

TABLE II
 5-SUBSTITUTED 5-(2-NAPHTHYL)HYDANTOINS

| R | Mp, °C ^a | Yield, % | Calcd, % | | | Found, % ^b | | |
|---|---------------------|----------|----------|------|-------|-----------------------|------|-------|
| | | | C | H | N | C | H | N |
| CH ₃ | 247-248 | 83 | 69.99 | 5.04 | 11.66 | 70.31 | 4.97 | 11.53 |
| <i>n</i> -C ₃ H ₇ | 239-240 | 78 | 71.62 | 6.01 | 10.44 | 71.84 | 6.09 | 10.30 |
| <i>i</i> -C ₃ H ₇ | 261-263 | 72 | ... | ... | 10.44 | ... | ... | 10.29 |
| <i>n</i> -C ₄ H ₉ | 201-202 | 76 | 72.32 | 6.43 | 9.92 | 72.21 | 6.49 | 9.85 |
| <i>i</i> -C ₄ H ₉ | 217-218 | 69 | ... | ... | 9.92 | ... | ... | 10.04 |
| <i>sec</i> -C ₄ H ₉ | 256-257 | 57 | ... | ... | 9.92 | ... | ... | 10.01 |
| <i>t</i> -C ₄ H ₉ | 292-293 dec | 43 | 72.32 | 6.43 | 9.92 | 71.99 | 6.42 | 10.09 |
| <i>n</i> -C ₅ H ₁₁ | 188-189 | 72 | 72.95 | 6.80 | 9.45 | 72.96 | 6.66 | 9.39 |
| <i>i</i> -C ₅ H ₁₁ | 244-245 | 87 | ... | ... | 9.45 | ... | ... | 9.32 |
| <i>n</i> -C ₆ H ₁₃ | 177-178 | 85 | ... | ... | 9.03 | ... | ... | 9.01 |
| <i>n</i> -C ₇ H ₁₅ | 167-168 | 95 | ... | ... | 8.63 | ... | ... | 8.74 |
| <i>n</i> -C ₈ H ₁₇ | 169-170 | 64 | ... | ... | 8.27 | ... | ... | 8.24 |
| <i>n</i> -C ₁₀ H ₂₁ | 167-168 | 73 | ... | ... | 7.65 | ... | ... | 7.62 |
| <i>n</i> -C ₁₂ H ₂₅ | 169-170 | 70 | ... | ... | 7.10 | ... | ... | 7.09 |
| C ₆ H ₅ | 281-282 | 63 | ... | ... | 9.27 | ... | ... | 9.32 |
| 1-C ₁₀ H ₇ | 323-324 | 68 | 78.39 | 4.58 | 7.95 | 77.82 | 4.29 | 8.33 |
| 2-C ₁₀ H ₇ | 313-314 | 64 | 78.39 | 4.58 | 7.95 | 78.39 | 4.51 | 7.92 |

^a All melting points were determined by the capillary method and are corrected. ^b Carbon, hydrogen, and nitrogen microanalyses were performed by the Huffman Laboratories, Inc., Wheatridge, Colo.

Heterocycles. II.¹ Synthesis of 3-Carbomethoxy-3-methyl-7,8-benzothiochromanone

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During an attempted syntheses of 11-thia steroid homologs, the title compound was synthesized as an intermediate. The method of synthesis is analogous to the route used by Bachmann, *et al.*,² for the preparation of equilenin.

Experimental Section

Methyl 7,8-Benzothiochromanone-3-glyoxalate.—To a suspension of 3.2 g of sodium methoxide in 40 ml of benzene was added 7.1 g of dimethyl oxalate, and the mixture was refluxed for 10 min. To the ice-cooled solution was added a solution of 6.4 g of 7,8-benzothiochromanone³ in 70 ml of benzene over a 10-min period, and the mixture was stirred at room temperature for 4 hr. Within a few minutes a light red solution resulted, which soon deposited a light yellow precipitate. The mixture was hydrolyzed with 100 ml of water. The benzene solution which separated was extracted twice with 60 ml of 2% NaOH solution and the combined aqueous solution was acidified with dilute HCl. The light yellow crystals were filtered off and dried. Recrystallization from ethanol gave 7.3 g (81%) of glyoxalate as pale yellow clusters which melted at 107-109°. Further recrystallizations from alcohol gave a pure sample of mp 108.5-109.5°.

Anal. Calcd for C₁₆H₁₂O₄S: C, 64.00; H, 4.03. Found: C, 64.08; H, 4.10.

3-Carbomethoxy-7,8-benzothiochromanone.—A mixture of 7.0 g of the above-mentioned glyoxalate and 3.5 g of powdered soft glass was heated at 180-200° for 1 hr with occasional stirring. After cooling, the dark brown product was dissolved in a mixture of benzene and acetone (1:1), and the solution was decanted from the glass. The solution was evaporated, and the residue was digested with methanol, whereupon crystallization took place. Recrystallization from ethyl acetate gave 5.1 g of product, mp 114-116°, as yellow needles.

Anal. Calcd for C₁₅H₁₂O₃S: C, 66.17; H, 4.44. Found: C, 66.21; H, 4.52.

3-Carbomethoxy-3-methyl-7,8-benzothiochromanone.—A warm solution of 3.6 g of 3-carbomethoxy-7,8-benzothiochromanone in 30 ml of benzene was added to a solution of sodium methoxide prepared from 1.6 g of sodium and 30 ml of methanol. The mixture was refluxed for 2 hr, cooled, and treated with 4 ml of methyl iodide. After 1 hr at room temperature, an additional 4 ml of methyl iodide was added. The resulting mixture was stirred at room temperature for 30 min, then refluxed for 2 hr, cooled, neutralized with acetic acid, and evaporated nearly to dryness. The residue was treated with benzene and water, and the organic solution after separating was washed with 5% NaOH solution with water, dried, and evaporated. Recrystallization of the residue from ethanol gave 3.5 g (92%) of the product, mp 112-113°, as tan needles.

Anal. Calcd for C₁₆H₁₄O₃S: C, 67.12; H, 4.93. Found: C, 67.30; H, 5.14.

Synthesis of Some 3-Arylacetyl- and 1,3-Di(arylacetyl)indoles¹

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The recent demonstration of anticonvulsant activity³ of certain 3-acylindoles has prompted us to report eighteen new 3-arylacetylindoles, of which compounds Ia-n (Table I) were all prepared by acylation of the corresponding indolylmagnesium bromides with the appropriate arylacetyl chloride, a method first described by Oddo⁴ and briefly elaborated by others.⁵ The 1,3-diacetyl derivatives (II) were also produced as coproducts, and could be obtained pure in several cases (Table II). The 3-arylacetyl-2-methylindoles (Io-r, Table I) were prepared by reac-

(1) This investigation was supported by research Grant C-4425 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) Abstracted in part from the Ph.D. Dissertation of M. F. M., Lehigh University, 1963.

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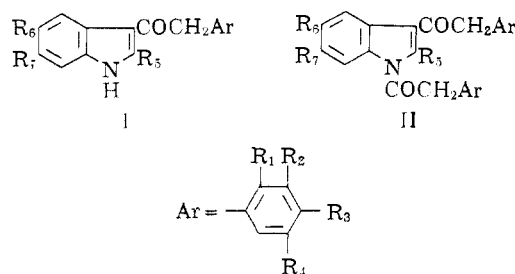
(2) W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, **61**, 974 (1939); **62**, 824 (1940); see also ref. 1.

(3) F. Krollpfeiffer and H. Schultze, *Ber.*, **56**, 1821 (1923).

TABLE I
 3-ARYLAZETYLINDOLES (I)

| Compd | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | R ₆ | R ₇ | Mp, °C ^a | Yield, % | Method | Infrared, μ | | Calcd, % | | | Found, % | | | |
|-------|----------------|----------------------|----------------|----------------|----------------------|----------------|----------------|---------------------|----------|--------|-----------------|------|----------|-------|------|----------|-------|------|------|
| | | | | | | | | | | | N-H | C=O | C | H | N | C | H | N | |
| a | Me | MeO | MeO | H | H | H | H | 246-248 | 48 | A | 3.10 | 6.08 | 73.76 | 6.19 | 4.53 | 73.83 | 6.48 | 4.42 | |
| b | MeO | MeO | H | H | H | H | H | 196-197 | 33 | C | 3.13 | 6.16 | 73.20 | 5.80 | 4.74 | 73.26 | 6.07 | 4.61 | |
| c | H | MeO | H | H | H | H | H | 160-162 | 9 | B | 3.14 | 6.15 | 76.96 | 5.70 | 5.28 | 77.05 | 5.87 | 5.35 | |
| d | Cl | MeO | MeO | H | H | H | H | 237-239 | 30 | C | 3.01 | 6.06 | 65.55 | 4.89 | 4.25 | 65.52 | 5.04 | 4.24 | |
| e | H | MeO | MeO | Cl | H | H | H | 216-217.5 | 24 | C | 3.20 | 6.17 | 65.55 | 4.89 | 4.25 | 65.87 | 4.96 | 4.30 | |
| f | Cl | H | MeO | MeO | H | H | H | 226-227 | 41 | C | 3.14 | 6.12 | 65.55 | 4.89 | 4.25 | 65.44 | 5.04 | 4.25 | |
| g | Br | H | MeO | MeO | H | H | H | 218-219.5 | 31 | C | 3.12 | 6.10 | 57.77 | 4.31 | 3.74 | 58.05 | 4.32 | 3.80 | |
| h | H | Me | Me | H | H | H | H | 214-216 | 15 | B | 3.12 | 6.08 | 82.09 | 6.50 | 5.32 | 82.26 | 6.64 | 5.22 | |
| i | H | Cl | Cl | H | H | H | H | 218-220 | 37 | B | 3.13 | 6.09 | 63.17 | 3.64 | 4.60 | 63.43 | 3.83 | 4.69 | |
| j | H | MeO | H | H | Br | H | H | 193-194 | 5 | C | 3.12 | 6.09 | 59.49 | 3.82 | 4.08 | 59.63 | 3.97 | 4.01 | |
| k | H | MeO | MeO | Cl | Br | H | H | 240-242 | 25 | B | 3.17 | 6.16 | 52.89 | 3.69 | 3.42 | 52.72 | 3.68 | 3.44 | |
| l | Br | H | MeO | MeO | Br | H | H | 258-260 | Trace | C | Broad | 6.08 | 3.34 | 47.71 | 3.34 | 3.09 | 47.72 | 3.42 | 3.21 |
| m | H | Me | Me | H | Br | H | H | 253 dec | 9 | B | 3.13 | 6.08 | 63.71 | 4.71 | 4.09 | 63.12 | 4.91 | 4.07 | |
| n | H | O-CH ₂ -O | H | H | O-CH ₂ -O | H | H | 256 dec | 10 | C | 3.13 | 6.12 | 66.87 | 4.05 | 4.35 | 66.90 | 4.20 | 4.38 | |
| o | H | O-CH ₂ -O | Me | H | H | H | H | 202-204 | 48 | D | 3.13 | 6.18 | 73.70 | 5.15 | 4.78 | 73.77 | 5.28 | 4.75 | |
| p | H | Me | Me | H | H | H | H | 168-169 | 42 | D | 3.06 | 6.17 | 82.27 | 6.90 | 5.05 | 82.08 | 6.37 | 5.01 | |
| q | H | Cl | Cl | H | Me | H | H | 168-169 | 70 | D | 3.06 | 6.16 | 64.16 | 4.11 | 4.40 | 64.26 | 4.20 | 4.55 | |
| r | Cl | H | Cl | H | Me | H | H | 209-211 | 42 | D | 3.08 | 6.15 | 64.16 | 4.11 | 4.40 | 64.21 | 4.03 | 4.46 | |

^a Analytical samples were purified from 95% ethanol except as follows: k was recrystallized from *n*-propyl alcohol, m was sublimed at 220° (0.1 mm), and o was sublimed at 200° (0.5 mm).
^b Over-all yield based on indole.



tion of known arylacetonitriles with 2-methylindole following Seka's original directions.⁶

Experimental Section⁷

2-Phenyl-4-(5-chloro-3,4-dimethoxybenzal)-5-oxazolone.—This precursor, obtained in 94% yield from 5-chloro-3,4-dimethoxybenzaldehyde⁹ by a standard procedure,^{10a} crystallized from 95% ethanol as yellow needles, mp 159-160°.

Anal. Calcd for C₁₈H₁₄ClNO₄: N, 4.07. Found: N, 4.11.

2-Phenyl-4-(2-chloro-3,4-dimethoxybenzal)-5-oxazolone.—2-Chloro-3,4-dimethoxybenzaldehyde¹¹ was analogously converted (99% yield) to this azlactone, which crystallized from 95% ethanol as bright yellow needles, mp 163-164°.

Anal. Calcd for C₁₈H₁₄ClNO₄: N, 4.07. Found: N, 3.89.

Preparation of Arylacetic Acids.—The foregoing azlactones and one additional isomer already reported¹² were all converted via a standard procedure^{10b} to the corresponding chlorodimethoxyphenylacetic acids, the properties of which are summarized in Table III along with the intermediate methyl esters. 2-Methyl-3,4-dimethoxyphenylacetic acid, also tabulated, was prepared from 3-methyl-4-chloromethylveratrole¹¹ via the nitrile route.¹³

Arylacetyl chlorides were all prepared by the familiar SOCl₂ method, and, with the exception of 2-chloro-4,5-dimethoxyphenylacetyl chloride (Table III), were all liquids purified by distillation. Because of the usual difficulties attending ultimate purification and analysis of these common derivatives, they were redistilled and used directly in the reactions with various indolylmagnesium halides. The identity of these acid chlorides was in each case confirmed by acceptable analysis of a subsequent transformation product (*viz.*, the indolyl ketones, Tables I and II). The aryl group, percentage yields, and boiling points, respectively, were as follows: 5-chloro-3,4-dimethoxyphenyl-, 63, 138-140° (2 mm); 2-chloro-3,4-dimethoxyphenyl-, 85, 145-149° (2 mm); 2-methyl-3,4-dimethoxyphenyl-, 82, 114-118° (1 mm); 3,4-dimethylphenyl-, 93, 102-104° (5 mm);^{14d} 3,4-dichlorophenyl-, 88, 158-161° (20 mm);^{14c} 2,3-dimethoxyphenyl-, 87, 113-115° (2 mm);^{14b} 2-bromo-4,5-dimethoxyphenyl-, 60, 158-

(6) R. Seka, *Ber.*, **56**, 2058 (1923); *cf. also* J. A. Ballantine, C. B. Barrett, R. J. S. Beer, B. G. Boggiano, S. Eardley, B. E. Jennings, and A. Robertson, *J. Chem. Soc.*, 2227 (1957); M. Kunori, *Nippon Kagaku Zasshi*, **83**, 841 (1962).

(7) Melting points were determined on a Mel-Temp apparatus and are corrected. Infrared spectra were determined in KBr on a Perkin-Elmer Model 21 spectrophotometer. Indole, 2-methylindole, and 5-bromoindole were obtained from the Aldrich Chemical Co., 5,6-Methylenedioxyindole was prepared by adaptation of Hoeber's catalytic reduction method for 5,6-dimethoxyindole.⁸ Microanalyses were performed by Dr. V. B. Fish of Lehigh University.

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(10) (a) J. S. Buck and W. S. Ide, "Organic Syntheses," Coll. Vol. 11, John Wiley and Sons, Inc., New York, N. Y., 1943, p 55; (b) H. R. Snyder, J. S. Buck, and W. S. Ide, *ibid.*, p 333.

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(12) 2-Phenyl-4-(2-chloro-4,5-dimethoxybenzal)-5-oxazolone; T. Kame-tani, O. Umezawa, Y. Sato, K. Ogasawara, S. Shibuya, M. Ishiguro, and D. Mizuno, *Vakugaku Zasshi*, **83**, 838 (1963); *Chem. Abstr.*, **60**, 447a (1964).

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(14) These acid chlorides were prepared from known arylacetic acids: (a) E. L. May and E. Mosettig, *J. Org. Chem.*, **11**, 632 (1946); (b) E. Späth and E. Mosettig, *Ann.*, **433**, 138 (1923); (c) R. Pschorr, *ibid.*, **391**, 35 (1912); (d) British Patent 869,504 (May 31, 1961); *Chem. Abstr.*, **55**, 24790f (1961); (e) J. S. Buck and W. H. Perkin, *J. Chem. Soc.*, 1675 (1924); (f) J. A. King and F. H. McMillan, *J. Am. Chem. Soc.*, **73**, 4911 (1951).

TABLE II
 1,3-DI(ARYLACETYL)INDOLES (II)

| Compd ^a | R ₁ , R ₆ , and R ₇ | | | | | Mp, °C | Yield, % ^b (pure) | Infrared, μ (C=O) | Formula | Calcd, % | | | Found, % | | |
|--------------------|--|----------------|----------------|----------------|----|-----------|------------------------------------|----------------------|---|----------|------|------|----------|------|------|
| | R ₂ | R ₃ | R ₄ | R ₅ | C | | | | | H | N | C | H | N | |
| c | H | MeO | H | H | H | 135.5-136 | 20 | 5.72, 5.92 | C ₂₆ H ₂₃ NO ₄ | 75.53 | 5.60 | 3.39 | 75.72 | 5.99 | 3.71 |
| h | H | Me | Me | H | H | 136-137 | 32 | 5.80, 5.95 | C ₂₈ H ₂₇ NO ₂ | 82.11 | 6.64 | 3.42 | 82.20 | 6.83 | 3.46 |
| i | H | Cl | Cl | H | H | 200-202 | 75 | 5.76, 5.95 | C ₂₄ H ₁₅ Cl ₂ NO ₂ | 58.68 | 3.08 | 2.85 | 58.73 | 3.13 | 2.85 |
| k | H | MeO | MeO | Cl | Br | 219-220.5 | 52 ^c | 5.51, 5.90 | C ₂₈ H ₂₄ BrCl ₂ NO ₆ | 54.13 | 3.89 | 2.25 | 54.17 | 4.06 | 2.27 |
| m | H | Me | Me | H | Br | 143-144 | 19 | 5.77, 5.96 | C ₂₈ H ₂₆ BrNO ₂ | 68.85 | 5.36 | 2.86 | 68.77 | 5.28 | 2.87 |

^a Letter designations and substituent distribution are consistent in Table I and II. ^b Yield based on arylacetyl chloride. ^c Recrystallized from aqueous acetone, the others from 95% ethanol.

 TABLE III
 SOME PHENYLACETIC ACID DERIVATIVES
 ArCH₂COX

| Ar | X | Bp (mm) or mp °C ^a | % yield | Formula | Calcd, % | | Found, % | |
|------------------------------|-----|----------------------------------|-----------------|--|----------|------|----------|------|
| | | | | | C | H | C | H |
| 5-Chloro-3,4-dimethoxyphenyl | OH | 94-95 | 56 ^b | C ₁₀ H ₁₁ ClO ₄ | 52.07 | 4.81 | 52.28 | 4.97 |
| 5-Chloro-3,4-dimethoxyphenyl | OMe | 114-115.5 (0.05) | 61 ^b | C ₁₁ H ₁₃ ClO ₄ | 54.00 | 5.36 | 54.28 | 5.46 |
| 2-Chloro-3,4-dimethoxyphenyl | OH | 138-140 | 44 ^b | C ₁₁ H ₁₁ ClO ₄ | 52.07 | 4.81 | 52.22 | 4.90 |
| 2-Chloro-3,4-dimethoxyphenyl | OMe | 125-125.5 (0.12) | 47 ^b | C ₁₁ H ₁₃ ClO ₄ | 54.00 | 5.36 | 54.21 | 5.39 |
| 2-Chloro-4,5-dimethoxyphenyl | OH | 121-123 | 63 ^b | C ₁₀ H ₁₁ ClO ₄ | 52.07 | 4.81 | 52.18 | 4.98 |
| 2-Chloro-4,5-dimethoxyphenyl | OMe | 111-111.5 (0.05) | 69 ^b | C ₁₁ H ₁₃ ClO ₄ | 54.00 | 5.36 | 54.28 | 5.85 |
| 2-Chloro-4,5-dimethoxyphenyl | Cl | 73.5-75 | 84 | C ₁₂ H ₁₀ Cl ₂ O ₃ | 48.22 | 4.05 | 48.50 | 3.83 |
| 2-Methyl-3,4-dimethoxyphenyl | OH | 109-110 | 66 | C ₁₁ H ₁₄ O ₄ | 62.84 | 6.71 | 62.80 | 6.83 |

^a All acids were crystallized from benzene-petroleum ether (bp 60-70°), and the acid chloride from petroleum ether. ^b Yields based on azlactone.

162° (3 mm);^{14c} 3,4-methylenedioxyphenyl-, 79, 101-102° (1 mm);^{14c} 3-methoxyphenyl-, 70, 104-109° (2 mm).^{14f}

Acylation of Indoles via the Oddo Reaction. General Procedure.—A solution of 0.05 mole of indole (or 5,6-methylenedioxyindole or 5-bromoindole) in 25 ml of anhydrous benzene was added dropwise during 10 min to a vigorously stirred solution of 0.05 mole of phenylmagnesium bromide, prepared in the usual way, in 50 ml of anhydrous ether. The resulting mixture was refluxed for 2 hr, then cooled to -10° in a Dry Ice-methanol bath. A solution of 0.05 mole of the arylacetyl chloride in 20 ml of benzene was then added dropwise during 45 min while the temperature was maintained at -8 to -10°. The cooling bath was then removed, the mixture was stirred for another 30 min, and finally hydrolyzed by addition of 25 ml of 10% aqueous NH₄Cl. The resulting solid product was collected by filtration, washed several times with ether, and air dried. Further treatment of the crude product followed one of the three following procedures. Properties of the final pure products are summarized in Table I (3-arylacetylindoles) and Table II (1,3-di(arylacetyl)indoles).

Method A. Direct Formation of a 3-Arylacetylindole.—This situation occurred only in the case of 3-(2-methyl-3,4-dimethoxyphenylacetyl)indole (Ia), which was directly purified by recrystallization from 95% ethanol.

Method B. Predominant Formation of 1,3-Di(arylacetyl)indoles.—The crude products were purified by recrystallization from 95% ethanol (except where otherwise noted) and had the properties collected in Table II. These pure diacyl compounds (II) were hydrolyzed as illustrated by the following explicit example.

3-(3,4-Dichlorophenylacetyl)indole (Ii).—One gram (0.0021 mole) of (Ii) was refluxed for 5 min with a solution of 5 ml of 10% NaOH in 15 ml of 95% ethanol. The resulting solution was diluted with 20 ml of water and cooled. The precipitate was collected by filtration, washed with water, air dried, then recrystallized from 95% ethanol to yield 0.60 g (98%) of pure (Ii) (cf. Table I).

Method C. Formation of Gross Mixtures of Mono- and Diacylindoles.—In these cases the crude products, although distinctly crystalline, did not yield either pure 3-arylacetyl- or 1,3-di(arylacetyl)indoles even after repeated recrystallization. Such mixtures were therefore directly hydrolyzed with aqueous alcoholic NaOH, as described under method B, to yield the pure 3-arylacetylindoles.

Method D. Saka's Reaction.—The reactions of 2-methylindole with 3,4-methylenedioxyphenyl-,¹⁵ 3,4-dimethylphenyl-,¹⁶

3,4-dichlorophenyl-,¹⁶ and 2,4-dichlorophenylacetonitriles¹⁷ in anhydrous ethereal HCl solution were all accomplished by essentially the same procedures previously reported.⁶

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Derivatives of 4-Phenyl-Δ^{β,γ}-butenoides¹

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In our efforts to prepare physiologically active compounds we have prepared a series of α-arylidene-γ-substituted Δ^{β,γ}-butenoides²⁻⁶ (see Table I on following page).

These compounds were tested for antitumor, antischistosome, antiviral, and antibacterial activities. The lactones were inactive in these tests except that compounds 1, 9, and 12, which contain the nitrogen mustard group, showed slight antileukemia activity.⁷

Experimental Section

The α-arylidene-γ-phenyl-Δ^{β,γ}-butenoides were prepared by heating 0.05 mole of the appropriate β-arylpropionic acid, 0.055 mole of aldehyde, 8.2 g of sodium acetate, and 16 ml of acetic anhydride on a hot plate until homogeneous. The heating was continued on a steam bath until crystals separated. The reaction mass was allowed to cool, filtered, washed with water and sodium bicarbonate, and recrystallized from ethanol.

(1) Supported by a grant (Cy-03908) from the National Institutes of Health and a Faculty grant from North Texas State University.

(2) W. Borsche, *Ber.*, **47**, 1107, 2718 (1914).

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(6) C. Hana and F. W. Schueler, *J. Am. Chem. Soc.*, **75**, 741 (1953).

(7) The antileukemia tests were arranged through CCNSC and were carried out at the Department of Medicine, University of Miami, Miami, Fla.

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