Insect Sex Attractants. 13. Isolation, Identification, and Synthesis of Sex Pheromones of the Male Mediterranean Fruit Fly†,‡

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The sex pheromones produced by males of the Mediterranean fruit fly, *Ceratitis capitata* Wiedemann, a serious pest of citrus, were collected by air condensation, separated in pure form, and identified as methyl (*E*)-6-nonenoate (1) and (*E*)-6-nonen-1-ol (2). Both pheromones were synthesized and shown separately to be attractive and sexually excitatory to females in the laboratory. Field-cage attraction requires a combination of both pheromones and certain acids also produced by the males.

The Mediterranean fruit fly, *Ceratitis capitata* Wiedemann, or "medfly," is one of the world's worst insect pests of citrus fruits. It was eradicated from Florida in 1957[2] and again in 1962, and from Texas in 1966.[3] Although it is not now present on the mainland of the United States, the pest is abundant in Hawaii and Central America and presents a major threat to fruit production in the subtropical regions of the continent.

In 1959, Féron[4] reported that sexually mature male medflies in captivity release from their erectile anal ampoules a highly volatile chemical substance that sexually excites and attracts virgin females. This substance was described as having an odor, easily perceptible to humans, similar to that of sweat or stale urine. In a subsequent detailed report on the sexual behavior of the insect, Féron[5] showed that the attractive substance is produced only by the male and is readily absorbed by cotton wicks hung in a cage containing such males. These wicks were then attractive themselves to sexually mature females.

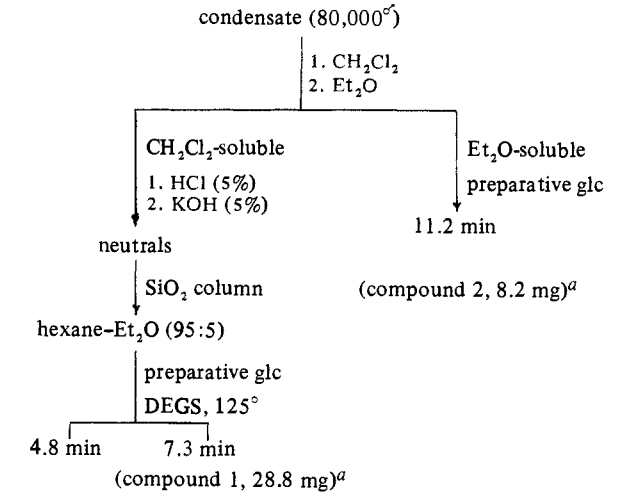
Lhoste and Roche[6] found that the two glands that probably produce the pheromone in the male are located in the last (seventh) abdominal segment. The attractive substance is apparently diffused from these glands to the surface of the erectile anal ampoule formed by pulsating pressure from the posterior portion of the rectum. Upon release, it is dispersed by air currents set up by the male's vibrating wings. Immature and fertilized females do not respond to the pheromone.

Since it was felt that the attractant might be useful in survey and control programs for this destructive insect, we began an investigation in 1969 aimed at isolating and identifying the substance. Medflies reared in large numbers at the U. S. Department of Agriculture Honolulu laboratories were utilized for both the collection and bioassay†† (described later) of the attractant.

Chemistry. During attempts to collect the attractant, it was found that solvent rinses of filter papers exposed to live males, water rinses, and benzene extracts of males were all unattractive to females. Methylene chloride homogenates, initially unattractive, yielded a fraction showing weak activity following chromatography on Florisil. Highly attractive materials were obtained by steam distillation of aqueous homogenates of males, as well as by passing a stream of air over caged live males and collecting the condensate in methylene chloride at Dry Ice-acetone temperature (−78°). Adsorption of the volatiles on glass plates coated with fatty material (enfleurage), followed by vacuum distillation of the fat, failed to give active material. Collection of the attractant from a steam distillate of aqueous homogenate was subsequently discarded in favor of the air-collection method when it was found that the former method gave at least four or five fractions with varying degrees of transient attractiveness by column chromatography on silicic acid; further attempts to purify these fractions by glc resulted in complete loss of activity. An inactive crystalline compound, mp 82°, with an odor of freshly roasted popcorn, was isolated from the basic fraction of the distillate and identified as 2-acetylpyrazine, a common constituent of roasted grains.[7] Its presence in the insects was traced to the wheat shorts and middlings used in the larval-rearing medium.[8]

The route used to isolate the pure pheromones from male medflies is shown in Scheme I. The condensate obtained by cold-trapping the air passed over 20,000-24,000, 4-14-day-old caged male flies for a total of 150-160 hr was extracted by shaking successively with ice-cold CH_2Cl_2 and Et_2O; the fractions soluble in each of these solvents were equally attractive to female medflies in the laboratory. The CH_2Cl_2-soluble portion was separated into basic, acidic, and neutral fractions and the latter was chromatographed on a column of silica gel, eluting successively with hexane and increasing percentages of Et_2O in hexane. The eluate collected with 5% Et_2O-hexane was subjected to preparative glc to give a major and a minor component. The former (compound

Scheme I



[a] Attractive to ♀.

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Table I. Test Reactions of Condensate Fractions

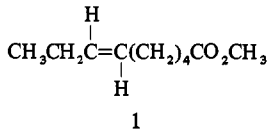
Fraction	Reagent	Activity
CH_2Cl_2-soluble	5% KOH (reflux)	Inactive
	$LiAlH_4$	Active
	$NaBH_4$	Active
Et_2O-soluble	5% KOH (reflux)	Active
	$LiAlH_4$	Active
	$NaBH_4$	Active
Saponified CH_2Cl_2-soluble	BF_3-CH_3OH	Active

1) consisted of 28.8 mg of colorless liquid with a floral odor. Preparative glc of the Et_2O-soluble portion of the condensate under the same conditions gave 8.2 mg of colorless liquid with a floral odor (compound **2**). Both **1** and **2** were equally attractive to female medflies and were found to be pure by glc on several column packings.

Test reactions carried out with the condensate fractions (Table I) had already indicated that **1** was probably an ester and **2** was probably an alcohol. This was confirmed by the ir spectra, **1** showing strong bands at 1730 (C=O stretching) and 1250, 1200, and 1160 cm^{-1} (CH_3 ester CO stretching[9]), and **2** showing strong bands at 3340 (OH stretching), 1370 (OH bending), and 1050 cm^{-1} (COH stretching); both spectra showed a very strong band at 963 cm^{-1} (trans unsaturation). The assignments of CH_3 ester and alcohol for **1** and **2**, respectively, were also supported by their nmr spectra. Comparison of the glc retention times of **1** and **2** with those of model compounds (Table II) indicated that **1** was the CH_3 ester of an unsaturated C_9 acid and **2** was an unsaturated C_9 alcohol.

The mass spectrum of **1** showed diagnostic peaks (mass to charge, *m/e*) at 170 (molecular ion, M), 138 (M – CH_3OH), and 74 (McLafferty rearrangement); **2** showed diagnostic peaks at 142 (molecular ion) and 124 (M – H_2O). The molecular formulas were assumed to be $C_{10}H_{18}O_2$ and $C_9H_{18}O$, respectively, each of which accommodates one double bond.

Spectral evidence supported the partial structures $CH_3(CH_2)_mCH{=}CH(CH_2)_nCO_2CH_3$ for **1** and $CH_3(CH_2)_mCH{=}CH(CH_2)_nOH$ for **2**, with *m* = at least 1 and *n* = at least 2 in each case as determined by nmr shift data. The position of the double bond in **1** and **2** was sought by oxidative degradation[10] with ozone; the fragments obtained were determined by glc comparison with those from model compounds. Compound **1** was found to be methyl (*E*)-6-nonenoate and **2** to be (*E*)-6-nonen-1-ol.



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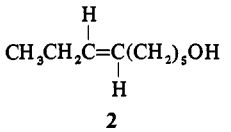

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The structures assigned to **1** and **2** were confirmed by synthesis. Compound **2** was synthesized by the method of Jacobson, *et al.*[11] Treatment of (*E*)-6-nonenoic acid[11] with methanol gave **1**. The synthetic compounds were identical in every respect with those isolated from the insect airstream condensate.‡‡

Although both **1** and **2** were highly excitatory and attractive to caged female medflies in the laboratory, they showed a low order of attractiveness in field cages when compared with crude male condensate. Mixing equal amounts of **1** and **2** failed to increase the activity, but attraction equal to that of the condensate was obtained only with a combination of **1**, **2**, and the inactive acidic fraction of the condensate (*cf.* Biological Activity). The basic fraction failed to synergize the attractiveness of the mixed pheromones. In an attempt to pinpoint the synergist, the crude acidic fraction was converted to the mixed CH_3 esters which were empirically identified by gas chromatography. The acids found are shown in Table III. Acids **6** and **8** are probably palmitoleic and oleic, respectively.[12] Admixture of of **1** + **2** with all possible combinations of the component acids failed to result in field attraction comparable with that of crude condensate. However, admixture of **1** + **2** with a mixture of all components was attractive.

‡‡Isomerizational analyses of both the natural and synthetic pheromones showed the presence of 6–7% of the corresponding cis form.

Table II. Glc Retention Times of Actives and Model Compounds[a]

Substance	Retention time, min	Substance	Retention time, min
1	6.0	1-Hexanol	3.4
Me octanoate	3.6	1-Octanol	5.8
Me nonanoate	4.8	1-Nonanol	7.8
Me decanoate	6.6	1-Decanol	11.0
2	9.8		

[a]Stainless steel column (0.635 cm × 3.66 m) of 5% DEGS on 60–80 mesh Gas-Chrom Q, temperature 125°, N_2 flow rate 44 ml/min.

Table III. Acid Composition of Male Medfly Condensate

No.	Acid	% of total acids
1	C_6 saturated	4.5
2	C_8 saturated	0.8
3	C_{10} saturated	8.2
4	C_{12} saturated	18.8
5	C_{14} saturated	8.7
6	C_{16} monounsaturated	14.3
7	C_{16} saturated	16.0
8	C_{18} monounsaturated	6.3
9	C_{18} saturated	1.4
10	Unidentified	21.0

It is of interest to note that the sex pheromones of a dermestid beetle, *Trogoderma inclusum* LeConte, have also been found to be an unsaturated CH_3 ester and the corresponding unsaturated alcohol, (–)-methyl 14-methyl-(*Z*)-8-hexadecenoate and (–)-14-methyl-(*Z*)-8-hexadecen-1-ol.[13]

Biological Activity. The fact that filter paper exposed in a cage to live male medflies became attractive to virgin females was made the basis of a laboratory bioassay method.†† The method was used to monitor all chemical fractions obtained during the isolation and purification procedure. Candidate test materials were bioassayed by exposing them on filter paper in small sticky cup traps to groups of 100 sexually mature, 4–5-day-old virgin female flies confined in 28-dm^3 screen cages. In each of a series of cages a "treated" cup and a "blank" cup (included to provide the flies a choice) were exposed to females for 30 min. The number of flies caught in this period in each treated cup was compared with the number caught in a "standard" treatment cup containing filter paper previously placed in a cage of 2000 4–5-day-old males for 17–18 hr. Whereas the catch in the blank cups was usually 0–2 females, that in the standard cup was usually 50 out of 100 in the 30-min period. Female response to cups containing the standard or an attractive candidate material was usually immediate; flies clustered around the entrance hole of the cup trap and entered after a brief session of wing-beating and aggressive bumping of neighboring flies. Females entering the 3-oz cups were caught on the adhesive which lined the inner walls of the trap. The female response was characterized not

Table IV. Laboratory Response of Female Medflies to Male Fractions

Test substance	Dose, M.E.[a]	No. of females caught in Blank[b]	Test	Standard[c]
Male condensate, crude	5,000	1	52	59
Male condensate, acids	400	0	5	39
Male condensate, bases	400	2	11	39
Male condensate, neutral	400	1	36	39
Natural 1	10,000	2	63	53
	1,500	1	19	39
	400	1	16	56
Synthetic 1	1,500	0	23	56
	400	1	31	39
Natural 2	10,000	1	58	53
	1,500	0	17	56
	400	3	36	56
	100	1	43	56
Synthetic 2	2,000	0	18	53
	400	3	35	50
	100	0	33	50
Natural 1 + 2	400	0	38	49
Synthetic 1 + 2	400	0	36	50

[a]M.E. = male equivalents (that amount of material calculated to have been obtained from one of the 80,000 males used for collecting the pure pheromones). [b]Filter paper treated with 1 ml of Et_2O. [c]Filter paper exposed to 2000 males for 17–18 hr.

Table V. Field-Cage Response of Female Medflies to Male Fractions

Test substance	Dose, M.E.[a]	No. of females caught in Blank[b]	Test	Standard[c]
Natural 1	1000	0	34	64
Synthetic 1	1000	0	27	64
Natural 2	1000	1	30	64
Synthetic 2	1000	0	32	64
Male condensate, acids	5 mg	0	0	98
Male condensate, bases	5 mg	0	0	98
Synthetic 1 + 2	1000	0	18	98
Synthetic 1 + 2 + 5 mg acids	1000	0	120	98
Synthetic 1 + 2 + 5 mg bases	1000	0	10	98

[a]M.E. = male equivalents. [b]Filter paper treated with 1 ml of Et_2O. [c]Filter paper exposed to 2000 males for 17–18 hr.

only by the numbers caught in the trap but also by the rapid orientation of the flies to the source of the odor. The tests were conducted between 8:30 and 11 A.M. in a 15.6-m^3 room illuminated by two 40-W fluorescent lamps.

Outdoor trapping tests were conducted in 7.6-m^3 cages containing approximately 1000 5-day-old female medflies. Test materials impregnated on filter paper were placed in 3-oz cup traps whose inner walls were coated with adhesive. The traps were positioned randomly on a 1.2-m diameter wheel rotating at 0.3 rpm. Counts were made after 30 min to 1 hr. Laboratory test results are reported in Table IV and field-cage test results are reported in Table V.

Experimental Section

Melting points were determined in a Mel-Temp apparatus and are uncorrected. Boiling points are uncorrected. Ir spectra were determined with a Perkin-Elmer Model 521 spectrophotometer. Nmr spectra were recorded with a Varian HA-100 spectrometer. Mass spectra were obtained with a Perkin-Elmer Model 270 GC-mass spectrometer. Gas chromatography was carried out with an F & M Model 500 gas chromatograph equipped with a Model 1609 flame ionization attachment. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. The mention of a proprietary product in this paper does not constitute an endorsement of this product by the U. S. Department of Agriculture.

Collection of the Sex Pheromones. Preparations attractive to females were obtained by steam distillation, into pentane, of aqueous homogenates prepared from 4–5-day-old males in an electric blender. However, more highly attractive material was obtained by passing a stream of air through cages of live males and trapping the condensate in reagent-grade CH_2Cl_2 at −78°. Absorbing the condensate on glass plates coated with Myverol Distilled Monoglycerides (Type 18-00, Distillation Products Industries, Rochester, N. Y.), scraping the plates, and extracting the solid fat with CH_2Cl_2 failed to give an active extract. Distilled H_2O rinses and benzene extracts of whole males and CH_2Cl_2 rinses of filter papers exposed to live males were likewise unattractive. Although column chromatography on Florisil (60–100 mesh) of an inactive crude CH_2Cl_2 extract of males yielded an active fraction following elution with 5% Et_2O–hexane, the activity was of a very low order.

Successive treatment of the steam distillate from aqueous homogenates of 52,433 males with cold 5% HCl solution and cold 5% KOH solution yielded an active neutral fraction (30.5 mg) and inactive acidic (42.8 mg) and basic (8.5 mg) fractions. Chromatography of the neutral fraction on a column (1.8 × 24 cm) of silicic acid (Bio-Sil HA, minus 325 mesh, obtained from Bio-Rad Laboratories, Richmond, Calif.), using successive elution with hexane and increasing amounts of Et_2O in hexane, gave five inactive fractions and at least four active fractions; however, the activity of the latter was transient and poorly defined. Sublimation of the odoriferous basic fraction of the steam distillate at 75° and 0.2 mm of pressure yielded 5.2 mg of colorless crystals, mp 82°, with a strong odor of freshly roasted popcorn. The crystals were identified as 2-acetylpyrazine by mixture melting point with an authentic specimen. The same compound was obtained from an Et_2O extract of the medium, containing wheat shorts and middlings, used to rear the flies in the laboratory.

Isolation of the Pheromones. A moderate stream of air (*ca.* 7 l./min) passed through a 225-dm^3 Plexiglas box containing 12 screen cages of 2000 4–14-day-old males/cage was collected in CH_2Cl_2 at −78°. A volume of condensate representing a collection over a total period of 150–160 hr was separated from the CH_2Cl_2 layer and the cold aqueous layer was shaken successively with five portions of cold CH_2Cl_2 followed by three portions of Et_2O. The CH_2Cl_2-soluble fraction was separated into acidic, basic, and neutral portions by shaking successively with cold 5% KOH solution and cold 5% HCl solution. The neutral portion was chromatographed, in lots of 10,000 male equivalents, on columns (1.8 × 28 cm) of silicic acid, eluting successively with hexane and 5, 10, 20, and 30% Et_2O in hexane. The 5% Et_2O–hexane eluates containing all the activity were combined and subjected to preparative glc on a stainless steel column (0.635 cm × 3.66 m) packed with 5% stabilized DEGS on 60–80 mesh Gas-Chrom Q (column temperature 125°, He flow rate 32 ml/min). The chromatogram showed a minor and a major peak with retention times of 4.8 and 7.3 min, respectively. The compound, **1**, responsible for the major peak was collected and found to be attractive to female medflies in the laboratory; it consisted of 28.8 mg of colorless liquid with a floral odor and was determined to be pure by glc on OV-1 and DEGS columns. Retention times for **1** and the methyl esters of the saturated C_8, C_9, and C_{10} acids are shown in Table II.

Direct preparative glc of the Et_2O-soluble fraction of male condensate on DEGS under conditions identical with those described above gave 8.2 mg of attractive colorless liquid with a floral odor, having a retention time of 11.2 min. The compound, **2**, was found to be pure by glc on OV-1 and DEGS columns. Retention times for **2** and the saturated C_6, C_8, C_9, and C_{10} alcohols are shown in Table II.

Compound **1** showed ir (film) 2950, 2920, 2862, 1730, 1455, 1430, 1355, 1250, 1200, 1160, 1110, 1060, 963, 722 cm^{-1}; nmr ($CDCl_3$ with tetramethylsilane) 0.95 (CH_3), 1.2–1.8 (CH_2 chain), 2.00 (allylic CH_2), 2.30 ($-CH_2COO-$), 3.64 ($-COOCH_3$), 5.40 ppm (−CH=CH−); the mass spectrum showed diagnostic peaks (mass to charge, *m/e*) at 170 (molecular ion, M^+), 138 ($M^+ - CH_3OH$), and 74 (McLafferty rearrangement); molecular formula $C_{10}H_{18}O_2$.

Compound **2** showed ir (film) 3340, 2950, 2920, 1456, 1370, 1065 (inflection), 1050, 963, 890, 722 cm^{-1}; nmr ($CDCl_3$ with tetramethylsilane) 0.94 (CH_3), 1.2–1.8 (CH_2 chain), 2.00 (allylic CH_2), 3.62 ($-CH_2OH$), 5.41 ppm (−CH=CH−); the mass spectrum showed diagnostic peaks (*m/e*) at 142 (M^+) and 124 ($M^+ - H_2O$); molecular formula $C_9H_{18}O$.

Ozonolysis of 1 and 2. Compound **1** (0.2 μl) was mixed with 200 μl of PrOAc and ozonized,[10] 1 mg of powdered Ph_3P was added, and the mixture was shaken. When the solution reached room temperature a 0.4-μl aliquot was analyzed by glc on a stainless steel column (0.32 × 3.05 m) of 10% DEGS on 60–80 mesh Chromosorb W, N_2 flow rate 26 ml/min. The temperature control, initially at ambient temperature, was raised to 75° 4 min following injection of the sample and again raised to 150° after an additional 12 min. The products formed, EtCHO and 6-acetoxyhexanal, emerged in 2.8 and 28.1 min, respectively.

Compound **2** (0.2 μl) was mixed with 150 μl of *i*-AmOAc and ozonized, 1 mg of powdered Ph_3P was added, and the mixture was shaken. When the solution reached room temperature a 0.4-μl aliquot was analyzed under the same glc conditions as above except that the final temperature control was set at 165° instead of 150°. The products formed, EtCHO and 6-hydroxyhexanal, emerged in 2.9 and 29.5 min, respectively.

Synthesis of 1. (*E*)-6-Nonenoic acid,[11] bp 95–102° (0.4 mm), $n^{25}D$ 1.4462, was converted to **1** by refluxing for 4 hr a solution of 30 g of the acid and 4 drops of concentrated HCl in 100 ml of CH_3OH, removing the latter under reduced pressure, dissolving the residue in Et_2O, and washing with cold 10% $NaHCO_3$ solution followed by cold H_2O. Distillation of the dried solution gave 29.2 g (89%) of colorless liquid, bp 105–107° (10 mm), $n^{25}D$ 1.4345. *Anal.* Calcd for $C_{10}H_{18}O_2$: C, 70.59; H, 10.59. Found: C, 70.62; H, 10.58.

Synthesis of 2. The compound was prepared by reducing (*E*)-6-nonenoic acid with $LiAlH_4$.[11] The product was a colorless liquid, bp 76–84° (0.2 mm), $n^{25}D$ 1.4471. *Anal.* Calcd for $C_9H_{18}O$: C, 76.06; H, 12.67. Found: C, 75.93; H, 12.68.

Isomerizational Analysis of Natural and Synthetic 1 and 2. Analyses were conducted by the capillary glc method of Warthen and Green[14] on a stainless steel column (0.49 mm × 91.5 m) coated with DEGS, He flow rate 5 ml/min, at a column temperature of 107° for **1** and 125° for **2**. Both natural and synthetic **1** showed two peaks with retention times of 19.8 and 20.6 min, respectively, corresponding to 96% trans and 4% cis for natural **1** and 93.5% trans and 6.5% cis for synthetic **1**. Natural and synthetic **2** were converted to the acetates with AcCl; the products showed two peaks with retention times of 15.2 and 15.9 min, respectively, corresponding to 94% trans and 6% cis for natural **2** and 93% trans and 7% cis for synthetic **2**.

Determination of the Medfly Condensate Acids. The acidic portion (78 mg) obtained from the CH_2Cl_2-soluble fraction of the condensate was converted to the mixed methyl esters with BF_3-CH_3OH and subjected to glc on a column (0.32 cm × 3.05 m) of 5% SE-30 on 60–80 mesh acid-washed Chromosorb W, N_2 flow rate 44 ml/min. The column was heated isothermally at 75° for 4 min, programmed at 5.6°/min to 225°, and continued isothermally at that temperature. Retention times were also determined on a column (0.32 cm × 3.05 m) of 5% DEGS on 60–80 mesh Gas-Chrom Q, N_2 flow rate 48 ml/min, under the same temperature regimen except that the maximum column temperature was 175°. The acid composition is shown in Table III.

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Synthesis and Antiinflammatory Activity of Some 2,2-Dimethyl-1,2-dihydroquinolines

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The syntheses of 2,2-dimethyl-1,2-dihydroquinolines and 4-chloro-2,2-dimethyl-1,2-dihydroquinolines from 1,1-dimethyl-2-propynylanilines are described. These compounds showed inhibition of uv-induced erythema in guinea pigs. The 8-alkyl derivatives were the most active members of the series.

The intramolecular cyclization of 1,1-dimethyl-2-propynylanilines to 1,2-dihydroquinolines was reported by Easton and Cassady.[1] We investigated this cyclization and found that a second product, 4-chloro-1,1-dimethyl-1,2-dihydroquinoline, also could be isolated from this cyclization by varying the reaction conditions. Unlike the thermal rearrangement of aryl 1,1-dimethyl-1-propynyl ethers,[2] the aniline rearrangement was catalyzed by cuprous salts. Because these compounds were active in broad-screen tests, this series and some structurally related compounds were prepared and evaluated for antiinflammatory activity using an ultraviolet-induced erythema inhibition test in guinea pigs.

Chemistry. Although Easton[1] reported the use of wet ether as solvent in the Cu^+-catalyzed cyclization, we have found dioxane to be a more effective solvent. When **1a** was stirred with a 10 mol % solution of CuCl for 2 hr at 75°, **6a** was isolated in 66% yield. Excluding oxygen from the reaction mixture greatly increased the isolated yield of **6a**. Purified Cu metal was not effective in this cyclization.

When **1a** was treated with a large excess of CuCl (200 mol %) at 25°, **6a** was obtained in 41.5% yield, and a second product, 4-chloro-1,1-dimethyl-1,2-dihydroquinoline (**7a**), was isolated in 8.5% yield. Substituting CuBr for CuCl in the above reaction gave 4-bromo-1,1-dimethyl-1,2-dihydroquinoline (**8**). The use of CuCN was not effective in this reaction. Treatment of **6a** with CuCl under identical conditions did not give any **7a**.

Apparently the NH was necessary for cyclization to take place. When *N*-(1,1-dimethyl-2-propynyl)-*N*-methylaniline was treated with CuCl under various conditions, only a cleavage product, *N*-methylaniline, was isolated.

The dihydroquinolines could be obtained directly from the condensation of 3-chloro-3-methyl-1-butyne with the substituted anilines using dioxane as the solvent and CuCl as the catalyst, presumably going through the 2-propynylaniline intermediates. The proposed mechanism of these reactions in outlined in Scheme I.

Chlorodihydroquinolines (**7**) were formed presumably from the CuCl chlorination of the copper complex **2** with subsequent conversion to **7** or from the chlorination of **5** to give the same products.

For further evaluation of the series, several chemical