Intramolecular Nitrene Insertion into Nitrogen Containing Rings. Pyrolyses of 3-(1-Methyl-2-imidazolyl)- and 3-(1-Methyl-5-pyrazolyl)-2,1-benzisoxazole (Anthranils)

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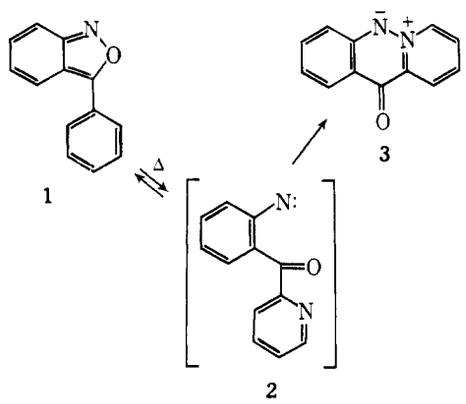
The pyrolyses of 5-chloro-3-(1-methyl-2-imidazolyl)-2,1-benzisoxazole (**5**) and 5-chloro-3-(1-methyl-5-pyrazolyl)-2,1-benzisoxazole (**9**) in trichlorobenzene (about 215 °C) led mainly to the nitrene-induced rearrangement products 1-chloro-1-methylimidazo[2,1-*b*]quinazolin-5-one (**6**, 63%) and 6-chloro-4,9-dihydro-1-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-4-one (**10**, 68%), respectively. Unrearranged nitrene insertion products were also obtained in small yields. For example, 8-chloro-5,10-dihydro-1-methyl-10-oxo-1*H*-imidazo[1,2-*b*]cinnolin-4-ium hydroxide inner salt (**7**) was obtained from **5** in 3% yield and 7-chloro-4,9-dihydro-1-methyl-1*H*-pyrazolo[4,3-*b*]quinolin-9-one (**11**) was obtained from **9** in 4% yield. The structures of **6** and **7** were unambiguously established by x-ray crystallography. The structure of **10** was secured by x-ray crystallographic analysis of its *O*-methyl derivative **12c**.

In our search for novel heterocyclic systems,[1,2] we have been intrigued by the intramolecular interactions[3,4] of nitrenes[4] and nitrenoid species with nitrogen atoms. Of special interest is the possibility of nitrogen–nitrogen bond formation in situations where potential competitive processes exist.[1,2,5] We have reported earlier[2] that the aryl nitrene **2**, generated thermally from 3-(2-pyridyl)-2,1-benzisoxazole[6] (**1**), gave exclusively nitrogen–nitrogen bond formation yielding the tricyclic compound **3**. Extension of this work to the 3-(1-methyl-2-imidazolyl)- and the 3-(1-methyl-5-pyrazolyl)-2,1-benzisoxazoles, compounds **5** and **9**, has resulted in sharply contrasting findings, which we now wish to record.



Compounds **5** and **9** were prepared by triethyl phosphite reduction[4c,8] of the corresponding nitro ketones[9] **4** and **8**. Pyrolysis of **5** in refluxing 1,2,4-trichlorobenzene (about 215 °C) afforded the anticipated N–N bonded product, compound **7**, but in only 3% yield. The major product (63%) was the isomeric quinazolinone, compound **6**, which was obviously a product of nitrene-induced rearrangement. The structures **6** and **7** were unambiguously established by x-ray crystallographic analyses. When the pyrazolyl anthranil **9** was pyrolyzed, the major product, compound **10** (68% yield), was also derived from a nitrene-induced rearrangement. An unrearranged tricyclic product, the pyrazolo[4,3-*b*]quinolinone **11**, was isolated in 4% yield. The structures of **10** and **11** were assigned on the basis of single crystal x-ray analysis. Owing to difficulty in growing suitable single crystals of **10**, we utilized a crystal of one of its derivatives, compound **12c**. The unambiguous structural analysis of **12c** also confirmed the observation that when the anion of **10** was treated with ethyl bromoacetate, it alkylated predominantly on oxygen to give the ester **12a**. The corresponding carboxylic acid **12b**, obtained by careful saponification, readily decarboxylated to give the 4-methoxy derivative **12c**. The structure of **11** was assigned on the basis of spectral comparisons with **10** and **12**.

These pyrolytic reactions of anthranils most probably proceed via initially formed nitrenes,[2,10,11] such as A, which could then yield the spiro intermediates B and E. Such spiro intermediates have been frequently invoked in similar systems.[3,11] Their formation would be particularly favorable in these two cases, owing to the availability of the electron pairs on the tertiary amino groups of the imidazolyl and the pyrazolyl rings, which would effectively stabilize the positive charges that are generated, as indicated in B and E. The spiro intermediates could then open up to form the conjugated ketenes[11,12] C and F, members of a class of heterocumulenes,[13] which would then readily cyclize to give the major products **6** and **10**, respectively. The minor products **7** and **11** can also be derived from the spiro intermediates via the tetracyclic intermediates D and G, respectively.

This proposed mechanism also provides an explanation for the contrasting result observed in the pyrolysis of the 3-(2-pyridyl)-2,1-benzisoxazole (**1** → **2** → **3**). In this case the spiro intermediate analogous to B and E would not form, owing to the inability of the pyridyl ring to stabilize the positive charge. The preferred process then becomes the formation of **3** either through a direct attack of the electrophilic nitrene on the lone pair of the pyridyl nitrogen, or through a two-step process involving a *direct* insertion of the nitrene into the carbon–nitrogen double bond to give a diaziridine (such as D) followed by ring opening.

X-Ray Crystallography. The structures of 1-chloro-1-methylimidazo[2,1-*b*]quinazolin-5-one (**6**), 8-chloro-5,10-dihydro-1-methyl-10-oxo-1*H*-imidazo[1,2-*b*]cinnolin-4-ium hydroxide inner salt (**7**), and 6-chloro-1-methyl-4-methoxy-1*H*-pyrazolo[3,4-*b*]quinoline (**12c**), all planar tricyclic molecules, were unambiguously determined by x-ray crystal structure analyses. The crystal data for the three compounds are given in Table I. The intensity data were measured on Hilger-Watts diffractometers (Ni filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). The structures of the first two compounds were solved by a multiple solution procedure.[14] In the case of **12c**, the *E* map calculated for the "best" phase set obtained from the multiple solution procedure showed an image of the molecule which was displaced from its correct position in the unit cell. An electron density map, calculated in the noncentric space group $P1$, revealed the other molecule in the unit cell. The location of the center of symmetry was obtained from these two molecules and used to correctly position the molecule in the centric space group $P\bar{1}$. The experimental details for the three analyses are summarized in Table II.

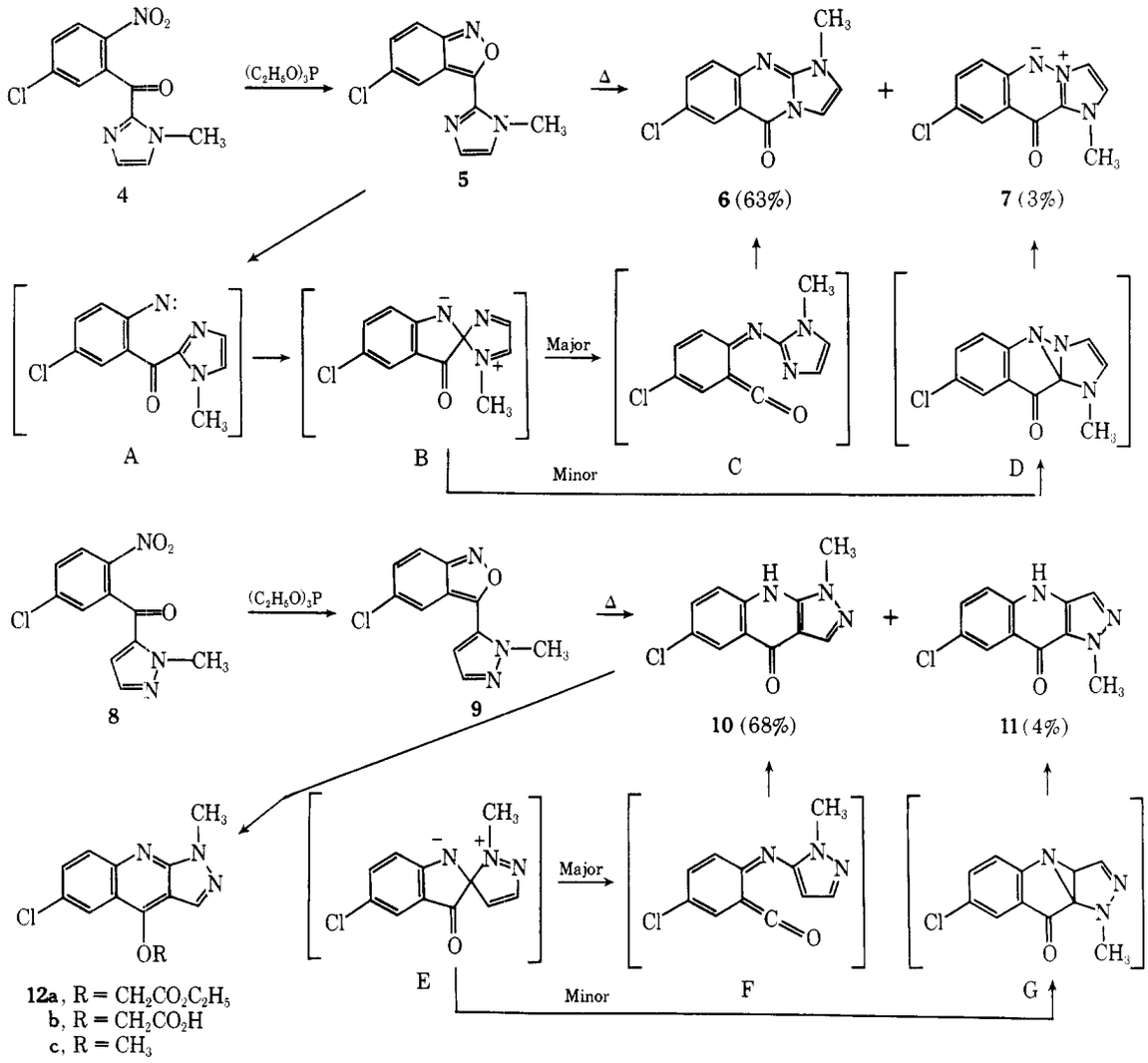


Table I. Crystal Data

	Compound 6[a]	Compound 7[b]	Compound 12c[c]
Formula	$C_{11}H_8ClN_3O$	$C_{11}H_8ClN_3O$	$C_{12}H_{10}ClN_3O$
Formula weight	233.66	233.66	247.68
Space group	*Aa*	$P\bar{1}$	$P\bar{1}$
a, Å	16.632 (8)	7.369 (2)	7.992 (7)
b, Å	10.402 (5)	10.907 (4)	8.953 (5)
c, Å	11.941 (6)	12.999 (5)	9.368 (5)
α, deg		86.90 (3)	73.37 (4)
β, deg	96.81 (5)	89.92 (3)	65.37 (4)
γ, deg		87.17 (2)	74.84 (6)
Z	8	4	2
d_{calcd}, g cm^{-3}	1.512	1.489	1.427
μ (Cu Kα), cm^{-1}	31.5	31.0	28.4

[a] Registry no., 61689-18-7. [b] Registry no., 61689-19-8. [c] Registry no., 61689-20-1.

Experimental Section[15]

5-Chloro-3-(1-methyl-2-imidazolyl)-2,1-benzisoxazole (5). A mixture of 54.0 g (0.212 mol) of 5-chloro-2-nitrophenyl 1-methyl-2-imidazolyl ketone (4),[9] 500 mL of ethanol, and 200 mL of triethyl phosphite was heated to reflux under nitrogen for 16 h. On cooling, the yellow prisms that separated were collected by filtration, washed with ethanol, and dried in vacuo for 2 h at 100 °C to afford 31.70 g (67%) of **5**, mp 188–192 °C. An analytical sample was prepared by recrystallization from ethanol to afford yellow prisms: mp 189–192 °C; IR ($CHCl_3$) no NH or carbonyl bands; NMR ($CDCl_3$) δ 4.10 (s, 3, CH_3) and 7.0–8.3 ppm (m, 5, aromatic); mass spectrum *m/e* 233 (M^+); UV max (EtOH) 220 nm (ϵ 16 600), 255 (7800), 262 (7700), and 367 (15 800).

Anal. Calcd for $C_{11}H_8ClN_3O$: C, 56.55; H, 3.45; N, 17.98; Cl, 15.17. Found: C, 56.81; H, 3.55; N, 17.90; Cl, 15.21.

7-Chloro-1-methylimidazo[2,1-*b*]quinazolin-5-one (6) and 8-Chloro-5,10-dihydro-1-methyl-10-oxo-1*H*-imidazo[1,2-*b*]-cinnolin-4-ium Hydroxide Inner Salt (7). A mixture of 11.50 g (0.049 mol) of 5-chloro-3-(1-methyl-2-imidazolyl)-2,1-benzisoxazole (**5**) and 50 mL of 1,2,4-trichlorobenzene was heated to reflux for 16 h. On cooling, the precipitated solids were collected and washed with petroleum ether, then ethanol, and dried to yield 10.50 g of a brown, amorphous solid. This product mixture was separated by column chromatography on 500 g of silica gel packed in ethyl acetate. The mixture was treated with ethyl acetate (200 mL) and filtered to remove 3.5 g of a black, polymeric material. The filtrate was applied to the column. The column was eluted with 4.0 L of a mixture of 5% (v/v) methanol in ethyl acetate. A fraction of 500 mL of 5% methanol–ethyl acetate was discarded, followed by elution with 2.5 L of a mixture of 20% methanol in ethyl acetate to elute the second component. The 4.0 L of 5% methanol–ethyl acetate was evaporated and the residue was crystallized from ethanol, to yield 4.9 g (63%) of **6** as cream prisms, mp 202–204 °C. An analytical sample was prepared by recrystallization from a mixture of methylene chloride and petroleum ether to afford light brown prisms: mp 202–205 °C; IR (KBr) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.71 ppm (s, 3, CH_3); UV (2-PrOH) 210 nm (ϵ 23 600), 236 (26 300), 265 (24 000), 293 (12 900), 302 (14 050), 364 (6650), and 380 (5600); mass spectrum *m/e* 233 (M^+).

Anal. Calcd for $C_{11}H_8ClN_3O$: C, 56.54; H, 3.44; N, 17.98. Found: C, 56.46; H, 3.67; N, 18.16.

The 2.5-L fraction of 20% methanol in ethyl acetate on evaporation, followed by crystallization of the residue from a mixture of methylene chloride and petroleum ether, afforded 220 mg (3%) of **7** as a yellow, amorphous solid, mp 208–210 °C. The crystal form and melting point remained unchanged after recrystallization from the same solvent:

Table II. Crystallographic Details

	Compound 6	Compound 7	Compound 12c
Crystal size, mm	0.20 × 0.25 × 0.30	0.10 × 0.30 × 0.30	0.15 × 0.20 × 0.75
Maximum θ, deg	57	57	76
Number of reflections	1389	2801	2344
Number of observed reflections	1244	2284	1970
Absorption correction	No	No	No
Least-squares refinement	Full matrix	Block diagonal (two blocks)	Full matrix
Heavier atoms	Anisotropic	Anisotropic	Anisotropic
Hydrogen atoms	Iso (fixed)	Iso (fixed)	Iso (refined)
Final R	0.056	0.069	0.060
Final wR	0.071	0.078	0.071
Final difference map—largest peak, e A^{-3}	<±0.1	<±0.2	<±0.3

IR (KBr) 1585 cm^{-1} (strong); NMR ($CDCl_3$–Me_2SO-d_6) δ 4.44 (s, 3, CH_3); mass spectrum m/e 233 (M^+).

Anal. Calcd for $C_{11}H_8ClN_3O$: C, 56.54; H, 3.44; N, 17.98. Found: C, 56.35; H, 3.68; N, 17.78.

5-Chloro-3-(1-methyl-5-pyrazolyl)-2,1-benzisoxazole (9). A mixture of 13.50 g (51.0 mmol) of 5-chloro-2-nitrophenyl 1-methyl-5-pyrazolyl ketone (8),[9] 50 mL of ethanol, and 50 mL of triethyl phosphite was heated to reflux under nitrogen for 16 h. On cooling the yellow prisms that separated were collected by filtration, washed with ethanol, and dried in vacuo at 100 °C to afford 9.20 g (77%) of **9**, mp 142–144 °C. An analytical sample was prepared by recrystallization from ethanol to afford yellow prisms: mp 142–144 °C; IR ($CHCl_3$) no NH or carbonyl bands; NMR ($CDCl_3$) δ 4.23 (s, 3, CH_3) and 6.8–7.7 ppm (m, 5, aromatic); mass spectrum m/e 233 (M^+); UV max (EtOH) 216 nm (ϵ 21 200), 250 (11 700), and 352 (12 700).

Anal. Calcd for $C_{11}H_8ClN_3O$: C, 56.54; H, 3.45; N, 17.98; Cl, 15.17. Found: C, 56.37; H, 3.33; N, 18.08; Cl, 15.35.

6-Chloro-4,9-dihydro-1-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-4-one (10) and 7-Chloro-4,9-dihydro-1-methyl-1*H*-pyrazolo[4,3-*b*]quinolin-9-one (11). A mixture of 25.30 g (0.110 mol) of 5-chloro-3-(1-methyl-5-pyrazolyl)-2,1-benzisoxazole (**9**) and 150 mL of 1,2,4-trichlorobenzene was heated to reflux for 16 h. On cooling the precipitated solids were collected by filtration and washed with hexane followed by ethyl acetate to afford 20.0 g of a light brown, amorphous solid. This solid was recrystallized from dimethylformamide to afford 17.20 g (68%) of **10** as colorless needles, mp above 360 °C. An analytical sample was prepared by recrystallization from dimethylformamide to afford colorless needles: mp above 360 °C; IR 3280, 3210, 3170, 3090, 1645, 1620, and 1590 cm^{-1}; UV max (EtOH) 212 nm (ϵ 19 600), 238 (42 000), 251 (25 700), 259 (25 300), 343 (6200), 357 (6130), and 395 (440); mass spectrum m/e 233 (M^+).

Anal. Calcd for $C_{11}H_8ClN_3O$: C, 56.55; H, 3.45; N, 17.98. Found: C, 56.71; H, 3.47; N, 18.23.

The dimethylformamide mother liquors from which **10** was isolated were evaporated to dryness to afford 5.0 g of a brown solid. A solution of this solid in ethyl acetate was applied to a column of 100 g of silica gel packed in ethyl acetate. The column was eluted with 2.5 L of ethyl acetate. The solvent was evaporated, and the residue on crystallization from acetonitrile afforded 500 mg (4%) of **11** as buff prisms, mp 355–358 °C. The melting point remained unchanged after recrystallization from acetonitrile: IR (KBr) 3260, 3195, 3140, 3090, 1630, 1620, and 1595 cm^{-1}; UV max (2-PrOH) 247 nm (ϵ 43 500), ~256 (shoulder 37 000), 372 (9700), and 390 (11 100); NMR ($CDCl_3$–Me_2SO-d_6) δ 4.37 (s, 3, CH_3), 7.50 (m, 2, H-5 and H-6), 7.57 (s, 1, H-3), 8.29 (d, 1, H-8) and 11.54 ppm (broad, 1, NH); mass spectrum m/e 233 (M^+).

Anal. Calcd for $C_{11}H_8ClN_3O$: C, 56.54; H, 3.44; N, 17.98. Found: C, 56.54; H, 3.51; N, 18.08.

6-Chloro-1-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-4-yloxyacetic Acid Ethyl Ester (12a). A mixture of 2.33 g (10.0 mmol) of **10**, 600 mg of sodium hydride as a 50% dispersion in oil (12.5 mmol of hydride), and 30 mL of dimethylformamide was stirred at room temperature for 0.5 h. To this mixture was added 2.5 mL (22.60 mmol) of ethyl bromoacetate and the mixture was heated on a steam bath for 2 h. The mixture was poured into ice–water. The precipitated solids were collected by filtration, then dissolved in methylene chloride. The methylene chloride solution was washed with brine, dried (Na_2SO_4), and evaporated to dryness. The residue on slurrying with ether afforded 2.40 g (75%) of **12a** as a colorless solid, mp 168–170 °C. An analytical sample was prepared by recrystallization from acetonitrile to afford colorless needles: mp 172–175 °C; IR (KBr) no NH, 1768 cm^{-1} (ester); NMR ($CDCl_3$) δ 1.30 (t, 3, CH_2CH_3), 4.11 (s, 3, NCH_3), 4.30 (q, 2, CH_2CH_3), 5.28 (s, 2, NCH_2), 7.57 (q, 1, H-7), 7.86 (d, 1, H-8), 8.08 (s, 1, H-3), and 8.30 ppm (d, 1, H-5); UV max (CH_3CN) 213 nm (ϵ 15 000), 247 (86 000), 290 (2130), 302 (2900), 316 (2700), 370 (7210), and 389 (7220); mass spectrum m/e 319 (M^+).

Anal. Calcd for $C_{15}H_{14}ClN_3O_3$: C, 56.34; H, 4.41; N, 13.14. Found: C, 56.18; H, 4.43; N, 13.17.

6-Chloro-1-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-4-yloxyacetic Acid (12b). A mixture of 1.0 g (3.12 mmol) of ethyl ester **12a**, 1.0 mL of 5 M sodium hydroxide in methanol, 25 mL of methanol, and 25 mL of water was stirred at room temperature for 3 h. This clear solution was concentrated to remove methanol. Some insoluble materials were removed by filtration. The aqueous solution was acidified with glacial acetic acid. The colorless solids precipitated were collected by filtration, washed with methanol followed by ether, and dried to afford 760 mg (85%) of **12b** as a colorless solid, mp above 350 °C. An analytical sample was prepared by recrystallization from dimethylformamide to afford colorless prisms: mp above 350 °C; IR (KBr) 3460, 2740, 2500, and 1755 cm^{-1}.

Anal. Calcd for $C_{13}H_{10}ClN_3O_3$: C, 53.52; H, 3.45; N, 14.40. Found: C, 53.51; H, 3.49; N, 14.53.

6-Chloro-1-methyl-4-methoxy-1*H*-pyrazolo[3,4-*b*]quinoline (12c). A mixture of 291 mg (1.0 mmol) of **12b**, 40 mg (1.0 mmol) of sodium hydroxide, and 10 mL of methanol was heated to reflux for 0.50 h. On cooling the reaction mixture afforded 165 mg (67%) of **12c** as colorless needles, mp 163–165 °C. An analytical sample was prepared by recrystallization from methanol to afford colorless prisms: mp 163–165 °C; IR (KBr) no carbonyl; NMR (DMF-d_7) δ 4.03 (s, 3, NCH_3), 4.58 (s, 3, OCH_3), 7.63 (q, 1, H-7), 7.83 (d, 1, H-8), 8.07 (d, 1, H-5), and 8.59 (s, 1, H-3); mass spectrum m/e 247 (M^+).

Anal. Calcd for $C_{12}H_{10}ClN_3O$: C, 58.19; H, 4.06; N, 16.96. Found: C, 58.29; H, 4.21; N, 17.07.

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Registry No.—**4**, 39264-30-7; **5**, 61689-21-2; **8**, 39264-10-3; **9**, 61689-22-3; **10**, 61689-23-4; **11**, 61689-24-5; **12a**, 61689-25-6; **12b**, 61689-26-7; ethyl bromoacetate, 105-36-2.

Supplementary Material Available. Tables of the positional and thermal parameters for the structures of **6**, **7** and **12c** (5 pages). Ordering information is given on any current masthead page.

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Notes

Stereoselective Synthesis of Racemic Occidentalol and Related Cis-Fused Hexahydronaphthalenes from *m*-Toluic Acid

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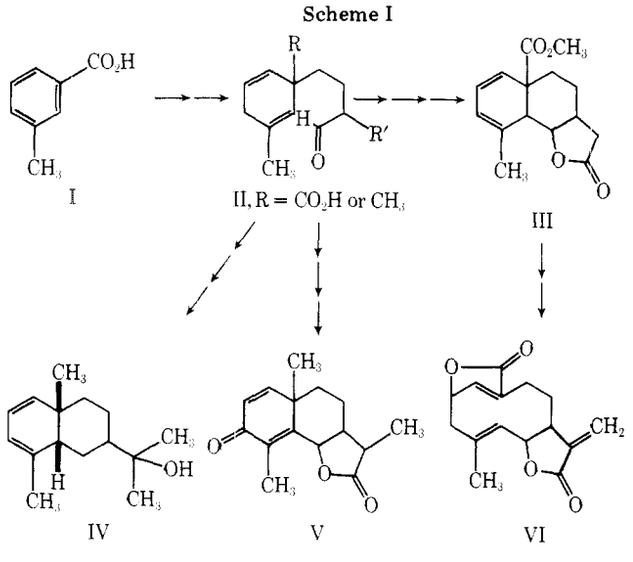
In connection with a program aimed at the development of new synthetic routes to sesquiterpenes of possible medicinal interest we wished to evaluate the potential of Scheme I as a

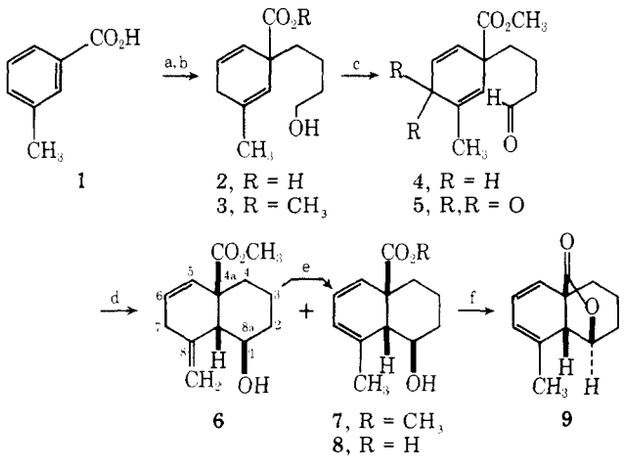
Scheme I



general approach to eudesmanes and germacranes.[1] The crux of this approach depends upon the cyclization of a suitably substituted 3-methyl-2,5-cyclohexadienyl aldehyde II, derivable through reduction–alkylation of a *m*-toluic acid precursor (I), to a eudesmanolide (e.g., V) or eudesmane (e.g., IV). Conceivably such a scheme could also lead to substances with the interesting germacranolide skeleton VI containing two α,β-unsaturated γ-butyrolactones.[2,3] Clearly the attainment of even the simplest of the synthetic objectives depicted above will require experimentally derived knowledge of the stereochemistry and regiochemistry of the cyclohexadienyl aldehyde cyclization process. This note describes our work on the synthesis and cyclization of dienic ester aldehyde II (R = CO_2CH_3; R′ = H), the methyl analogue (II, R = CH_3; R′ = H), and the α-methylene derivative (II, R = CH_3; R′ = CH_2) and the subsequent conversion of the cyclization product of the latter aldehyde to racemic occidentalol (IV), a cis-fused eudesmane sesquiterpene containing a homoannular 1,3-diene moiety.[4]

The hydroxy acid **2** was efficiently prepared by treating *m*-toluic acid (**1**) with lithium in ammonia to generate the carboxylic dianion which was alkylated in situ[5] with commercially available 4-phenoxybutyl bromide.[6] The ammonia solution was then treated with lithium and *tert*-butyl alcohol to reduce the phenoxy ring. Removal of the ammonia and acidic hydrolysis cleaved the resulting dihydrophenyl (enol) ether[7] and afforded the crystalline hydroxy acid **2** in 95% yield. Esterification with methanolic *p*-toluenesulfonic acid yielded the ester **3** quantitatively. Oxidation of this substance with

Chart I[a]



[a] a, Li, NH_3; $Br(CH_2)_4OPh$; Li, NH_3, *t*-BuOH; HCl, H_2O; b, CH_3OH, *p*-TsOH; c, $C_5H_5N{\cdot}CrO_3{\cdot}HCl$; d, ZnI_2, CH_2Cl_2; e, KOH, *t*-BuOH; f, DCC.

pyridinium chlorochromate[8] gave the ester aldehyde **4** in 70–80% yield along with the product of allylic oxidation, dienone aldehyde **5**. The Collins' chromium trioxide–pyridine reagent[9] was somewhat less effective (60–70% yield of **4**) as were several variations of the DCC–Me_2SO Moffatt procedure[10] for primary alcohol oxidation.

After examining numerous Lewis acids we found zinc iodide in methylene chloride to most effectively catalyze the cyclization of diene aldehyde **4**.[11] The product obtained in quantitative yield consisted of a 1:3 mixture of dienic alcohols **6** and **7** which could be separated by high-pressure liquid chromatography. Interestingly, we found that the nonconjugated isomer **6** could be smoothly converted to the conjugated dienic acid **8** upon saponification of the crude cyclization mixture and esterification of the crystalline acid **8**. The stereochemistry of this hydroxy ester was assigned on the basis of the NMR spectrum which showed axial–axial coupling for the ring fusion hydrogen (H-8a) and conversion of the acid **8** to lactone **9** whose NMR spectrum showed no H-8a axial–axial coupling (see below). These findings are uniquely satisfied by the *cis,anti* isomer **7**.