TABLE I. 2,5-BIS(ALKYLAMINO)-3,6-DIMETHOXY-*p*-BENZOQUINONES (1)

Amine	R	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Yield, %
Ethyl-	CH_3CH_2-	162	$C_{12}H_{18}N_2O_4$	56.7	7.1	56.8	7.1	90
Propyl-	$CH_3CH_2CH_2-$	161	$C_{14}H_{22}N_2O_4$	59.6	7.8	59.6	8.1	79
Isopropyl-	$(CH_3)_2CH-$	205	$C_{14}H_{22}N_2O_4$	59.6	7.8	59.8	7.9	74
Butyl-	$CH_3(CH_2)_3-$	113	$C_{16}H_{26}N_2O_4$	61.9	8.4	62.0	8.7	95
Isobutyl-	$(CH_3)_2CHCH_2-$	148	$C_{16}H_{26}N_2O_4$	61.9	8.4	62.1	8.3	89
sec-Butyl-	$CH_3CH_2CH(CH_3)-$	145	$C_{16}H_{26}N_2O_4$	61.9	8.4	61.9	8.6	61
t-Butyl-	$(CH_3)_3C-$	182	$C_{16}H_{26}N_2O_4$	61.9	8.4	61.9	8.3	91
Pentyl-	$CH_3(CH_2)_4-$	118	$C_{18}H_{30}N_2O_4$	63.9	8.9	63.6	8.8	90
Hexyl-	$CH_3(CH_2)_5-$	108	$C_{20}H_{34}N_2O_4$	65.5	9.3	65.7	9.6	88
Octyl-	$CH_3(CH_2)_7-$	86	$C_{24}H_{42}N_2O_4$	68.2	10.0	68.1	10.2	87
2,4-Dimethylaniline	$2,4-(CH_3)_2C_6H_3-$	245	$C_{24}H_{26}N_2O_4$	70.9	6.4	70.8	6.6	67
p-Methoxyaniline	$4-CH_3OC_6H_4-$	229	$C_{22}H_{22}N_2O_6$	64.4	5.4	64.5	5.5	98
p-Toluidine	$4-CH_3C_6H_4-$	277	$C_{22}H_{22}N_2O_4$	69.8	5.9	69.6	6.1	97

Tetramethoxyquinone also suffered cleavage to 2,5-dihydroxy-3,6-dimethoxy-*p*-benzoquinone under mild acid treatment.

Grateful acknowledgment is given to the Michigan Cancer Foundation for partial support of this research. Preliminary results indicate some aminoquinones of structure **1** show activity against Sarcoma 180.

Experimental Section

Melting points were determined on a Kofler micro hot stage and are corrected. The infrared spectra were obtained in Nujol mulls on a Perkin-Elmer Infracord, Model 137.

The procedure for the preparation of 2,5-bis(pentylamino)-3,6-dimethoxy-*p*-benzoquinone illustrates the general preparation of 2,5-bis(alkylamino)-3,6-dimethoxy-*p*-benzoquinones with the exception of 2,5-bis(*t*-butylamino)-3,6-dimethoxy-*p*-benzoquinone (*vide infra*) and of the last three quinones listed in Table I. These three quinones were prepared in methanol (30 ml of methanol/g of tetramethoxyquinone) with a reflux time of 24 hr. Table I lists the yields obtained under these conditions.

2,5-Bis(pentylamino)-3,6-dimethoxy-*p*-benzoquinone.—Tetramethoxyquinone (920 mg), pentylamine (5 ml), and water (3 ml) were warmed at 75° for 2 min. When the mixture was let stand overnight, crystals of 2,5-bis(pentylamino)-3,6-dimethoxy-*p*-benzoquinone separated, 1.23 g (90%), which crystallized from ethanol as blue-black needles. For physical data, see Table I.

Reaction of Tetramethoxyquinone and *t*-Butylamine in Aqueous Solution.—Tetramethoxyquinone (272 mg) was refluxed in a nitrogen atmosphere with 4 ml of *t*-butylamine and 4 ml of water. After the reaction was heated for 4 hr, solvent was stripped, 10 ml of water was added, and the aqueous solution was extracted with ether. Acidification of the aqueous layer yielded a red solution from which 83 mg (30%) of 2,5-dihydroxy-3,6-dimethoxy-*p*-benzoquinone, mp 236°, lit.[1] mp 236°, separated on concentration. The ether layer was extracted with several portions of 6 *N* hydrochloric acid. Neutralization of the acid extracts yielded 30 mg (8%) of 2,5-bis(*t*-butylamino)-3,6-dimethoxy-*p*-benzoquinone, mp 182°. Both 2,5-dihydroxy-3,6-dimethoxy-*p*-benzoquinone and 2,5-bis(*t*-butylamino)-3,6-dimethoxy-*p*-benzoquinone were identified with authentic samples (*vide infra*) by mixture melting point determination and comparison of the infrared spectra.

2,5-Bis(*t*-butylamino)-3,6-dimethoxy-*p*-benzoquinone.—Tetramethoxyquinone (187 mg) was refluxed for 40 hr with 10 ml of *t*-butylamine. When the mixture was let stand overnight, crystals of 2,5-bis(*t*-butylamino)-3,6-dimethoxy-*p*-benzoquinone separated, 231 mg (91%), which were purified by crystallization from ethanol.

Tetramethoxyquinone.—A slurry of 24.6 g (0.1 mole) of chloranil in 50 ml of methanol was added to a solution of 9.2 g (0.4 mole) of sodium in 200 ml of methanol. During addition the temperature was kept at 30° by means of an ice bath. The resulting mixture was autoclaved at 85° for 6 hr. The cooled reaction mixture deposited bright orange crystals which were collected and dissolved in methylene chloride. This solution was treated with charcoal and filtered, and the filtrate was evaporated to dryness. The residue crystallized from methanol to give 13.5 g (57%) of bright orange crystals, mp 135°, lit.[1] mp 135–136°. These were identified as tetramethoxyquinone by mixture melting point determination and comparison of infrared spectra with that of an authentic sample.[1]

2,5-Dihydroxy-3,6-dimethoxy-*p*-benzoquinone.—Tetramethoxyquinone (367 mg) was refluxed in a nitrogen atmosphere with 10 ml of 2 *N* hydrochloric acid for 1 hr. When the reaction mixture was cooled, black crystals separated, 249 mg (77%), mp 236°, lit.[1] mp 236°. These were identified as 2,5-dihydroxy-3,6-dimethoxy-*p*-benzoquinone by mixture melting point determination and comparison of infrared spectra with that of an authentic sample.[1]

Amine Exchange Reaction.—The following procedure illustrates the amine exchange reaction. A solution of 199 mg of 2,5-bis(isopropylamino)-3,6-dimethoxy-*p*-benzoquinone in 2 ml of octylamine and 3 ml of water was refluxed for 1 hr. When the reaction mixture was cooled, crystals separated, which were filtered and washed with dilute acetic acid and then with water. The 2,5-bis(octylamino)-3,6-dimethoxy-*p*-benzoquinone thus obtained, 260 mg (87%), proved to be identical with an authentic sample prepared from tetramethoxyquinone.

7-Hydroxy-11,12-dimethoxycoumestan. Characterization and Synthesis

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A new compound, $C_{17}H_{12}O_6$, isolated from alfalfa has been characterized. Analysis of the compound, its acetate, and methyl ether indicated that it was a dimethoxy derivative, containing one hydroxyl group. Its methyl ether was identical with authentic 7,11,12-trimethoxycoumestan.[2] Since λ_{max} 346 mμ in ethanol underwent a bathochromic shift in the presence of sodium acetate to 367 mμ, the hydroxyl group must be located at the 7-position.[3] Thus, the structure of the new compound is 7-hydroxy-11,12-dimethoxycoumestan, closely related to medicagol.[2]

This structure assignment was confirmed by its synthesis from 7,11,12-trihydroxycoumestan (Ia) in the following manner. The 11,12-positions of Ia were first blocked by the formation of the diphenylmethylenedioxy derivative IIa. Benzoylation to IIb, followed by acid hydrolysis, regenerated the 11,12-

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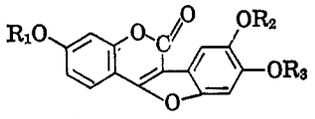
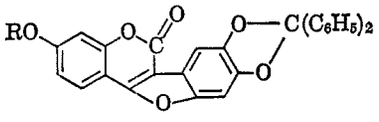


Ia, $R_1=R_2=R_3=H$
b, $R_1=Bz$, $R_2=R_3=H$
c, $R_1=Bz$, $R_2=R_3=CH_3$
d, $R_1=H$, $R_2=R_3=CH_3$



IIa, R=H
b, R=Bz

dihydroxy derivative Ib, which gave the expected bathochromic shift in the presence of boric acid for an *o*-dihydroxyl grouping[4] (355–382 mμ). Methylation of the 11- and 12-positions then gave 7-O-benzoyl-11,12-dimethoxycoumestan (Ic), identical with the benzoate prepared from the natural material. Basic hydrolysis of the synthetic benzoate gave a compound, Id, which was identical with the natural material in all respects.

Experimental Section

Purification.—The new phenolic compound was isolated from dehydrated alfalfa and purified by recrystallization from ethyl acetate, mp 306° (compound VIII in ref. 5).

Anal. Calcd for $C_{17}H_{12}O_6$: C, 65.4; H, 3.85; OCH_3, 19.8. Found: C, 65.5; H, 3.85; OCH_3, 19.6.

Acetate.—A mixture of the compound (60 mg) and anhydrous sodium acetate (250 mg) in 5.0 ml of acetic anhydride was heated at reflux for 5 min, cooled, and poured into ice–water. A white solid (69 mg) precipitated. An analytical sample, mp 213–215°, was prepared by recrystallization from acetone.

Anal. Calcd for $C_{19}H_{14}O_7$: C, 64.4; H, 3.96; OCH_3, 17.5; CH_3CO, 12.1. Found: C, 64.5; H, 4.02; OCH_3, 17.3; CH_3CO, 12.0.

Methyl Ether.—A mixture of the compound (100 mg), anhydrous potassium carbonate (300 mg), and dimethyl sulfate (0.5 ml) in 20 ml of dry acetone was heated at reflux under nitrogen for 1.5 hr, cooled, and poured into ice–water. A white solid (110 mg) precipitated. Recrystallization from methanol gave colorless crystals, mp 246°.

Anal. Calcd for $C_{18}H_{14}O_6$: C, 66.3; H, 4.30; OCH_3, 28.5. Found: C, 65.9; H, 4.35; OCH_3, 28.2.

Admixture with an authentic sample of 7,11,12-trimethoxycoumestan did not depress the melting point of the natural ether. Ultraviolet and infrared spectra were identical.

7-Hydroxy-11,12-diphenylmethylenedioxycoumestan (IIa).—Using the procedure of Jurd,[6] a mixture of 7,11,12-trihydroxycoumestan (Ia) (1.5 g) and α,α-dichlorodiphenylmethane[7] (2.8 g) was heated at 210° for 5 min. The resulting dark brown solids were purified by countercurrent distribution in a robot-operated, 100-tube instrument with Skellysolve B–methanol (2:1) as the developing system. After 250 transfers, tubes 49–80 in the instrument were combined and taken to dryness, giving 720 mg of a white solid. Recrystallization from methanol gave an analytical sample, mp 293.5–294°.

Anal. Calcd for $C_{28}H_{16}O_6$: C, 75.0; H, 3.60. Found: C, 75.0; H, 3.81.

7-O-Benzoyl-11,12-dihydroxycoumestan (Ib).—A solution of IIa (200 mg) in 10 ml of pyridine was mixed with 100 mg of anhydrous sodium acetate and 0.3 ml of benzoyl chloride. After standing for 45 min at room temperature, the reaction mixture was poured into ice-cold aqueous sodium acetate solution and the intermediate IIb was removed with chloroform. The chloroform was evaporated *in vacuo*, and the crude syrup was dissolved in 50 ml of glacial acetic acid–hydrochloric acid (15:1) and heated at reflux for 10 min. After the addition of 5.0 ml of water, the mixture was further heated on a steam bath for 5 min and cooled, and the white solids (230 mg) were collected. Recrystallization from acetic acid gave an analytical sample, mp 301–302°.

Anal. Calcd for $C_{22}H_{12}O_6$: C, 68.1; H, 3.11. Found: C, 68.5; H, 3.69.

7-O-Benzoyl-11,12-Dimethoxycoumestan (Ic). Synthetic.—A mixture of the 7-O-benzoyl derivative Ib (115 mg), dimethyl sulfate (0.2 ml), and anhydrous potassium carbonate (250 mg) in 50 ml of dry acetone was heated at reflux for 3 hr. The reaction mixture was cooled and poured into ice–water, giving 121 mg of a white solid. Recrystallization from acetone gave an analytical sample, mp 227–228°.

Anal. Calcd for $C_{24}H_{16}O_6$: C, 69.2; H, 3.87; OCH_3, 14.9. Found: C, 69.4; H, 4.11; OCH_3, 14.9.

Natural.—A mixture of the natural compound (75 mg) with benzoyl chloride (0.5 ml) in 3.5 ml of pyridine, was heated on the steam bath for 1 hr while protected from moisture. The reaction mixture was added dropwise to a well-stirred mixture of ice and saturated aqueous sodium bicarbonate solution. A white solid (80 mg) precipitated. Recrystallization from acetone gave an analytical sample, mp 227.5°, identical with the comparable synthetic derivative.

7-Hydroxy-11,12-dimethoxycoumestan (Id).—The synthetic preparation of the 7-O-benzoate of the dimethyl ether (Ic) (82 mg) was stirred with 5.0 ml of 0.5% potassium hydroxide in methanol for 0.5 hr at 0–5°. Acidification with dilute hydrochloric acid gave 48.4 mg of a tan solid. Recrystallization from ethyl acetate gave a white solid, mp 303–305°, which was identical in all respects with the natural material.

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Alkylation of N,N-Dimethylamides *via* Carbanion Intermediates

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Alkylation of several 2-aryl-N,N-dialkylacetamides[2–6] and 2,2-diaryl-N,N-dialkylacetamides[6–10] at the α-carbon *via* carbanion intermediates has been reported; however, we have found no examples in the literature of alkylation of simple N,N-dialkylamides. Generally, substitution of an activating aryl group at the 2-position has been considered a necessary condition for carbanion formation to take place in N,N-dialkylamides. We wish to report alkylation at the α-carbon *via* carbanion intermediates of three simple N,N-dimethylamides (see Table I).

Formation of carbanions of the N,N-dimethylamides was effected by refluxing the amide with finely divided sodium amide in benzene or toluene. Attempts to use lithium amide or sodium ethoxide in place of so-

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