Synthesis of Some Ethyl-6,7-dimethoxycarbazoles and Interpretation of Their Nuclear Magnetic Resonance Spectra

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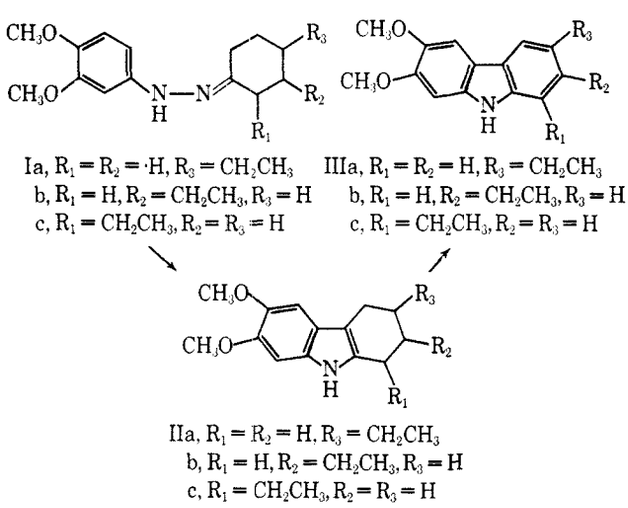
The preparation of 1-, 2-, 3-, and 4-ethyl-6,7-dimethoxycarbazole is described. Their nmr spectra are compared and evaluated in terms of electronic, ring current, and steric effects. The ABX spectrum depicted by the C-2, C-3, and C-4 protons of the 1-ethyl isomer has been completely analyzed.

As part of the structural studies on a new alkaloid,[2] it was degraded to an ethyl-6,7-dimethoxycarbazole. Conclusions based on possible structures for this alkaloid led originally to the assignment of 3-ethyl-6,7-dimethoxycarbazole as the structure of this degradation product, and this assignment was reconciled with its nmr spectrum. However, comparison with a synthetic sample showed that this assignment was in error and that the nmr spectrum had been misinterpreted. In order to establish the correct structure for the degradation product and to clarify the subtle differences in nmr spectra, the 1-, 2-, and 4-ethyl isomers also were synthesized. The preparation of these compounds and the discussion of their nmr spectra is the subject of the present report.

Synthesis.—1-, 2-, and 3-ethyl-6,7-dimethoxycarbazole were obtained by catalytic dehydrogenation of the corresponding 1,2,3,4-tetrahydrocarbazole, the tetrahydrocarbazole being conveniently prepared by the classical Fischer ring closure of the 3,4-dimethoxyphenylhydrazone of the appropriate ethylcyclohexanone. Cyclization of Ia was straightforward and gave the only possible product (IIa) in glacial acetic acid (eq 1). Cyclization of Ib in glacial acetic acid led to the

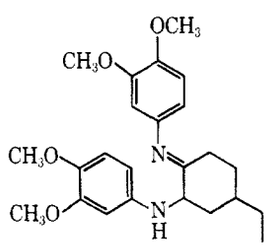


Ia, $R_1 = R_2 = H, R_3 = CH_2CH_3$ IIIa, $R_1 = R_2 = H, R_3 = CH_2CH_3$
b, $R_1 = H, R_2 = CH_2CH_3, R_3 = H$ b, $R_1 = H, R_2 = CH_2CH_3, R_3 = H$
c, $R_1 = CH_2CH_3, R_2 = R_3 = H$ c, $R_1 = CH_2CH_3, R_2 = R_3 = H$

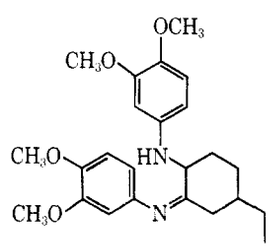
IIa, $R_1 = R_2 = H, R_3 = CH_2CH_3$
b, $R_1 = H, R_2 = CH_2CH_3, R_3 = H$
c, $R_1 = CH_2CH_3, R_2 = R_3 = H$

2-ethyl isomer IIb and none of the much more hindered 4-ethyl isomer was found. Cyclization of Ic to IIc however, was carried out in methanolic sulfuric acid instead of glacial acetic acid to prevent the formation of undesired 2,3,4,4a-tetrahydro-4a-ethyl-6,7-dimethoxy-1H-carbazole. The phenylhydrazones Ia, Ib, and Ic were best prepared by treating 3,4-dimethoxyphenylhydrazine hydrochloride with 2-ethyl-, 3-ethyl-, and 4-ethylcyclohexanone, respectively, in the presence of pyridine.

The tetrahydrocarbazole IIa was also obtained in 10% yield using a method described by Campbell and McCall[3] in which 4-aminoveratrole and 4-ethyl-2-chlorocyclohexanone were condensed in absolute ethanol in the presence of anhydrous sodium acetate. As it has been reported[4] that tetrahydrocarbazole formation proceeds through intermediate tautomers which would have structures IV and V in our specific case, we expected to obtain a mixture of IIa and IIb. The nmr spectrum of the crude indolic product, however, showed it to be exclusively IIa.



IV



V

The preparation of 4-ethyl-6,7-dimethoxycarbazole (XI) was straightforward, even though it entailed more steps. The first and only critical step in the synthesis, which required the coupling of a 4-halo-5-nitroveratrole and an *o*-haloethylbenzene in a mixed Ullmann reaction, proceeded cleanly with the appropriate halo substituents. *o*-Iodoethylbenzene was chosen as one moiety since the rate of self coupling was unobservably slow and the rate of mixed coupling with an active aromatic halo compound relatively rapid.[5] The mixed Ullmann reaction of 4-chloro-5-nitroveratrole (VI) and *o*-iodoethylbenzene gave a 42% yield of 2-nitro-4,5-dimethoxy-2′-ethylbiphenyl (VIII) as the only product while the substitution of 4-iodo-5-nitroveratrole (VII) resulted in a 28% yield of VIII and a 44% yield of 2,2′-dinitrobiveratrole. In both preparations the yield of the desired product VIII was low; in the former, the rate of coupling of VI and *o*-iodoethylbenzene was slow enough so that considerable VI was decomposed during the course of the reaction, whereas in the latter, the rate of self coupling of VII was comparable with the rate of mixed coupling. The best yield of VIII probably would have been obtained using 4-bromo-5-nitroveratrole.

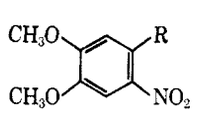
(1) National Institutes of Health Predoctoral Fellow.

(2) The details of isolation and structural elucidation of this alkaloid will be presented in a forthcoming publication.

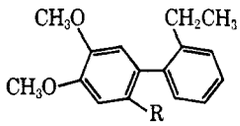
(3) N. Campbell and E. B. McCall, *J. Chem. Soc.*, 2870 (1950).

(4) P. L. Julian, E. W. Meyer, and H. C. Printy, "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p 24.

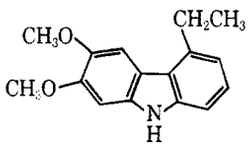
(5) *o*-Bromoethylbenzene could not be used since the rate of mixed coupling was slow enough to result in the complete self coupling of the 4-halo-5-nitroveratrole.



VI, R = Cl
VII, R = I



VIII, R = NO_2
IX, R = NH_2
X, R = N_3



XI

Reduction of VIII with hydrazine in ethanol catalyzed by Raney nickel gave the amine IX. Diazotization of IX followed by treatment of the diazonium compound with sodium azide afforded 2-azido-4,5-dimethoxy-2′-ethylbiphenyl (X). The azide X showed remarkable stability to heat and could be recovered unchanged after an hour reflux in *n*-hexyl ether (235°). Only in the presence of 30% palladium–charcoal did decomposition of X in refluxing *n*-hexyl ether ensue to give 4-ethyl-6,7-dimethoxycarbazole (XI), and even with the catalyst the evolution of nitrogen was relatively slow.

Interpretation of Nmr Spectra.—Frequently assignments of aromatic signals in nmr spectra can be made through consideration of electron densities. An LCAO–MO calculation has shown the electron density in carbazole[6] to be smallest at C-2, followed by C-4, C-3, and C-1, respectively. In this computation the electron density at C-2 was found to be an order of magnitude smaller than electron densities at C-4, C-3, and C-1 (Table I). If electron density alone imparts the major effect on the chemical shift of aromatic protons, then this calculation predicts that the C-2 proton should resonate at lowest field. On studying electrophilic substitution of carbazole, it was found[7] that C-2 was nitrated an order of magnitude more slow than C-1 or C-3 (Table I), indicating the electron density to be much smaller at C-2 than at C-1 and C-3. It was also found[7] that the rate of nitration at C-4 was small, but there was no indication of how much smaller in comparison to C-2. This order could be reproduced by appropriate MO calculations using reasonable parameters. The authors concluded that the electron density was smallest at C-4 and did not consider the influence of steric hindrance on the nitration rate at this position.

TABLE I

COMPARISON OF CALCULATED ELECTRON DENSITIES IN CARBAZOLE WITH PARTIAL RATE FACTORS OF NITRATION

Ring position	Frontier electron density[a]	Rate of nitration in acetic anhydride[b,c]
1	0.268	3.2×10^4
2	0.007	0.11×10^4
3	0.224	7.8×10^4
4	0.108	Small

[a] From ref 6. [b] From ref 7. [c] Relative to benzene nitration at 0°.

(6) K. Fukui, T. Yonezawa, C. Nagata, and H. Shingu, *J. Chem. Phys.*, **22**, 1433 (1954).

(7) R. D. Brown and B. A. W. Coller, *Australian J. Chem.*, **12**, 152 (1959), using the nitration data of M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.*, 3079 (1958).

In Table II the chemical shifts[8] of the various protons of IIIa, IIIb, IIIc, and XI are compared. The chemical shifts of the aromatic C-1, C-2, and C-3 protons are essentially the same, whereas that of the C-4 proton is distinctly different. Obviously the electron density does not play the major role in determining the chemical shifts of the carbazole protons, since the C-2 proton does not resonate at lowest field as MO calculations of electron density predict. The resonance of the C-4 proton at lowest field is not attributed to the low electron density at C-4 but to a ring-current effect and a steric interaction with the C-5 proton.[9] For similar reasons the position of the C-5 hydrogen is displaced from that of the C-8 proton. This effect is observed in many aromatic compounds; for example, in the nmr spectrum of phenanthrene, where the C-4 and C-5 protons exhibit the lowest field signal, about 1 ppm removed from the complex multiplet for the other aromatic proton.[9] The paramagnetic displacement of the quartet for the methylene protons of the ethyl substituent at C-4 also is explained by this phenomenon. In simplest terms the signal of a proton-bearing substituent at the C-4 or C-5 position is shifted downfield owing to the anisotropy of the neighboring aromatic system.

TABLE II

COMPARISON OF PROTON CHEMICAL SHIELDING PARAMETERS OF SOME ETHYL-6,7-DIMETHOXYCARBAZOLES

	Chemical shift, δ			
Protons	1-Ethyl	2-Ethyl	3-Ethyl	4-Ethyl
H-1[a]		7.08	7.18	7.2
H-2[a]	7.19		7.18	7.2
H-3[a]	7.19	7.08		7.2
H-4	7.81	7.84	7.80	
H-5	7.51	7.48	7.52	7.63
H-8[b]	6.92	6.78	6.72	6.87
OCH_3	3.90	3.88	3.87[b]	3.93
	3.97	3.97	3.98	4.03
NH[b]	7.94	7.67	7.72	7.92
CH_2[c]	2.88	2.79	2.83	3.25
CH_3[c]	1.38	1.30	1.33	1.47

[a] Center of multiplet. [b] Concentration dependent or position sensitive to small amount of impurity. [c] J = 7.5 cps.

The abstraction of the correct coupling constants from a three-spin spectrum is important since from them the structural relationship of the three protons can be deduced. Very often the small lines of a three-spin spectrum cannot be observed because of an unfavorable signal to noise ratio. If this is so, then the determination of the coupling constants becomes impossible. In the case of IIIc, where the C-4 proton forms the X part and the C-3 and C-2 protons the A and B parts, respectively, of an ABX spectrum, only the principal lines, appearing essentially as a triplet for the X proton and a doublet for the AB protons, were immediately apparent. Only after a thorough examination of this region of the spectrum were the small lines found.

(8) The nmr measurements were obtained on a Varian A-60 instrument in deuteriochloroform solution. Chemical shifts are reported in cycles per second or parts per million as δ units relative to internal tetramethylsilane (δ = 0).

(9) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 250.

Our initial error in assigning structure IIIa to the degradation product can be ascribed to the following reasons: (1) an erroneous assignment, based only on electron densities, of the signal at δ 7.81 to the C-2 proton, (2) failure to recognize the effect of the anisotropy of the neighboring aromatic system on the C-4 proton, and (3) the inability to observe the smaller lines of the ABX spectrum and extract the coupling constants.

With the aid of a generalized three-spin program for the IBM 7090 high-speed digital computer,[10] an accurate match between the experimental spectrum of the C-2, C-3, and C-4 protons of IIIc and the calculated spectrum was achieved. The experimental energy levels and their errors were first calculated from the observed spectrum. Next the energy levels were calculated from a set of trial parameters where the three coupling constants were all assumed positive and the program then iterated to obtain a better agreement with the experimental energy levels. Finally the spectrum was calculated from the set of final parameters and the calculated frequencies. Calculated line intensities are summarized in Table III. When the calculated spectrum was plotted,[10] it was readily apparent that the intensities of the small lines did not coincide with those of the observed spectrum (Figure 1). Another discrepancy in this calculation was the somewhat large *meta*-coupling constant (J_{BX} = 3.27 cps) and the small *ortho*-coupling constant (J_{AX} = 5.80 cps).

TABLE III

OBSERVED AND CALCULATED FREQUENCIES AND CALCULATED LINE INTENSITIES OF THE ABX SPECTRUM OF THE C-2, C-3, AND C-4 PROTONS OF 1-ETHYL-6,7-DIMETHOXYCARBAZOLE

Obsd frequency	Calcd frequency[a]	Calcd intensity[a]	Calcd frequency[b]	Calcd intensity[b]
Unobsd	−392.80	0.00	−392.78	0.00
−420.8	−420.88	0.09	−420.88	0.07
−425.8	−425.58	0.02	−425.58	0.01
−428.1	−428.13	1.66	−428.13	1.64
−428.8	−428.80	1.65	−428.79	1.67
−433.0	−432.83	2.21	−432.82	2.18
−433.0	−433.15	2.24	−433.14	2.24
−436.0	−436.05	0.13	−436.04	0.14
−440.3	−440.40	0.01	−440.39	0.04
−460.6	−460.91	0.04	−460.92	0.17
−464.3	−464.13	1.26	−464.13	1.25
−468.7	−468.48	0.95	−468.48	0.87
−468.7	−468.83	0.95	−468.83	0.86
−473.2	−473.17	0.78	−473.18	0.78
Unobsd[c]	−476.40	0.02	−476.40	0.07

[a] Spectrum satisfied by the chemical shifts ν_A = −429.68, ν_B = −432.06, and ν_X = −468.36 cps and spin-spin coupling constants J_{AB} = 7.23, J_{AX} = 5.80, and J_{BX} = 3.27 cps. [b] Spectrum satisfied by the chemical shifts ν_A = −430.53, ν_B = −431.27, and ν_X = −468.30 cps and spin-spin coupling constants, J_{AB} = 7.26, J_{AX} = 7.09, and J_{BX} = 1.95 cps. [c] Masked by NH signal.

The differences can only be rationalized with another set of parameters. Four sets of coupling constants will satisfy this spectrum: one set where all three coupling constants have the same sign and three sets where one of the coupling constants has an opposite sign with respect to the other two. The two possibilities in which the coupling constants J_{AX} and J_{AB} have opposite signs

(10) J. D. Swalen and C. A. Reilly, *J. Chem. Phys.*, **37**, 21 (1962).

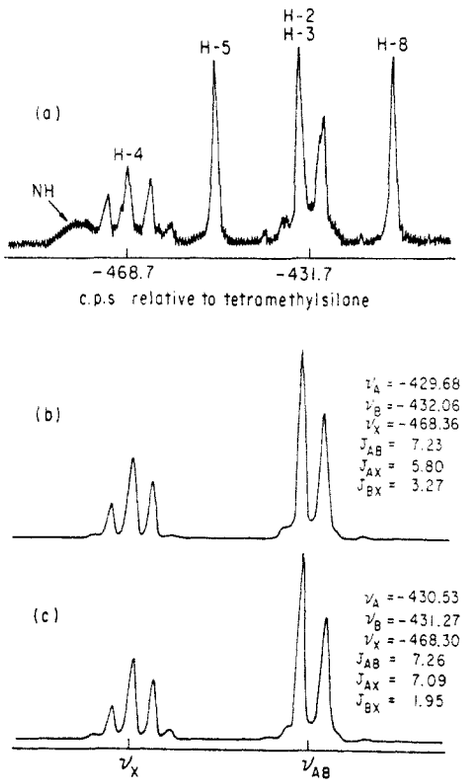


Figure 1.—Comparison of (a) observed and (b, c) calculated ABX spectra of H-2, H-3, and H-4 of 1-ethyl-6,7-dimethoxycarbazole (IIIc).

can be rejected, since the B (C-2) and X (C-4) protons are vicinal to the A (C-3) proton. In an attempt to find a solution of this spectrum with a small negative value for the *meta*-coupling constant J_{BX}, another set of coupling constants with all like signs was converged on by the iterative process of the program to match the calculated and experimental energy levels. The coupling constants J_{AX} = 7.09 and J_{BX} = 1.95 cps from this computed spectrum, however, were now much more reasonable for *ortho* and *meta* coupling, respectively. Moreover, the line intensities of the calculated nmr plot agreed excellently with those experimentally observed (Figure 1). The frequencies and line intensities from this computation are also given in Table III. This ABX spectrum represents a rare example with its two sets of coupling constants with all like signs.

The ABX spectra of IIIa and IIIb were not analyzed with the aid of the computer. The ABX spectrum exhibited by the C-1, C-3 and C-4 protons of IIIb is satisfied approximately by the chemical shifts ν_A = −422.6, ν_B = −427.0, and ν_X = −470.4 cps and the spin-spin coupling constants J_{AB} = 1.5, J_{AX} = 8.0, and J_{BX} = 0.5 cps. The parameters could not be abstracted from the ABX spectrum displayed by the C-1, C-2, and C-4 protons of IIIa since $\nu_A - \nu_B$ is very small (< 0.5 cps), resulting in the appearance of essentially a singlet with small lines which could not be adequately seen above the noise; furthermore, the signal for the C-4 proton was unresolved because of long-range coupling to the methylene protons of the ethyl substituent. The C-1, C-2, and C-3 protons of XI exhibit a complex ABC spectrum.

The NH proton appears as a broad band due to quadrupole relaxation of the nitrogen, the chemical shift of which is influenced by concentration of sample,

solvent, and the presence of impurities. The chemical shifts of the C-1 and C-8 protons, especially in the spectrum of IIIa, and the methoxy signal at highest field in the spectrum of IIIa are affected by these factors.

Experimental Section[11]

3-Ethyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole (IIa).—A solution of 1.05 g of 3,4-dimethoxyphenylhydrazine hydrochloride[12] and 0.65 g of 4-ethylcyclohexanone in 50 ml of methanol–benzene (1:1) was heated to reflux in a nitrogen atmosphere, 0.76 ml of pyridine was added, and the resulting solution was refluxed for 15 min and then evaporated *in vacuo*. The crystalline residue was treated with 25 ml of glacial acetic acid, the mixture was heated on a steam bath for 10 min and again evaporated, and the residual solid was distributed between 1 *N* hydrochloric acid and ether. The product crystallized when the washed (bicarbonate) and dried ether layer was slowly evaporated under a stream of nitrogen. It was removed by filtration, washed with cold, peroxide-free ether and cold ethanol, and dried, 0.63 g (48%), mp 121–123°.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.1; H, 8.2. Found: C, 74.3; H, 8.2.

2-Ethyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole (IIb).—The indolic product was prepared (using the procedure described above) from 400 mg of 3,4-dimethoxyphenylhydrazine hydrochloride and 250 mg of 3-ethylcyclohexanone. The oil that was obtained was fractionally distilled at 80° (0.3 mm) and 130° (0.3 mm), giving a gum at 130° which readily crystallized when triturated with ethanol. Washing with cold ethanol and drying gave 195 mg (42%), mp 119–122° with a change of crystalline form at 80–90°.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.1; H, 8.2. Found: C, 73.5; H, 7.9.

2,3-Dimethoxycarbazole.—A mixture of 300 mg of 1,2,3,4-tetrahydro-6,7-dimethoxycarbazole (mp 108–110°, lit.[12] mp 105–106°) and 450 mg of 30% palladium–charcoal in 10 ml of *n*-hexyl ether was refluxed (stirring) for 1.5 hr in a nitrogen atmosphere, cooled, and filtered. The catalyst was extracted with several portions of hot methanol and the methanol extract was concentrated to give the crystalline carbazole which was recrystallized from methanol and dried at 80° (0.1 mm) for 20 hr, mp 187–188° (lit.[13] mp 125°); the ultraviolet spectrum gave λ_{max} 216 mμ (ε 23,400), 235 (44,800), 250 sh (16,100), 263 (13,400), 304 (17,900), 327 sh (5520), 342 (5170), and λ_{min} 224 mμ (ε 20,400), 260 (13,200), 277 (3640), 338 (4930).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.8. Found: C, 74.3; H, 5.7.

3-Ethyl-6,7-dimethoxycarbazole (IIIa).—3-Ethyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole (IIa) was dehydrogenated in refluxing *n*-hexyl ether in the presence of 30% palladium–charcoal for 5 hr. The mixture was filtered hot, the filtrate was diluted with petroleum ether (bp 60–90°), and the resulting mixture was cooled strongly for several hours. The crystalline carbazole was removed by filtration, sublimed at 140° (0.2 mm), recrystallized several times from absolute ethanol, and dried at 80° (0.3 mm) for 18 hr, mp 156.5–157.5° with change of crystalline form at 145–146°.

Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7. Found: C, 75.3; H, 6.5.

2-Ethyl-6,7-dimethoxycarbazole (IIIb).—The dehydrogenation of 2-ethyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole (IIb) was performed using the procedure described above. The product was sublimed at 120° (0.3 mm) and recrystallized twice from benzene–petroleum ether, mp 137–138°.

Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7. Found: C, 74.9; H, 6.5.

1-Ethyl-6,7-dimethoxycarbazole (IIIc).—A solution of 2.05 g of 3,4-dimethoxyphenylhydrazine hydrochloride and 1.26 g of 2-ethylcyclohexanone in 100 ml of methanol–benzene (1:1) was heated to reflux in a nitrogen atmosphere, 1.5 ml of pyridine was added, and the resulting solution was refluxed for 15 min. The benzene and methanol were removed *in vacuo* and the residue was dissolved in 40 ml of absolute ethanol; 3 ml of concentrated sulfuric acid was added dropwise with swirling, and this solution was refluxed in a nitrogen atmosphere for 10 min. Thirty milliliters of water was added to the cooled solution, most of the ethanol was evaporated under reduced pressure, and the concentrated mixture was extracted with peroxide-free ether. The dried ethereal layer was evaporated to give crude 1-ethyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole (IIc) as a yellow gum: ultraviolet spectrum, λ_{max} 285, 228, 302 sh mμ, and λ_{min} 255 mμ. The indole was dehydrogenated in 10 ml of *n*-hexyl ether in the presence of 1 g of 30% palladium–charcoal by refluxing the mixture in a nitrogen atmosphere for 3 hr. The mixture was filtered while hot and 1.01 g (40%) of 1-ethyl-6,7-dimethoxycarbazole crystallized from the cooled filtrate, mp 157.5–158° after repeated sublimation at 140° (0.3 mm) and recrystallization from absolute ethanol: ultraviolet spectrum, λ_{max} 210 mμ (ε 28,000) 235 (44,300), 250 sh (19,400), 262 (15,600), 303 (17,500), 328 (5730), 340 (5280), and λ_{min} 217 mμ (ε 25,700), 259 (15,400), 277 (3960), 322 (5600), 335 (5190).

Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.3; N, 5.5. Found: C, 75.0; N, 5.5.

Reaction of 4-Aminoveratrole and 2-Chloro-4-ethylcyclohexanone.—2-Chloro-4-ethylcyclohexanone was prepared from 4-ethylcyclohexanone using the procedure described for the preparation of 2-chlorocyclohexanone.[14] Fractional distillation of the chlorination product afforded a 30% yield of 2-chloro-4-ethylcyclohexanone, bp 103–104° (3.5 mm); nmr spectrum in carbon disulfide showed a quartet at 4.50 (H-2). The compound was not characterized further.

A mixture of 3.8 g of 4-aminoveratrole, 4.2 g of 2-chloro-4-ethylcyclohexanone, and 2.5 g of anhydrous sodium acetate in 100 ml of absolute ethanol was refluxed for 6 hr in a nitrogen atmosphere and then was evaporated. The residue was refluxed for 6 hr in a nitrogen atmosphere and then evaporated. The residue was distributed between water and ether and the ethereal layer was washed with 0.5 *N* hydrochloric acid and water, dried, and evaporated, leaving a gum which produced 640 mg (10%) of crystalline 3-ethyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole (IIa) after vacuum sublimation and trituration with ethanol. Positive identification of the product was obtained by dehydrogenation of the indole to 3-ethyl-6,7-dimethoxycarbazole (IIIa), identical in all respects with the carbazole prepared above.

4-Iodo-5-nitroveratrole (VII).—A suspension of 2.8 g of powdered 4-amino-5-nitroveratrole[15] in 15 ml of concentrated hydrochloric acid and 5 ml of water was heated on a steam bath for 5 min and then cooled to *ca.* 5° with stirring. A solution of 1 g of sodium nitrite in 15 ml of water was added dropwise and then water was added until all the solid dissolved; the solution was stirred for 5 min longer. A solution of 2.5 g of potassium iodide in water was added rapidly with vigorous stirring at 5°. There was an immediate evolution of nitrogen and the brown precipitate which formed was removed by filtration, washed with water, recrystallized from ethanol, and sublimed at 100° (0.2 mm) to give 2.6 g (60%) of yellow-orange crystals, mp 149.5–150.5°.

Anal. Calcd for $C_8H_8NO_4I$: C, 31.1; H, 2.6; I, 41.1. Found: C, 31.3; H, 2.6; I, 41.3.

4-Chloro-5-nitroveratrole (VI).—When the diazonium solution described above was poured into a well-stirred solution of 2.8 g of cuprous chloride in 100 ml of 6 *N* hydrochloric acid, there was an immediate evolution of nitrogen and the formation of a tan precipitate. The solid was removed by filtration, washed with water, recrystallized from ethanol, and sublimed at 80° (0.3 mm) to give 2.0 g (65%) of pale yellow crystals, mp 114.5–115.5°.

Anal. Calcd for $C_8H_8NO_4Cl$: C, 44.1; H, 3.7; Cl, 16.3. Found: C, 44.4; H, 3.8; Cl, 16.2

2-Nitro-4,5-dimethoxy-2′-ethylbiphenyl (VIII). A. From 4-Chloro-5-nitroveratrole (VI) and *o*-Iodoethylbenzene.—A mixture of 2.60 g of 4-chloro-5-nitroveratrole, 3.5 g of *o*-iodoethylbenzene, and 6 g of copper powder[16] was heated in a salt bath at 235–240° in a nitrogen atmosphere for 20 hr. The cooled mixture was digested in chloroform and the chloroform extract was filtered

(11) All melting points were taken on a Kofler hot stage; microanalyses were performed by the Microchemical Laboratory, University of California at Berkeley; ultraviolet spectra were determined in ethanol; nmr spectra are reported as δ values relative to internal TMS (δ = 0).

(12) R. J. S. Beer, L. McGrath, A. Robertson, A. B. Woodier, and J. S. E. Holker, *J. Chem. Soc.*, 2061 (1949).

(13) G. H. Hughes, F. Lions, J. J. Maunsell, and L. E. A. Wright, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 428 (1938).

(14) M. S. Newman, M. D. Farbman, and H. Hipsher, *Org. Syn.*, **3**, 188 (1955).

(15) T. G. H. Jones and R. Robinson, *J. Chem. Soc.*, **111**, 903 (1917).

(16) Baker and Adamson copper powder was used.

through a short column of alumina (Woelm, neutral) to remove considerable tar. The filtrate was evaporated and the residual resin was extracted several times with boiling *n*-hexane. The *n*-hexane extract was introduced onto an alumina column (Woelm, neutral; 10 g), the column was washed with *n*-hexane, and the product was eluted with benzene–hexane (1:1). 2-Nitro-4,5-dimethoxy-2′-ethylbiphenyl (VIII) could not be induced to crystallize and was purified only by a short-path distillation at 100° (0.3 mm) to give 1.45 g (42%) of a yellow oil; nmr spectrum in carbon disulfide showed a singlet at 7.45 (H-3) and a singlet at 6.51 (H-6).

Anal. Calcd for $C_{16}H_{17}NO_4$: N, 4.9. Found: N, 4.6.

B. From 4-Iodo-5-nitroveratrole (VII) and *o*-Iodoethylbenzene.—A mixture of 1.55 g of 4-iodo-5-nitroveratrole and 2.3 g of *o*-iodoethylbenzene was heated to 190° in a nitrogen atmosphere and 2.5 g of copper powder[16] was added over 1 hr. The resulting mixture was then heated to 210–215° for 2 hr, cooled, and extracted with hot methanol. On concentrating and cooling the methanol extract, 0.4 g (44%) of 2,2′-dinitrobiveratrole was obtained, mp 218–220° after recrystallization from ethanol; nmr spectrum in deuteriochloroform showed a singlet at 7.83 (H-3 and H-3′), a singlet at 6.72 (H-6 and H-6′), and a singlet at 3.95 and 4.05 (OCH_3).

Anal. Calcd for $C_{16}H_{16}N_2O_8$: C, 52.8; H, 4.4. Found: C, 52.3; H, 4.3.

The 2,2′-dinitrobiveratrole mother liquors were evaporated and the residual oil was extracted with several portions of hot *n*-hexane. After chromatography of the hexaneextracted material on alumina (Woelm, neutral; 3 g), followed by a short-path distillation at 100° (0.3 mm) of the crude product eluted from the column with benzene–hexane (1:1), 0.40 g (28%) of 2-nitro-4,5-dimethoxy-2′-ethylbiphenyl (VIII) was obtained as a yellow oil.

4-Ethyl-6,7-dimethoxycarbazole (XI).—2-Nitro-4,5-dimethoxy-2′-ethylbiphenyl (VIII) was reduced to the corresponding amine in quantitative yield by hydrazine–Raney nickel.[17] The crude amine was purified by short-path distillation at 80° (0.3 mm) to give 2-amino-4,5-dimethoxy-2′-ethylbiphenyl (IX) as a colorless oil; nmr spectrum (carbon disulfide) showed a singlet at 6.13 (H-3) and a singlet at 6.40 (H-6).

(17) D. Balcom and A. Furst, *J. Am. Chem. Soc.*, **75**, 4334 (1953).

A solution of 600 mg of the amine IX in 1 ml of concentrated sulfuric acid and 5 ml of water was cooled to 5° and treated dropwise with a solution of 160 mg of sodium nitrite in 2 ml of water. After allowing the diazonium solution to stand for 5 min at 5°, 200 mg of sodium azide in 5 ml of water was added all at once. As the mixture stood at room temperature overnight, nitrogen was slowly evolved and a dark orange oil was deposited on the wall of the flask. The mixture was extracted with chloroform and the dried chloroform extract evaporated *in vacuo* at 30–35° to give 490 mg (74%) of quite pure 2-azido-4,5-dimethoxy-2′-ethylbiphenyl (X) as a light brown oil: nmr spectrum, singlet at 6.56 (H-3 and H-6).

The azido compound was dissolved in 10 ml of *n*-hexyl ether, 100 mg of 30% palladium–charcoal was added, and the mixture was heated to 235–240°[18] in a nitrogen atmosphere. After 1 hr the evolution of nitrogen ceased and the mixture was refluxed for 15 min longer and then filtered while hot. The product crystallized from the cooled filtrate and was removed by filtration, washed with *n*-hexane, recrystallized from ethanol, and sublimed at 135° (0.3 mm) to give 253 mg (58%) of 4-ethyl-6,7-dimethoxycarbazole (XI): mp 144–146°; ultraviolet spectrum, λ_{max} 237 mμ (ε 47,400), 265 (16,300), 302 (18,500), 328 (5740) 340 (5740), and λ_{min} 220 mμ (ε 25,200), 260 (15,400), 279 (6400), 319 (5270), 331 (5650).

Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7; N, 5.5. Found: C, 75.0; H, 6.6; N, 5.7.

Registry No.—IIa, 14171-79-0; IIb, 14120-07-1; IIc, 14120-08-2; IIIa, 14120-09-3; IIIb, 14120-10-6; IIIc, 14120-11-7; VI, 3899-65-8; VII, 14120-13-9; VIII, 14120-14-0; XI, 14120-16-2; 2,3-dimethoxycarbazole, 14120-17-3; 2-chloro-4-ethylcyclohexanone, 14120-18-4; 2,2′-dinitrobiveratrole, 14172-77-1; IX, 14120-15-1; X, 14271-19-3.

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(18) Nitrogen was evolved smoothly at this temperature; however, no decomposition of the azide occurred during 1 hr in the absence of a catalyst.

Cyclizations of Anthranilate–Acetylenedicarboxylate Adducts. A Facile Route to 2,8-Dicarboalkoxy-4(1H)-quinolinones[1]

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Isatoic anhydrides (**1**) and anthranilic esters (**2**) react with acetylenedicarboxylates to give Michael adducts (**3**) which cyclize to 2,8 dicarboalkoxy-4(1H)-quinolinones (**4**) upon heating. The synthesis is limited by steric and electronic features in the initial anhydrides and esters which inhibit formation of the intermediate enamines (**3**).

The Conrad–Limpach reaction of β-dicarbonyl compounds with arylamines[2,3] is traditionally employed as the most general synthesis of 4(1H)-quinolinones; it was used for the preparation of the majority of quinolinones examined in the antimalarial program during World War II. This method, however, suffers from several significant disadvantages. A major problem has been the direction of the reactants, arylamine and β-keto ester, toward formation of the desired cyclization precursor, a substituted aminocrotonate, rather than toward the competitive product, an anilide, which leads to 2(1H)-quinolinones (Knorr synthesis).[4] In some cases no aminocrotonate formation was observed.[5] Similar problems are encountered with the closely related Gould–Jacobs reaction, which involves thermal cyclization of α-carbethoxy-β-anilinoacrylic esters.[6]

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