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**.

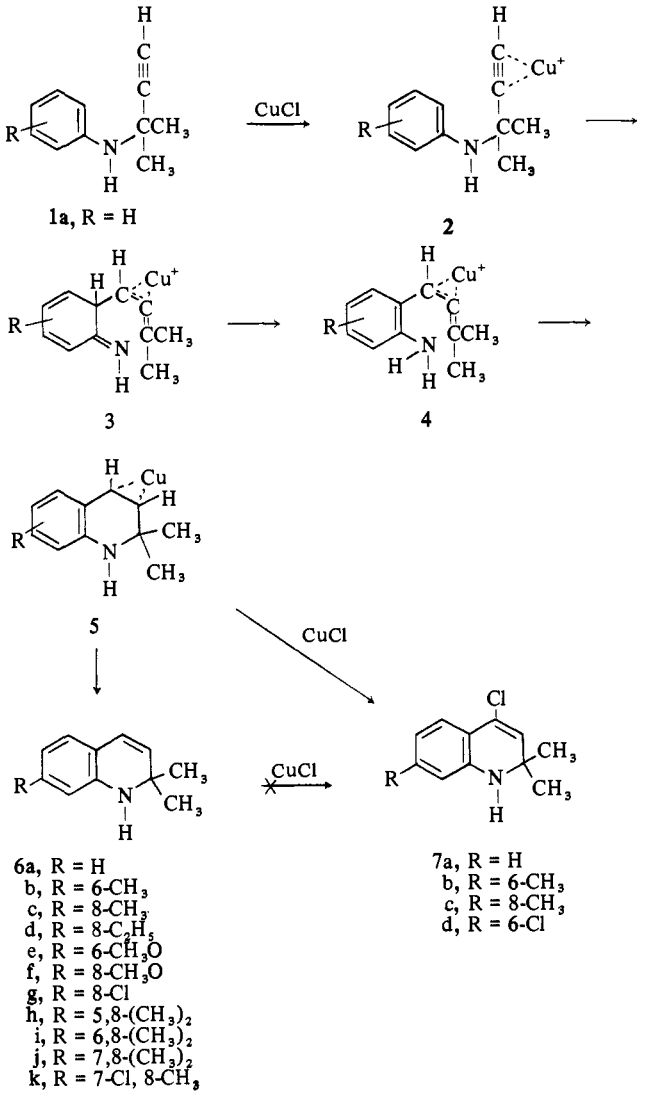
Apparently the NH was necessary for cyclization to take place. When *N*-(1,1-dimethyl-2-propynyl)-*N*-methylaniline was treated with CuCl under various conditions, only a cleavage product, *N*-methylaniline, was isolated.

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.

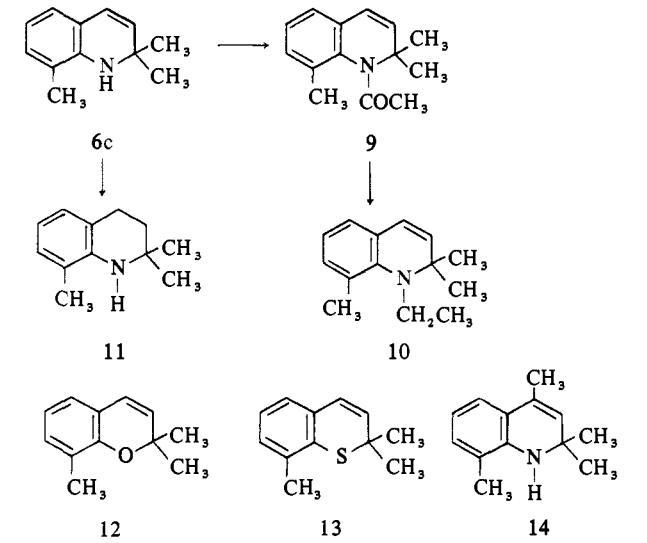
Chlorodihydroquinolines (**7**) were formed presumably from the CuCl chlorination of the copper complex **2** with subsequent conversion to **7** or from the chlorination of **5** to give the same products.

For further evaluation of the series, several chemical

Scheme I



modifications were made on **6c**. The *N*-acetyl compound **9** was made readily and reduced to the *N*-ethyl derivative **10** with $LiAlH_4$. Catalytic reduction of **6c** gave tetrahydroquinoline **11**. Related compounds **12**, **13**, and **14** were made by conventional methods[2] (see Table I).



Pharmacology. In reviewing the results described in Table II, some general observations can be made. Although unsubstituted compound **6a** does have good erythema blocking activity, substituting **6a** with alkyl groups in the 6 or 8 position does increase potency to some extent. When the substituent in the 8 position was ethyl (**6d**), optimum activity was obtained. Compounds disubstituted in the 5, 6, 7, or 8 positions (**6h–k**) or substituted in the 4 position (**7a–d**) were less effective. Substitutions on the N (**9**, **10**) or replacing N with O or S did not increase potency. When the double bond was reduced to give **11**, some activity was retained.

Experimental Section

Pharmacological Test Methods. The antiinflammatory effects of these 1,1-dimethyl-1,2-dihydroquinolines were determined by using a modification of the method of Winder, *et al.* (1958).[3] Male albino guinea pigs weighing 225–300 g were shaved on the back and chemically† depilated 18–20 hr before exposure to ultraviolet light. The animals were fasted overnight. Immediately after the guinea pigs were treated with the compounds, the back of each guinea pig was exposed to a high intensity ultraviolet light for 7 sec. The ultraviolet light source was a Hanovia lamp (Kromayer Model 10) which was placed in contact with the skin of the guinea pig's back.

A gummed notebook paper reinforcement was placed on the lamp face. This unexposed area under the reinforcement provided an area of contrast for grading the erythema. The animals were randomized and placed in clear plastic partitioned holders 10 × 20 cm wide and 15 cm high. Beginning 1 hr after exposure and thereafter at 0.5-hr intervals for another 1.5 hr, the degree of resulting erythema was graded by an arbitrary scoring system based upon the degree of contrast and redness formed. Antiinflammatory agents delay the development of erythema and have their greatest effect at the initial grading periods. Therefore, the scores were weighted by a factor of 3, 2, 1, and 0 at the 1.0, 1.5, 2.0, and 2.5 hr scoring times, respectively. The erythema was graded as shown in Table III.

Total scores from each treatment group of four guinea pigs were compared to the control treatment, and the per cent inhibition was calculated as follows.

$$100 \times \frac{\text{control} - \text{treatment}}{\text{control}} = \% \text{ inhibition}$$

Suspensions of the compounds were prepared in 1% methylcellulose in water. Guinea pigs were treated with 2.0 ml/kg orally of the treatment suspension. Control animals received comparable amounts of the vehicle.

The compounds were administered at an initial screening dose of 50 mg/kg. In those cases where there was a greater than 50% inhibition at the 50 mg/kg dose, lesser dose levels were administered and an ED_{50} was estimated. The ED_{50} is that estimated dose of the compound which causes a 50% inhibition of the erythema.

Results are given in Table II. In this test system, acetylsalicylic acid has an ED_{50} of 50 mg/kg.

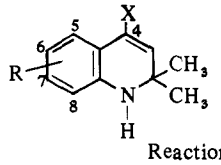
General Chemistry. All physical data were determined by the Physical Chemistry Department in our laboratories. The nmr spectra were determined on a Varian Associates spectrophotometer, Model HA60, and the ir spectra on a Perkin-Elmer 221 spectrophotometer. All spectra were consistent with the structures proposed. Compound purity was checked also by glc analyses. Analytical data in Table I are within ±0.4% of calculated values. The melting points are uncorrected. The intermediate 2-propynylanilines were made by the AgCl catalyzed condensation of the appropriately substituted anilines with 3-chloro-3-methyl-1-butyne as described by Easton[1] and in some cases were used in their crude state.

2,2-Dimethyl-1,2-dihydroquinolines (6) and/or 4-Chloro-2,2-dimethyl-1,2-dihydroquinolines (7). General Procedures. Method A. The appropriate anilines (0.1 mol), 0.1 mol of triethylamine, and 22 g of CuCl were placed in 100 ml of dioxane, and 0.1 mol of 3-chloro-3-methyl-1-butyne was added dropwise while the stirred mixture was cooled at 20°. After stirring at 20° for 1 hr and at 25° for 2 hr, H_2O and ether were added; the organic layer was separated, washed several times with water, and dried ($MgSO_4$), and the solvent was removed at reduced pressure. The residue was placed on a silica gel column and eluted with benzene. The products (7), if solids, were recrystallized and approximately 5% yields were obtained.

Method B. A mixture of 0.1 mol of the *N*-propynylaniline 1, 10 g of CuCl, and 10 ml of H_2O in 50 ml of ether was heated to maintain reflux for 48 hr. After cooling, the ether was filtered,

†Nair, Lotion Hair Remover, Carter Products, New York, N. Y.

Table I. 2,2-Dimethyl-1,2-dihydroquinolines



Compd no.	R	X	Reaction solvent	Method[a]	Reaction temp, °C	Bp (mm) or mp, °C	Formula	Analyses[b]
6a	H	H	Dioxane	C	75	50–51 (0.07)	$C_{11}H_{13}N$	C, H, N
6b	6-CH_3	H	Dioxane	C	75	55–56 (0.2)	$C_{12}H_{15}N$	C, H, N
6c	8-CH_3	H	Ether	B	37	103 (4)	$C_{12}H_{15}N$	C, H, N
6d	8-C_2H_5	H	Dioxane	C	75	55–57 (0.1)	$C_{13}H_{17}N$	C, H, N
6e	6-CH_3O	H	Dioxane	C	*c*	81–83 (0.1)	$C_{12}H_{15}NO$	C, H, N
6f	8-CH_3O	H	Ether	B	37	65 (0.07)	$C_{12}H_{15}NO$	C, H, N
6g	8-Cl	H	Dioxane	C	75	*e*	$C_{11}H_{12}ClN$	C, H, N
6h	5,8-$(CH_3)_2$	H	Dioxane	C	75	60–62 (0.1)	$C_{13}H_{17}N$	C, H, N
6i	6,8-$(CH_3)_2$	H	Dioxane	C	75	65–66 (0.1)	$C_{13}H_{17}N$	C, H, N
6j	7,8-$(CH_3)_2$	H	Dioxane	C	75	65–66 (0.1)	$C_{13}H_{17}N$	C, H, N
6k	7-Cl, 8-CH_3	H	Dioxane	C	75	70–72 (0.05)	$C_{12}H_{14}ClN$	C, H, N
7a	H	Cl	Dioxane	A	*c*	37–38[d]	$C_{11}H_{12}ClN$	C, H, N, Cl
7b	6-CH_3	Cl	Dioxane	C	*c*	65–67[d]	$C_{12}H_{14}ClN$	C, H, N, Cl
7c	8-CH_3	Cl	Dioxane	A	*c*	*e*	$C_{12}H_{14}ClN$	C, H, N
7d	6-Cl	Cl	Dioxane	A	*c*	*e*	$C_{11}H_{11}Cl_2N$	C, H, N

[a] See Experimental Section. [b] Analytical data within ±0.4% of calculated value. [c] Ambient temperature. [d] Crystallized from petroleum ether (bp 35–60°). [e] Purified by silica gel column chromatography.

Table II. Ultraviolet-Induced Erythema Inhibition in Guinea Pigs

Compd no.	% erythema inhibition at 50 mg/kg po	Estd ED_{50}, mg/kg po
6a	60	42
6b	62	34
6c	66	31
6d	68	23
6e	52	47
6f	35	>50
6g	50	50
6h	17	>50
6i	22	>50
6j	42	>50
6k	27	>50
7a	41	>50
7b	0	>50
7c	13	>50
7d	7	>50
9	16	>50
10	22	>50
11	35	>50
12	18	>50
13	0	>50
14	36	>50

Table III. Erythema Scoring System

Score	Appearance of exposed area
0	No redness and no contrast
1	Slight redness with a faint reinforcement outline
2	Slight to moderate redness with a distinct outline
3	Marked redness with a distinct circular outline

washed with H_2O, and dried ($MgSO_4$), and the ether solution was distilled to give products 6 in approximately 25% yields. No 7 was obtained.

Method C. A mixture of 0.1 mol of 1 and 0.1 mol of CuCl in 150 ml of dioxane was placed in an oil bath at 75° with stirring for 2 hr. After cooling and filtering, the mixture was diluted with ether and washed with H_2O. The organic layer was dried ($MgSO_4$) and distilled. Yields ranged from 25 to 66%. In the case of **6a**, a 66% yield was obtained.

Approximately 5–10% yields of 7 could be isolated by column chromatography (silica gel, benzene) when the above reaction was run at room temperature for 48 hr and a 200 mol % of CuCl was used. Under these conditions, **1a** was converted to a mixture from which was isolated **6a** in 41.5% yield and **7a** in 8.4% yield.

Treatment of *N*-Methyl-*N*-(1,1-dimethyl-2-propynyl)aniline with CuCl. A mixture of 1 g of *N*-methyl-*N*-(1,1-dimethyl-2-propynyl)aniline and 2 g of CuCl in 10 ml of ether was stirred at room temperature, and the reaction was followed by glc. After 48 hr, complete conversion to *N*-methylaniline had taken place. Complete conversion occurred within 3 hr when dioxane was the solvent instead of ether.

4-Bromo-1,2-dihydro-2,2-dimethylquinoline (8). A mixture of 0.1 mol of **1a** and 32 g of CuBr in 200 ml of dioxane was stirred 168 hr at 25°. After filtering off the salts and removing the solvent, the crude residue was purified by a silica gel column (benzene) to give 0.5 g (4% yield) of **8**. *Anal.* ($C_{11}H_{12}BrN$) C, H, N.

1,2-Dihydro-2,2,4,8-tetramethylquinoline (14). Acetone (284 ml) was added dropwise to 107 g of *o*-toluidine and 3 g of I_2, heated at 170–175°. After 210 ml of distillate was collected (1.5 hr), the reaction mixture was cooled, taken up in ether, washed with H_2O, and dried ($MgSO_4$), and the ether was removed. Pure **14** (1 g) was isolated in an overall 15% yield from a 3-g sample of this residue by preparative glc. *Anal.* ($C_{13}H_{17}N$) C, H, N.

1-Acetyl-1,2-dihydro-2,2,8-trimethylquinoline (9). Acetyl chloride (0.08 mol) was added to a solution of 0.04 mol of **6c** and 0.1 mol of *N,N*-dimethylaniline in dichloromethane. After stirring at 25° for 24 hr and washing with dilute HCl and $NaHCO_3$ solution, **9** was obtained by distillation in 66.5% yield, bp 70–74° (0.1 mm) (5.7 g). *Anal.* ($C_{14}H_{17}NO$) C, H, N.

1-Ethyl-1,2-dihydro-2,2,8-trimethylquinoline (10). Treatment of 0.04 mol of **9** with 0.2 mol of $LiAlH_4$ in ether gave **10** in 66% yield, bp 98–100° (4 mm). *Anal.* ($C_{14}H_{19}N$) C, H, N.

1,2,3,4-Tetrahydro-2,2,8-trimethylquinoline (11). Low-pressure hydrogenation of 6.4 g of **6c** in EtOH using PtO_2 as catalyst gave **11** in 61% yield, bp 54–56° (0.1 mm). *Anal.* ($C_{12}H_{17}N$) C, H, N.

2,2,8-Trimethyl-2*H*-1-benzopyran (12). 3-Chloro-3-methyl-1-butyne (30.8 g) was added dropwise to a mixture of 97.2 g of *o*-cresol and 33.6 g of KOH in 800 ml of 50% EtOH, cooled to 20°, and the resulting mixture was stirred for 4 hr. After diluting with water and extracting the product with ether, distillation gave 16.8 g of crude *o*-tolyl 1,1-dimethyl-2-propynyl ether. The crude ether in *N,N*-diethylaniline was heated to maintain reflux for 4 hr and cooled; the *N,N*-diethylaniline was washed out with dilute HCl; and 5.5 g of pure **12** was obtained in 33% yield from a Florisil column that was eluted with benzene. *Anal.* ($C_{12}H_{14}O$) C, H.

2,2,8-Trimethyl-2*H*-1-benzothiopyran (13). Using the procedures described for **12**, *o*-thiocresol was converted to crude *o*-tolyl 1,1-dimethyl-2-propynyl sulfide bp 60–65° (0.1 mm), which was converted to **13** in 20% yield, bp 70–72° (0.3 mm). *Anal.* ($C_{12}H_{14}S$) C, H.

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