TABLE I. Effect of Methscopolamine Bromide (Methsc) on Steroid Induced Ulcers (Glandular portion) and on Fasting Ulcers (Forestomach).

Group	1	2	3	4	5	6	7	8
						Δ^1-COL		
		Methsc				Methsc,	Methsc,	Methsc,
Treatment	CMC	1 mg/kg	3 mg/kg	5 mg/kg	Δ^1-COL	1 mg/kg	3 mg/kg	5 mg/kg
Initial body wt	155	155	156	155	155	156	155	156
Final " "	111	110	110	109	102	101	100	101
Difference	−44	−45	−46	−46	−53	−55	−55	−55
Forestomach								
Edema, %	40	0	0	0	0	0	0	0
Ulcers, %	40	0	0	0	0	0	0	0
No./rat	4.1							
Glandular ulcers								
%	20	0	0	0	100	100	90	20
Severity (+)	.2				1.8	1.1	.6	.2
No./rat	.4				6.8	4.1	1.6	.4
Ulcer index*	2.6	0	0	0	18.6	15.2	11.2	2.6

* "Ulcer index" for glandular portion of stomach is determined by calculating the sum of: incidence in % divided by 10, severity (in pluses) and No. of ulcers/rat. A maximum "ulcer index" is around 20.

due to corticoid therapy. In this same connection, Carbone *et al.*(4) made the interesting observation that while prednisone increased both gastric pepsin and urinary uropepsin in normal subjects, addition of an anticholinergic drug nullified these effects of the steroids. According to our results, there is also a possibility that part of the protection afforded by methscopolamine was due to stimulation of mucus secretion.

Summary. Ulcers were produced in glandular portion of stomach of fasting rats with Δ^1-cortisol (Δ^1-COL). When methscopolamine bromide, an anticholinergic, was administered, these steroid induced ulcers were prevented proportionately to dose. Methscopolamine, given alone, increased the amount of visible mucus on mucosal surface. Methscopolamine would protect by counteracting some effects of corticoids on gastric secretion and perhaps also by stimulating mucus formation.

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Coenzyme Q. IV. Coenzyme Activity of 6-Isoprenoid and Other Derivatives of 2,3-Dimethoxy-5-Methylbenzoquinone. (24711)

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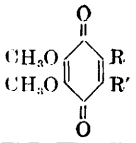
Discovery(1) and chemical structures(2) of the coenzyme Q group and additional characterization of ubiquinone(3) have been described recently. Synthesis of 6-(3′-methyl-2′-butenyl)-, (IV), 6-geranyl-, (V) and 6-farnesyl-, (VI), derivatives of 2,3-dimethoxy-5-methylbenzoquinone has been reported(4). These 3 compounds are lower isoprenoid analogs of the coenzyme Q group and may be considered as coenzyme Q_1, Q_2, and Q_3, respec-

TABLE I. Coenzyme Q Assay on 2,3-Dimethoxybenzoquinone and Certain Derivatives.

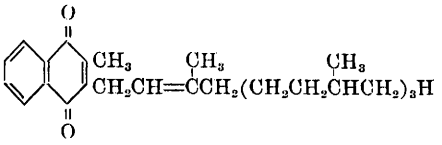


	Compound	Sample, mg	Specific activity succinoxidase	△S.A./μM
I	R = R′ = -H	.025	.00	.0
II	R = $-CH_3$	"	.00	.0
	R′ = -H	.05	.00	.0
III	R = R′ = $-CH_3$	.025	.06	.47
		.05	.08	.31
IV	R = $-CH_3$ CH_3	.025	.11	1.0
	R′ = $-CH_2CH=CCH_3$	.049	.16	.73
	(coenzyme Q_1)			
V	R = $-CH_3$ CH_3	.0094	.19	5.9
	R′ = $(-CH_2CH=C-CH_2)_2H$	.047	.28	
	(coenzyme Q_2)			
VI	R = $-CH_3$ CH_3	.011	.14	4.8
	R′ = $(-CH_2CH=C-CH_2)_3H$	.053	.29	
	(coenzyme Q_3)			
VII	R = $-CH_3$ CH_3 CH_3	.025	.19	3.5
	R′ = $-CH_2CH=C-CH_2(CH_2CH_2CHCH_2)_3H$	(-phytyl)		
	(hexahydrocoenzyme Q_4)	.05	.25	
VIII	R = $-CH_3$ CH_3	.025	.15	5.0
	R′ = $(CH_2CH=C-CH_2)_{10}H$	.05	.25	
	(coenzyme Q_{10})	.25	.28	
	None		0	
	Mixture of II and Q_{10}	.025	0	
		"		
	Mixture of III and Q_{10}	"	.10	
		"		

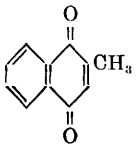
tively. The 6-phytyl derivative (VII) of 2, 3-dimethoxyl-5-methylbenzoquinone (hexahydrocoenzyme Q_4) was also synthesized(4). VII and Vit. K_1 have the same isoprenoid substituent. These 4 new isoprenoid compounds and the unsubstituted, 5-methyl-, and 5,6-dimethyl- derivatives of 2,3-dimethoxybenzoquinone have been tested for activity as coenzymes in the succinoxidase system; the data are in Table I.

Methods. The electron transport particle (5) was extracted at room temperature with 4 volumes of isooctane by rapid shaking for 1 hour on a reciprocal machine in presence of pH 5.5 potassium acetate buffer (0.4 M) and versene (0.002 M). Succinoxidase activity of the extracted particle was assayed manometrically as described previously(6) with mitochondrial phospholipid as supplement (.03 mg/flask). The extraction procedure removes coenzyme Q completely but does not remove other lipid components required for reactivation of more extensively extracted particles. The assay system used to collect data here reported did not contain the neutral lipid (NL II)(5) as supplement. Oxidation rates in the assay system were linear over a 20 minute period.

Results. (Data in Table I) 2,3-Dimethoxybenzoquinone (I) showed no activity. 2,3-Dimethoxy-5-methylbenzoquinone (II) also showed no activity, and when tested in pres-



IX



X

ence of coenzyme Q_{10} completely inhibited oxidation. This 5-methyl derivative (II) has the same structural relationship to 2,3-dimethoxy-5-methyl-6-phytylbenzoquinone (VII) (and essentially to Q_{10} also) as menadione (X) has to Vit. K_1 (IX).

2,3-Dimethoxy - 5,6-dimethylbenzoquinone (III) elicited very low activity and did not restore the full rate, even at higher concentrations. When this 5,6-dimethyl derivative (III) was tested in presence of coenzyme Q_{10}, there was inhibition.

Coenzyme Q_1 (IV) showed low activity and did not restore full rate. Coenzymes Q_2 (V) and Q_3 (VI) showed the same specific activity and restored the full rate. The hexahydrocoenzyme Q_4 (VII) showed full activity, and is of particular interest; it is an isoprenoid analog of intermediate chain length which is readily synthesized, because of availability of phytol. Furthermore, the 6-phytyl derivative possesses a 2'-double bond adjacent to the quinoid nucleus which may contribute to maximal electron functionality of the nucleus and coenzymatic activity.

Importance of the 6-isoprenoid substituent in coenzyme Q_{10} (VIII) to its lipid characteristics is more evident if one considers that the molecule has a 9-carbon quinoid nucleus attached to a 50-carbon hydrocarbon side chain. Although the coenzymatic activity of Q_6, Q_7, Q_8 and $Q_9(1)$ and some of the synthetic analogs described herein show that considerable variation of the 9-carbon/50-carbon ratio is possible with retention of activity, it is evident that excessive reduction of the 50-carbon side chain destroys the dominant lipid characteristics and coenzymatic activity of the molecule.

Studies on structure-activity relationships in the coenzyme Q group are being extended.

Summary. 2,3 - Dimethoxybenzoquinone and 2,3 - dimethoxy - 5-methylbenzoquinone showed no coenzymatic activity in a succinoxidase system. 2,3-Dimethoxy-5,6-dimethylbenzoquinone and coenzyme Q_1 showed low activity. Coenzyme Q_2, Q_3 and hexahydrocoenzyme Q_4 showed activity comparable to that of coenzyme Q_{10}.

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