as described above. The basic fraction afforded 22,25-diazacholesterol (7, 120 mg): mp 110–112° (lit.[3] mp 112–114°); nmr ($CDCl_3$) δ 0.70 (C-18 CH_3), 1.00 (C-19 CH_3), 1.08 (d, J = 6.5 Hz, C-21 CH_3), 2.17 (-$N(CH_3)_2$). The neutral fraction (1 g) was acetylated and chromatographed on silicic acid impregnated with 5% $AgNO_3$. Elution with hexane–C_6H_6 (9:1, 200 ml) gave *cis*-3β-acetoxy-5,20(21)-pregnadiene (8, 200 mg, 16%): mp 87–89° (from MeOH); [α]D −65° (lit.[18] mp 89°; [α]D −70°). Further elution with the same solvent gave a mixture of 8 and 3 (200 mg). This was followed by a fraction (200 ml) contg pure 3 (100 mg, 8%). The next fraction eluted from the column contained a mixture of 3 and 4 (150 mg). This was followed by a fraction contg only 4 (110 mg). Further elution with hexane–C_6H_6 (7:3) gave the *D*-homoacetate 5 (100 mg).

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3(2*H*)-Isoquinolones. 1. 3-Oxygenated Analogs of Papaverine as Peripheral Vasodilators†

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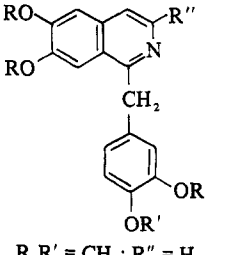
Two types of papaverine analogs, *N*-substituted-6,7-dialkoxy-1-(3,4-dialkoxybenzyl)-3(2*H*)-isoquinolone hydrochlorides (**5**, **10**) and 3-alkoxypapaverines (**6**) were prepared, and the cardiovascular effects of representative compounds were studied in comparison with papaverine and ethaverine. The 3(2*H*)-isoquinolone derivatives elicit a rapid lowering of blood pressure when administered iv or id to anesthetized dogs. The *N*-methyl-3(2*H*)-isoquinolone derivative (**5a**) shows relatively less positive inotropic effect than papaverine hydrochloride, both iv and id, and produces a longer vasodilator response. Compounds **6b** and **10** exhibit greater vascular selectivity than **5a** upon rapid iv administration in dogs, although **6b** is much less effective when given id in the rat. Although no obvious structure–activity relationship is evident among the N-substituents in the isoquinolones studied, it is apparent that the *N*-substituted-3(2*H*)-isoquinolone variation of papaverine allows enhanced selectivity and/or duration of peripheral vasodilator activity in the dog.

Clinically interesting 1-benzylisoquinolines include such compounds as papaverine (**1**),[1] dioxyline (**2**),[2] and ethaverine (**3**).[3] Although papaverine enjoys considerable use as an antispasmodic and peripheral vasodilator, its utility is hampered by untoward cardiac effects and short duration of action.

We have investigated the synthesis and vasodilator properties of isoquinoline derivatives, structurally related to papaverine, but having oxygen functions in the 3 position.

Chemical Synthesis. The reaction of 2-[(3,4-dimethoxyphenyl)acetyl]-4,5-dimethoxyphenyl acetic acid (**7**) with NH_4OAc was reported to give the 3(4*H*)-isoquinolone (**4a**).[4,5] However, our spectral data support the existence of **4** under most conditions as the 3(2*H*)-isoquinolone, **4b**,

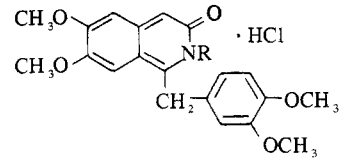


1, R,R' = CH_3; R'' = H
2, R,R'' = CH_3; R' = C_2H_5
3, R,R' = C_2H_5; R'' = H

in agreement with a recent communication.[6] Other workers[7,8] have demonstrated an equilibrium between 3(2*H*)-isoquinolones and 3-isoquinolinols, in which polar solvents (H_2O, EtOH) favor the lactam form and nonpolar solvents (Et_2O, dioxane) allow the lactim to predominate.

†Presented in part before the Medicinal Division, 163rd National Meeting of the American Chemical Society, Boston, Mass., April 10, 1972.

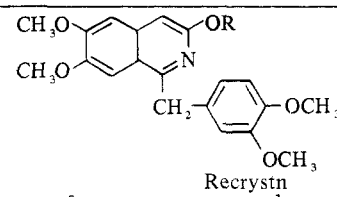
Table I. 2-Substituted 6,7-Dimethoxy-1-veratryl-3(2*H*)-isoquinolone Hydrochlorides



Compound	R	Method	% yield	Mp, °C[a]	Recrystn solvent[b]	Formula	λ_{max},[c] nm (ε)	Anal.
5a	CH_3	A	43	223.0–225.0	M-EA	$C_{21}H_{23}NO_5 \cdot HCl$	400 (6300)	C, H, N
		B	39	227.5–228.5	M-EA			
		C	76	228.0–230.0	M-EA			
5b	C_2H_5	B	30	219.5–221.5	M-EA	$C_{22}H_{25}NO_5 \cdot HCl$	402 (5400)	C, H, N
5c	$CH_2CH{=}CH_2$	C	23	182.5–184.5	E-EA	$C_{23}H_{25}NO_5 \cdot HCl$	403 (4900)	C, H, N
5d	$CHCH_2CH_2$	C	82	214.0–215.0	M-I	$C_{23}H_{25}NO_5 \cdot HCl$	400 (5400)	C, H, N
5e	$CH_2C_6H_5$	B	25	145.0[d]	M-EA	$C_{27}H_{27}NO_5 \cdot HCl$	400 (5300)	C, H, N
5f	$CH_2CH_2C_6H_3$-3,4$(OCH_3)_2$	B	10	215.5–219.0	I	$C_{30}H_{33}NO_7 \cdot HCl$	400 (6500)	C, H, N
5g	OH	*e*	74	205.5–210.0	M	$C_{20}H_{21}NO_6 \cdot HCl$	394 (4400)	C, H, N
5h	NH_2	*e*	39	206.0–207.0	M-E	$C_{20}H_{22}N_2O_5 \cdot HCl$	400 (6400)	C, H, N
5i	$N(CH_3)_2$	C	59	156.0–163.0	M-EA	$C_{22}H_{26}N_2O_5 \cdot HCl$	400 (4300)	C, H, N

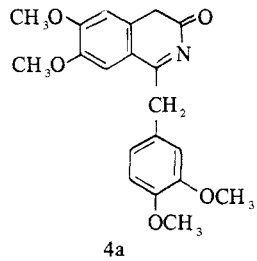
[a]Mp's are corrected and include decomposition. See footnote ‡. [b]M = MeOH, EA = EtOAc, I = *i*-PrOH, E = abs EtOH. [c]Longest wavelength uv absorption in 95% EtOH at 10 μg/ml. [d]Resolidifies and melts again at 208.5–209.5°. [e]See Experimental Section.

Table II. 3-Alkoxy-6,7-dimethoxy-1-veratrylisoquinolines

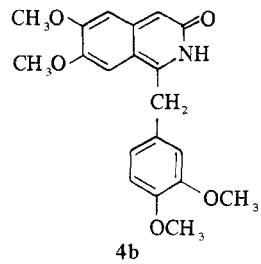


Compound	R	% yield	Mp, °C[a]	Recrystn solvent[b]	Formula	λ_{max},[c] nm (ε)	*Anal.*
6a	CH_3	49	135.0–136.0	D-C	$C_{21}H_{23}NO_5$	346 (5500)	C, H, N
6b	CH_2CH_3	43	110.0–112.0	M-I	$C_{22}H_{25}NO_5$	348 (5500)	C, H, N
6c	$CH_2C_6H_5$	72	114.0–115.5	M-I	$C_{27}H_{27}NO_5$	348 (5500)	C, H, N
6d	$CH_2CH{=}CH_2$	58	108.0–109.5	M-I	$C_{23}H_{25}NO_5$	347 (5900)	C, H, N

[a]Mp's are corrected. [b]D = Et_2O, C = CH_2Cl_2, M = MeOH, I = *i*-PrOH. [c]Longest wavelength uv absorption in $CHCl_3$ at 10 μg/ml.



4a

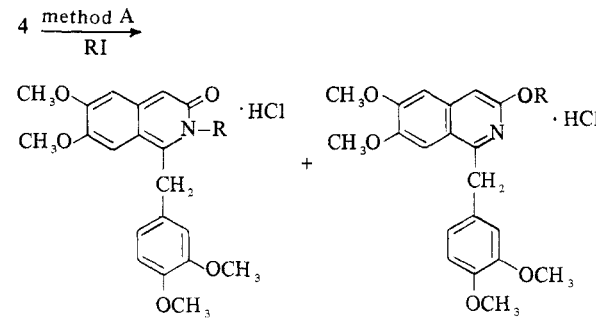


4b

Interestingly, **4** is amphoteric,[9] forming both a sodium salt and a stable hydrochloride (Experimental Section).

Alkylation of **4** with CH_3I in alkaline MeOH (method A, R = CH_3) affords a mixture of N- and O-methylated materials. Uv spectral evidence supports *N*-alkyl as the major product (43% yield) and *O*-alkyl as the minor product (10% yield). The major product (**5a**) absorbs at 400 nm in EtOH and at 395 nm in both H_2O and 0.1 *N* NaOH solution.‡ 6,7-Dimethoxy-1,2-dimethyl-3(2*H*)-isoquinolone, the 1-methyl congener of **5a**, absorbs at 395 nm.[11] Moreover, absorption of the 1-methyl congener of **6b** at 343 nm[7] is nearly identical with that of our minor product (base), 346 nm.

‡Uv spectra of the major alkylation product (HCl salt) in EtOH, H_2O, and 0.1 *N* NaOH are identical; however, a strong hypsochromic shift to 367 nm occurs in 0.1 *N* HCl, apparently due to 3-hydroxy quaternary formation (see ref 9). We make the assumption with 5·HCl that the very weakly basic parent allows virtually complete dissociation of the HCl, resulting in a spectrum of the base in all but very strongly acidic solutions. See also ref 10.

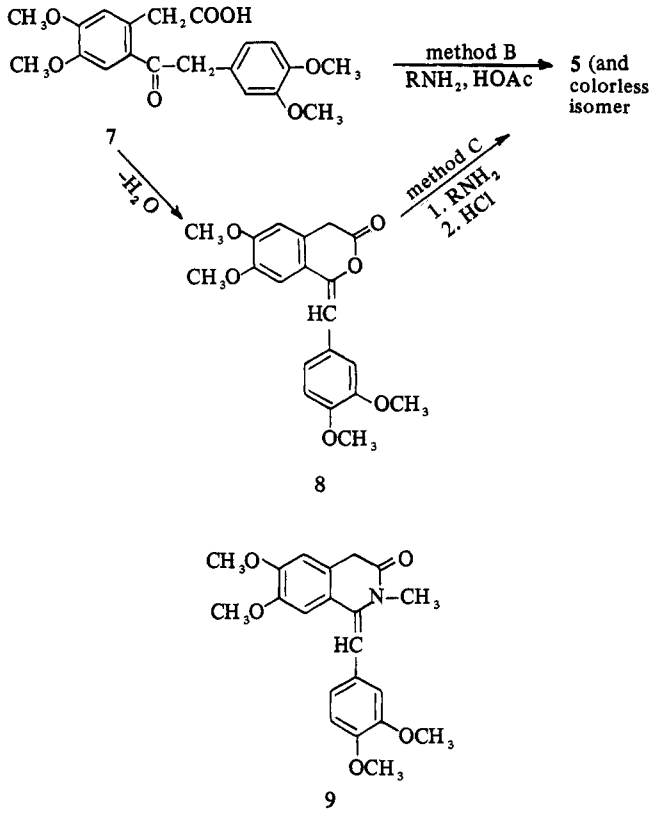


5a-i (Table I) 6a-d (Table II)

Assignment of the major product as *N*-methyl material was confirmed by its unequivocal synthesis from **7** and methylamine (method B, R = CH_3). Moreover, if keto acid **7** is first dehydrated to lactone **8**, the latter allowed to react in dry THF with CH_3NH_2, and the product acidified with HCl-EtOH at 25° (method C), **5a** is produced in quantitative yield (tlc).

The reaction of both **7** and **8** with CH_3NH_2 was first reported[5] to give **9**, an isomer of **5a** base. Our spectral studies clearly confirm structure **5a** as the product of this reaction, which is in agreement with a recent communication.[6]

As further support of the *O*-alkyl assignment, 3-ethoxypapaverine, **6b**, was prepared by allowing **4** to react with triethyloxonium fluoroborate, a reagent which effectively converts lactams to imino ethers;[12] **6b** is nearly colorless,

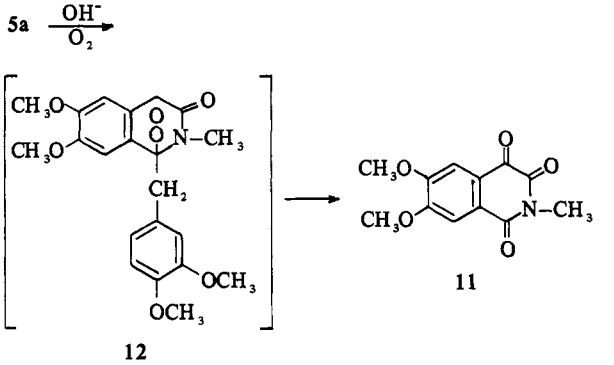


having a long wavelength uv absorption at 348 nm. In addition, **6a** base has been prepared from the Ag salt[10] of **4** by stirring with CH_3I in Et_2O and is identical (mmp, ir) with material obtained by method A. Two other O-substituted derivatives (**6c, d**) were prepared from **4** and the appropriate alkyl halide in K_2CO_3-Me_2CO. The *O*-brosyl derivative (**6e**) was isolated when brosyl chloride was allowed to react with **4** in pyridine-$CHCl_3$.

The interesting cardiovascular pharmacology shown by **5a** prompted us to prepare several additional 3(2*H*)-isoquinolones (Table I). Although **5a** has been prepared by methods A, B, and C, it is generally more convenient to obtain the *N*-alkyl members of the series by method B or C. The synthesis was extended to include *N*-hydroxyl, *N*-amino, and *N*-dimethylamino derivatives (**5g-i**) as well as the tetraethoxy analog of **5a**, compound **10**.

During the preparation of *N*-alkyl-3(2*H*)-isoquinolones by method B, a colorless isomer of the yellow product was isolated in each case; in fact, as R increases in size and bulk, the colorless isomer becomes the predominant product. The structure of these isomers will be the subject of another paper.

There is evidence for reactivity[7,11] and instability[7,13,14] of 3(2*H*)-isoquinolones in the free base form. Attempts to purify **5a** as the free base result in unsatisfactory elemental analyses and isolation of an additional substance (**11**). It is likely that **5a**·base readily absorbs a molecule of oxygen forming **12**, which in the presence of alkali rapidly disproportionates, losing the 1-substituent and forming **11**.



Cardiovascular Effects.§ The 3(2*H*)-isoquinolone derivatives elicit a lowering of diastolic blood pressure (DBP) similar in magnitude to that of **1** and **3** in normotensive, anesthetized dogs following rapid iv administration of compound at a dose of 1.28 mg/kg (Table III). Most of the isoquinolone derivatives also directly stimulate both right ventricular contractile force, as measured by Walton-Brodie strain gauge, and heart rate at doses which lower blood pressure. However, two congeners, the *N*-methyl-3(2*H*)-isoquinolones **5a** and **10**, produce minimal direct myocardial stimulant activity. This is in contrast to the pronounced augmentation of contractile force elicited by **1**[15] and a few of the 3(2*H*)-isoquinolones. Although **3**, administered iv, exhibits vasodilator selectivity with respect to contractile force and heart rate, its potency appears greatly reduced upon intraduodenal (id) administration (Tables III and IV).

The oral effectiveness of the isoquinolone derivatives in lowering blood pressure was inferred by id administration of the *N*-alkyl compounds in anesthetized dogs. Although **4** fails to demonstrate significant hypotensive activity in the dog at a dose of 20 mg/kg, the *N*-alkylisoquinolones (Table IV) cause a rapid lowering of blood pressure within 5 min of drug administration, suggesting that the latter are rapidly absorbed from the digestive tract. The hypotensive response is prolonged (*ca.* 4 hr) and appears to be due to a reduction in total peripheral resistance (TPR) as it occurs without significant change in aortic blood flow (cardiac output minus coronary blood flow). Although **1** at 20 mg/kg id lowers TPR for approximately 2 hr, it is minimally effective at 5 mg/kg by the same route. In contrast, the *N*-alkyl-3(2*H*)-isoquinolones cause a significant fall in TPR at the lower dose. The *N*-methyl compound, **5a**, is the most selective

Table III. Changes in Cardiovascular Parameters Following Rapid Intravenous Administration in Dogs[a]

Compound	n[b]	DBP	CF	HR
4	3	−52.7 ± 4.9	43.0 ± 13.2	26.0 ± 13.6
5a	4	−34.5 ± 3.6	21.8 ± 6.1	19.8 ± 6.1
5b	4	−39.5 ± 1.0	46.3 ± 3.4	26.5 ± 3.7
5c	4	−40.3 ± 3.4	41.8 ± 6.5	30.5 ± 4.9
5d	4	−39.3 ± 4.4	38.5 ± 7.5	26.5 ± 4.3
5g	2	−18.0	8.0	8.0
5h	4	−41.8 ± 2.1	30.5 ± 8.1	24.5 ± 4.3
5i	4	−35.5 ± 3.4	33.5 ± 5.1	17.0 ± 1.3
6b	4	−40.0 ± 2.7	6.5 ± 4.9	8.0 ± 2.9
10	4	−50.0 ± 0.7	6.8 ± 5.7	15.0 ± 4.1
Papaverine·HCl	4	−47.5 ± 6.1	50.0 ± 3.8	31.0 ± 4.3
Ethaverine·HCl	4	−33.0 ± 4.4	11.8 ± 3.5	22.8 ± 10.7

[a] Max change (±SE of mean) in diastolic blood pressure (DBP, Δmm of Hg), right ventricular contractile force (CF, Δg), and heart rate (HR, Δbpm) at a dose of 1.28 mg/kg. [b] Number of dogs.

§ Mongrel dogs (11-14 kg) were anesthetized with sodium thiopental (15 mg/kg) and sodium barbital (275 mg/kg), iv. Systemic blood pressure was monitored from the left carotid artery using a Statham pressure transducer. A tracheotomy was performed, and the animals were ventilated mechanically (Harvard Respirator) with room air. A Walton-Brodie strain gauge arch was sutured to the epicardial surface of the right ventricle through a right-side or midline thoracotomy. Total peripheral resistance (TPR) was calcd as mean systemic blood pressure (mm) divided by mean aortic blood flow (l./min). Test compds were dissolved in distd H_2O, 10-40% DMF-distd H_2O, or DMF for intraduodenal (id) administration and in saline or 10% DMF-saline for iv use, depending upon solubility. Control observations established that the vehicles did not influence the parameters studied.

Table IV. Changes in Cardiovascular Parameters Following Intraduodenal Administration in Dogs

Compound	Dose, mg/kg id	n^a	TPR[b]	CF[c]	DBP[d]
4	20	3	4	8	14
5a	20	3	31	25	51
	5	3	19	20	30
5b	20	1	45	110	66
	5	1	14	110	13
5c	20	1	47	58	67
	5	1	35	57	52
5d	20	1	58	95	70
	5	1	20	51	28
5e	20	1	34	34	41
	5	1	13	10	10
5f	20	1	20	27	20
6a	20	3	12	22	9
Papaverine	20	3	25	85	25
	5	3	5	14	7
Ethaverine	20	3	13	5	8

[a]Number of dogs. [b]Max decrease (%) in total peripheral resistance. [c]Max increase (%) in contractile force. [d]Max decrease (%) in diastolic blood pressure.

member of the series, producing a significant hypotensive response with minimal cardiac stimulation. Compound **10**, however, attenuates blood pressure for a significantly longer period than **1**, **3**, or **5a**, when given id in the anesthetized rat.

Cardiovascular properties of the 3-alkoxypapaverines **6a,-b** were also evaluated in dogs. Although **6a** elicits changes in contractile force (id) comparable to those produced by **5a**, its effect on DBP and TPR is considerably less (Table IV). Compound **6b**, on rapid iv administration, selectively lowers diastolic blood pressure and minimally augments heart rate and contractile force (Table III), but it is much less effective upon id adminstration in the rat.

The *N*-methyl compounds, **5a** and **10**, have been selected for further evaluation. In oral, acute toxicity studies in nonfasted mice, **5a** demonstrates weak CNS depression accompanied by ptosis ($TD_{50} \cong 30$ mg/kg, $LD_{50} \cong 1000$ mg/kg); compound **10** exhibits general CNS depression accompanied by ataxia and dyspnea at higher doses ($TD_{50} = 65$-125 mg/kg, $LD_{50} \cong 1000$ mg/kg). Oral toxicity of **5a** in fasted dogs ($LD_{50} = 304$ mg/kg) may have been affected by emesis.

Although no obvious structure-activity relationship is evident among the N-substituents in the isoquinolones studied, it is apparent that the *N*-substituted-3(2*H*)-isoquinolone variation of papaverine allows enhanced selectivity and/or duration of peripheral vasodilator activity in the dog.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within ±0.4% of the theoretical values. Thin-layer chromatograms were obtained on EM silica gel GF-254, developed in $CHCl_3$–MeOH (9 : 1) and visualized under a Mineralight UVS-12 lamp. Mp's are corrected, as determined on a Thomas-Hoover mp apparatus in open capillary tubes.# Longest wavelength uv bands are reported in nanometers, infrared bands in cm^{-1}, and nmr peaks in ppm (δ) from Me_4Si.

6,7-Dimethoxy-1-veratryl-3(2*H*)-isoquinolone, Sodium Salt (4, Na Salt). A suspn of 4 (3.6 g, 0.01 mole) in 90 ml of 0.2 *N* NaOH was stirred (25°) until all the yellow solid had turned white, and the supernatant was colorless. Chilling overnight and filtering afforded a white solid which was washed (THF) and dried in air to give 4.0 g (99%), sintering above 235°. The nmr spectrum and elemental analysis are consistent with the monohydrate. *Anal.* ($C_{20}H_{20}NNaO_5 \cdot H_2O$) C, H, N.

6,7-Dimethoxy-1-veratryl-3(2*H*)-isoquinolone Hydrochloride (4·HCl). Recrystn of 4 from an equal volume of H_2O and 5 *N* HCl–EtOH afforded a faintly yellow cryst solid: mp 207.0–209.5° dec. Elemental and spectral data are consistent with the hemihydrate. *Anal.* ($C_{20}H_{21}NO_5 \cdot HCl \cdot 0.5H_2O$) C, H, N.

6,7-Dimethoxy-2-methyl-1-veratryl-3(2*H*)-isoquinolone Hydrochloride (5a). Method A. To a refluxing suspn of 28.4 g (0.08 mole) of 4, in 224 g (1.60 moles) of MeI and 400 ml of MeOH, was added 26.0 g of MeONa, in portions over 24 hr, until the starting material was consumed (tlc). Insoluble material was filtered (discarded), and the filtrate was concd to an oil. The oil was taken up in EtOAc, washed with three 300-ml portions of H_2O, dried [K_2CO_3–Darco G-60), and filtered, and the filtrate was acidified (5 *N* HCl–EtOH) to give a yellow solid which was purified as indicated in Table I. Tlc showed one spot (R_f 0.46), fluorescing sky-blue under uv light: ν_{max} (KBr) 1625 (strong, C=O); δ (DMSO-d_6) 3.7–4.2 (5s, 15, N-CH_3, OCH_3), 4.9 (s, 2, CH_2), 6.3–7.2 (3, ArH), 7.3–7.6 (3, ArH).

Method B. A soln of 10 g (0.027 mole) of keto acid 7 and 40 g (0.44 mole) of $CH_3NH_2 \cdot AcOH$ in HOAc (40 ml) was stirred at 130° for 2 hr, then poured into 800 ml of ice water. Concd NH_4OH was added to the mixt until no more ppt formed and the suspn was extd with $CHCl_3$. Sepn and acidification of the organic layer (5 *N* HCl–EtOH to pH 2), followed by removal of the volatile material *in vacuo*, yielded 9 g of brown solid. Fractional recrystn from MeOH–EtOAc gave a yellow powder identical with the material obtained by method A and 700 mg (6.4%) of a colorless isomer: mp 242–244° dec; λ_{max} (95% EtOH) 345 nm (ϵ 11,320). *Anal.* ($C_{21}H_{23}NO_5 \cdot HCl$) C, H, N.

6,7-Diethoxy-1-(3,4-diethoxybenzyl)-2-methyl-3(2*H*)-isoquinolone Hydrochloride (10). {2-[(3,4-Diethoxyphenyl)acetyl]-4,5-diethoxyphenyl}acetic Acid. A procedure[4] using PPA as solvent and catalyst was adapted to prepare the keto acid from (3,4-diethoxyphenyl)acetic acid[16] in 42% yield (EtOAc): mp 151–154°. *Anal.* ($C_{24}H_{30}O_7$) C, H. Method B applied to the keto acid afforded the 3(2*H*)-isoquinolone (**10**) in 54% yield (MeOH–EtOAc): mp 182.5–187.5° dec; λ_{max} (95% EtOH) 400 nm (ϵ 6200). *Anal.* ($C_{25}H_{31}NO_5 \cdot HCl$) C, H, N.

3,6,7-Trimethoxy-1-veratrylisoquinoline Hydrochloride (6a). Method A. The recrystn liquors from the prepn of **5a** were evapd to 100 ml and chilled overnight to afford 5.9 g of yellow solid. Recrystn from MeOH–EtOH gave 3.5 g (mp 189–192° dec) which was converted with NH_4OH to the free base (2.9 g, mp 135–137°). Reconversion to the HCl salt and recrystn from MeOH–*i*-PrOH gave 2.8 g (10%) of light yellow powder, mp 190.5–194.0° dec. Tlc showed one spot (R_f 0.90), fluorescing red-violet under uv light: ν_{max} (KBr) 2650, 1920 (HN^+), 1640 (C=N); δ (DMSO-d_6) 3.8–4.1 (5s, 15, OCH_3), 4.9 (s, 2, CH_2), 7.0–7.7 (6, ArH). *Anal.* ($C_{21}H_{23}NO_5 \cdot HCl$) C, H, N.

***Via* the Silver Salt.** One gram (0.0025 mole) of 4·Na salt (monohydrate) was suspd in 20 ml of abs EtOH and treated dropwise with 2% $AgNO_3$–EtOH until further addn caused no more yellow-orange ppt to form. The resulting suspn was stirred (25° for 1 hr) in the dark and filtered; the yellow filter cake was washed (5 ml of abs EtOH followed by 20 ml of Et_2O) and then dried in air to give 1 g of crude Ag salt. The salt was stirred overnight in the dark with 15 ml of Et_2O and 34 g (0.24 mole) of MeI after which the mixt was diluted to 125 ml (THF) and filtered. Evapn of the filtrates and recrystn of the residues afforded pale yellow crystals of the base (Table II). The ir spectrum is superimposable on that of **6a**·base obtained by method A.

3-Ethoxy-6,7-dimethoxy-1-veratrylisoquinoline (6b). To a soln of triethyloxonium tetrafluoroborate[17] (0.036 mole) in 100 ml of dry CH_2Cl_2 was added a suspn of 10.8 (0.03 mole) of 4 in 200 ml of CH_2Cl_2. The resulting soln was stirred at 25° overnight, chilled, and washed with aqueous K_2CO_3. The organic layer was separated, washed with three 300-ml portions of H_2O, dried ($MgSO_4$–Darco G-60), filtered, and evapd to an oil. The oil, which crystd from MeOH–*i*-PrOH, was recrystd to give a white solid (Table II).

General Reaction of 6,7-Dimethoxy-1-veratryl-3(2*H*)-isoquinolone (4) with Alkyl Halides. Preparation of 3-Alkoxy-6,7-dimethoxy-1-veratrylisoquinolines (6c, d). A procedure[18] using anhyd K_2CO_3–acetone was adapted to prepare these derivatives. The reactions generally required 3 days reflux.

6,7-Dimethoxy-1-veratrylidene-3-isochromanone (8). A soln of keto acid 7 (3.0 g, 0.008 mole) in a mixt of 5 ml of glac AcOH, 5 ml of Ac_2O, and 1 drop of concd H_2SO_4 was heated at 90° for 4 hr. The mixt was allowed to stand overnight, chilled, and filtered to afford 2 g of material which was recrystd (MeCN–Darco G-60) to give

#Corrected melting points were obtained according to USP XVI, class I, which requires immersion at 30° below the expected melting point. Samples which decompose upon melting generally give higher melting points and narrower ranges if immersed at 25°.

1.3 g (45%) of beige flakes: mp 166.0–168.0° (lit.[5] 166–167°); ν_{max} (KBr) 1760 (C=O). *Anal.* ($C_{20}H_{20}O_6$) C, H.

2-Cyclopropyl-6,7-dimethoxy-1-veratryl-3(2*H*)-isoquinolone (5d). Method C. A soln of lactone 8 (10.7 g, 0.03 mole) and cyclopropylamine (5 g, 0.088 mole) in 500 ml of THF was stirred 18 hr at 25°. The volatile material was removed *in vacuo* (85°), and the residue, dissolved in 50 ml of EtOAc, was warmed with excess 5 *N* HCl–EtOH. Evapn of the solvents and recrystn of the residue afforded a yellow solid.

2-Hydroxy-6,7-dimethoxy-1-veratryl-3(2*H*)-isoquinolone Hydrochloride (5g). {2-[3,4-(Dimethoxyphenyl)acetyl]-4,5-dimethoxyphenyl}acetic Acid Oxime. The oxime was prepd[19] by heating 7 with $NH_2OH \cdot HCl$ for 1 hr in aqueous alkali. Recrystn from EtOAc afforded off-white crystals: mp 137–139°. *Anal.* ($C_{20}H_{23}NO_7$) C, H, N. A soln of 7 oxime (2.6 g or 0.0066 mole) in 100 ml of AcOH and 2 ml of 12 *N* HCl was stirred at 25° for 16 hr and concd *in vacuo*. The residue was leached with 100 ml of hot MeOH, and the extracts were evapd to dryness. Recrystn of the residue gave yellow prisms (5g): δ (DMSO-d_6) 3.8–4.0 (12, OCH_3), 4.9 (s, 2, CH_2), 6.9–7.6 (6, ArH). 10.5 (s, 2, OH, H^+).

2-Amino-6,7-dimethoxy-1-veratryl-3(2*H*)-isoquinolone Hydrochloride (5h). A soln of 7 (9.4 g or 0.025 mole), 1.25 g (0.025 mole) of 98% $N_2H_4 \cdot H_2O$, and 150 ml of abs EtOH was refluxed 5 hr. The EtOH was distilled and replaced with 75 ml of *i*-PrOH; 5 *N* HCl–EtOH was added to pH 2, after which the soln was refluxed 1 hr and chilled. The solidified mass, when diluted with Et_2O and filtered, afforded 7.3 g of crude solid which was taken up in hot 0.1 *N* HCl. The soln was filtered and basified with 20% NaOH soln to yield a solid which was purified as the HCl salt to provide light yellow crystals: δ (DMSO-d_6) 3.8–4.0 (12, OCH_3), 5.0 (s, 2, CH_2), 6.9–7.5 (6, ArH), 8.2 (s, 3, NH_3^+).

6,7-Dimethoxy-1-veratrylisoquinolin-3-yl *p*-Bromobenzenesulfonate (6e). A soln of 8.9 g (0.025 mole) of 4, 6.4 g (0.025 mole) of *p*-bromobenzenesulfonyl chloride, 300 ml of $CHCl_3$, and 2.4 g of pyridine was refluxed for 4 hr and filtd (Darco G-60). The filtrate was washed with 150 ml of H_2O, sepd, dried (anhyd K_2CO_3), and evapd *in vacuo* to afford a yellow solid which was recrystd twice from butanone–$(i\text{-Pr})_2O$ to give 9 g (62%) of faintly yellow needles: mp 147–148°; λ_{max} ($CHCl_3$) 332 (ε 5200). *Anal.* ($C_{26}H_{24}BrNO_7S$) C, H, N.

6,7-Dimethoxy-2-methylisoquinoline-1,3,4(2*H*)-trione (11). Eight grams of analytically pure *N*-methyl lactam (5a) was converted to the free base in an open beaker with concd NH_4OH. The bright yellow ppt (mp 165–181°) was taken up in 200 ml of boiling EtOAc and filtered to separate 200 mg (4%) of insol yellow solid. The material is readily soluble in cold, concd H_2SO_4, yielding an orange-brown soln, and dissolves upon heating in dilute Na_2CO_3 to give a colorless soln.[20] One recrystn from CH_3CN afforded material: mp 275–276° (lit.[20] mp 270–271° dec). Ir and nmr spectra are consistent with structure 11. The EtOAc filtrates contained pure 5a (isolated as the HCl salt). *Anal.* ($C_{12}H_{11}NO_5$) C, H, N.

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Antimetabolites of Coenzyme Q. 17. Improved Synthesis of 5-Hydroxy-1,4-benzoquinone Analogs and Their Indices†

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Improvements in the synthesis of 5-hydroxy analogs of coenzyme Q having different aliphatic and isoprenoid substituents in the 6 position, as well as in the purification of these analogs, have been made. New 5-hydroxy analogs have been obtained by these modifications. These eight 2,3-dimethoxy-5-hydroxy-1,4-benzoquinones have the following 6 substituents: decyl-, 5-cyclohexylpentyl-, tetradecyl-, pentadecyl-, nonadecyl-, heneicosyl-, farnesyl-, and phytyl-. They were compared for inhibition of the CoQ_{10} enzymes DPNH-oxidase and succinoxidase. Inhibition is newly defined by an antimetabolite CoQ index which is the number of nmoles of analog/nmoles of CoQ_{10} in the enzyme preparation for 50% inhibition. The antimetabolite CoQ indices of the eight analogs ranged from 5 to 32 for NADH-oxidase and 5 to 14 for succinoxidase showing that these 5-hydroxy analogs are relatively potent antimetabolites of coenzyme Q.

Coenzyme Q has biologically important and indispensable functions in certain organelles of the cell. Its functions in mitochondria as an intrinsic component of the electron transfer processes of respiration and oxidative phosphorylation have now been recognized and studied for over a decade by many investigators. Two enzyme sites for its coenzymatic function in mitochondrial systems are well known. Lenaz, *et al.*,[1] found one site for succinoxidase and a second site for NADH-oxidase. The necessity of coenzyme Q for the interaction of NADH dehydrogenase, succinate dehydro-

†Coenzyme Q. 154.