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Electrochemical Oxidation of Tropanes

Bruce L. Laube, Margaret R. Asirvatham, and Charles K. Mann*

Department of Chemistry, Florida State University, Tallahassee, Florida 32306

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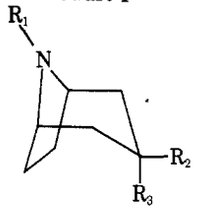
Tropane and nortropane were selected as examples of the tropane alkaloids for study of their anodic reactions. The tertiary amine, tropane, undergoes anodically induced dealkylation, and, like nortropane, does not show further cleavage of carbon–nitrogen bonds, presumably because of the presence of bridgehead carbon atoms α to nitrogen. Instead, reactions that involve formation of carbon–nitrogen and of nitrogen–nitrogen bonds are observed. These reactions involve reaction of the solvent, acetonitrile, with electrochemically generated intermediates. Evidence is presented to support a proposed reaction scheme that involves electrochemical reaction of the amine and of hydroxide ion.

The electrochemical oxidation of saturated aliphatic amines in wet acetonitrile proceeds through the aminium cation radical which typically loses a proton from an α carbon atom to form an intermediate that ultimately undergoes hydrolytic cleavage between the nitrogen atom and the adjacent carbon atom.[1,2] Thus a symmetrically substituted tertiary straight chain alkylamine forms the secondary amine and the aldehyde corresponding to the cleaved alkyl group. The process can be successively repeated to form a primary amine, ammonia, and nitrogen. By contrast, anodic oxidation of aromatic or olefinic amines may lead to formation of relatively stable intermediates owing to delocalization of the unpaired electron. In some cases, radical intermediates with appreciable lifetimes are observed; in others, products from coupling and polymerization are found.[3-6]

Complex amines of both aliphatic and aromatic character are formed in plants and animals. Those of plant origin fall in the general classification of alkaloids. The physiological function of alkaloids is often obscure, but it is generally accepted that chemical and enzymatic redox reactions occur. Electrochemistry provides a tool with which to study redox reactions of biogenic compounds outside living systems.[7-11]

The tropane alkaloids are nonaromatic bicyclic amines. The parent compounds of the series are nortropane (I) (8-azabicyclo[3.2.1]octane) and tropane (II) (8-methyl-8-azabicyclo[3.2.1]octane). Many compounds of this class exist; some, such as atropine, scopolamine, and cocaine, are very well known. Our attention has been attracted to them because of their pharmacological importance. Compounds studied in the work are identified in Chart I and Table I.

Chart I



Experimental Section

Apparatus. Electrolyses were performed with conventional potentiostats. Hydrogen–nitrogen gas coulometers or electronic integrators were used for current integration.[12] Cyclic voltammograms were obtained at a platinum button anode on a PAR Model 173 potentiostat equipped with a H-P model 300A function generator and an X-Y recorder.

Table I. Tropane Derivatives Cited in This Work

	Compd	R_1	R_2	R_3
I	Nortropane	H	H	H
II	Tropane	Me	H	H
III	Tropacocaine	Me	H	OCOPh
V	Atropine	Me	±-OCOCHPhCH$_2$OH	H
VI	3-Tropinone	Me	=O	H
VII	*N*-Formylnortropane	CHO	H	H
VIII	8,8′-Binortropane	$C_7H_{12}N$	H	H
IX	(*N*-Nortropanyl)nortropane carboxamide	$C_7H_{12}NCO$	H	H
X	*N*-Cyanomethylnortropane	CH_2CN	H	H

Various two-compartment H cells were used. The compartments were fitted with ground glass joints which permitted filling under an atmosphere of inert gas. Total solution volume ranged from 20 to 200 ml. Cylindrical perforated platinum sheet anodes and mercury pool cathodes were used. Asbestos fiber tipped reference electrodes consisting of a silver wire immersed in 0.1 M $AgClO_4$ in MeCN made contact with the anode solution by way of a fiber-tipped salt bridge which was filled with the anode supporting electrolyte solution. For electrolyses in benzonitrile, the reference electrode was a silver wire in contact with a 0.1 M $LiClO_4$ solution saturated with $AgClO_4$ in benzonitrile. It was used with the type of salt bridge described above. NMR spectra were obtained on 60-, 90-, or 270-MHz spectrometers. Mass spectra were obtained on a AEI MS902 instrument operated in high or low resolution mode as needed.

Electrolysis Procedures. Supporting electrolyte and solvent were mixed and degassed in a reservoir which provided for transfer to the cell without contact with the atmosphere. All oxidations were carried out at the voltammetric peak potentials observed in the respective solvents. Preelectrolyses were run at +0.75 V prior to the injection of reactant with a syringe. Nortropane was placed in the anode compartment as nortropanium perchlorate along with an excess of powdered NaOH prior to the addition of solvent and supporting electrolyte. Neutralization was allowed to occur before oxidations were begun. No preelectrolyses were possible when this procedure was used. A fivefold molar excess of water with respect to the amine concentration was added to the anode compartment before all electrolyses.

Reagents. The solvents, MeCN, PhCN, and benzene, and the supporting electrolytes, $NaClO_4$ and $LiClO_4$, were purified by established procedures.[13-15] Tropane (II) and tropacocaine (III), received as the hydrochlorides, and atropine (V) (Aldrich Chemical Co.) were used as received. 3-Tropinone (VI) (City Chemical Co.) was sublimed before use.

Nortropane (I). Compound I was prepared by the chemical[16] and electrochemical demethylation of II. That prepared chemically was freed of tertiary amine contaminants by the Hinsburg method[17] and converted to the perchlorate salt which was recrystallized from MeCN–Et_2O. The neutral compound has the following properties: bp 96–97 °C (104 mm) [lit.[18] 161 °C (760 mm)]; NMR ($CDCl_3$) 3.46 (m, 2 CH), 1.74–2.05 (s, 1, NH, shifts with concentration[19]), and 1.2–1.9 ppm (m, 10); mass spectrum (70 eV) *m/e* (rel intensity) 111 (60), 110 (5.3), 96 (4.2) 83 (69.5), 82 (87.4), 69 (23.2), 68 (100), 67 (12.6), 56 (14.7), 55 (12.1), 54 (13.7).[20]

Tropane (II). Compound II was prepared by the Huang-Minlon modification[21,22] of the Wolff–Kishner reduction of VI: bp 98–99 °C (107 mm) [lit.[18] 167 °C (760 mm)]; NMR ($CDCl_3$) 2.2 (s, 3, NCH_3), 3.1 (m, 2, CH), and 1.2–2.1 ppm (m, 10); mass spectrum (70 eV) *m/e* (rel intensity) 125 (23.2), 110 (2.6), 97 (58.9), 96 (84.2), 83 (35.8), 82 (100), 68 (18.9), 67 (12.6), 55 (29.5), 42 (75.8) (lit.[23-25] derivatives); mass spectrum (75 eV, high resolution) 125.1214 (calcd for $C_8H_{15}N$, 125.1204).

***N*-Formylnortropane (VII).** Compound VII was prepared by the formylation of I[26] and by the electrochemical oxidation of II in moist MeCN–$NaClO_4$ and moist MeCN–$NaClO_4$–NaOH and I in moist MeCN–$NaClO_4$–NaOH (Table III). Derivative VII exhibited the following properties: bp 95 °C (2 mm); IR (thin film) 1650 (amide I), 2748 (CH stretch), and 1381 cm^{-1} (CH in-plane deformation); NMR ($CDCl_3$) 8.11 (s, 1, CHO), 4.59 (m, 1, CH), 4.02 (m, 1, CH), and 1.4–2.2 ppm (m, 10); mass spectrum (70 eV) *m/e* (rel intensity) 139 (7.4), 111 (27.4), 110 (12.6), 97 (4.2), 96 (10.5), 95 (28.4), 83 (52.6), 82 (65.3), 69 (21.1), 68 (100), 67 (17.9), 56 (15.8), 55 (23.2), 53 (9.5).

8,8′-Binortropane (VIII). Compound VIII was prepared by the electrochemical oxidation of I in PhCN–$LiClO_4$–NaOH. Attempted preparations by oxidation of I with Ag_2O[27,28] and $KMnO_4$–acetone[29] at 0 °C failed. Derivative VIII has the following properties: NMR (C_6D_6) 3.31 (m, 4, CH), 1.7–2.3 (m, 8, CH_2CH_2), and 1,2–1.6 ppm (m, 12, $CH_2CH_2CH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 220 (100), 192 (10.5), 191 (21), 178 (11.6), 177 (75.6), 165 (6.3), 164 (14.7), 163 (16.8), 151 (25.3), 138 (25.3), 137 (41.1), 125 (27.4), 110 (100), 95 (23.2), 83 (44.2), 82 (62.1), 80 (42.1), 69 (30.5), 68 (88.4), 67 (43.2), 55 (58.9), 54 (33.7); mass spectrum (75 eV, high resolution) 220.1948 (calcd for $C_{14}H_{24}N_2$, 220.1939).

(*N*-Nortropanyl)nortropanecarboxamide (IX). Compound IX was prepared by the electrochemical oxidation of I in moist MeCN–$NaClO_4$–NaOH: mp 115.0–115.5 °C; IR (thin film) 1619 cm^{-1} (amide I); NMR (CCl_4) 4.07 (m, 4, CH) and 1.2–2.2 ppm (m, 20); mass spectrum *m/e* (rel intensity) 248 (63.2), 220 (9.5), 219 (12.6), 205 (16.8), 193 (3.2), 192 (4.2), 191 (2.1), 139 (17.9), 138 (100), 111 (6.3), 110 (22.1), 96 (18.9), 95 (100), 83 (13.7), 82 (4.2), 69 (5.3), 68 (14.7), 67 (23.2), 55 (20); mass spectrum (75 eV, high resolution) 248.1873 (calcd for $C_{15}H_{24}N_2O$, 248.1888).

***N*-Cyanomethylnortropane (X).** Compound X was synthesized from I by the procedure for cyanomethylation of amines:[26] NMR (in CCl_4) 3.69 (s, 2, CH_2), 3.38–4.2 (m, 2, CH), 1.44–2.78 (m, 10, CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 150 (38.2), 122 (26.5), 121 (44.1), 108 (47.1) 107 (100), 83 (38.2), 82 (41.2), 55 (47.1); IR (thin film) 2250 cm^{-1} (weak, nitrile).

Mass spectrometry was the major tool used in the identification of tropane derivatives. The bicyclic ring system undergoes characteristic cleavage under electron impact.[24-26] In addition to the parent ion peaks, most of the tropane derivative revealed peaks with *m/e* ratios of 111–110, 96–95, 83, 82, 68, and 55.

Product Analyses. Summarized results are collected in Table III.

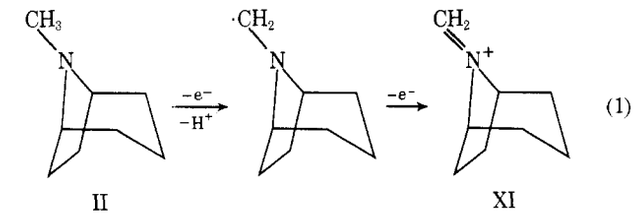
Tropane Oxidation. All basic material in the anolyte was protonated by the addition of 60% $HClO_4$ prior to solvent evaporation. The free bases were extracted into benzene or ether from a basic aqueous solution of these perchlorate salts. Reactants and products were separated and isolated by variable temperature gas chromatography on a 6 ft × 0.25 in. column of 17.5% Dowfax 9N9, 2.5% NaOH on Chromosorb W. Quantitative analyses were based on integration of gas chromatographic peak areas.

Nortropane Oxidation. In MeCN the anolyte was filtered, evaporated to dryness, and extracted into benzene. In PhCN the anolyte was acidified with concentrated $HClO_4$ or HCl and evaporated to dryness under vacuum at 70 °C. The residue was dissolved in MeCN, neutralized, filtered, concentrated, and extracted into benzene. Reactants and products were separated and isolated by variable temperature gas chromatography on a 3 ft × 0.25 in. column of 10% SE-30 on Chromosorb W.

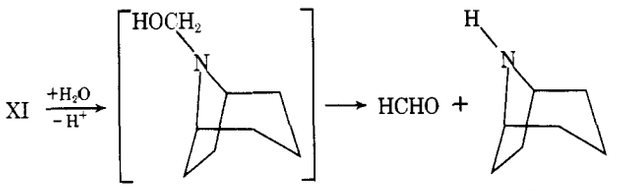
Results and Discussion

The voltammetric peak potentials (Table II) observed for the tropane alkaloids follow the general trends expected for aliphatic amines.[1] Tertiary amines are oxidized in the range of 0.5–0.8 V and secondary amines are oxidized at more anodic potentials of 0.9–1.2 V vs. $Ag/AgClO_4$ (0.1 M). As would be expected for an amide, *N*-formylnortropane reacts at much more anodic potentials.[30]

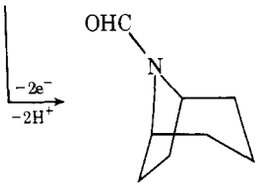
Reactions of Tropane (II). The pathway followed in the electrochemical oxidation of tropane corresponds to that observed for the oxidation of other tertiary aliphatic amines. Tropane reacts at the potential of its voltammetric peak to give 14.4 mol % of nortropane (I) and 4.2 mol % of *N*-formylnortropane (VII), with 64% recovery of starting material



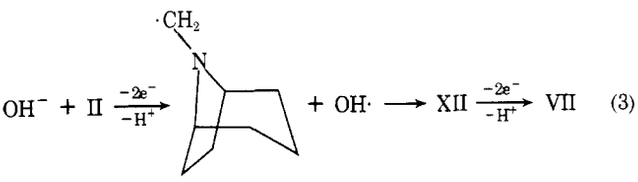
II XI (1)



XII I (2)



VII



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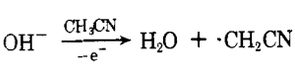

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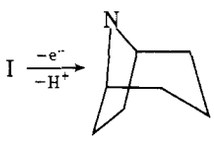
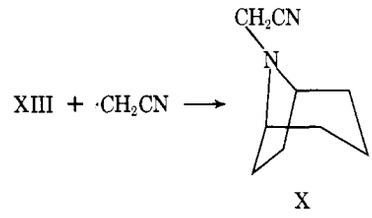
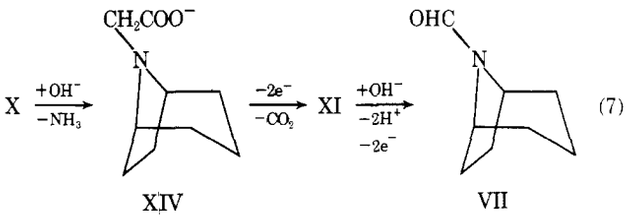


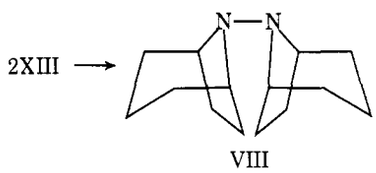
XIII (5)



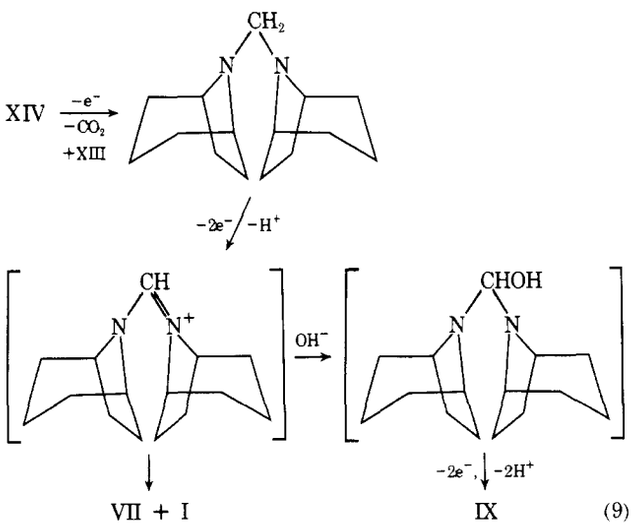
X (6)



XIV VII (7)



VIII (8)



VII + I IX (9)

(average of five runs). Oxidation of tropane in the presence of NaOH increases the yield of VII to 88%.

The previously reported sequence of reactions[1,2] (eq 1, 2) can account for the formation of I. Loss of an electron, a proton, and a second electron produces the ionic intermediate XI. This adds water to give XII which may be cleaved to formaldehyde and nortropane. A finite stability of XII would allow oxidation to the amide VII. Ring cleavage does not occur, presumably because the steric restrictions imposed by the bicyclic ring system do not allow formation of an intermediate endocyclic iminium ion.

Previously reported electrochemical oxidations of amines to amides have involved elemental oxygen,[1] making it unnecessary to postulate an intermediate amino alcohol such as XII. The situation is apparently different in this case. *N*-Formylnortropane (VII) is formed in solutions from which elemental oxygen has been excluded. Water is present; however, we have specifically determined that a 70 mM solution of water in MeCN–0.1 M $NaClO_4$ is not appreciably electrolyzed at +1.0 V. When the experiment was repeated at 0.75 V, the electrolysis current again substantially increased only when II was subsequently added. A small but significant quantity of amide (VII) was then formed.

The presence of NaOH in the electrolysis medium greatly increases the yield of VII. Since hydroxide ion apparently undergoes a one-electron oxidation near +0.75 V in MeCN,[31] the increased yield of VII may be due to participation of a hydroxyl radical in the oxidation of II (eq 3) or to proton scavenging by hydroxide. The amide yield in the presence of hydroxide is very much larger than has been observed in the oxidation of other amines, even when oxygen has been deliberately added. Similarly, chemical oxidations of *N*-methylamines to form amides occur in lower[29,32-38] yields.

Reactions of Nortropane (I). The major product of the oxidation of nortropane at +1.0 V in the presence of NaOH is *N*-formylnortropane (VII). Binortropane (VIII) and the urea (IX) are minor products, as shown in Table III. As the total electrolysis time is increased, the amount of VII and IX increases while that of VIII decreases. Semiquantitative analyses of the products in an exhaustive oxidation at a less positive potential, 0.9 V, showed increased yields of the hydrazine (VIII). Presumably the oxidation potential of VIII is slightly more positive than that of I. Such a large oxidation potential for a hydrazine may be expected in cases in which

Table II. Voltammetric Peak Potentials[a]

Compd	Sweep rate, mV/s	$+E_p$
Nortropane	650	1.00
Tropane	238	0.72
Tropine	632	0.72
Atropine	590	0.67
3-Tropinone	647	0.94
Tropacocaine	666	0.70
N-Formylnortropane	400	1.83

[a] $Ag/AgClO_4$ (0.1 M)–MeCN reference electrode.

Table III. Product Analyses[a]

Compd	Amount taken, mmol	Electrolysis time, h	Apparent-*n*, F/mol	Analysis results (mol %)
I	0.2464[c]	11.5	0.93	I (45.7), VII (15.3) VIII (1.7), IX (0.7)
I	0.2401[c]	19.9	1.09	I (31.9), VII (23.8) VIII (1.5), IX (1.2)
I	0.2427[c]	42.7	2.24	I (24.2), VII (42.5) VIII (1.10), IX (4.6)
I	0.2381[c]	57.3	3.46	I (35.7), VII (36.2) VIII (5.8), IX (5.8)
II	0.375[f]	5.2	0.79	I (13.6), II (57.6) VII (5.3)
II	0.1875[c,d]	18.5	2.07	VII (87.6)
I	0.2346[c,e]	27.8	0.97	VIII (58.1)
X	0.9596[c]	4.5	0.89	VII (24.8), X (74)

[a] Solvent MeCN–$NaClO_4$, reaction potential +1.00 V, except as noted. [b] Based upon starting material and including charge consumed by hydroxide ion. [c] Solid NaOH present during reaction. [d] Oxidation run at +0.65 V. [e] Oxidation at +1.05 V in PhCN–$LiClO_4$–NaOH. [f] Oxidation at +0.75 V.

ring strain restricts flattening of the tetrahedral geometry about nitrogen upon oxidation and steric interaction inhibits the formation of a 0° dihedral angle between the nitrogen lone pair orbital axes.[39]

The formation of *N*-formylnortropane by oxidation of nortropane was unexpected since it involves forming rather than breaking a carbon–nitrogen bond. The only sources of carbon atoms in this system are the solvent and carbon dioxide from the atmosphere. The latter is excluded, owing to the formation of very slightly soluble carbamates;[40,41] accordingly, we conclude that the solvent is involved.

Involvement of nitrile solvents in anodic reactions has often been observed;[42] however, these reactions have usually involved attack by an electrochemically generated positive ion on the nitrile nitrogen, followed by hydrolysis to an amide. The present example evidently does not follow that path, since the carbon–nitrogen bond formed involves the amine nitrogen.

Hydroxide ion has been shown to be oxidized at platinum and gold in Me_2SO–$NaClO_4$[31,43] and MeCN–Et_4NClO_4.[31] Although bulk electrolysis products eluded isolation and identification, the initial product of the diffusion-controlled oxidation at approximately +0.7 V vs. Ag/0.1 M $AgClO_4$ in MeCN was thought to be adsorbed or solvated hydroxyl radicals.

We suggest that in the system used in this work, these radicals decay by hydrogen atom abstraction from the solvent to form cyanomethyl radicals which can react with the electrochemically generated intermediate XIII to form the nitrile X as indicated in eq 4–6. The observed products are thought to be formed by hydrolysis of the nitrile to give the carboxylic acid salt which is oxidized to give the carbinol XV. This compound would be expected to lose water to form VII (eq 7).

To get further information about this, the nitrile X was synthesized. When it is electrolyzed under the conditions of this work, it forms VII, as indicated in Table III. When the nitrile is allowed to stand in the reaction mixture without electrolysis for a period of time comparable to that of an electrolytic run, only part of it is recovered. Hydrolysis of the nitrile under basic conditions is plausible.

In the proposed reaction scheme, the hydrazine VIII is formed by dimerization of radical XII (eq 8). When the reaction is carried out in PhCN–$LiClO_4$–NaOH, the hydrazine, formed in 58 mol % yield, is the major product. This is a very unusual result for anodic reactions of aliphatic amines. Presumably it occurs because the ordinarily reactive positions α to the amine nitrogen are inactivated by the bridgehead structure and because the solvent lacks hydrogen α to the nitrile, which would allow it to undergo reactions analogous to eq 4.

The urea IX may be formed as a result of reaction of intermediate XIII with the one-electron Kolbe product from XIV. This is shown in eq 9.

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Registry No.—I, 280-05-7; II, 529-17-9; III, 537-26-8; V, 51-55-8; VI, 532-24-1; VII, 56771-95-0; VIII, 56847-10-0; IX, 61064-10-6; X, 4903-43-9; tropine, 120-29-6.

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Dual Reactivity of 3,3-Dimethoxycyclopropene

R. M. Albert and G. B. Butler*[1]

Center for Macromolecular Science and Department of Chemistry, University of Florida, Gainesville, Florida 32611

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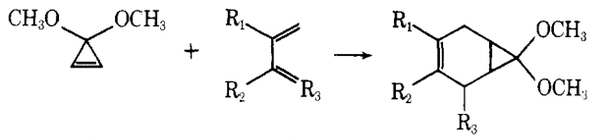
Charge transfer complex studies indicate that 3,3-dimethoxycyclopropene (I) is an electron-deficient olefin. Initial studies of its chemical reactivity were consistent with this conclusion. Diels–Alder reactions with electron-rich dienes (II) gave high yields of the postulated 7,7-dimethoxy-3-norcarenes (III) under mild conditions. Secondary amines (IV) reacted with I to give cyclopropylamines (V) and/or β-alanine derivatives (VI). Both products could arise from nucleophilic attack of the amine on the cyclopropene system. However, an alternative mechanism is also proposed. The reactions of I with tetracyclone (VII) and hexafluoroacetone (VIII) are best explained by nucleophilic attack of I on the carbonyl carbon of these compounds. The reaction with VII proceeds with cleavage of the cyclopropene ring and subsequent ring closure to a 2-furanone derivative (IXb). In the case of VIII, the adduct is a bicyclic oxetane (X). An improved synthesis of I is also reported. Also, cyclization of 1-bromo-3-chloro-2,2-ethylenedioxypropane (XII) to yield 3,3-ethylenedioxycyclopropene (XIII) along with 3,3-ethylenedioxycyclopropane (XIV) as a by-product is reported.

The synthesis of 3,3-dimethoxycyclopropene (I) in pure form was first accomplished in 1968.[2] Preliminary studies of its chemical reactivity indicated it to be a highly reactive species possessing a somewhat electron-deficient double bond. A study of charge transfer (CT) complexation using the NMR method now adds support to this conclusion. It was found that both styrene and divinyl ether, two electron-rich olefins, gave CT complexes with I. The equilibrium constants were 9.3×10^{-2} l. mol^{-1} for the styrene complex and 0.5×10^{-2} in the case of divinyl ether.

Diels–Alder Reactions of I. Diels–Alder reactions of I with electron-rich dienes (II) was therefore considered a favorable route to the unusual 7,7-dimethoxy-3-norcarenes. When I was mixed with an excess of IIa, IIb, or IIc and the solution allowed



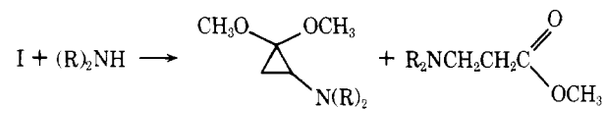
I IIa-d IIIa-d

R_1, R_2, R_3 = (a) H, H, H; (b) H, CH_3H; (c) CH_3, CH_3H; (d) H, H, OCH_3

to stand at room temperature for several days, the expected adducts were formed in high yield. Because of the symmetry of these systems, only one isomer was possible in each case. Pure samples were obtained by preparative gas chromatography (GC). Spectroscopy and elemental analysis (see Experimental Section) confirmed the predicted structures of IIIa–c. IIIa was hydrogenated to yield methyl cyclohexanecarboxylate.

When I and IId (threefold excess of diene) were mixed without solvent, high conversion to the adduct was observed. Analysis of the product after distillation (by GC) showed four components in the approximate ratio of 5:9:20:66. Isolation of the major component by preparative GC gave a product whose NMR, IR, and elemental analysis were completely consistent with the expected adduct, IIId. The second and third minor components were shown to consist largely of methyl benzoate. The first minor component was not identified (See supplementary material for further experimental details.)

Reactions of I with Secondary Amines. When I was added to excess diethylamine (IVa) and the mixture stored at room temperature for several days, the major product formed (60% by preparative GC) was 1,1-dimethoxy-2-diethylaminocyclopropane (Va). The NMR, IR, and mass spectra and elemental analysis gave data consistent with Va.



IVa-c Va-c VIa-c

R = (a) C_2H_5; (b) C_3H_7; (c) C_6H_5

Addition of I to IVb gave a considerably more complex product. Analysis by GC indicated that two major components comprised about 85% of the mixture and that these components were present in a ratio of 40:60. Pure samples of each were then obtained by preparative GC.

The first component was identified by spectroscopy as 1,1-dimethoxy-2-di-*n*-propylaminocyclopropene (Vb), the expected product. The second component was identified by spectroscopy as *N,N*-di-*n*-propyl-β-alanine methyl ester (VIb). Use of diphenylamine (IVc) in the reaction with I led predominantly to *N,N*-diphenyl-β-alanine methyl ester (VIc). Analysis of the crude reaction product by NMR revealed the absence of cyclopropyl protons; indicating only ring-opened product. Purification by silica gel chromatography yielded VIc in 65% recovery. NMR, IR, mass spectral, and elemental analyses were consistent with this structure. Mechanistically, the simple addition reaction may be considered as a nucleo-