(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]

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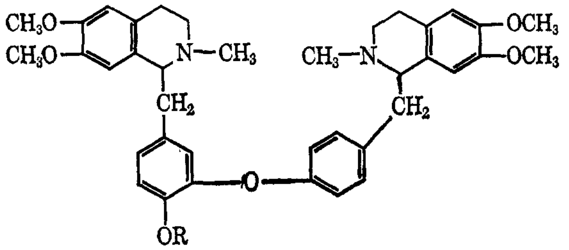
O-Methyldauricine (I, R = CH_3) has been synthesized by several paths from the Reissert compound, 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV). One approach involves the synthesis of two benzylisoquinolines which are then joined by an Ullmann reaction. The other approach involves the reaction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

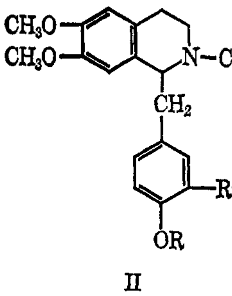
The bisbenzylisoquinoline alkaloid dauricine (I, R = H) has been isolated from *Menispermum dauricum* D. C.[3] and *Menispermum canadense* L.[4] Its methyl ether, O-methyldauricine (I, R = CH_3), has been the object of much study.

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]

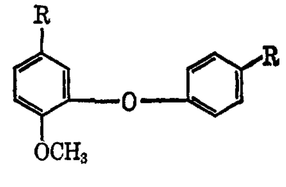
In view of the ability of Reissert compounds to condense with aldehydes[10,11] and with alkyl halides,[12] and



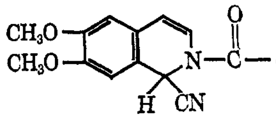
I



II



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



IV

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(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).

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(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).

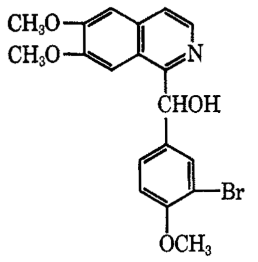
(10) L. R. Walters, N. T. Iyer, and W. E. McEwen, *J. Am. Chem. Soc.*, **80**, 1177 (1958).

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

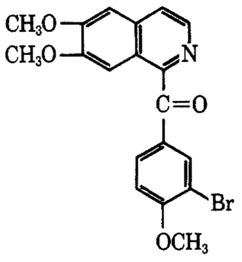
(12) V. Boekelheide and J. Weinstock, *J. Am. Chem. Soc.*, **74**, 660 (1952).

the previous utilization of these intermediates for alkaloid synthesis,[13–16] it appeared likely that O-methyldauricine could be synthesized from the Reissert compound, 2-benzoyl-6,7-dimethoxy-1,2-dihydrosisoquinaldonitrile (IV). In fact, our recent synthesis[16] of *dl*-armepavine (II, R = R′ = H) from the Reissert compound IV constitutes a synthesis of O-methyldauricine.[5]

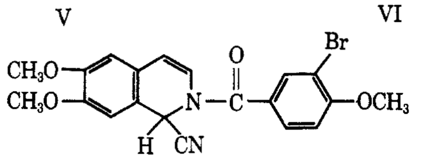
Another synthesis involves the preparation of II ($R = CH_3$, $R' = Br$), directly from IV rather than from armepavine. The synthesis of 1-(3-bromo-4-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (II, $R = CH_3$, $R' = Br$) proceeded in the same way as our synthesis of *dl*-armeparine.[16] Reaction of the anion of IV with 3-bromo-4-methoxybenzaldehyde yielded gummy 3-bromo-4-methoxyphenyl-1-(6,7-dimethoxyisoquinolyl)carbinyl benzoate hydrolysis of which afforded the carbinol V, a second gum, in 87% yield. Oxidation of V yielded 1-(3-bromo-4-methoxybenzoyl)-6,7-dimethoxyisoquinoline (VI) which was also prepared by the following method. 2-(3-Bromo-4-methoxybenzoyl)-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (VII) was prepared in 74% yield from 6,7-dimethoxyisoquinoline and 3-bromo-4-methoxybenzoyl chloride by methylene chloride method.[17] Rearrangement of this Reissert compound according to a new procedure using sodium hydride in dimethylformamide[18] led to the formation of 1-(3-bromo-4-methoxybenzoyl)-6,7-dimethoxyisoquinoline (VI) in 49% yield. This was readily reduced in 92% yield to carbinol V by means of sodium borohydride. Reduction of the carbinol V with hydrogen bromide–zinc dust gave rise to 1-(3-bromo-4-methoxybenzyl)-6,7-dimethoxyisoquinoline in 78% yield. Treatment with methyl iodide afforded the methiodide in 66% yield. Sodium borohydride reduction of the methiodide resulted in the formation of 84% of 1-(3-bromo-4-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (II, $R = CH_3$, $R' = Br$). Since these two fragments were joined by Tomita and co-workers,[5] synthesis of these two compounds constitutes a synthesis of O-methyldauricine *via* a Reissert compound.



V



VI

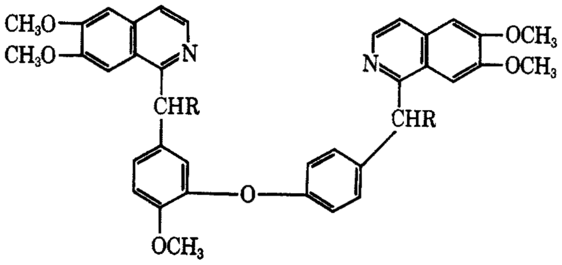


VII

The second and much shorter method of synthesis of O-methyldauricine approaches the problem from a different viewpoint. The diphenyl ether portion was prepared first and then joined to 2 moles of IV.

4′,5-Diformyl-2-methoxydiphenyl ether (VIII) was a requisite starting material. Its synthesis was reported in 1935 by Kondo and co-workers in 28% over-all yield from *p*-cresol and 3-bromo-4-methoxytoluene.[8] In our hands, however, their method did not proceed as favorably and several other synthetic approaches were investigated. The simplest approach proved to be the best. An Ullmann condensation between *p*-bromobenzaldehyde and isovanillin afforded the crude dialdehyde VIII in 53% yield.

Condensation of the anion of IV with the dialdehyde VIII at −40° gave the ether IX ($R = OCOC_6H_5$) in 83% yield. Hydrolysis of this dibenzoate with aqueous ethanolic potassium hydroxide resulted in the isolation of a quantitative amount of ether IX (R = OH). Oxidation of the diol (IX, R = OH) with sodium dichromate in acetic acid yielded α,α'-bis[1-(6,7-dimethoxyisoquinolyl)]-4′,5-diformyl-2-methoxydiphenyl ether in a quantitative yield. Attempts to reduce this diketone by the Huang-Minlon modification of the Wolff–Kishner reduction led to no isolable products.



IX

When the diol IX (R = OH) was treated with hydrogen bromide and zinc dust in acetic acid, α,α'-bis[1-(6,7-dimethoxyisoquinolyl)]-4′,5-dimethyl-2-methoxy-diphenyl ether (IX, R = H) resulted in a 91% yield as the dihydrate. Treatment with methyl iodide gave the dimethiodide in 95% yield. Reduction of this methiodide with sodium borohydride in methanol resulted in the formation of an 81% yield of O-methyldauricine (I, $R = CH_3$) as a solid, mp 88–100°. Although Tomita and co-workers[5] report obtaining a dimethiodide containing 2.5 moles of water, the dimethiodide obtained in this study could according to its elemental analysis contain either 2.5 or 2.0 moles of water. The infrared spectrum of the synthetic free base and its dimethiodide was identical with those of authentic O-methyldauricine obtained by methylation of natural dauricine[19] (I, R = H) with diazomethane.

The over-all yield of O-methyldauricine based upon 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (IV) and 4′,5-diformyl-2-methoxydiphenyl ether (VIII) was 52%. Based on β-(3,4-dimethoxyphenyl)ethylamine, the over-all yield was 41% compared with 10% yield based on the same starting material reported in the previous total synthesis.[7]

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[13] F. D. Popp and W. E. McEwen, *J. Am. Chem. Soc.*, **79**, 3773 (1957).

[14] F. D. Popp and W. E. McEwen, *ibid.*, **80**, 1181 (1958).

[15] H. W. Gibson, F. D. Popp, and A. Catala, *J. Heterocyclic Chem.*, **1**, 251 (1964).

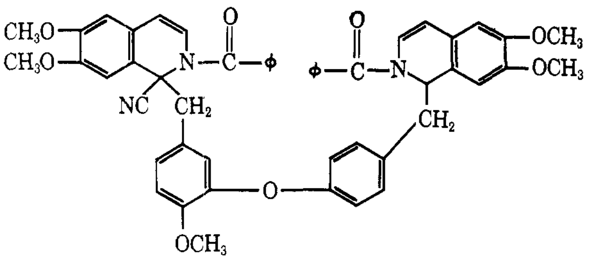
[16] H. W. Gibson, F. D. Popp, and A. C. Noble, *ibid.*, **3**, 99 (1966).

[17] F. D. Popp and W. Blount, *Chem. Ind.* (London), 550 (1961).

[18] Part XI.[1a]

[19] Kindly supplied by Professor M. Tomita.

Another synthesis of O-methyldauricine using a preformed diphenyl ether portion involved the reaction of 4′,5-bis(bromomethyl)-2-methoxydiphenyl ether (X), prepared in 50% yield by bromomethylation of 2-methoxydiphenyl ether, with the anion of the Reissert compound IV. Treatment of the anion of IV with X at −45° gave the intermediate XI, which was subjected to basic hydrolysis without isolation, yielding IX (R = H) in a 22% yield. The product obtained in this way was identical in all respects with the compound obtained by the sequence described above and was converted to O-methyldauricine (I, R = CH_3) by the same sequence of reactions described. The yield of O-methyldauricine based on Reissert compound IV was 17% and from β-(3,4-dimethoxyphenyl)ethylamine was 14%.



XI

In view of the results described above it appears that Reissert compounds warrant serious consideration in the synthesis of isoquinoline alkaloids, especially in the case of complex alkaloids (such as the bisbenzylisoquinolines) for which the greatest advantages seem to accrue.

Experimental Section[20]

1-(3-Bromo-4-methoxybenzoyl)-6,7-dimethoxyisoquinoline (VI).—The condensation of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile[15] with 3-bromoanisaldehyde[21] at −40° yielded a gum which could not be induced to crystallize. Hydrolysis of the gummy benzoate[10] yielded the gummy carbinol in 87% overall yield. The crude gummy carbinol was oxidized with sodium dichromate in acetic acid to the ketone in 45% yield. Recrystallizations from ethyl acetate, ethanol–water, and ethanol gave a colorless solid, mp 177–178°.

Anal. Calcd for $C_{19}H_{16}BrNO_4$: C, 56.73; H, 4.01; Br, 19.87; N, 3.48. Found: C, 56.67; H, 4.11; Br, 19.98; N, 3.54.

3-Bromo-4-methoxybenzoic Acid.—A mixture of 18.3 g (0.0851 mole) of 3-bromoanisaldehyde, 37.0 g of potassium permanganate, 50 ml of 20% sodium hydroxide, and 200 ml of water was refluxed for 1.25 hr. After filtration, the solution was made acidic with hydrochloric acid. Filtration and washing with water gave 13.4 g (68%) of colorless solid, mp 215–217°, lit.[22] mp 215°.

2-(3-Bromo-4-methoxybenzoyl)-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile. (VII).—A mixture of 13.4 g of the above acid and 50 ml of thionyl chloride was refluxed for 2 hr. The excess thionyl chloride was removed *in vacuo*, leaving a crystalline solid which was used without further purification. Treatment of 5.2 g (0.0287 mole) of 6,7-dimethoxyloquinoline with potassium cyanide and the crude acid chloride by the methylene chloride method[17] afforded a 74% yield of the compound, mp 157–157.5°, after recrystallization from ethanol.

Anal. Calcd for $C_{20}H_{17}BrN_2O_4$: C, 55.95; H, 3.99; N, 6.53. Found: C, 55.73; H, 3.95; N, 6.29.

Sodium Hydride Rearrangement of 2-(3-Bromo-4-methoxybenzoyl)-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile.—This is the general procedure of Wefer.[18] To a solution of 0.50 g (0.00116 mole) of the Reissert compound in 25 ml of dimethylformamide was added 0.10 g (0.00125 mole) of 30% sodium hydride. The mixture was stirred 30 min and poured into an ice–water mixture. Filtration yielded 0.23 g (49%) of 1-(3-bromo-4-methoxybenzoyl)-6,7-dimethoxyisoquinoline identical with that reported above.

1-(3-Bromo-4-methoxybenzyl)-6,7-dimethoxyisoquinoline.—Reduction of the corresponding ketone with sodium borohydride gave rise to a carbinol in 92% yield. Its spectra was identical with that of the carbinol reported above. When the carbinol was treated with hydrogen bromide and zinc dust, this material was obtained in 78% yield as an amorphous solid, for which no suitable recrystallization solvent could be found. The picrate after recrystallization from ethanol melted at 177–179°.

Anal. Calcd for $C_{25}H_{21}BrN_4O_{10}$: C, 48.63; H, 3.43; Br, 12.95; N, 9.08. Found: C, 48.87; H, 3.56; Br, 12.80; N, 9.28.

The methiodide was obtained in 66% yield; recrystallization from ethyl acetate–methanol gave mp 195–196°.

Anal. Calcd for $C_{19}H_{18}BrNO_3 \cdot CH_3I \cdot H_2O$: C, 43.82; H, 4.23; N, 2.56. Found: C, 43.86; H, 3.90; N, 2.52.

1-(3-Bromo-4-methoxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline.—To a solution of 0.40 g (0.000755 mole) of 1-(3-bromo-4-methoxybenzyl)-6,7-dimethoxyisoquinoline methiodide in 25 ml of methanol and 2 ml of water was added 0.80 g of sodium borohydride. The mixture was refluxed 2 hr and then poured into ice–water. The pink solid, 0.26 g (84%), turned to a gum on the filter. This was dissolved in ether, treated with hydrogen chloride, and recrystallized from methanol–benzene; it had mp 211–213°.

Anal. Calcd for $C_{20}H_{25}NBrClO_3$: C, 54.25; H, 5.69; Br, 18.05; Cl, 8.01; N, 3.16. Found: C, 54.04; H, 5.66; Br, 17.84; Cl, 8.07; N, 3.18.

4′,5-Diformyl-2-methoxydiphenyl Ether (**VIII**).—A mixture of 6.08 g (0.04 mole) of *p*-bromobenzaldehyde, 5.60 g (0.04 mole) of potassium carbonate, and 0.5 g of copper powder[23] was ground thoroughly together and then 0.1 ml of pyridine was added. The mixture was heated to 190° and maintained there for 1 hr. After cooling, the hard mass was stirred with 15% sodium bisulfite until it was broken up and dissolved. The copper was filtered and the solution treated with 50% sodium hydroxide until a cloudiness developed and a gummy sludge precipitated. Continuous extraction with ether for 25 hr yielded 5.45 g (53%) of yellow gum. Careful recrystallization from ethanol-water gave material (3.4 g, 33%) pure enough for use, mp 63–70°. A pure sample had mp 72–74°, lit.[24] mp 72°. The semicarbazone (226–228°) and the phenylhydrazone (215–218°) also had melting points corresponding to the reported[24] value.

α,α'-Bis(benzoyloxy)-α,α'-bis-1-(6,7-dimethoxyisoquinolyl)-4′,5-dimethyl-2-methoxydiphenyl Ether (IX, R = $OCOC_6H_5$).—The condensation of the Reissert compound IV (18.4 g, 0.0567 mole) and the ether VIII (7.38 g, 0.0288 mole) was carried out at −30° to −40° with phenyllithium. The reaction mixture was extracted with water, 20% sodium bisulfite, and 0.5 *M* hydrochloric acid. The latter was washed with ether and made basic with sodium hydroxide and filtered; the cream colored solid was washed and dried to give 15.31 g, mp 105–115°. From the reaction mixture was recovered 4.35 g of IV. The yield based on unrecovered starting material was thus 83%. The product yielded a dihydrochloride upon treatment with gaseous hydrogen chloride. After recrystallization from methanol–ether, it melted at 169–172°, after turning pink at 161°.

Anal. Calcd for $C_{51}H_{42}N_2O_{10} \cdot 2HCl \cdot 4H_2O$: C, 62.00; H, 5.31; Cl, 7.18; N, 2.84. Found: C, 61.64; H, 5.08; Cl, 7.57; N, 3.13.

α,α'-Di(hydroxy)-α,α'-bis-1-(6,7-dimethoxyisoquinolyl)-4′,5-dimethyl-2-methoxydiphenyl Ether (IX, R = OH).—Hydrolysis of the above dibenzoate with sodium hydroxide yielded a solid, mp 145–165°, in quantitative yield. A picrate, mp 213.5–217.5°, was obtained. Acidification of the reaction mixture gave benzoic acid.

α,α'-Bis-1-(6,7-dimethoxyisoquinolyl)-4′,5-diformyl-2-methoxydiphenyl Ether.—Oxidation of the above diol with sodium dichromate in acetic acid gave a solid, mp 155–165°, in quantitative yield. The bispicrate after recrystallization from ethanol had mp 148–151°.

Anal. Calcd for $C_{49}H_{36}N_8O_{22}$: C, 54.05; H, 3.33; N, 10.29. Found: C, 54.18; H, 3.49; N, 10.10.

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(20) All melting points were taken in capillaries and are corrected. Analyses by Spang Microanalytical Laboratories, Ann Arbor, Mich., and Gailbraith Laboratories, Knoxville, Tenn.

(21) O. Brady and L. Manjunath, *J. Chem. Soc.*, 1060 (1924).

(22) H. Bretschneider and R. Lutz, *Monatsh.*, **84**, 575 (1953).

(23) R. Q. Brewster and T. Groening, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 446.

(24) F. V. Bruchhausen and P. Gericke, *Arch. Pharm.*, **269**, 115 (1931).

4′,5-Bis(bromomethyl)-2-methoxydiphenyl Ether (X).—This procedure is analogous to one used to prepare the bis(chloromethyl) compound.[7] Hydrogen bromide gas was passed through a stirred solution of 10.58 g (0.529 mole) of 2-methoxydiphenyl ether,[25] 10 ml of 40% formalin, and 75 ml of acetic acid for 2 hr. The mixture was poured onto about 200 ml of ice and allowed to stand overnight. The chloroform extract was washed with water, sodium bicarbonate solution, water, sodium carbonate solution, and water. After drying over magnesium sulfate, evaporation yielded 19.3 g (95%) of yellow-brown oil. Crystallization from hexane–petroleum ether (bp 30–60°), followed by recrystallizations from hexane, gave colorless crystals, mp 103–104°, in about 50% yield.

Anal. Calcd for $C_{15}H_{14}Br_2O_2$: C, 46.66; H, 3.66; Br, 41.40. Found: C, 46.78; H, 3.74; Br, 41.49.

α,α'-Bis-1-(6,7-dimethoxyisoquinolyl)-4′,5-dimethyl-2-methoxydiphenyl Ether (IX, R = H). Method A.—Application of the hydrogen bromide–zinc dust reduction method to the diol mentioned above gave an 81% yield of a solid, mp 109–112°, after recrystallization from ethanol–water and then benzene–hexane.

Anal. Calcd for $C_{37}H_{34}N_2O_6\cdot 2H_2O$: C, 69.58; H, 6.00; N, 4.39. Found: C, 69.45; H, 5.75; N, 4.16.

Method B.—IV (3.48 g, 0.0109 mole) and X (2.15 g, 0.00557 mole) were condensed in the presence of phenyllithium at −40° to yield 5.77 g of cream colored solid, mp 113–120°. The solid (XI) was subjected to hydrolysis by refluxing with 1.54 g of potassium hydroxide, 100 ml of ethanol, and 50 ml of water for 2.5 hr. After dilution with water, filtration yielded 0.77 g (22%) of a brown solid. A solid identical with that obtained in method A could be obtained by extraction with 15% hydrochloric acid, followed by basification with ammonium hydroxide and filtration. The methiodide, prepared from either solid, mp 196–198° (from methanol–ethyl acetate), was obtained in 95% yield.

Anal. Calcd for $C_{37}H_{34}N_2O_6\cdot 2CH_3I$: C, 52.83; H, 4.55; I, 28.63; N, 3.16. Found: C, 52.60; H, 4.69; I, 28.48; N, 3.01.

Both solids gave the same picrate, mp 141–145° from ethanol.

Anal. Calcd for $C_{49}H_{40}N_8O_{20}$: N, 10.56. Found: N, 10.46.

O-Methyldauricine (I, R = CH_3).—A solution of 0.4 g (0.000452 mole) of the dimethiodide salt above in 50 ml of methanol and 10 ml of water was treated with 1.5 g of sodium borohydride and the resulting mixture refluxed for 2.5 hr. It was filtered hot and reduced in volume by evaporation. After pouring onto ice, filtering, and washing with water, 0.23 g (81%) of cream colored solid, mp 88–100°, was obtained. The bispicrate was prepared and after recrystallization from ethanol melted at 137–140°.

Anal. Calcd for $C_{51}H_{52}N_8O_{20}$: C, 55.84; H, 4.78; N, 10.22. Found: C, 55.58; H, 4.63; N, 10.02.

The material gave a dimethiodide in quantitative yield. Recrystallization from methanol-ethyl acetate gave material of mp 186–190°.

Anal. Calcd for $C_{41}H_{52}N_2I_2O_6\cdot 2.5H_2O$ (as reported by Tomita and co-workers[5]): C, 50.88; H, 5.94; N, 2.90. Calcd for $C_{41}H_{52}N_2I_2O_6\cdot 2H_2O$: C, 51.36; H, 5.89; N, 2.92. Found: C, 51.22; H, 5.68; N, 2.77.

Authentic O-Methyldauricine (I, R = CH_3).—This material was prepared by reaction of dauricine·$CHCl_3$[20] with diazomethane. A cream colored solid, mp 54–64°, whose infrared spectra was identical with the above synthetic O-methyldauricine resulted. The dimethiodide had mp 184–188°, lit.[5] mp 181–182°. It did not depress the melting point of the above synthetic dimethiodide and had an infrared spectra identical with that of the synthetic material.

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[25] H. E. Ungnade and E. F. Orwoll, ref 24, Coll. Vol. III, 1955, p 566.

Solvent Effects in Aromatic Nitration. Nitration by Acyl Nitrates

ALLEN K. SPARKS

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A study of aromatic nitration by nitric acid in acetic anhydride shows this reagent affords a lower *ortho/para* ratio with halobenzenes than is obtained from mixed nitric–sulfuric acids, while toluene yields essentially the same product distribution with either reagent. The use of a cosolvent with acetic anhydride can bring about substantial changes in the orientation from nitration of chlorobenzene, although toluene again is insensitive to changes in the reaction medium. These results are interpreted in terms of interaction between charge induced at the *ortho* position of the substrate by the substituent-ring dipole and the electrophilic species, with the strength of the interaction showing a dependency on solvent polarity.

Acetyl nitrate has been the subject of a number of recent investigations, and an excellent description of the nitric acid–acetic anhydride system has been given by Bordwell and Garbisch[1] in connection with a study of the nitration of olefins. The anomalously high *ortho/para* ratios obtained from nitration of anisole[2] and acetanilide[3] with acetyl nitrate are well documented, while more recently similar behavior has been observed with other substrates, including methyl phenethyl ether[4] and cyclopropylbenzene.[5]

The first systematic study[6] of acyl nitrates was a part of Ingold's pioneering work in the field of aromatic nitration. It was adduced from kinetic evidence that benzoyl nitrate was a precursor of dinitrogen pentoxide and that the latter species effected substitution; a similar mechanism was presumed to operate in the acetyl nitrate system. More recently, however, Paul[7] found the kinetics of nitration of benzene by nitric acid in acetic anhydride to be inconsistent with attack by dinitrogen pentoxide. The susceptibility of the reaction to acid catalysis and inhibition by nitrate and acetate ion suggested that nitronium ion was the electrophilic moiety. It was also reported[8] that the same system affords a significantly lower *ortho/para* ratio of nitrohalobenzenes than does mixed acid, although these data apparently contravene the results of earlier investigations,[9,10] which indicate that the orientation is the same in either system. To accommodate his data, Paul suggests that the dipole between the nucleus and halogen, with the negative end directed out, induces a slight positive charge at the *ortho* position (relative to *para*). The interaction of this charge with nitronium ion is enhanced by solvents of low dielectric constant (acetic anhydride *vis-a-vis* sulfuric acid), and *ortho* substitution is correspondingly

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