A Substituent Sensitive Acylation and Intramolecular Alkylation. The Synthesis of the Ring B Analog of Dehydrogriseofulvin[1a]

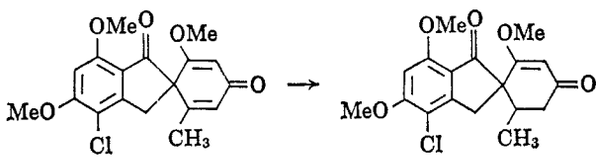
HOWARD NEWMAN AND ANTHONY DURANTE[1b]

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

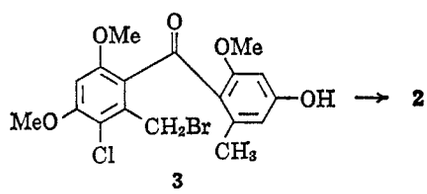
Received March 24, 1966

The straightforward behavior of 3,5-dimethoxytoluene, its α-acetoxy derivative, and 2-chloro-3,5-dimethoxybenzyl bromide toward acylation with isoeverninic acid acetate (**5**) is contrasted with the behavior of 3,5-dimethoxybenzyl bromide and chloride toward the same reagent. The intramolecular alkylation of the phenol **3**, derived from **5** and 2-chloro-3,5-dimethoxybenzyl bromide, is described, as is the attempt to effect this same type of reaction with **9** derived from **5** and 3,5-dimethoxybenzyl chloride.

We have recently described a synthesis of the griseofulvin carbon analog **1**.[1c] An alternate approach to the synthesis of this compound which we have also investigated involved the preparation of the dehydro derivative **2** which, it was anticipated, would be convertible to **1** *via* hydrogenation, by analogy with the facile conversion of dehydrogriseofulvin to griseofulvin.[2] We considered as an attractive route to **2**, the intramolecular alkylation of the benzophenone **3**. This latter transformation would represent an extension

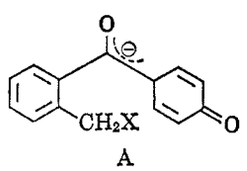


2 **1**



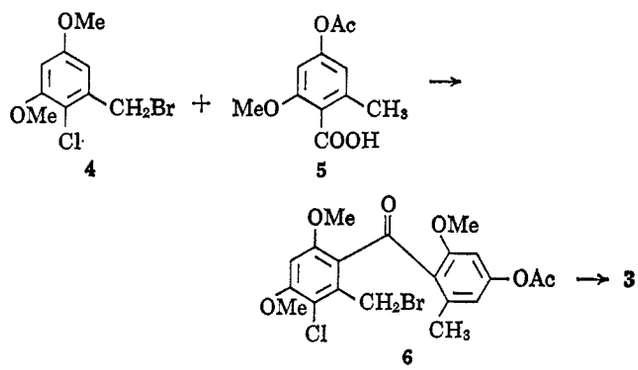
3

of the so called Ar_1-5 assisted reaction, first demonstrated by Winstein and Baird,[3] to systems in which the *para* substituent on the phenol ring involved in the intramolecular cyclization was a group other than alkyl. In addition, the ambident nature of the intermediate anion A undergoing alkylation would provide information on the interesting problem of intramolecular C *vs.* O alkylation, a point which, to the best of our knowledge, has not previously received attention.[4]

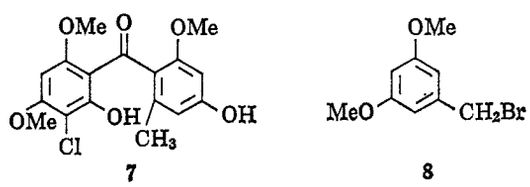


A

We considered as a likely route to **3** the acylation of 3,5-dimethoxy-2-chlorobenzyl bromide (**4**) with isoeverninic acid acetate (**5**)[5] followed by hydrolysis of the resultant benzophenone acetate **6** [*cf.* the preparation of 2,4′-dihydroxy-4,6,2′-trimethoxy-6′-methyl-3-chlorobenzophenone (**7**)].[2] In order to develop conditions suitable for affecting this transformation we first investigated the acylation of the simpler, more readily



4 **5** **6**



7 **8**

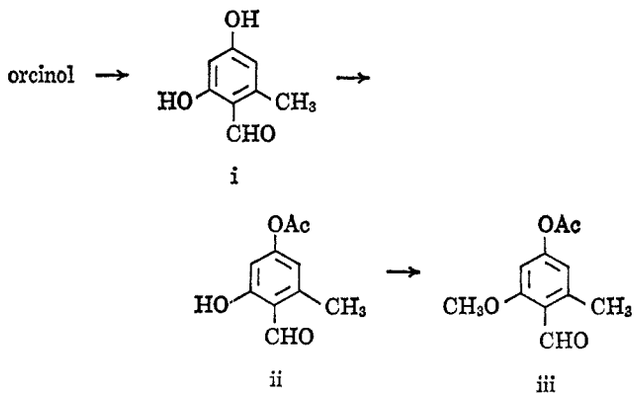
(1) (a) Griseofulvin Analogs IV; Griseofulvin Analogs III, ref 1c; (b) Summer Employee, Career Training Program, 1965; (c) H. Newman and R. B. Angier, *J. Org. Chem.*, **31**, 1462 (1966).

(2) D. Taub, C. H. Kuo, H. L. Slates, and N. L. Wendler, *Tetrahedron*, **19**, 1 (1963).

(3) S. Winstein and R. Baird [*J. Am. Chem. Soc.*, **79**, 756 (1957)] reported the conversion of 4-*p*-hydroxyphenyl-1-butyl *p*-bromobenzenesulfonate to spiro[4.5]deca-1,4-dien-3-one. Related transformations were subsequently reported by A. S. Dreiding [*Helv. Chim. Acta*, **40**, 1812 (1957)] and S. Masamune [*J. Am. Chem. Soc.*, **83**, 1009 (1961)].

(4) The behavior of ambident nucleophiles in intermolecular reactions has been extensively investigated and has been recently reviewed by R. Gompper [*Angew. Chem.*, **76**, 412 (1964); *Angew. Chem. Intern. Ed. Engl.*, **3**, 560 (1964)].

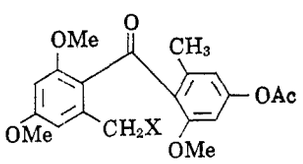
(5) Isoeverninic acid acetate (**5**) was obtained by permanganate oxidation of the corresponding aldehyde iii[6] according to the procedure of Taub, *et al.*[2] The latter compound was obtained much more conveniently than previously described[6a] according to the following route (see Experimental Section). This route to iii is a modification of that described by Canter, *et al.*,[6b] in which i is acetylated rather than carbomethoxylated, thus obviating the necessity to hydrolyze and acetylate after methylation.



i ii iii

(6) (a) A. S. Pfau, *Helv. Chim. Acta*, **11**, 876 (1928); K. Hoesch, *Ber.*, **46**, 886 (1913); (b) F. W. Canter, A. Robertson, and R. B. Waters, *J. Chem. Soc.*, 493 (1933).

available 3,5-dimethoxybenzyl bromide (**8**). The attempted acylation of **8** with isoeverninic acid acetate (**5**) in trifluoroacetic anhydride at room temperature[7] did not proceed cleanly. The reaction mixture began darkening soon after the reagents were mixed and was practically black at the end of 13 min. Work-up of the reaction gave an intractable black gum whose infrared spectrum showed absorption in the carbonyl region at 5.7 and 6.1 μ as might be expected for the benzophenone acetate **9** (X = Br). That the likely source of the difficulty was the relatively good leaving potential of the bromine substituent on the benzylic carbon was indicated by the fact that both 3,5-dimethoxytoluene and 3,5-dimethoxybenzyl acetate were cleanly and rapidly acylated to give the benzophenone acetate **9** (X = H) and **9** (X = OAc), respectively,



9

whereas 3,5-dimethoxybenzyl chloride behaved in a manner similar to that of the bromide. The reaction mixture involving the latter substrate darkened at a somewhat slower rate and it was possible to isolate the desired benzophenone **9** (X = Cl) in poor yield, by working on a very small scale (*ca.* 150 mg) and using very short (5 min) reaction times. The product decomposed on heating (capillary tube) at *ca.* 100° and yielded an intractable tar on warming in methanol whereas the corresponding acetate **9** (X = OAc) could be readily recrystallized from this solvent.

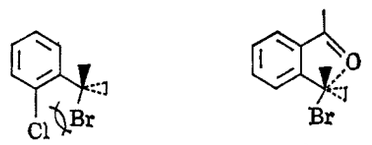
On the basis of the foregoing, it would appear reasonable to conclude that when the substituent X in **9** is a fairly good leaving group it is relatively unstable even under the conditions of its formation.

A completely different result was obtained when the acylation of 3,5-dimethoxy-2-chlorobenzyl bromide (**4**) was attempted! The reaction of **4** with isoeverninic acid acetate (**5**) in trifluoroacetic anhydride proceeded smoothly and cleanly at 75° (*ca.* 23 hr) to give the desired benzophenone acetate **6** in 59% yield as a readily isolable, stable crystalline solid.

This dramatic difference in behavior between 3,5-dimethoxybenzyl bromide (**8**) and its 2-chloro analog **4** would appear to be most reasonably explained on the basis of steric hindrance to free rotation of the bromomethyl substituent in **4** owing to the proximity of the relatively bulky (compared to hydrogen) chloro substituent. The conformation that would be particularly affected would be that one in which the carbon–bromine bond is parallel to the plane of the aromatic ring (see structure a), since this would result in a very serious bromine–chlorine buttressing. In the benzophenone **6** formed from **4** this conformation is precisely the one required for backside displacement of bromine by the carbonyl oxygen (see structure b), a reaction which is thus rendered highly unfavorable.

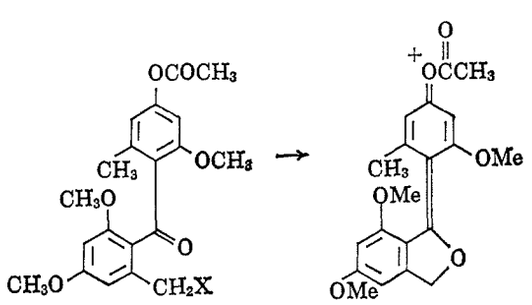
(7) Acylations in this medium were first reported by E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder [*J. Chem. Soc.*, 718 (1951)] and subsequently used by Taub, *et al.*,[8] in their elegant work on the synthesis of griseofulvin and its analogs.

(8) D. Taub, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, **28**, 2752, 3344 (1963), and preceding papers.



a b

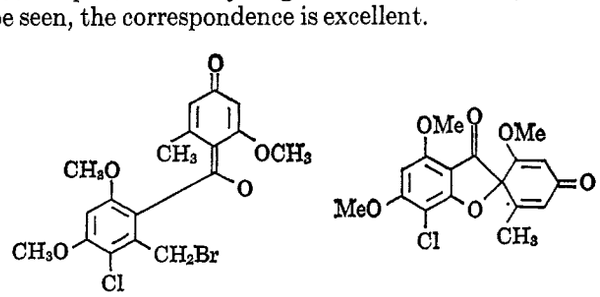
In the case of the benzophenone **9** (X = Br) derived from the dechloro analog **8** this particular conformation is not nearly so unfavorable sterically, and, to the extent that it contributes to the conformational equilibrium, provides the ideal geometrical arrangement for backside displacement of bromine by oxygen. The quinoidal intermediate **10** (one resonance form shown) can thus readily form, thereby providing a pathway for the further transformation of the initially formed **9** (X = Br) under the reaction conditions. (Even if a full carbon–oxygen bond does not form, the availability of an anchimerically assisted pathway for the ionization of bromine in **9** but not in **6** would also account for the difference in behavior observed. In this situation it is the benzylcarbonium ion formed from **9** which is further transformed.)[9]



9 **10**

The phenol **3** was obtained from **6** in 95% yield by brief treatment of the latter with 2 equiv of base at room temperature.

An examination of Stuart–Breigleb models (a model of **3** and B were used to approximate anion A) indicated that although the geometry required for backside displacement of bromine by oxygen was sterically prohibited, that required for backside displacement by carbon (C_4 of the phenol ring) could be realized. In fact when a 0.003 *M* solution of **3** was heated under reflux for 22 hr with 1 equiv of potassium *t*-butoxide in dry *t*-butyl alcohol the anticipated intramolecular C-alkylation did take place to give the spirodienone **2** in *ca.* 30% yield. In Table I the chemical shift values of the various protons in **2** are compared with their counterparts in dehydrogriseofulvin **11** and, as can be seen, the correspondence is excellent.



B **11**

(9) A related *ortho*-substituent effect on the rate of lactonization of 2-(hydroxymethyl)benzoic acids has been observed by Tirouflet[10a] and Bunnett.[10b]

(10) (a) J. Tirouflet, *Bull. Soc. Chim. France*, 769 (1954); (b) J. F. Bunnett and C. F. Hauser, *J. Am. Chem. Soc.*, **87**, 2214 (1965).

TABLE I[a]

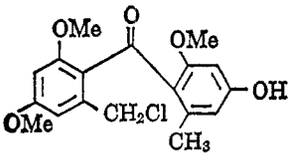
COMPARISON OF THE CHEMICAL SHIFT VALUES OF PROTONS IN 2 AND 11

	Chemical shift, ppm					
	Aromatic[b] proton	Vinyl protons	Aromatic methoxyls	Vinyl methoxyl	Vinyl methyl	Ring-B CH_2[c]
Spirodienone 2	6.52	6.17,[d] 5.70[e]	4.07, 4.00	3.62	1.75, 1.73	3.40, 3.32
Dehydrogriseofulvin[f] 11	6.15	6.15, 5.59	4.04, 3.98	3.63	1.80, 1.77	...

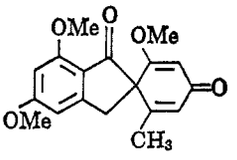
[a] Chemical shift values are in parts per million from tetramethylsilane (internal standard); solvent, $CDCl_3$. [b] The chemical shift values of the aromatic protons in the two compounds would be expected to differ most as a result of the ring substituent change from oxygen to methylene: P. L. Corio and B. P. Dailey, *J. Am. Chem. Soc.*, **78**, 3043 (1956). [c] The CH_2 protons of **2** would be expected to show a four-line spin pattern characteristic of an AB system. Two peaks at the positions indicated were clearly visible; the other two are presumably too weak to distinguish from the background noise. [d] Triplet (J = <1 cps). [e] Doublet (J = <1 cps). [f] B. H. Arison, N. L. Wendler, D. Taub, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, and N. R. Trenner, *J. Am. Chem. Soc.*, **85**, 627 (1963).

Another major product isolated from the reaction was a very high-melting (324–326° dec) colorless solid, insoluble in organic solvents (including dimethyl sulfoxide). These properties together with its infrared spectrum and elemental analysis (see Experimental Section) suggested a dimeric (polymeric, or both) structure for the material, presumably the result of an intermolecular condensation reaction of **3**. The yield of this material increased at the expense of the spirodienone **2** when the reaction was conducted at higher (0.03 *M*) concentration. [At 0.03 *M* concentration Winstein and Baird reported[3] the conversion to spirodienone to take place "in >50% yield." The considerably lower yield (*ca.* 20%) of **2** obtained at that concentration is consistent with a higher energy transition state for intramolecular condensation in our case which would allow the intermolecular reaction course to compete more effectively. The yield is improved (32%) under more dilute conditions since higher dilution decreases the rate of the intermolecular reaction only.]

While enough of the benzophenone acetate **9** (X = Cl) could not be accumulated, because of the difficulties attending its preparation, to make a complete study of its conversion to the phenol **12** and the behavior of the latter on attempted intramolecular alkylation to **13**, the following observations appear relevant.



12

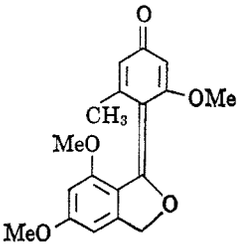


13

An attempt was made to achieve the transformation of **9** (X = Cl) to **13** in a single operation by deacylation, with 1 equiv of methoxide in 1,2-dimethoxyethane at room temperature (*cf.* conversion of **6** to **3** in 5 min at room temperature with 1 equiv of base) followed by heating for a short while or keeping at room temperature for some hours. The experiment in which heat was applied gave only a very dark intractable gum, while the room temperature reaction gave a very dark crude reaction product from which a dark green amorphous solid could be obtained on trituration with ether. The infrared spectrum of the initially isolated crude product obtained from either of the two reactions showed *no* absorption at *ca.* 5.8 μ as would be expected for **13** (*cf.* infrared spectrum of **2**).[11a]

(11) (a) The possibility that **9** (X = Cl) underwent chloride ion displacement by methoxide faster than it was deacetylated would appear to be ruled out by the lack of *any* absorption in the acetoxyl region in the infrared. Since only 1 molar equiv of methoxide was used, one would have expected the acetoxy substituent to remain intact if the methoxide ion was preferentially consumed in a displacement reaction. (b) For related destabilizing factors in quinonemethide systems, see R. D. Kimbrough, Jr., *et al.*, *J. Org. Chem.*, **30**, 4333 (1965).

Again the contrast in behavior of the chloro and dechloro compounds **3** and **12** is spectacular. Whereas **3** reacted cleanly in base to give the spirodienone **2** (along with some intermolecular condensation product), **12** presumably formed *in situ* from **9** (X = Cl) gave an uncharacterizable mixture. Here too, the difference in behavior is most reasonably attributed to the ability of **12** but not **3** to undergo intramolecular O-alkylation. The resulting quinoidal product **14** is apparently unstable under the reaction conditions, possibly because of the adverse steric interaction resulting from the



14

proximity of the methyl (or methoxyl) substituent on the quinonemethide moiety to the aromatic methoxyl substituent.[11b]

On the basis of the foregoing results it would appear reasonable to conclude that where both intramolecular C and O alkylation are possible the latter reaction course is strongly favored. Intramolecular O-alkylation can, however, be suppressed by imposing suitable conformational restrictions, thus permitting the alternative C-alkylation to take place.

The relatively poor yield in which the spirodienone **2** was obtained and the development of another route to the desired griseofulvin C-analog **1**[1b] combined to discourage efforts to effect the further conversion of **2** to **1**.

Experimental Section[12]

Isoeverninic Acid Acetate (**5**).—The acid **5** was obtained by permanganate oxidation of O-acetylisoeverninaldehyde (iii) according to the procedure of Taub, *et al.*[2] The latter compound

(12) Melting points were taken in a Hershberg apparatus using a 3-in. immersion thermometer. Infrared spectra were determined either neat (liquids or oils) or in KBr disks (solids) on a Perkin-Elmer infracord spectrophotometer. Nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Ultraviolet spectra were measured in methyl alcohol on a Cary 11MS spectrophotometer. Magnesium sulfate was used for drying. The petroleum ether used boiled at 30–60°.

was obtained either as reported[6] or preferably in the following manner (see equations in ref 5). 2,4-Dihydroxy-6-methylbenzaldehyde[13] was monoacetylated to give 2-hydroxy-4-acetoxy-6-methylbenzaldehyde as follows. To a stirred, cooled solution of 5.6 g (0.037 mole) of aldehyde in 150 ml of anhydrous ether–methylene chloride (commercial grade) (1:1, v/v) was added 2.63 ml (0.037 mole) of acetyl chloride followed by 5.15 ml (0.037 mole) of triethylamine. A solid separated immediately. Stirring was continued at room temperature for 24 hr (a 2-hr reaction time gave comparable results). Cold water was added; the organic phase was separated, washed, dried, and evaporated to yield a somewhat pasty orange solid which was purified by heating in boiling petroleum ether–ether. A nearly colorless, crystalline solid (3.5 g) was collected; it had mp 93–95.5°. Further concentration of the mothr liquor gave an additional 1.5 g of pale yellow crystals, mp 88–95.5°, total yield 5 g (70%). The analytical sample, mp 96.5–98.5°, was obtained by recrystallizing twice from aqueous acetone.

Anal. Calcd for $C_{10}H_{10}O_4$ (194.18): C, 61.85; H, 5.19. Found: C, 61.85; H, 5.27.

2-Hydroxy-4-acetoxy-6-methylbenzaldehyde was converted to the 2-methoxy derivative according to the general procedure of Canter, *et al.*[6b] A solution of 2 g (0.01 mole) of 2-hydroxy-4-acetoxy-6-methylbenzaldehyde, mp 96.5–97.5°, in 45 ml of acetone and 2.8 g (0.012 mole) of silver oxide (Merck) was heated under vigorous reflux with 5.5 ml (0.088 mole) of methyl iodide for 4 hr. The reaction mixture was filtered through Celite to separate the silver oxide, the filter cake was washed with acetone, and the combined acetone filtrates were evaporated *in vacuo*. The yellow liquid residue crystallized almost immediately to give a somewhat sticky solid. This was heated in petroleum ether–ether and collected: yield 1.8 g (87%), mp 78–82° (lit.[6b] 85°).

In order that the product crystallize directly, it is essential that the 2-hydroxy-4-acetoxy-6-methylbenzaldehyde used is of the highest purity.

2,6′-Dimethyl-4,6,2′-trimethoxy-4′-acetoxybenzophenone (9, X = H).—A solution (orange) of 0.5 g (0.0022 mole) of isoeverninic acid acetate (**5**) and 0.35 g (0.0022 mole) of 3,5-dimethoxytoluene[14] in 5 ml of trifluoroacetic anhydride was kept at room temperature for 2 hr. The excess anhydride was removed *in vacuo* and the residue was partitioned between water and ether. The ethereal solution was washed with 10% aqueous sodium carbonate and water, dried, and evaporated to yield 0.75 g of a yellow gum which was suspended in ether–petroleum ether. The product crystallized in *ca.* 3.5 hr, yield 0.32 g (41%), mp 105–110°. The colorless analytical sample was obtained by recrystallization from methyl alcohol: mp 115–117°; λ_{max}^{Nujol} 5.70 μ (OAc) and 6.05 μ (ArCOAr); λ_{max}^{MeOH} 302 (sh) (ϵ 7150), 281 (ϵ 8750), 233 mμ (sh) (ϵ 15,000), and end absorption.

Anal. Calcd for $C_{20}H_{22}O_6$ (358.38): C, 67.02; H, 6.19. Found: C, 67.13; H, 6.25.

2-Acetoxymethyl-4,6,2′-trimethoxy-4′-acetoxy-6′-methylbenzophenone (9, X = OAc).—A solution of 5 g (0.022 mole) of isoeverninic acid acetate (**5**) and 4.7 g (0.022 mole) of 3,5-dimethoxybenzyl acetate[15] in 75 ml of trifluoroacetic anhydride was kept at room temperature for 30 min. The excess anhydride was removed *in vacuo* and the residue was partitioned between methylene chloride and water. The methylene chloride solution was washed with aqueous bicarbonate, dried, and evaporated, and the residue was treated with ether. The product which crystallized melted at 102–104.5° (softened *ca.* 95°), yield 5.5 g (60%). Recrystallization from ether–acetone furnished the analytical sample: mp 103–105°; λ_{max}^{Nujol} 5.70 (ArOAc), 5.78 ($ArCH_2OAc$), and 6.02 μ [ArC(=O)Ar]; λ_{max}^{MeOH} 300 (ϵ 7700), 277 (ϵ 9350), 235 mμ (ϵ 15,600), and end absorption.

Anal. Calcd for $C_{22}H_{24}O_8$ (416.41): C, 63.45; H, 5.81. Found: C, 63.42; H, 5.92.

3,5-Dimethoxybenzyl Bromide (8).—The title compound was prepared according to the general procedure of Haworth and Perkin.[16] Gaseous hydrogen bromide was bubbled through a cooled (ice–water) solution of 3.8 g (0.023 mole) of 3,5-dimethoxybenzyl alcohol[15] in benzene for *ca.* 30 min. The flask was stoppered and kept at room temperature for an additional 1.5 hr. Most of the excess hydrogen bromide was then removed in a stream of nitrogen, ether was added, and the mixture was poured into cold water. The organic phase was washed with bicarbonate solution, dried, and evaporated to yield 3.6 g (68%) of a green-tinged white solid. The analytical sample was obtained by percolating a solution of this in ether through a column of Woelm nonalkaline, almost neutral, alumina, activity I. Evaporation of the ether eluates (*ca.* 100 ml) left a colorless solid which was recrystallized from cyclohexane and sublimed at 80–90° (bath temperature) under oil pump vacuum for 15 min. The product which collected on the cold finger melted at 74.5–75.5°.

Anal. Calcd for $C_9H_{11}BrO_2$ (231.10): C, 46.77; H, 4.80; Br, 34.59. Found: C, 46.72; H, 4.99; Br, 34.85.

Reaction of Isoeverninic Acid Acetate (5) and 3,5-Dimethoxybenzyl Bromide (8).—Compound **5** (59 mg, 0.27 mmole) and 62 mg (0.27 mmole) of 3,5-dimethoxybenzyl bromide were dissolved in 1.5 ml of trifluoroacetic anhydride. The reaction mixture began darkening quite rapidly [contrast with the acylations of **9** (X = H) and **9** (X = OAc)] and was opaque after 13 min. The excess anhydride was removed *in vacuo* (without heating) and the residue was worked up as described for the acylations of **9** (X = H) and **9** (X = OAc). Evaporation of the methylene chloride extracts gave 86 mg of a dark syrupy residue whose infrared spectrum showed bands in positions not inconsistent with those expected for the desired product (*viz.*, 5.70, 6.10, and 6.30 μ). The product was taken up in acetone and the solvent was permitted to evaporate slowly at room temperature overnight (open beaker). A practically black intractable tar remained.

In another experiment in which a 1.75-hr reaction time was employed, the very dark product isolated also showed infrared absorption bands at positions indicated above.

3,5-Dimethoxybenzyl chloride was prepared from the alcohol and thionyl chloride according to the procedure of Adams, *et al.*[17]

Reaction of Isoeverninic Acid Acetate (5) and 3,5-Dimethoxybenzyl Chloride. 2-Chloromethyl-4,6,2′-trimethoxy-4′-acetoxy-6′-methylbenzophenone (9, X = Cl).—A solution of 110 mg (0.59 mmole) of 3,5-dimethoxybenzyl chloride and 130 mg (0.59 mmole) of **5** in 1.5 ml of trifluoroacetic anhydride was kept at room temperature for 5 min (the rate at which the solution was darkening appeared somewhat slower than in the case of **8**), the excess anhydride was removed *in vacuo* (without heating), and the residue was processed as described for **9** (X = H) and **9** (X = OAc). Evaporation of the lime-colored methylene chloride extracts *in vacuo* (without heating) left a green-purple residue; it crystallized on rubbing (metal spatula) in a small amount of ether to give a tan solid. This was collected and washed with a small amount of ether: yield 60 mg (26%); mp 100–103° dec (sample began darkening at *ca.* 94°); λ_{max}^{Nujol} 5.70 μ and 5.98 μ. The analytical sample was obtained from another experiment in which the residue remaining after evaporating the methylene chloride was crystallized by rubbing in ether containing some methyl alcohol. While this solvent system gave a poorer yield of product, the product obtained appeared cleaner. The light yellow solid obtained in this manner had mp 104–105° dec (sample began darkening at *ca.* 95°). The sample was kept at room temperature overnight before submitting it for analysis, during which time its color changed to light brown.

Anal. Calcd for $C_{20}H_{21}ClO_6$ (392.83): C, 61.14; H, 5.38; Cl, 9.03. Found: C, 61.33; H, 5.62; Cl, 8.85.

Approximately 300 mg of **9** (X = Cl) was accumulated from a number of small-scale experiments using the above procedure, and was stored at −5°. (An infrared spectrum of a sample of this material taken after 3 months was identical with that taken initially.)

The product did not crystallize so readily and was obtained in inferior yield when the reaction was run on twice the scale. Color changes of the methylene chloride extracts during the work-up which had been observed when longer reaction times were employed, and which were hardly noticeable when the reaction was run on a 130-mg scale, were again observed in the larger scale run. (Perhaps the increased work-up time required in the larger run results in the formation of more impurities and makes product isolation more difficult.)

An attempt to recrystallize **9** (X = Cl) from luke warm methyl alcohol [**9** (X = OAc) could be cleanly recrystallized from this solvent] resulted in the formation of a deep red-purple solution

(13) R. Adams and J. Levine, *J. Am. Chem. Soc.*, **45**, 2373 (1923).
(14) S. Ludwinowsky and J. Tambor, *Ber.*, **39**, 4037 (1906).
(15) H. E. Zimmerman and V. Sandel, *J. Am. Chem. Soc.*, **85**, 915 (1963).
(16) R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, Part 1, 1434 (1925).
(17) R. Adams, S. MacKenzie, Jr., and S. Loewe, *J. Am. Chem. Soc.*, **70**, 664 (1948).

from which a dark red, intractable tarry residue was obtained on evaporation *in vacuo*.

Attempted Conversion of 9 (X = Cl) to 13 in a Single Operation.—To a solution of 52 mg (0.13 mmole) of 9 (X = Cl) in 2 ml of dry 1,2-dimethoxyethane was added 0.08 ml of 1.66 *N* (determined titrimetrically) sodium methoxide in methyl alcohol (0.13 mmole). Within 10 min the solution became turbid and within 2.5 hr a fine white solid (sodium chloride?) had separated. After *ca.* an additional 2.5 hr, a quite sudden darkening of the reaction mixture took place, making it almost opaque. The reaction mixture was worked up after a total reaction time of 5.5 hr by diluting with methylene chloride and pouring the mixture into cold water containing a few drops of acetic acid. The maroon organic phase was separated, washed with bicarbonate solution, and dried. During the drying process the solution became green. Evaporation of the methylene chloride left a dark, very viscous syrup (47 mg) which showed only very weak absorption in the 5.6–6.0-μ region of the infrared. The compound also showed a strong broad band in the 3.0-μ region and a sharp strong band at 6.1 μ. Trituration of the material with ether resulted in the formation of an amorphous, dark olive green solid (20 mg). On melting, the material appeared to shrink somewhat at *ca.* 100° and gradually became darker. The melting point bath temperature was raised to 200°. By the time this temperature was reached, the sample had turned black but did not melt. The infrared spectrum of the amorphous solid showed no absorption in the 5.8-μ region.

Anal. Calcd for 12 ($C_{18}H_{19}ClO_5$): C, 61.63; H, 5.46; Cl, 10.01. Calcd for **13** ($C_{18}H_{18}O_5$): C, 68.78; H, 5.77. Found: C, 65.00; H, 6.20; Cl, 3.64.

Thus, the product apparently lost chloride ion in a reaction which did not lead to the spirodienone **13**.[11a]

When a solution of 9 (X = Cl) and 1 equiv of methoxide in 1,2-dimethoxyethane was heated under reflux under nitrogen after standing at room temperature for 1.25 hr, the reaction mixture turned practically black within 2 min, and a black solid separated. Nothing characterizable could be isolated from the reaction mixture.

2-Bromomethyl-3-chloro-4,6,2′-trimethoxy-4′-acetoxy-6′-methylbenzophenone (**6**).—A mixture of 9.8 g (0.037 mole) of isoeverninic acid acetate (**5**) and 2-chloro-3,5-dimethoxybenzyl bromide (**4**)[1] in 300 ml of trifluoroacetic anhydride (**4** was not very soluble in the trifluoroacetic anhydride) was heated and stirred at 75° (oil bath temperature) in a sealed (rubber stopper) 500-ml Parr pressure bottle for 23.25 hr. The excess trifluoroacetic anhydride was removed *in vacuo*, the residue was dissolved in methylene chloride, and the organic solution was washed with aqueous bicarbonate, dried, and evaporated. A solid was obtained by manipulating the residue in ether (metal spatula) which was collected and washed with ether: yield 10.4 g (59%); mp 163–165° (darkens at *ca.* 156°). Recrystallization from benzene–ether gave 9 g of pale yellow solid melting at 168–170°: λ_{max}^{KBr} 5.70 μ (OAc) and 6.02 μ [ArC(=O)Ar]; λ_{max}^{MeOH} 318 mμ (ϵ 6600) and end absorption.

The colorless analytical sample, mp 168–169°, was obtained from a second recrystallization of a small portion of the product from ether–acetone.

Anal. Calcd for $C_{20}H_{20}BrClO_6$ (471.59): C, 50.94; H, 4.25; Br, 16.95; Cl, 7.52. Found: C, 50.98; H, 4.56; Br, 16.87; Cl, 7.60.

The nmr spectrum in deuteriochloroform showed the following peaks: δ 2.22 (three-proton singlet, aromatic methyl), δ 2.32 (three-proton singlet, acetoxyl CH_3), δ 3.45, 3.47, and 3.85 (nine protons, aromatic OCH_3) δ 4.67 (two-proton singlet, ArCH_2Br), δ 6.42 [two-proton poorly resolved doublet (J = 2 cps), acetylated aromatic ring protons], and δ 6.58 (one-proton poorly resolved doublet, chlorinated aromatic ring proton).

2-Bromomethyl-3-chloro-4,6,2′-trimethoxy-4′-hydroxy-6′-methylbenzophenone (**3**).—To a suspension of 6.77 g (0.014 mole) of the acetylbenzophenone **6** in 300 ml of methyl alcohol was added 14.4 ml of 1 *N* aqueous sodium hydroxide (0.014 mole) and the mixture was stirred at room temperature for 40 min to give a homogeneous reaction mixture which was acidified with 1 *N* hydrochloric acid. A good portion of the methanol was removed *in vacuo*, water was added, and the solid which separated was collected, washed with water, and air dried: yield, 5.9 g (95%); mp 175–176° dec; λ_{max}^{KBr} 3.0 and 6.1 μ.

The analytical sample, mp 182–184° dec, was obtained by repeated trituration with fresh portions of ether.

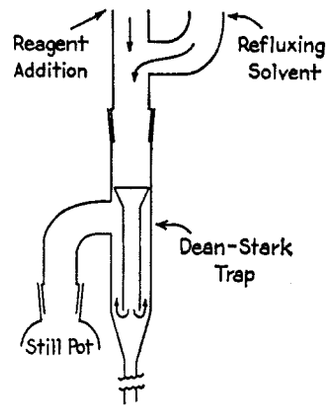


Figure 1.

Anal. Calcd for $C_{18}H_{18}BrClO_5$ (429.70): C, 50.31; H, 4.18; Br, 18.60; Cl, 8.25. Found: C, 50.17; H, 4.53; Br, 18.12; Cl, 8.47; λ_{max}^{MeOH} 315 mμ (ϵ 9500), 281 mμ (ϵ 8200), and end absorption.

The hydrolysis of **6** (118 mg) was effected in 83% yield using a 5-min reaction time.

The nmr spectrum of **3** in $CDCl_3$-d_6–DMSO exhibited the following absorptions: δ 2.37 (three-proton singlet, aromatic CH_3), δ 3.45, 3.65, and 3.97 (nine protons, aromatic OCH_3), δ 4.62 (two-proton singlet, ArCH_2Br), δ 6.24 and 6.33 [two poorly resolved one-proton doublets (J = 2 cps), phenolic ring protons], and δ 6.58 (aromatic proton of chlorinated ring).

An attempt to effect the hydrolysis of **6** to **3** by treating the former with 1 equiv of sodium methoxide in methyl alcohol for 16.5 hr at room temperature also led to considerable bromine displacement as indicated by the low bromine content of the product obtained.

Anal. Calcd: Br, 18.60. Found: Br, 3.08.

4′-Chloro-2,5′,7′-trimethoxy-6-methylspiro(2,5-cyclohexadiene-1,2′-indan)-1′,4-dione (**2**).—To 1.29 g (0.003 mole) of **3** in 1 l. of anhydrous (distilled from calcium hydride) *t*-butyl alcohol was added 2.9 ml of 1.04 *M* (determined titrimetrically) solution of potassium *t*-butoxide in *t*-butyl alcohol (0.003 mole, prepared from metallic potassium). The yellow solution was heated under reflux for 22 hr during which time the yellow color was discharged and a nearly colorless solid separated. The *t*-butyl alcohol was removed *in vacuo*, the residue was dissolved in methylene chloride, and the organic solution was washed with water, dried, and evaporated to yield a tan solid which partially melted and darkened 135–300°, and whose infrared spectrum exhibited absorption in the carbonyl region at 5.86 and 6.07 μ (expected for **2**). The solid was triturated with methyl alcohol and filtered to separate 0.2 g of a colorless solid, insoluble in organic solvents including DMSO, which melted at 324–326° dec and whose infrared spectrum showed a band at 6.1 but not at 5.9 μ in the carbonyl region. The elemental analysis of this product agreed fairly well with values calculated assuming a dimeric (or polymeric or both) structure.

Anal. Calcd for $C_{36}H_{34}Cl_2O_{10}$ (698): C, 61.89; H, 4.87; Cl, 10.03. Found: C, 60.55; H, 5.29; Cl, 10.32.

The methyl alcohol filtrate was evaporated and the residue (1 g) cleanly separated into two main fractions by dissolving in benzene–ethyl acetate (1:1) and chromatographing on 300 g of silica gel (Camag, with fluorescent indicator) according to the recently described procedure of Loev and Snader[18] using benzene–ethyl acetate (1:1) as the developing solvent. The positions of the components on the column were determined by observing their fluorescence when the column was exposed to a 366-mμ ultraviolet lamp. The faster moving fraction (consisting of *ca.* five subfractions) did not show any absorption in the infrared at *ca.* 5.9 μ. It thus clearly did not contain any of the desired spirodienone **2** and was not investigaged further.

The slower moving fraction did show infrared bands at *ca.* 5.9 and 6.1 μ as expected for **2**. It proved to be essentially homogenous by thin layer chromatography (Camag silica gel with fluorescent indicator; developing solvent, benzene–ethyl acetate

(18) B. Loev and K. M. Snader, *Chem. Ind.* (London), 15 (1965).

(1:1); detector, ultraviolet light; R_f *ca.* 0.2): yield 0.34 g (32%). After recrystallization from methanol–acetone, the product had mp 241–244° dec (softened *ca.* 235°); λ_{max}^{KBr} 5.85 μ (indanone carbonyl), 6.05 μ (dienone carbonyl) (roughly equal intensity strong bands), 6.20 μ (sh), and 6.30 μ (aliphatic and aromatic unsaturation); λ_{max}^{MeOH} 318 (ϵ 12,000), 280 (ϵ 29,400), and 236 mμ (ϵ 32,000).

Anal. Calcd for $C_{18}H_{17}ClO_5$ (348.5): C, 61.98; H, 4.88; Cl, 10.20. Found: C, 61.92; H, 5.07; Cl, 10.33.

The nmr spectrum of **2** is presented in the Discussion.

The reaction was also conducted at 0.03 *M* concentration. The crude reaction mixture obtained was separated into a methyl alcohol insoluble (74% by weight of the total crude) and methyl alcohol soluble fraction (26%). The amount of **2** present in the soluble fraction was estimated at *ca.* 75% from the ratio of the intensities of the 5.85- and 6.05-μ bands in its infrared spectrum compared to that in pure **2**. The yield of **2** obtained from the 0.03 *M* run thus drops to *ca.* 20%.

Compound **3** was recovered unchanged when its reaction with 1 equiv of *t*-butoxide in *t*-butyl alcohol was attempted at room temperature (17 hr) and was recovered unchanged from refluxing (3 days) anhydrous *t*-butyl alcohol in the absence of base.

The yield of **2** was not improved over that obtained at 0.03 *M* concentration when the reaction was performed under high dilution (attained with the apparatus shown in Figure 1). The reason for this appears to be that the reaction takes place at too slow a rate. The yellow color of the refluxing reaction mixture, presumably the phenolate anion of **2**, was still present after the 6 hr required to add the solution of **2** in *t*-butyl alcohol containing 1 equiv of potassium *t*-butoxide.

Acknowledgments.—We thank Dr. R. B. Angier for his continued interest. Analyses were performed by L. Brancone and staff; ultraviolet and nmr spectra were determined by W. Fulmor and staff.

Reissert Compound Studies. XII. Synthesis of O-Methyldauricine[1]

FRANK D. POPP, HARRY W. GIBSON,[2] AND ADRIA CATALA NOBLE

Department of Chemistry, Clarkson College of Technology, Potsdam, New York

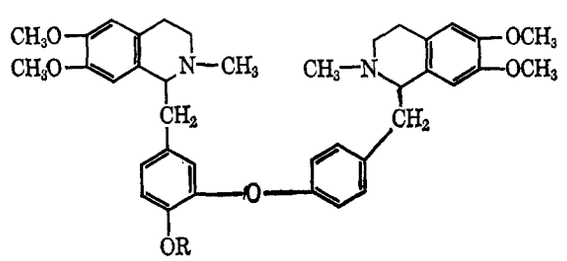
Received March 10, 1966

O-Methyldauricine (I, R = CH_3) has been synthesized by several paths from the Reissert compound, 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV). One approach involves the synthesis of two benzylisoquinolines which are then joined by an Ullmann reaction. The other approach involves the reaction of 2 moles of IV with an appropriate diphenyl ether derivative.

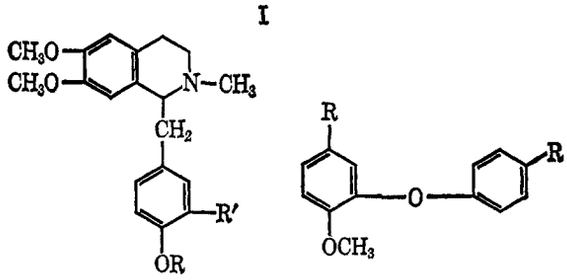
The bisbenzylisoquinoline alkaloid dauricine (I, R = H) has been isolated from *Menispermum dauricum* D. C.[3] and *Menispermum canadense* L.[4] Its methyl ether, O-methyldauricine (I, R = CH_3), has been the object of much study.

In 1955 a partial synthesis of O-methyldauricine was achieved from one of dauricine's degradation products, armepavine (II, R = R′ = H).[5] Armepavine was converted through a series of reactions to II (R = CH_3, R′ = Br) and the Ullmann reaction of the latter compound with armepavine gave O-methyldauricine (I, R = CH_3), albeit in low (2.4%) yield. In 1957, Russian workers reported a synthesis of two potential precursors of O-methyldauricine (II, R = CH_3, R′ = Br and II, R = $CH_2C_6H_5$, R′ = H)[6] *via* the Bischler–Napieralski reaction. These workers, however, reported no attempts to join these two fragements. In the same year this group also reported a total syntheis of O-methyldauricine.[7] Condensation of III with β-(3,4-dimethoxyphenyl)ethylamine gave a diamide which was subjected to the Bischler–Napieralski ring closure. Reduction and N-methylation of this intermediate, which Japanese workers had prepared by a similar route more than 20 years earlier,[8] afforded O-methyldauricine in 6.5% over-all yield. Dauricine itself has recently been synthesized through a somewhat similar sequence.[9]

In view of the ability of Reissert compounds to condense with aldehydes[10,11] and with alkyl halides,[12] and

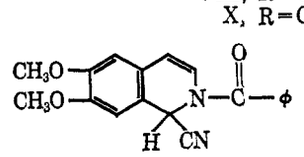


I



II

III, R = CH_2COCl
VIII, R = CHO
X, R = CH_2Br



IV

(1) (a) Presented at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966. (b) Part XI: F. D. Popp and J. M. Wefer, *Chem. Commun.*, 207 (1966).

(2) Taken from the Ph.D. Dissertation of H. W. Gibson, Clarkson College of Technology, Oct 1965. National Defense Educational Act Fellow.

(3) H. Kondo and Z. Narita, *J. Pharm. Soc. Japan*, **542**, 279 (1927); *Chem. Abstr.*, **21**, 2700 (1927).

(4) R. H. F. Manske, *Can. J. Res.*, **21B**, 17 (1943).

(5) M. Tomita, K. Ito, and H. Yamaguchi, *Pharm. Bull.* (Tokyo), **3**, 449 (1955).

(6) I. Gorbacheva, L. Nikolaeva, and N. Preobrazhenskii, *Zh. Obshch. Khim.*, **27**, 3367 (1957).

(7) I. Gorbacheva, G. Bushbek, L. Varnakova, L. Shulov, and N. Preobrazhenskii, *ibid.*, **27**, 2297 (1957).

(8) H. Kondo, Z. Narita, and S. Uyeo, *Ber.*, **68B**, 519 (1935).

(9) T. Kametani and K. Fukumoto, *Tetrahedron Letters*, 2271 (1964).

(10) L. R. Walters, N. T. Iyer, and W. E. McEwen, *J. Am. Chem. Soc.*, **80**, 1177 (1958).

(11) F. D. Popp and H. W. Gibson, *J. Heterocyclic Chem.*, **1**, 51 (1964).

(12) V. Boekelheide and J. Weinstock, *J. Am. Chem. Soc.*, **74**, 660 (1952).