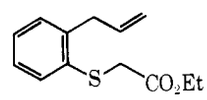

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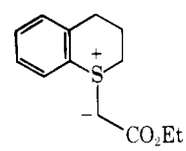

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in the catalyzed reaction suggests that the intermediate copper–carbenoid complex may be trapped by the sulfur site of thianaphthene (**1a**),[7] e.g., in the form of ylide **6**, and thus form a reagent for cyclopropanation[8] of the common products of the decomposition of ethyl diazoacetate, diethyl maleate, and fumarate.[6] The conversion of thiochromane (**7**) into sulfide **8** on thermal, copper-catalyzed decomposition of ethyl diazoacetate in the presence of the heterocycle illustrates the intermediacy of a sulfur ylide. In this case, presumably compound **9** is formed and undergoes thermally induced, intramolecular elimination.[7]

Indoles **2** have been shown to undergo β-alkylation on reaction with diazoacetic ester under the influence of copper or its salts.[5a,9,10] Whereas no intermediates have been isolated heretofore, the reactions have been assumed to be cyclopropanation–isomerization processes.[4b,11] It now became of interest to test the fate of the reaction in the case of a β-alkylindole and to attempt to trap cyclopropane intermediates.

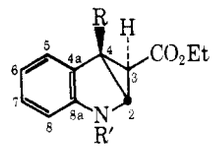
Table I. Carbon Shifts of 2,4-Dehydro-1,2,3,4-tetrahydroquinolines[a]

	10a[b,g]	11a[b,g]	10b[c,g]	11b[c,g]	10c[c,d,g]	11c[c,e,g]
C(2)	46.0	44.1	45.0	43.4	49.3	49.0
C(3)	25.0	20.0	24.1	18.2	28.8	24.4
C(4)	29.2	27.5	28.2	27.1	33.7	33.7
C(4a)	130.1	*f*	130.0	126.5	134.8	130.0
C(5)	124.1	124.7	124.1	124.6	122.6	123.2
C(6)	123.3	123.2	122.4	122.1	122.4	122.1
C(7)	127.7	127.8	127.4	127.4	127.4	127.5
C(8)	117.1	116.4	115.1	114.1	115.0	114.1
C(8a)	141.7	*f*	140.8	144.1	140.1	143.3
CO	171.2	166.4	171.3	166.5	170.6	166.5
OCH_2	60.9	60.4	60.6	59.8	60.4	59.8
Me	14.0	13.7	13.9	13.6	14.0	13.6
NCO	168.5	169.3	152.7	153.7	152.7	153.1

[a] In parts per million downfield from Me_4Si; δ (Me_4Si) = δ ($CDCl_3$) + 76.9 ppm. [b] δ (Me^{NAc}) = 24.2 ppm. [c] δ (OMe) = 52.6 ppm. [d] δ (4-Me) = 10.9 ppm. [e] δ (4-Me) = 18.5 ppm. [f] Missing signal. [g] Registry no.: **10a**, 63703-19-5; **11a**, 63730-21-2; **10b**, 63703-20-8; **11b**, 63730-22-3; **10c**, 63703-21-9; **11c**, 63730-23-4.

Copper-catalyzed decomposition of ethyl diazoacetate in 1,3-dimethylindole (**2d**) led in minute yield (7%) to an indoleacetic ester, whose transformation into 1,2,3-trimethylindole (**2g**) by alkaline hydrolysis and thermal decarboxylation of the resultant acid[12] showed it to be an α- or β-acetic ester. Its nonidentity with the β-ester (**2e**)[13] indicated it to be the indole derivative **2f**.[14] Thus, despite the predilection of indoles to form β-acetic esters, the aromatic heterocycle tolerates the equivalent of α-alkylation in an already β-substituted case.[15]

On the assumption of a decrease of electron availability on the indole nitrogen enhancing the stability of possible cyclopropanecarboxylate intermediates in the reaction of indoles with diazoacetic ester,[16] *N*-acetylindole (**2h**),[17] *N*-carbomethoxyindole (**2i**),[18] and *N*-carbomethoxyskatole (**2j**) were prepared and involved in a copper-catalyzed decomposition of ethyl diazoacetate. The products proved to be *exo*- and *endo*-cyclopropanecarboxylate isomers **10a** and **11a** (ca. 7:1



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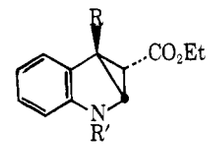

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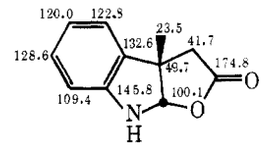
a, R = H; R′ = Ac
b, R = H; R′ = CO_2Me
c, R = Me; R′ = CO_2Me

ratio), **10b** and **11b** (ca. 3:1 ratio) and **10c** and **11c** (ca. 4:1 ratio), respectively. The stereoisomers were differentiated from each other by ^1H- and ^{13}C NMR spectral analysis (cf. Table I). The α-ketomethine hydrogen of the exo isomers and the carboethoxy hydrogens of the endo esters are shielded strongly anisotropically by the aromatic rings.[19] The effect is exhibited even by the carbon shifts of the *endo*-carboethoxycarbonyl and oxymethylene units.[20]

The successful cyclopropanation of the *N*-acylindoles exclusively at the C(α)–C(β) bond site is suggestive, albeit not proof, of cyclopropanecarboxylates serving as intermediates in the conversion of indoles into indoleacetic esters by copper-catalyzed diazoacetic ester decompositions (vide supra). Cyclopropane ring scission of one of the esters, **10c**, by alkaline hydrolysis yielded indolinelactone **12**,[21] an indole-β-acetic acid equivalent. The carbon shifts of this eserine alkaloid model are depicted on the formula.[22]



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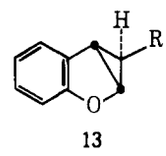
The thermal decomposition of diazoacetic ester in benzofuran (**3a**) has been reported to lead to a cyclopropanecarboxylate whose structure implied the carbenoid trapping of the enol ether double bond of **3a** and whose alkaline hydrolysis yielded a single crystalline carboxylic acid.[5a] The copper-catalyzed decomposition of ethyl diazoacetate in benzofuran (**3a**) now could be shown to produce a ca. 7:1 mixture of *exo*- and *endo*-cyclopropane esters **13a** and **14a**, respectively, in



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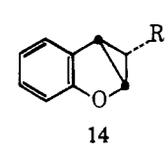

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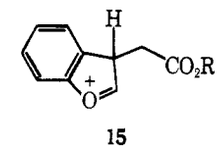

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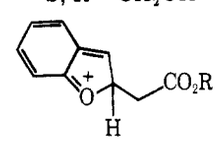
a, R = CO_2Me
b, R = CH_2OH



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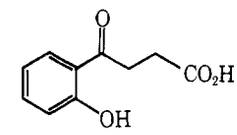

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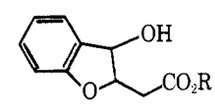

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62% yield. The β-oxycyclopropylcarbonyl nature of these substances could be expected to make them susceptible to acid-induced ring opening with the formation of γ-keto acid equivalents.[4] However, the tendency for the customary ring fission, i.e., toward intermediate **15**, should be lessened by the lowered electron availability on the ether oxygen because of its conjugation with the benzene ring and might be in competition with ring scission of the type leading to intermediate **16** because of the ester also being a β-(*o*-oxyphenyl)cyclopropanecarboxylate, i.e., a β-oxycyclopropylcarbonyl vinylogue. In view of the unpredictability of the reaction path, the behavior of a cyclopropane ester toward acid became of interest.

Treatment of the ester **13a** with methanolic acid afforded a 97% yield of a 4:1 mixture of the benzofuranacetic esters[23] **3b** and **3c**, respectively, thus indicating both types of ring opening being operative. When the cyclopropanecarboxylate **13a** was treated with aqueous, methanolic acid, the β-alkylbenzofuran **3b** was again a product, but it was accompanied by the ketophenol **17**[24] in lieu of the α-alkylbenzofuran **3c**. Apparently, in this instance hydration of intermediate **16** intercedes in the reaction sequence, and the resultant 3-hydroxy-2,3-dihydrofuran **18** (or its lactone) undergoes acid-catalyzed elimination of the aryloxy unit.

Reduction of esters **13a** and **14a** with lithium aluminum hydride yielded alcohols **13b** and **14b**, respectively. Acid-catalyzed dehydration of carbinol **13b** yielded an ca. 2:1 mixture of vinylbenzofurans **3e** and **3d**, respectively. Thus, the unravelling of the cyclopropane initiated by the dissociation of the external carbon–oxygen bond system follows the two paths indicated above for a cyclopropane carboxylate, although the product preference is inverse that of the reaction with the ester.

Experimental Section

Melting points were recorded on a Reichert micro hot stage and are uncorrected. Infrared spectra were measured on a Perkin-Elmer 137 spectrophotometer and ^1H NMR spectra on a Varian A-60 spectrometer. Low-resolution mass spectra were obtained on a Varian CH-7 GC–MS instrument.

Cyclopropanation of Thianaphthene (1a). A solution of 35.0 g of ethyl diazoacetate and 45 g of **1a** was added dropwise evenly during a 24-h period to stirring **1a**, 45g, at 150 °C. Thereupon, the mixture was stirred at 150 °C for 1 h more, and the excess thianapthene (72 g) was removed by distillation at 2 Torr. Chromatography of the viscous, orange residue, 42 g, on 200 g of silica gel and elution with hexane gave 5 g of **1a**, and with 49:1 to 19:1 hexane–ether 300 mg of a 2:1 mixture (by GPC and ^1H NMR analyses) of ester **4a** (vide infra) and benzocyclopropanated ester [^1H NMR (CCl_4) δ 0.73 (t, 1, J = 4 Hz, c-Pr H), 1.23 (t, 3, J = 7 Hz, Me), 2.4–2.8, 3.0–3.5 (m, 1 each, c-Pr H_2), 4.08 (q, 2, J = 7 Hz, OCH_2), 6.08 (dd, 1, J = 10, 5 Hz, olefinic H), 6.40 (d, 1, J = 10 Hz, olefinic, benzyl H), 7.0–7.1 (m, 2, H-2, H-3)]. Elution with 19:1 hexane–ether yielded 800 mg of colorless, liquid ester **4a**: IR ($CHCl_3$) C=O 1710 (s) cm^{-1}; ^1H NMR (CCl_4) δ 1.23 (t, 3, J = 7 Hz, Me), 1.28 (m, 1, c-Pr COCH), 3.40 (t, 2, J = 4 Hz, ArCH, SCH), 4.08 (q, 2, J = 7 Hz, OCH_2), 6.9–7.4 (m, 4, Ar H's). A solution of 200 mg of the latter and 2 g of sodium hydroxide in 30 mL of ethanol was refluxed for 4 h, and then poured onto ice, acidified with 1 N hydrochloric acid, and extracted with ether. The extract was washed with water and evaporated under vacuum. Crystallization of the residue, 100 mg, from petroleum ether gave 21 mg of crystalline acid **4c**: mp 147 °C; ^1H NMR ($CDCl_3$) δ 1.33 (t, 1, J = 4 Hz, COCH), 3.55 (t, 2, J = 4 Hz, ArCH, SCH), 6.8–7.5 (m, 4, Ar H's).

Continuation of the elution with 9:1 hexane–ether yielded 400 mg of a 3:2 mixture (by GPC and ^1H NMR analyses) of ester **1b** (vide infra) and its isomer (possibly **1c**) [^1H NMR (CCl_4) δ 1.08 (t, 3, J = 7 Hz, Me), 3.67 (s, 2, CH_2), 4.00 (q, 2, J = 7 Hz, OCH_2), 6.8–7.7 (m, 4, Ar H's)]. Chromatography of 300 mg of this mixture on silica gel and elution with 19:1 hexane–ether gave 135 mg of colorless, liquid ester **1b**: IR ($CHCl_3$) C=O 1725 (s) cm^{-1}; ^1H NMR (CCl_4) δ 1.17 (t, 3, J = 7 Hz, Me), 3.71 (s, 2, CH_2), 4.04 (q, 2, J = 7 Hz, OCH_2), 7.0–7.7 (m, 4, Ar H's); identical with IR and ^1H NMR spectra of an authentic specimen.[25] Further elution with 9:1 hexane–ether yielded 4 g of a mixture of **1b**, its isomer (possibly **1c**), **4b**, and the benzocyclopropanated ester. Rechromatography of 300 mg of this mixture on silica gel and elution with hexane led to 100 mg of liquid ester **4b**: IR ($CHCl_3$) C=O 1726 (s) cm^{-1}; ^1H NMR (CCl_4) δ 0.99 (t, 3, J = 7 Hz, Me), 2.00 (t, 1, J = 8 Hz, COCH), 3.32, 3.40 (d, 1 each, J = 8 Hz, ArCH, SCH), 3.80 (q, 2, J = 7 Hz, OCH_2), 6.8–7.3 (m, 4, Ar H's).

Anal. Calcd for $C_{12}H_{12}O_2S$: C, 65.44; H, 5.49; S, 14.54. Found: C, 64.94: H, 5.32; S, 14.22.

Heating of 50 mg of ester **4a** at 150 °C for 24 h, extraction of the product with ether, and evaporation yielded 40 mg of starting ester, as identified by GPC.

Triethyl 1,2,3-Cyclopropanetricarboxylate (5). A solution of 6.37 g of ethyl diazoacetate in 7 mL of anhydrous xylene was added over a 6-h period to a stirring mixture of 15 g of thianaphthene (**1a**) and 0.5 g of copper bronze in 8 mL of xylene at 90 °C, and the mixture was stirred at 100 °C for 12 h. It then was filtered and the filtrate evaporated under vacuum. Distillation of the residue led to the recovery of xylene and 14 g of thianapthene (**1a**). Chromatography of the distillation residue, 2 g, on 40 g of silica gel and elution with benzene yielded 500 mg of a mixture of the products of the uncatalyzed reaction and 1.40 g of oily triester: IR ($CHCl_3$) C=O 1725 (s) cm^{-1}; ^1H NMR (CCl_4) δ 1.26, 1.30 (t, 9 total, J = 7 Hz, Me), 2.3–2.7 (m, 3, CH) 4.05, 4.06 (q, 2 total, J = 7 Hz, OCH_2); spectra identical with those reported previously.[26]

Ethyl *o*-Allylphenylthioacetate (8). Ethyl diazoacetate, 4.00 g, was added dropwise over a 5-h period to a stirring mixture of 7.00 g of thiochromane (**7**) and 0.4 g of copper bronze in 8 mL of benzene under nitrogen at 60 °C, and the mixture was stirred at 40 °C for 12 h. It then was filtered and the filtrate evaporated under vacuum. Distillation of the residue under vacuum led to the recovery of 4.3 g of thiochromane (**7**) and chromatography of the residue on silica gel, followed by elution with benzene, yielded 1.80 g of ester **8**: IR (CCl_4) C=O 1735 (s), C=C 1700 (m), 1600 (w) cm^{-1}; ^1H NMR (CCl_4) δ 1.15 (t, 3, J = 7 Hz, Me), 3.44 (s, 2, CH_2), 3.49 (d, 2, J = 6 Hz, CH_2), 4.00 (q, 2, J = 7 Hz, OCH_2), 4.7–5.1, 5.5–6.2 (m, 3, olefinic H's), 6.8–7.4 (m, 4, Ar H's).

Anal. Calcd for $C_{13}H_{16}O_2S$: C, 66.08; H, 6.83; S, 13.55. Found: C, 66.18; H, 6.92; S, 13.60.

Ethyl (1-Methyl-3-indolyl)acetate (2c). A solution, 4.20 g, of ethyl diazoacetate (80%, w/w) in methylene chloride was added dropwise over a 5-min period to a stirring suspension of 0.5 g of copper bronze in 2.10 g of *N*-methylindole (**2b**), and the stirring was continued for 4 h. Chromatography of the mixture on 100 g of alumina, activity III, and elution with 1:1 hexane–benzene yielded 815 mg of recovered starting material **2b** (39%) and an ester mixture. Chromatography of the latter on 50 g of silica and elution with methylene chloride gave 952 mg of liquid ester **2c**[5a] (27%): ^1H NMR ($CDCl_3$) δ 1.04 (t, 3, J = 7 Hz, Me), 3.20 (s, 3, NMe), 3.60 (s, 2, $COCH_2$), 3.99 (q, 2, J = 7 Hz, OCH_2), 6.72 (s, 1, NCH), 7.0–7.2 (m, 3, aromatic H's), 7.5–7.7 (m, 1, indole H-4).

Ethyl (1,3-Dimethyl-2-indolyl)acetate (2f). The identical procedure as for the preparation of **2c** above, except for the use of 2.30 g of 1,3-dimethylindole (**2d**), gave 1.19 g of recovered indole **2d** (52%) and 130 mg of liquid ester **2f**[14] (3.5%): ^1H NMR ($CDCl_3$) δ 1.20 (t, 3, J = 7 Hz, Me of Et), 2.21 (s, 3, Me), 3.59 (s, 3, NMe), 3.67 (s, 2, $COCH_2$), 4.06 (q, 2, J = 7 Hz, OCH_2), 7.0–7.3 (m, 3, aromatic H's), 7.3–7.5 (m, 1, indole H-4). A solution of 10 mL of 20% aqueous potassium hydroxide and 100 mg of ester **2f** in 5 mL of ethanol was refluxed under nitrogen for 3 h and then washed with ether. The aqueous solution was acidified with 10% hydrochloric acid and extracted with ether. The extract was evaporated and the solid residue heated at 210 °C under nitrogen for 5 min. It was reextracted with ether and the extract evaporated. Filtration of a 1:1 hexane–benzene solution through alumina yielded 30 mg of 1,2,3-trimethylindole[12] (**2g**): ^1H NMR ($CDCl_3$) δ 2.21, 2.27 (s, 3 each, Me_2), 3.56 (s, 3, NMe), 6.9–7.1 (m, 3, aromatic H's), 7.2–7.4 (m, 1, indole H-4).

Ethyl (1,2-Dimethyl-3-indolyl)acetate (2e). 1-Methyl-1-phenylhydrazine, 15.2 g (85%, 15% *N*-methylaniline impurity), was added dropwise during a 1-h period to a refluxing solution of 18.8 g of ethyl levulinate in 50 mL of acetic acid, and the heating was continued for another 1 h. The mixture was poured into water and extracted with ether. The extract was washed with 5% sodium bicarbonate and brine solution, dried (Na_2SO_4), and evaporated. Distillation of the residue gave some starting ester in a forerun and 10.5 g of liquid ester **2e** (51%): bp 160–162 °C (2 Torr); IR (neat) C=O 1730 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (t, 3, J = 7 Hz, Me of Et), 2.25 (s, 3, Me), 3.40 (s, 3, NMe), 3.63 (s, 2, $COCH_2$), 4.05 (q, 2, J = 7 Hz, OCH_2), 7.0–7.3 (m, 3, aromatic H's), 7.4–7.7 (m, 1, indole H-4); not identical with **2f** above.

Anal. Calcd for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.70; H, 7.41; N, 5.97.

Ethyl *exo*- and *endo*-1-Acetyl-2,4-dehydro-1,2,3,4-tetrahydroquinoline-3-carboxylate (10a and 11a). A mixture of a methylene chloride solution of 3.90 g of ethyl diazoacetate (80%, w/w) and 2.60 g of *N*-acetylindole (**2h**)[17] in 9 mL of cyclohexane was added dropwise over a 4-h period to a refluxing suspension of 0.5 g of copper bronze in 3 mL of dry cyclohexane. Ether, 20 mL, was added and the mixture filtered. The filtrate was evaporated and the residue chromatographed on alumina, activity III. Elution with hexane and benzene yielded 765 mg of starting indole **2h** (30%), 355 mg of ethyl maleate and fumarate, and 1.29 g of ester **10a** (32%) in the form of rosettes: mp 88–89 °C (hexane–ether); ^1H NMR ($CDCl_3$) δ 1.25 (t, 3, J = 7 Hz, Me), 1.32 (dd, 1, J = 3, 2 Hz, H-3), 2.34 (s, 3, COMe), 3.22 (dd, 1, J = 7, 3 Hz, H-4), 4.19 (q, 2, J = 7 Hz, OCH_2), 4.39 (dd, 1, J = 7, 2 Hz, H-2), 6.9–7.5 (m, 3, aromatic H's), 8.17 (br d, 1, J = 7 Hz, H-8); MS *m/e* 245 (M^+), 174, 172, 129 (base), 43.

Anal. Calcd for $C_{14}H_{15}O_3N$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.64; H, 6.15; N, 5.63.

Another eluate gave 193 mg of needles of ester **11a** (5%): mp 75–77 °C (hexane–ether); ^1H NMR ($CDCl_3$) δ 0.92 (t, 3, J = 7 Hz, Me), 2.03 (dd, 1, J = 9, 6 Hz, H-3), 2.37 (s, 3, COMe), 3.27 (dd, 1, J = 9, 7 Hz, H-4), 3.86 (q, 2, J = 7 Hz, OCH_2), 4.31 (dd, 1, J = 7, 6 Hz, H-2), 6.9–7.5 (m, 3 aromatic H's), 8.19 (br d, 1, J = 7 Hz, H-8); MS *m/e* same as for **10a**.

Anal. Calcd for $C_{14}H_{15}O_3N$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.64; H, 6.07; N, 5.68.

Ethyl *exo*- and *endo*-2,4-Dehydro-1-methoxycarbonyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (10b and 11b). Sodium hydride (from a mineral oil suspension, washed with hexane), 5.40 g of 50%, was added over a 20-min period to a solution of 11.7 g of indole (**2a**) in 80 mL of dry hexamethylphosphoramide under nitrogen at 0 °C, and the mixture was then stirred at room temperature for 4 h. It was cooled to −25 °C and 9.70 g of freshly distilled methyl chloroformate (bp 69–70 °C) was added at a rate maintaining a reaction temperature of −5 to 10 °C. The mixture was stirred at room temperature for 12 h, 120 mL of 2 N hydrochloric acid was added, and the mixture was extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residue, 14.9 g (85%), consisted of a 8:1 mixture of methyl 1- and 3-indolecarboxylate whose distillation led to 11.2 g of liquid urethane **2i**[18] (64%): bp 91–92 °C (0.3 Torr);

IR (neat) C=O 1740 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.58 (s, 3, Me), 6.20 (d, 1, J = 4 Hz, H-3), 6.8–7.3 (m, 4, aromatic H's), 7.8–8.0 (m, 1, H-7).

Anal. Calcd for $C_{10}H_9O_2N$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.80; H, 5.20; N, 7.97.

A mixture of a methylene chloride solution of 3.90 g of ethyl diazoacetate (80%, w/w) and 2.80 g of **2i** in 13 mL of cyclohexane was added dropwise over a 5-h period to a refluxing suspension of 0.5 g of copper bronze in 3 mL of cyclohexane, and the mixture was then filtered. Two consecutive additions of 20 mL of 9:1 hexane–benzene solutions each precipitated 975 mg of crystalline solid, identified subsequently as **10b**. Evaporation of the filtrates and chromatography of the residue on alumina, activity III, led to 1.12 g of starting indole **2i** (40%), 252 mg of ethyl maleate and fumarate, and 441 mg of more crystalline ester **10b** (36% total yield): mp 127–128.5 °C (hexane–benzene); ^1H NMR ($CDCl_3$) δ 1.20 (m, 1, H-3), 1.27 (t, 3, J = 7 Hz, Me), 3.25 (dd, 1, J = 3 Hz, H-4), 3.92 (s, 3, OMe), 4.21 (q, 2, J = 7 Hz, OCH_2), 4.65 (dd, 1, J = 7, 2 Hz, H-2), 6.9–7.5 (m, 3, aromatic H's), 7.82 (br d, 1, J = 7 Hz, H-8).

Anal. Calcd for $C_{14}H_{15}O_4N$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.47; H, 5.62; N, 5.27.

Another eluate yielded 486 mg of needles of **11b** (12%): mp 67–68.5 °C (hexane–benzene); ^1H NMR ($CDCl_3$) δ 0.91 (t, 3, J = 7 Hz, Me), 1.87 (dd, 1, J = 9, 6 Hz, H-3), 3.12 (dd, 1, J = 9, 7 Hz, H-4), 3.74 (q, 2, J = 7 Hz, OCH_2), 3.84 (s, 3, OMe), 4.41 (dd, 1, J = 7, 6 Hz, H-2), 6.8–7.4 (m, 3 aromatic H's), 7.80 (br d, 1, J = 7 Hz, H-8).

Anal. Calcd for $C_{14}H_{15}O_4N$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.41; H, 5.79; N, 5.36.

Ethyl *exo*- and *endo*-2,4-Dehydro-1-methoxycarbonyl-4-methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (10c and 11c). The procedure for the preparation of **2i** above was used identically on 13.10 g of skatole (**2**, R = Me, R′ = R″ = H). Distillation of the oily product yielded 11.00 g of liquid *N*-carbomethoxyskatole (**2j**) (58%): bp 101–102 °C (0.5 Torr); IR (neat) C=O 1735 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (d, 3, J = 1 Hz, Me), 3.67 (s, 3, OMe), 6.8–7.2 (m, 4, aromatic H's), 7.7–7.9 (m, 1, H-7).

Anal. Calcd for $C_{11}H_{11}O_2N$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.96; H, 5.90; N, 7.31.

The procedure for the preparation of **10b** and **11b** above was followed identically with the use of 3.08 g of **2j**. Chromatography of the product on alumina, activity III, yielded 1.24 g of starting indole **2j** (40%), 338 mg of ethyl maleate and fumarate, and 1.24 g of crystalline plates of ester **10c** (28%): mp 122–124 °C (hexane–benzene); ^1H NMR ($CDCl_3$) δ 1.25 (t, 3, J = 7 Hz, Me of Et), 1.29 (d, 1, J = 2 Hz, H-3), 1.69 (s, 3, Me), 3.84 (s, 3, OMe), 4.13 (q, 2, J = 7 Hz, OCH_2), 4.50 (d, 1, J = 2 Hz, H-2), 6.7–7.3 (m, 3, aromatic H's), 7.67 (br d, 1, J = 7 Hz, H-8).

Anal. Calcd for $C_{15}H_{17}O_4N$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.28; H, 6.20; N, 4.92.

Another eluate gave 357 mg of liquid ester **11c** (8%): ^1H NMR ($CDCl_3$) δ 0.90 (t, 3, J = 7 Hz, Me of Et), 1.59 (s, 3, Me), 1.83 (d, 1, J = 6 Hz, H-3), 3.74 (q, 2, J = 7 Hz, OCH_2), 3.78 (s, 3, OMe), 4.15 (d, 1, J = 6 Hz, H-2), 6.7–7.3 (m, 3, aromatic H's), 7.72 (br d, 1, J = 7 Hz, H-8).

Anal. Calcd for $C_{15}H_{17}O_4N$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.42; H, 6.42; N, 4.94.

(2-Hydroxy-3-methyl-3-indolinyl)acetic Acid Lactone (12). A solution of 114 mg of ester **10c** and 120 mg of 85% potassium hydroxide in 10 mL of 1:1 ethanol–water was refluxed for 2.5 h. Ice was added and the mixture extracted with ether. The aqueous solution was brought to pH 7 with sodium dihydrogenphosphate and extracted exhaustively with ether. The extract was dried ($MgSO_4$) and evaporated, yielding 72 mg of crystalline lactone **12** (92%): mp 99–101 °C (hexane–benzene) (lit.[21] mp 100 °C); ^1H NMR ($CDCl_3$) δ 1.43 (s, 3, Me), 2.79, 2.96 (AB dd, 2, J = 18, 2 Hz, CH_2), 5.62 (s, 1, OCH), 6.5–7.2 (m, 4, aromatic H's).

Anal. Calcd for $C_{11}H_{11}O_2N$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.74; H, 5.90; N, 7.35.

Ethyl *exo*- and *endo*-2,4-Dehydrochroman-3-carboxylate (13a and 14a). The procedure by Sörm[27] for the catalyzed reaction of α-diazoketo compounds with furans was applied to benzofuran and ethyl diazoacetate and produced a 62% yield of a ca. 7:1 mixture of cyclopropanecarboxylates[5a] **13a** and **14a**. Chromatography of 8.00 g of the ester mixture on 250 g of silica gel and elution with hexane yielded 6.84 g of liquid exo isomer **13a** (86%): bp 89–90 °C (0.25 Torr); IR (neat) C=O 1725 (s) cm^{-1}; ^1H NMR (CCl_4) δ 1.17 (dd, 1, J = 2, 3 Hz, H-3), 1.23 (t, 3, J = 7 Hz, Me), 3.15 (dd, 1, J = 3, 6 Hz, H-4), 4.05 (q, 1, J = 7 Hz, OCH_2), 4.92 (dd, 1, J = 2, 6 Hz, H-2), 6.73, 7.25 (d, 1 each, J = 7 Hz, aromatic H's), 6.78, 7.01 (t, 1 each, J = 7 Hz, aromatic H's). Elution with 9:1 hexane–benzene afforded 1.01 g of a liquid 5:1 **14a–13a** mixture (14%) whose endo isomer (**14a**) component revealed the following properties: bp 90–91 °C (0.13 Torr); IR (neat) C=O 1745 (s) cm^{-1}; ^1H NMR (CCl_4) δ 0.93 (t, 3, J = 7 Hz, Me), 1.67 (dd, 1, J = 6, 9 Hz, H-3), 3.10 (dd, 1, J = 6, 9 Hz, H-4), 3.76 (q, 2, J = 7 Hz, OCH_2), 4.99 (t, 1, J = 6 Hz, H-2), 6.70, 7.20 (d, 1 each, J = 7 Hz, aromatic H's), 6.76, 6.98 (t, 1 each, J = 7 Hz, aromatic H's).

***exo*-2,4-Dehydro-3-hydroxymethylchroman (13b).** A solution of 2.04 g of ester **13a** and 410 mg of lithium aluminum hydride in 30 mL of ether was refluxed under nitrogen for 1 h, and then treated with moist sodium sulfate, shaken thoroughly, and filtered. Drying (Na_2SO_4) of the filtrate and evaporation yielded 1.56 g of oily carbinol (96%), which solidified on cooling. Crystallization from hexane–methylene chloride gave 1.53 g of needles of alcohol **13b**: mp 74.5–75 °C; IR (KBr) OH 3350 (m), C=C 1610 (m), 1590 (w) cm^{-1}; ^1H NMR (CCl_4) δ 0.88 (ddt, 1, J = 2, 4, 7 Hz, H-3), 1.86 (s, 1, OH), 2.60 (dd, 1, J = 4, 6 Hz, H-4), 3.54 (d, 2, J = 7 Hz, CH_2), 4.60 (dd, 1, J = 2, 6 Hz, H-2), 6.73, 7.24 (d, 1 each, J = 7 Hz, aromatic H's), 6.78, 7.01 (t, 1 each, J = 7 Hz, aromatic H's).

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.00; H, 6.26.

***endo*-2,4-Dehydro-3-hydromethylchroman (14b).** An identical reduction of 1.00 g of endo ester **14a** with lithium aluminum hydride furnished 0.77 g of crystalline alcohol **14b**: mp 66–67 °C (hexane–methylene chloride); IR (KBr) OH 3370 (m) cm^{-1}; ^1H NMR (CCl_4) δ 1.05 (m, 1, H-3), 2.61 (dd, 1, J = 6, 9 Hz, H-4), 3.04 (d, 2, J = 7 Hz, CH_2), 3.68 (s, 1, OH), 4.61 (t, 1, J = 6 Hz, H-2), 6.57, 7.10 (d, 1 each, J = 7 Hz, aromatic H's), 6.68, 6.92 (t, 1 each, J = 7 Hz, aromatic H's).

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.18; H, 5.98.

Methyl 3- and 2-Benzofuranylacetate (3b and 3c) and o-(β-Carboxypropionyl)phenol (17). A solution of 5.18 g of ester **13a** in 70 mL of methanol, saturated with hydrogen chloride gas, was refluxed under anhydrous conditions for 1.5 h. The dark mixture was made alkaline with 10% potassium hydroxide and extracted with ether. The extract was dried ($MgSO_4$) and evaporated. Distillation of the residue gave 4.69 g of a 4:1 liquid mixture of benzofuranacetic esters[23] (97%) **3b** (vide infra) and **3c**: bp 94–96 °C (0.25 Torr); ^1H NMR ($CDCl_3$) δ 3.59 (s, 3, Me), 3.67 (s, 2, CH_2), 6.49 (s, 1, furan H). The basic, aqueous solution was acidified with 10% hydrochloric acid and extracted with ether. Drying ($MgSO_4$) of the extract and evaporation yielded 15 mg of acid **17** (0.4%) (vide infra).

A mixture of 8.00 g of ester **13a** and 80 mL of concentrated hydrochloric acid in 100 mL of methanol and 150 mL of water was refluxed for 2 h. It then was made alkaline with 10% potassium hydroxide solution and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated. Distillation of the residual oil, 2.92 g, yielded 2.41 g of liquid ester **3b**[23] (30%): bp 90–93 °C (0.25 Torr); IR (neat) C=O 1740 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.54 (s, 2, CH_2), 3.59 (s, 3, Me), 7.50 (s, 1, furan H); MS *m/e* 190 (M^+), 131 (base). [Alkaline hydrolysis of this ester gave 3-benzofuranylacetic acid, mp 89.5–91 °C (lit.[23] mp 89–90 °C).] The basic, aqueous solution was acidified with 10% hydrochloric acid and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated. Crystallization of the solid residue, 4.75 g, from hexane–methylene chloride yielded 4.10 g of crystalline acid **17**[24] (54%): mp 139–140 °C (lit.[24] mp 139–140 °C); IR (KBr) C=O 1725 (s), C=C 1660 (s) cm^{-1}; ^1H NMR (acetone-d_6) δ 2.73 (t, 2, J = 6 Hz, CH_2CO_2), 3.40 (t, 2, J = 6 Hz, $COCH_2$), 6.7–8.1 (m, 4, aromatic H's); MS *m/e* 194 (M^+), 121 (base).

3- and 2-Vinylbenzofuran (3d and 3e). A mixture of 530 mg of alcohol **13b** and 1 g of dried Amberlite ir-120-H cation-exchange resin in 30 mL of dry benzene was refluxed for 5 h and then filtered. The filtrate was evaporated and the fluorescent, residual oil, 501 mg, chromatographed on 10 g of neutral alumina, activity III. Elution with hexane yielded 292 mg of an inseparable, liquid, 2.3:1 mixture of vinylfurans (62%) **3e**: ^1H NMR (CCl_4) δ 5.27 (dd, 1, J = 2, 11 Hz, vinyl H), 5.85 (dd, 1, J = 2, 17 Hz, vinyl H), 6.44 (s, 1, furan H), 6.50 (dd, 1, J = 11, 17 Hz, vinyl H), 7.0–7.3 (m, 4, aromatic H's); and **3d**: ^1H NMR (CCl_4) δ 5.24 (dd, 1, J = 2, 12 Hz, vinyl H), 6.62 (dd, 1, J = 12, 17 Hz, vinyl H), 7.11 (dd, 1, J = 2, 17 Hz, vinyl H), 7.0–7.3 (m, 4, aromatic H's), 7.50 (s, 1, furan H).

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Registry No.—**1a,** 95-15-8; **1b,** 7597-68-4; **2a,** 120-72-9; **2b,** 603-76-9; **2c,** 56999-62-3; **2d,** 875-30-9; **2e,** 63703-22-0; **2f,** 14190-79-5; **2g,** 1971-46-6; **2h,** 576-15-8; **2i,** 39203-20-8; **2j,** 63703-23-1; **2** (R = Me; R′

= R″ = H), 83-34-1; **3a**, 271-89-6; **3b**, 26278-23-9; **3c**, 39581-61-8; **3d**, 63703-24-2; **3e**, 7522-79-4; **4a**, 63703-25-3; **4b**, 63730-24-5; **4c**, 63703-29-7; **5**, 729-87-3; **7**, 2054-35-5; **8**, 63703-26-4; **12**, 54124-39-9; **13a**, 63703-27-5; **13b**, 63703-28-6; **14a**, 63730-25-6; **14b**, 63730-26-7; **17**, 39560-34-4; ethyl diazoacetate, 623-73-4; 1-methyl-1-phenylhydrazine, 618-40-6; ethyl levulinate, 539-88-8.

References and Notes

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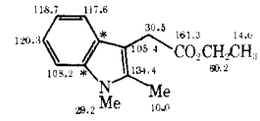

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Vicinal π Interactions in the Electrochemical Oxidation of a Carboxylic Acid

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Cyclic voltammetry of 5-carboxy-1,3-diphenyl-5-methyl-2-pyrazoline in acetonitrile reveals the presence a small peak at ca. 0.5 V lower overpotential than the usual peak position for diphenylpyrazolines. The peak is due to the anion form produced in the double layer and is attributed to the presence of through space interactions between the pyrazoline π system and the carboxylate group. The anodic oxidation reaction proceeds with decarboxylation to produce the aromatized pyrazole.

Although the Kolbe reaction with simple carboxylic acids appears to proceed via a concerted electron transfer–decarboxylation step to produce dimeric product,[1] in the case of phenyl-substituted propionic acids[2,3] the formation of cyclized products demonstrates that the acyloxy radical can affiliate the π system at some stage of the reaction. We should now like to present some results which show that the affiliation between the carboxyl group and a vicinal π system under anodic conditions occurs early in the reaction.

Results

5-Carbomethoxy-1,3-diphenyl-5-methyl-2-pyrazoline (I-$COOCH_3$) is produced as the only isomer in the addition reaction of diphenylnitrilimine to methyl methacrylate.[4] Saponification of I-$COOCH_3$ in methanolic sodium hydroxide produces I-COOH in good yields. The *N*-*p*-anisyl analogues, II-COOH and II-$COOCH_3$, were prepared in the same manner. The carboxylic acids are not very stable and they decarboxylate to produce the corresponding pyrazole derivative. For example, I-COOH produces ca. 1% 1,3-diphenyl-5-methylpyrazole during the saponification reaction, while II-COOH produces ca. 12% 1-anisyl-5-methyl-3-phenylpyrazole.

Electrolytic Measurements. Cyclic voltammetry measurements for these compounds were performed in anhydrous acetonitrile containing 0.1 M tetraethylammonium tetrafluoroborate using a platinum button electrode plus a Ag/Ag^+ (0.01 M in CH_3CN) reference electrode. The cyclic voltammogram for I-COOH shows two irreversible peaks at a 200 mV/s scan rate as shown in Table I. The peak ratio varies with the basicity of the solvent. With the addition of excess sodium bicarbonate or sodium methoxide the peak at lower overpotential increases with almost the complete disappearance of the peak at +0.6 V. The reverse situation is not accomplished with the additions of methanol or benzoic acid. This result is most likely due to the fact that the inherent basicity of the double layer[5] is not completely affected by the acidity of the bulk solution. Finally, when an inherently basic electrode surface is used, e.g., Sb-doped SnO_2, the first peak is ca. 1.5 greater than the second peak.