

*Anal.* Calcd for  $C_{18}H_{12}O_9S_3$ : C, 22.22; H, 3.73; S, 29.65. Found: C, 22.30; H, 3.80; S, 29.70.

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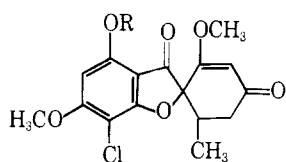
### Synthesis of Grisan and Coumaran-3-one Derivatives with Potential Insect-Repellent Properties<sup>1</sup>

VASU DEV, RONALD P. QUINTANA, AND ANDREW LASSLO

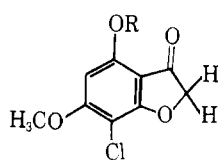
Department of Pharmaceutical and Medicinal Chemistry,  
University of Tennessee College of Pharmacy,  
Memphis, Tennessee 38103

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In developing structural designs for compounds which would prove effective as systemically administered insect repellents, we sought to combine within a *single molecule* (1) a component known to have affinity for dermal tissue with (2) a component possessing certain insect-repellent (or prophylactic or therapeutic) properties. In the initial phase of our exploratory work, we have synthesized a series of compounds (I–III and VI–VIII) combining into one molecular entity a moiety (IV) known to be transported to and found in epidermal tissue in significant quantities<sup>2</sup> [or a component (IX) of the latter], with moieties ascertained to have mosquito-repellent properties (anisyl alcohol,<sup>3a</sup> *N,N*-diethyl-*m*-toluamide,<sup>3b</sup> and citronellol<sup>3c</sup>).



- I, R =  $p\text{-CH}_2\text{C}_6\text{H}_4\text{OCH}_3$   
 II, R =  $m\text{-CH}_2\text{C}_6\text{H}_4\text{CON}(\text{C}_2\text{H}_5)_2$   
 III, R =  $\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{-CH}_2\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$   
 IV, R =  $\text{CH}_3$   
 V, R = H



- VI, R =  $p\text{-CH}_2\text{C}_6\text{H}_4\text{OCH}_3$   
 VII, R =  $m\text{-CH}_2\text{C}_6\text{H}_4\text{CON}(\text{C}_2\text{H}_5)_2$   
 VIII, R =  $\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{-CH}_2\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$   
 IX, R =  $\text{CH}_3$   
 X, R = H

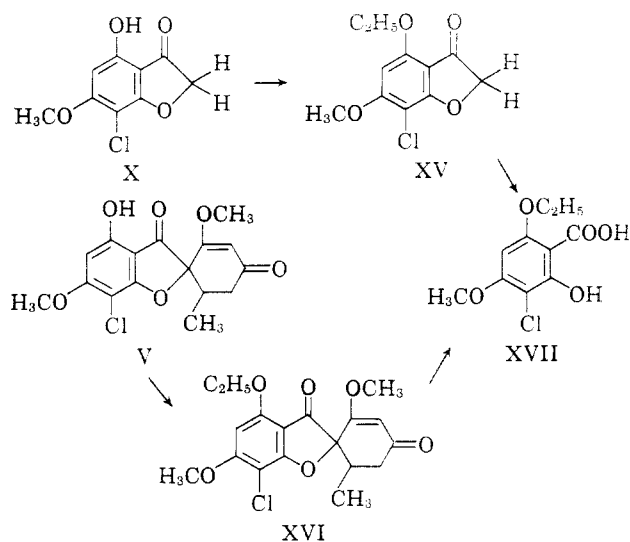
**Chemistry.**—The subject compounds could be viewed, basically, as condensation products of 4-demethylgriseofulvin<sup>4</sup> (V) and of the corresponding coumaran-3-one (X) with anisyl alcohol, *N,N*-diethyl-*m*-toluamide, and citronellol.

Compounds I, II, and III were actually obtained by treating V with anisyl bromide<sup>5</sup> (XI), 3-(*N,N*-diethylcarbamoyl)benzyl bromide (XII), and citro-

nellyl bromide<sup>6</sup> (XIII) in acetone and/or dimethylformamide, in the presence of potassium carbonate.

7-Chloro-4-hydroxy-6-methoxycoumaran-3-one (X), a hitherto unreported moiety, was obtained by the selective demethylation of 7-chloro-4,6-dimethoxycoumaran-3-one (IX) using a modification of the procedure employed in the demethylation of griseofulvin by Arkley, *et al.*<sup>4</sup>

The structure of the hydroxycoumaranone (X) was established by chemical and spectral evidence. Oxidative degradation of X in anticipation of obtaining the known<sup>7</sup> 3-chloro-2,6-dihydroxy-4-methoxybenzoic acid proved unsuccessful. Our inability to isolate a product from this direct oxidation appears to be consistent with the observation of Molho<sup>8</sup>; according to his interpretation, the corresponding salicylic acid derivative could not be obtained from a 4-hydroxy-substituted coumaranone because it is destroyed under the prevailing reaction conditions. Since our attempts to oxidize 7-chloro-4,6-dimethoxycoumaran-3-one (IX) met with success and yielded the expected 3-chloro-2-hydroxy-4,6-dimethoxybenzoic acid<sup>9</sup> (XIV), we were led to the following approach. Both the hydroxycoumaranone (X) and the known<sup>4</sup> 7-chloro-4-hydroxy-6,2'-dimethoxy-6'-methylgris-2'-ene-3,4'-dione (V), upon conversion to the respective ethyl ether derivatives (XV and XVI<sup>4</sup>) and subsequent oxidation with potassium permanganate, yielded the same acid, 3-chloro-6-ethoxy-2-hydroxy-4-methoxybenzoic acid (XVII), as confirmed by the melting and mixture melting points of the acids as well as their superimposable infrared spectra, and the elemental analyses of the acid and its anilide derivative (XVIII). Moreover, had the hydroxycoumaranone been the isomeric 7-chloro-



6-hydroxy-4-methoxycoumaran-3-one, oxidative degradation of its ethyl ether derivative would have afforded the known 3-chloro-4-ethoxy-2-hydroxy-6-methoxybenzoic acid,<sup>10</sup> mp 179–181° dec.

(1) This investigation was supported by Research Contract No. DA-49-193-MD-2636 from the U. S. Army Medical Research and Development Command, Washington, D. C.

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TABLE I  
ULTRAVIOLET ABSORPTION CHARACTERISTICS OF 7-CHLORO-4-HYDROXY-6-METHOXYCOUMARAN-3-ONE (X)  
AND SELECTED REFERENCE COMPOUNDS

Ref compd <sup>a</sup>	K-band									
	In 95% EtOH		In 95% EtOH with 2% HCl				In aqueous 0.1 N NaOH			
	Found <sup>b</sup>	$\lambda_{\max}$ , m $\mu$	Ref <sup>c</sup>	$\lambda_{\max}$ , m $\mu$	log $\epsilon$	$\lambda_{\max}$ , m $\mu$	Ref <sup>d</sup>	$\lambda_{\max}$ , m $\mu$	log $\epsilon$	$\lambda_{\max}$ , m $\mu$
XIX, R <sub>1</sub> = OH; R <sub>2</sub> = OCH <sub>3</sub> ; R <sub>3</sub> = H	4.33	283	4.31	280	4.31	284	4.35	285	4.25	284
XX, R <sub>1</sub> = OCH <sub>3</sub> ; R <sub>2</sub> = OH; R <sub>3</sub> = H	...	...	4.35	284	...	...	4.53	318	...	...

<sup>a</sup> Summarized from a paper by Duncanson, *et al.*<sup>10</sup> <sup>b</sup> For 7-chloro-4-hydroxy-6-methoxycoumaran-3-one (X).

We obtained additional confirmation for the structure of X by determining its ultraviolet absorption characteristics (see Table I). It can be seen that the spectral characteristics of X are in excellent agreement with those reported by Duncanson<sup>10</sup> for the similarly substituted 4-hydroxy-6-methoxycoumaran-3-one (X-IX), and are consistent with the observations of Cram and Cranz<sup>11</sup> on the spectra of *o*- and *p*-hydroxyacetophenones in ionizing and nonionizing media. Compound X must be a 4-hydroxycoumaran-3-one since its K-band, like that of Duncanson's 4-hydroxy derivative, has maxima of similar intensity and wavelength in both ionizing as well as nonionizing media; those of Duncanson's 6-hydroxycoumaran-3-one occur at considerably longer wavelengths and with significantly greater intensity in ionizing media.<sup>10</sup>

Compounds VI, VII, and VIII were prepared by the interaction of X with XI, XII, and XIII in dimethylformamide in the presence of potassium carbonate.

**Evaluation of Repellency.**—The compounds synthesized have been subjected to screening for mosquito repellency by Dr. C. N. Smith and Mr. H. K. Gouck of the Entomology Research Division, U. S. Department of Agriculture at Gainesville, Fla., by their standardized test.<sup>12</sup> Preliminary tests have shown that the six compounds evaluated possessed no repellent activity against *Aedes aegypti* mosquitoes.

#### Experimental Section<sup>13,14</sup>

**3-(N,N-Diethylcarbamoyl)benzyl Bromide (XII).**—To an ice-cold solution of 61.4 g (0.221 mole) of 3-bromomethylbenzoyl bromide<sup>15</sup> (XXI) in 200 ml of anhydrous benzene, a solution of diethylamine (32.3 g, 0.442 mole) in 150 ml of anhydrous benzene was added dropwise. After the reaction mixture was stirred at room temperature for 3 hr, the precipitated diethylamine hydrobromide was removed by filtration and washed with anhydrous benzene. The filtrate and washing were combined and the solvent was removed under reduced pressure. The residual oily liquid (57.0 g, 95.5%) was used without further purification after

drying at 100° (0.5 mm) for 3 hr, since it decomposed during all attempts to purify it by vacuum distillation.

**8-Bromo-2,6-dimethyloctene-2 (citronellyl bromide) (XIII)** was prepared according to the procedure reported for the synthesis of 5-bromo-2-pentene by Goering and co-workers.<sup>16</sup> Phosphorus tribromide (24.5 g, 0.090 mole) was added slowly to a cold solution of citronellol (31.2 g, 0.200 mole) ( $[\alpha]^{25}_D +1.2981^\circ$  (neat,  $l = 1$  dm),  $d^{25}_4$  0.8557) and pyridine (6.32 g, 0.090 mole), maintaining the reaction temperature below  $-20^\circ$ ; the reaction mixture was stirred for 0.5 hr subsequently. The crude product (38.3 g) obtained by a preliminary distillation under reduced pressure was dissolved in ether and washed successively with ice water, 5% NaHCO<sub>3</sub>, and saturated NaCl solution. After drying (Na<sub>2</sub>SO<sub>4</sub>), the ether was removed by distillation, and fractionation through a 22.5-cm Vigreux column yielded a colorless liquid (31.8 g, 72.6%), bp 104–108° (5–6 mm),  $n^{25}_D$  1.4764,  $[\alpha]^{25}_D -2.9182^\circ$  (neat,  $l = 1$  dm),  $d^{25}_4$  1.0946; lit.<sup>6</sup> bp 111° (12 mm),  $n^{20}_D$  1.4756,  $[\alpha]^{20}_D -6.93^\circ$ ,  $d^{20}_4$  1.1105.

**7-Chloro-4-hydroxy-6,2'-dimethoxy-6'-methylgrise-2'-ene-3,4'-dione (V)** was synthesized by the method of Arkley and co-workers.<sup>4</sup> The analytical sample, obtained as the monohydrate by recrystallization from aqueous acetic acid and aqueous methanol, melted at 113.8–115.0° (fusion) in accordance with the observation of Boothroyd, *et al.*<sup>17</sup> While Arkley and co-workers<sup>4</sup> reported the melting point as 140–143°, their value for the specific rotation was in agreement with our findings,  $[\alpha]^{25}_D +322.4^\circ$  (c 1.250, acetone).

*Anal.* Calcd for C<sub>16</sub>H<sub>15</sub>ClO<sub>6</sub>·H<sub>2</sub>O: C, 53.87; H, 4.80; Cl, 9.94. Found: C, 53.78; H, 4.78; Cl, 10.15.

Prior to use as a reactant in the synthesis of I, II, III, and XVI, this material was dried at 100° (2 mm) for 3 hr.

**7-Chloro-4-hydroxy-6-methoxycoumaran-3-one (X).**—To a refluxing mixture of 27.8 g (0.110 mole) of iodine in 80 ml of anhydrous ether and 100 ml of anhydrous benzene, 5.6 g (0.230 g-atom) of magnesium turnings was added gradually. The reaction mixture was refluxed for 4 hr and was allowed to stand overnight at room temperature. The clear solution obtained by decantation from this reaction mixture was added slowly to 27.8 g (0.122 mole) of 7-chloro-4,6-dimethoxycoumaran-3-one<sup>18,19</sup> (IX) in 2 l. of refluxing anhydrous benzene. After refluxing for 24 hr, the solvent was removed by distillation under reduced pressure. The residue was treated with 300 ml of 3 N HCl and the resulting yellow solid was treated with 150 ml of boiling chloroform. Upon cooling, the resulting solid was filtered off and suspended in 200 ml of boiling dioxane; to this mixture 300 ml of 3 N HCl, and subsequently, 200 ml of water were added. The yellow solid so obtained crystallized in the form of yellow needles (12.2 g, 46.6%) from 88% dioxane-water; recrystallized from 85% dioxane-water, it melted at 241.5–242.7° dec;  $\lambda^{EtOH}_{max}$  210 m $\mu$  ( $\epsilon$  20,200), 235 (18,200), 283 (21,600), 325 (4200);  $\lambda^{EtOH-2\% HCl}_{max}$  210 m $\mu$  ( $\epsilon$  20,000), 236 (17,800), 284 (20,200), 325 (4200);  $\lambda^{0.1N NaOH}_{max}$  219 m $\mu$  ( $\epsilon$  17,600), 240 (17,000), 284 (17,600), 355 (6200);  $\lambda^{CHCl_3}_{max}$  5.90  $\mu$  (C=O).

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(13) The authors acknowledge the technical assistance of Miss Linda F. Lorenzen and Miss Patricia J. Ward.

(14) Melting points were determined with a Swiseco melting point apparatus containing silicone fluid and are corrected. Boiling points are uncorrected. Ultraviolet spectra and infrared spectra were obtained, respectively, with the Perkin-Elmer Model 202 and 137B spectrophotometers. A Rudolph Model 62 polarimeter was employed to determine optical rotations. Analyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England.

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*Anal.* Calcd for  $C_9H_7ClO_4$ : C, 50.37; H, 3.29; Cl, 16.52;  $OCH_3$ , 16.02. Found: C, 50.32; H, 3.36; Cl, 16.30;  $OCH_3$ , 15.92.

**3-Chloro-2-hydroxy-4,6-dimethoxybenzoic Acid (XIV).**—To a solution of 2 g (8.75 mmoles) of 7-chloro-4,6-dimethoxycoumaran-3-one (IX) in 700 ml of anhydrous acetone, 8 g of powdered  $KMnO_4$  was added. The mixture was stirred at room temperature for 24 hr, and the resulting brown solid obtained by filtration was washed with acetone, dried at  $120^\circ$  for 15 min, and ground with 40 ml of 10%  $NH_4OH$  solution. The filtrate and washing were combined and added to 100 g of crushed ice, and this mixture was carefully acidified with concentrated  $H_2SO_4$ . The gelatinous-type precipitate was filtered off, dried, and recrystallized from ethyl acetate. The resulting tan needles (0.51 g) melted at  $222.0$ – $223.0^\circ$  dec in accordance with the literature.<sup>9</sup>

**7-Chloro-4-ethoxy-6-methoxycoumaran-3-one (XV).**—To a mixture of 30 g of anhydrous  $K_2CO_3$  and 4.29 g (0.020 mole) of 7-chloro-4-hydroxy-6-methoxycoumaran-3-one (X) in 120 ml of dimethylformamide, a solution of ethyl bromide (3.27 g, 0.030 mole) in 40 ml of dimethylformamide was added. The reaction mixture was slowly heated to  $65^\circ$  and maintained at this temperature for 5 hr. It was then added to 800 ml of ice water, and the resulting red precipitate was washed with water. Recrystallization from aqueous ethanol gave orange-red needles (3.1 g, 63.9%); after recrystallization from 95% ethanol, a melting point of  $180.7$ – $182.2^\circ$  dec was obtained;  $\lambda_{max}^{EtOH}$  210  $m\mu$  ( $\epsilon$  18,927), 235 (18,200), 286 (19,656), 322 (5996);  $\lambda_{max}^{CHCl_3}$  5.88  $\mu$  ( $C=O$ ).

*Anal.* Calcd for  $C_{11}H_{11}ClO_4$ : C, 54.45; H, 4.57; Cl, 14.61. Found: C, 54.58; H, 4.58; Cl, 14.70.

**7-Chloro-4-ethoxy-6,2'-dimethoxy-6'-methylgris-2'-ene-3,4'-dione (XVI).**—Compound XV (2.0 g, 8.24 mmoles) was oxidized by the procedure described for oxidation of IX. The product (0.47 g), recrystallized from ethyl acetate, melted at  $210.0$ – $211.7^\circ$  dec;  $\lambda_{max}^{KBr}$  3.15 ( $OH$ ), 3.77 (bonded  $OH$ ), 5.92  $\mu$  ( $C=O$ ).

*Anal.* Calcd for  $C_{10}H_{11}ClO_5$ : C, 48.70; H, 4.50; Cl, 14.38. Found: C, 48.62; H, 4.55; Cl, 14.29.

**B. From the Oxidation of 7-Chloro-4-ethoxy-6-methoxycoumaran-3-one (XV).**—Compound XV (2.0 g, 8.24 mmoles) was oxidized by the procedure described for oxidation of IX. The product (0.47 g), recrystallized from ethyl acetate, melted at  $210.0$ – $211.7^\circ$  dec;  $\lambda_{max}^{KBr}$  3.15 ( $OH$ ), 3.77 (bonded  $OH$ ), 5.92  $\mu$  ( $C=O$ ).

**3-Chloro-6-ethoxy-2-hydroxy-4-methoxybenzoic Acid (XVII).**—A solution of 8.0 g (0.022 mole) of XVI in 1.8 l. of anhydrous acetone was treated with 32 g of powdered  $KMnO_4$  by the procedure described for the oxidation of XV. The acid obtained from this reaction melted at  $204.7$ – $206.7^\circ$  dec after recrystallization from ethyl acetate; mixture melting point with the acid obtained in part A above was  $207.7$ – $209.0^\circ$  dec. The infrared spectrum (in  $KBr$ ) was superimposable on that of the acid obtained in part A.

**3-Chloro-6-ethoxy-2-hydroxy-4-methoxybenzanilide (XVIII).**—It was prepared in the customary manner from 0.40 g of 3-chloro-6-ethoxy-2-hydroxy-4-methoxybenzoic acid (XVII) and 1 ml of aniline. Recrystallization from benzene yielded 0.092 g of silky white needles, mp  $210.0$ – $210.5^\circ$ ,  $\lambda_{max}^{KBr}$  3.03 ( $NH$ ,  $OH$ ) and 6.08  $\mu$  ( $N=C=O$ ).

*Anal.* Calcd for  $C_{16}H_{16}ClNO_4$ : C, 59.73; H, 5.01; Cl, 11.02; N, 4.35. Found: C, 59.68; H, 5.30; Cl, 11.08; N, 4.53.

**7-Chloro-6,2'-dimethoxy-4-(p-methoxybenzyloxy)-6'-methylgris-2'-ene-3,4'-dione (I).**—A benzene solution of freshly prepared and vacuum dried (at  $25^\circ$ ) crude *p*-methoxybenzyl bromide (XI, prepared from 3.45 g (0.025 mole) of anisyl alcohol) was added slowly to a stirred mixture of 6.77 g (0.020 mole) of anhydrous 7-chloro-4-hydroxy-6,2'-dimethoxy-6'-methylgris-2'-ene-3,4'-dione (V), 25 g of anhydrous  $K_2CO_3$ , and 200 ml of anhydrous acetone. After the reaction mixture was refluxed for 16 hr, the solid separated by filtration was washed with two 40-ml portions of boiling acetone and the filtrate and washings were combined and concentrated to dryness. The resulting solid product (8.5 g, 92.5%) was recrystallized from dioxane-absolute ethanol; it melted at  $201.6$ – $202.2^\circ$  dec;  $[\alpha]_D^{20} +246.32^\circ$  ( $c$  1.224, dioxane);  $\lambda_{max}^{EtOH}$  231  $m\mu$  ( $\epsilon$  36,712), 292 (22,027), 335 (6425);  $\lambda_{max}^{CHCl_3}$  5.82 ( $C=O$ ), 6.0  $\mu$  ( $COC=O$ ).

*Anal.* Calcd for  $C_{24}H_{23}ClO_7$ : C, 62.82; H, 5.05; Cl, 7.73. Found: C, 62.69; H, 4.83; Cl, 8.02.

**7-Chloro-4-[3-(N,N-diethylcarbamoyl)benzyloxy]-6,2'-dimethoxy-6'-methylgris-2'-ene-3,4'-dione (II).**—It was prepared from V (3.39 g, 0.010 mole) and XII (3.0 g, 0.011 mole) by the procedure described for the synthesis of I. The crude product (4.7 g, 89.0%), recrystallized from benzene, gave white crystalline plates; mp  $191.0$ – $192.0^\circ$ ;  $[\alpha]_D^{20} +215.41^\circ$  ( $c$  1.012, acetone);  $\lambda_{max}^{EtOH}$  214  $m\mu$  ( $\epsilon$  35,641), 235 (29,569), 292 (21,912), 330 (5808);  $\lambda_{max}^{CHCl_3}$  5.85 ( $C=O$ ), 6.02  $\mu$  ( $COC=O$ ).

*Anal.* Calcd for  $C_{28}H_{35}ClNO_7$ : C, 63.69; H, 5.73; Cl, 6.72; N, 2.65. Found: C, 63.61; H, 5.81; Cl, 6.61; N, 2.51.

**7-Chloro-6,2'-dimethoxy-4-(3,7-dimethyl-6-octenyl-1-oxy)-6'-methylgris-2'-ene-3,4'-dione (III).**—It was prepared from V (6.8 g, 0.020 mole) and XIII (4.6 g, 0.021 mole) by the procedure described for the synthesis of I except that dimethylformamide was employed as the solvent and the reaction temperature was held at  $25^\circ$  for 1 hr and  $70^\circ$  for 4 hr. The crude product (7.8 g, 80.0%) crystallized from 80% methanol in the form of white crystalline plates; mp  $136.5$ – $137.5^\circ$ ;  $[\alpha]_D^{20} +252.33^\circ$  ( $c$  0.988, acetone);  $\lambda_{max}^{EtOH}$  218  $m\mu$  ( $\epsilon$  24,327), 235 (23,135), 291 (22,658), 327 (5963);  $\lambda_{max}^{CHCl_3}$  5.82 ( $C=O$ ), 6.02  $\mu$  ( $COC=O$ ).

*Anal.* Calcd for  $C_{36}H_{39}ClO_7$ : C, 65.47; H, 6.97; Cl, 7.43. Found: C, 65.42; H, 6.91; Cl, 7.60.

**7-Chloro-6-methoxy-4-(p-methoxybenzyloxy)coumaran-3-one (VI).**—It was prepared from X (2.15 g, 0.010 mole) and XI (2.61 g, 0.013 mole) by the procedure described for the synthesis of III. The solid product (3.1 g, 92.6%) was recrystallized from dioxane giving the analytical sample; mp  $182.6$ – $183.2^\circ$  dec;  $\lambda_{max}^{EtOH}$  232  $m\mu$  ( $\epsilon$  26,446), 285 (17,408), 322 (5021);  $\lambda_{max}^{p-dioxane}$  236  $m\mu$  ( $\epsilon$  23,768), 283 (18,914), 317 (5858);  $\lambda_{max}^{CHCl_3}$  5.87  $\mu$  ( $C=O$ ).

*Anal.* Calcd for  $C_{17}H_{17}ClO_5$ : C, 60.99; H, 4.52; Cl, 10.59. Found: C, 60.94; H, 4.76; Cl, 10.55.

**7-Chloro-4-[3-(N,N-diethylcarbamoyl)benzyloxy]-6-methoxycoumaran-3-one (VII).**—It was prepared from X (2.15 g, 0.010 mole) and XII (2.97 g, 0.011 mole) by the procedure described for the synthesis of III. The product (2.9 g, 71.8%) was recrystallized from ethyl acetate giving cream-colored microcrystalline needles; mp  $141.0$ – $143.0^\circ$  dec;  $\lambda_{max}^{EtOH}$  208  $m\mu$  ( $\epsilon$  37,157), 235 (26,252), 286 (19,790), 320 (6866);  $\lambda_{max}^{CHCl_3}$  5.87 ( $C=O$ ), 6.18  $\mu$  ( $N=C=O$ ).

*Anal.* Calcd for  $C_{21}H_{22}ClNO_5$ : C, 62.45; H, 5.49; Cl, 8.78; N, 3.47. Found: C, 62.69; H, 5.46; Cl, 9.00; N, 3.50.

**7-Chloro-6-methoxy-4-(3,7-dimethyl-6-octenyl-1-oxy)coumaran-3-one (VIII).**—It was prepared from X (2.15 g, 0.010 mole) and XIII (2.63 g, 0.012 mole) by the procedure described for the synthesis of III. The product (2.1 g, 59.5%) was recrystallized from methanol, yielding the analytical sample; mp  $75.2$ – $76.0^\circ$ ;  $\lambda_{max}^{EtOH}$  209  $m\mu$  ( $\epsilon$  20,643), 235 (18,349), 285 (18,173), 320 (4940);  $\lambda_{max}^{CHCl_3}$  5.85  $\mu$  ( $C=O$ ).

*Anal.* Calcd for  $C_{30}H_{33}ClO_5$ : C, 64.67; H, 7.14; Cl, 10.05. Found: C, 64.67; H, 7.05; Cl, 10.05.

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## The Synthesis of *p*-Guanidinobenzamides

VICTOR J. BAUER AND S. R. SAFIR

Organic Chemical Research Section, Lederle Laboratories,  
A Division of American Cyanamid Company,  
Pearl River, New York

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Phenethylbiguanide hydrochloride (**1**) is a clinically effective drug for the control of selected cases of diabetes.<sup>1</sup> We have sought to develop for hypoglycemic

(1) J. Pomeranze, H. Fujii, and G. T. Muratoff, *Proc. Soc. Exptl. Biol. Med.*, **95**, 193 (1957).