Model Reactions for the Biosynthesis of Thyroxine. XIII. Preparation and Reactions of Hindered *p*- and *o*-Quinol Ethers[1,2]

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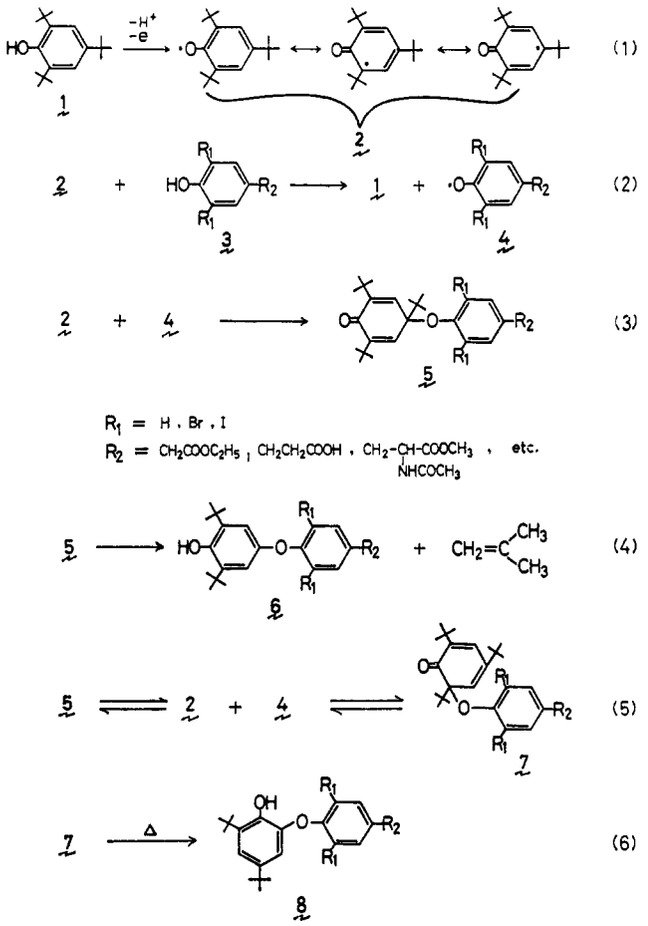
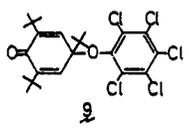
Hydroxydiphenyl ethers which had been previously obtained by de-*t*-butylation of *p*-quinol ethers of type **5** at elevated temperatures were found to be *o*-hydroxydiphenyl ethers of type **8** instead of *p*-hydroxydiphenyl ethers of type **6**. However, acid treatment of **5c** at room temperature leads to a *p*-hydroxydiphenyl ether **6c**. This represents a model for the hypothetical mechanism which has been postulated for the biosynthesis of thyroxine by Johnson and Tewkesbury. In contrast to other phenolic compounds, *p*-hydroxybenzoic acid or its methyl ester reacts with 2,4,6-tri-*t*-butylphenoxyl (**2**) to form a mixture of *p*- and *o*-quinol ethers **5** and **7**. Similarly, reaction of **2** with phenols bearing an electron-withdrawing group at the *para* position (NO_2 and $COCH_3$) results in the formation of a *p*-quinol ether of type **5** and an *o*-hydroxydiphenyl ether of type **8** which in turn most likely is formed *via* an *o*-quinol ether **7**. Various reactions of these two quinol ethers are described.

It has been reported in the previous papers of this series[3,4] that various *p*-quinol ethers of type **5** were synthesized from derivatives of tyrosine and of halogenated tyrosines and also from their side-chain analogs in a free-radical reaction involving the tri-*t*-butylphenoxyl radical (**2**) (eq 1–3), and that some of these quinol ethers were converted by acid catalysis in boiling ethyl acetate or by pyrolysis to the corresponding analogs (**6**) of thyroxine (eq 4). We also mentioned that this sequence of reactions represents a model for the hypothetical mechanism which had been postulated by Johnson and Tewkesbury[5] for the biosynthesis of throxine.



Müller and his collaborators[6] have reported the preparation of a *p*-quinol ether (**9**) of type **5** from 2,4,6-tri-*t*-butylphenoxyl (**2**) and pentachlorophenol in a similar manner. They found that **9**, on heating with trifluoroacetic acid, was converted into an *o*-hydroxydiphenyl ether of type **8**, presumably *via* an *o*-quinol ether of type **7** (eq 5 and 6). Accordingly, they assumed that the thyroxine analogs, which were prepared by us, might have an *o*-hydroxydiphenyl ether structure (**8**) rather than that of a *p*-hydroxydiphenyl ether (**6**). This report prompted us to reinvestigate the conversion of the *p*-quinol ethers **5** to thyroxine analogs to which we had previously assigned structure **6**. This reinvestigation showed that the compounds obtained by us have indeed an *o*-hydroxydiphenyl ether structure (**8**). We found, however that under appropriate conditions, the *p*-quinol ethers **5** can be converted to the true thyroxine analogs of structures **6**.



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Structure of Quinol Ethers and Hydroxydiphenyl Ethers.—It has been reported by us[3,4] as well as by Müller, *et al.*,[6,7] that quinol ethers obtained in the reaction of 2,4,6-tri-*t*-butylphenoxyl with various phenols (eq 2 and 3) have structure **5**. The structure assignment is confirmed by nmr data, which are summarized in Table I. In accordance with the symmetrical structure of the *p*-quinol ethers **5a–m** the pair of *t*-butyl protons at positions 2 and 6 appear magnetically equivalent. The same holds true for the pair of olefinic protons (H_A), and also for the pair (or two pairs) of aromatic protons (H_B or H_B and H_C). A similar magnetic equivalence cannot be expected for quinol ethers which have an *o*-quinol ether structure **7**. In fact, in the nmr spectrum of an *o*-quinol ether (**7**, R_1 = H, R_2 = $COOCH_3$), which will be described later, protons of three *t*-butyl groups appear as three individual

(1) Part XII: A. Nishinaga, H. J. Cahnmann, H. Kon, and T. Matsuura, *Biochemistry*, **7**, 388 (1968).

(2) This work was supported by U. S. Public Health Service Grant AM-07955 from the National Institute of Arthritis and Metabolic Diseases.

(3) T. Matsuura and H. J. Cahnmann, *J. Am. Chem. Soc.*, **83**, 2055 (1960).

(4) T. Matsuura and A Nishinaga, *J. Org. Chem.*, **27**, 3072 (1962).

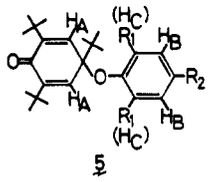
(5) T. B. Johnson and L. B. Tewkesbury, Jr., *Proc. Natl. Acad. Sci., U. S.*, **28**, 73 (1942).

(6) E. Müller, A. Rieker, and A. Schick, *Ann.*, **673**, 40 (1964).

(7) E. Müller, K. Ley, and G. Schlechte, *Chem. Ber.*, **90**, 2660 (1957).

TABLE I

THE NMR DATA FOR *p*-QUINOL ETHERS 5



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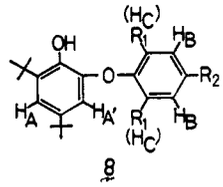
No.	R_1	R_2	*t*-Butyl	*p*-*t*-Butyl	Chemical shift, δ value (J_{BC}, Hz) H_A	H_B	H_C	Other protons
5a	H	$CH_2COOC_2H_5$	1.19	1.07	6.62	6.98	6.78 (9.0)	
5b	H	$(CH_2)_2COOC_2H_5$	1.16	1.04	6.60	6.88	6.72 (8.5)	
5c	H	$(CH_2)_2COOH$	1.14	1.03	6.59	6.89	6.72 (9.0)	
5d	Br	$(CH_2)_2COOH$	1.14	1.24	7.12	7.21		
5e	Br	$(CH_2)_2COOC_2H_5$	1.13	1.24	7.13	7.21		
5f	I	$(CH_2)_2COOH$	1.17	1.29	7.22	7.42		
5g	I	$(CH_2)_2COOC_2H_5$	1.22	1.34	7.30	7.48		
5h	I	$CH_2COOC_2H_5$	1.18	1.29	7.29	7.53		
5i	H	$COOCH_3$	1.21	1.08	6.60	6.80	6.84 (10.5)	3.80 ($COOCH_3$)
5j	H	COOH						
5k	H	$COCH_3$	1.26	1.10	6.68	6.90	7.75 (9.0)	2.52 ($COCH_3$)
5l	H	NO_2	1.25	1.09	6.64	6.94	8.04 (10.0)	
5m	NO_2	$(CH_2)_2COOH$	1.12	1.14	6.38	7.70		

TABLE II

THE NMR DATA FOR *o*-HYDROXYDIPHENYL ETHERS 8



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No.	R_1	R_2	*t*-Butyl	Chemical shift, δ values (*J*, Hz) H_A	$H_{A'}$	H_B	H_C	Other protons
8a	H	CH_2CH_2COOH	1.44, 1.23	7.07 (2.2)	6.80	6.92 (8.5)	7.18	2.5–3.1 (CH_2CH_2)
8i	H	$COOCH_3$	1.44, 1.25	7.18 (2.2)	6.87	8.03 (8.5)	7.04	3.91 ($COOCH_3$), 5.66 (OH)
8e	Br	CH_2CH_2COOH	1.46, 1.17	7.03 (2.0)	6.31	7.50		2.70–3.05 (CH_2CH_2COO)
8f	Br	$CH_2CH(NH_2)COOCH_3$	1.44, 1.16	6.98 (2.2)	6.25	7.47		3.74 (ester), 2.70–3.05 (side chain)
8k	H	$COCH_3$	1.46, 1.29	7.12 (2.8)	6.82	7.90 (9.0)	7.00	5.64 (OH), 2.54 ($COCH_3$)
8l	H	NO_2	1.28, 1.46	7.17 (2.9)	6.84	8.20 (9.5)	7.05	

singlets and two olefinic protons as two doublets with J = 2.5 Hz.

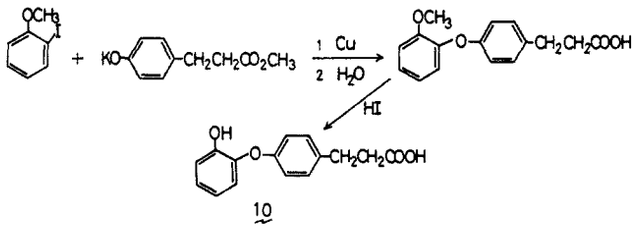
The hydroxydiphenyl ethers which had been previously obtained by us by acid catalysis of the *p*-quinol ethers **5** have nmr spectra which confirm their *o*-hydroxydiphenyl ethers structure (**8**) (Table II).[7a] The nmr signals of the protons on the nonphenolic ring of **8a–e** reflect the symmetrical structure of that ring. [Letters following numbers of compounds refer to the nature of the side chain R_2 in the formulas (see Tables I and II).]

(7a) NOTE ADDED IN PROOF.—The same conclusion has been recently reported by Bowie and Bedford [R. A. Bowie and G. R. Bedford, *Tetrahedron Lett.*, 5471 (1968)].

On the other hand, the methyl protons of the two *t*-butyl groups appear as two singlets and two aromatic protons (H_A and $H_{A'}$) as a pair of doublets with J = 2 Hz. The structure of the *o*-hydroxydiphenyl ethers (**8**) was further confirmed by de-*t*-butylation of **8a** with aluminum chloride. The product obtained was found to be identical with 3-[4-(2-hydroxyphenoxy)phenyl]-propionic acid (**10**) which was synthesized by an unambiguous route as shown in Chart I.

Conversion of a *p*-Quinol Ether to a *p*-Hydroxydiphenyl Ether.—From the above results, it can be concluded that a thermal equilibrium exists between the *p*-quinol ether (**5**) and *o*-quinol ether (**7**) *via* dis-

CHART I



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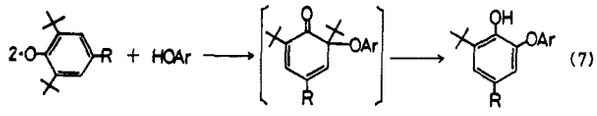
sociation into the parent phenoxyl radicals **2** and **4** as suggested by Müller, *et al.*[6] (eq 5), and that the unstable *o*-quinol ether is decomposed with the elimination of isobutylene to give an *o*-hydroxydiphenyl ether of type **8**. It has been reported[8] that 2,4-cyclohexadienones bearing a *t*-butyl group at position 6 are very unstable and the 6-*t*-butyl group is eliminated as isobutylene to form the corresponding phenols with only a few exceptions.[9] Therefore, the *p*-quinol ethers (**5**) may be expected to be converted to the corresponding *p*-hydroxydiphenyl ethers (**6**) by acid catalysis at low temperature at which the dissociation of **5** into two parent phenoxy radicals **2** and **4** is suppressed. In fact, treatment of **5c** with boron trifluoride at room temperature yielded the corresponding *p*-hydroxydiphenyl ether **6c** which was not isolated in pure form but gave 3-[4-(4-hydroxyphenoxy)phenyl]propionic acid (thyropropionic acid) by de-*t*-butylation with aluminum chloride. Thus, we can now complete a model for Johnson–Tewkesbury's mechanism for the biosynthesis of thyroxine from diiodotyrosine. On the other hand, treatment of **5c** with hydrobromic acid and acetic acid at room temperature gave 2,4,6-tri-*t*-butylphenol (**1**) and 3-bromophloretic acid as the only isolable products.

Isolation of Stable *o*-Quinol Ethers of Type 7.—The question arises whether or not in the coupling reaction of tri-*t*-butylphenoxyl (**2**) with various phenols (**3**), a quinol ether of type **7** is formed besides the quinol ether of type **5**. In order to check this, we carefully analyzed by tlc the reaction products from **2** and phloretic acid (**3**, R_1 = H, R_2 = CH_2CH_2COOH). The bulk of the coupling products was found to consist of the *p*-quinol ether **5c**, which was accompanied by a trace of an unknown product, presumably **7** (R_1 = H, R_2 = CH_2CH_2COOH). The minor reaction product could not be isolated. From this result and from the fact that *p*-quinol ethers of type **5** were usually obtained in excellent yield in the coupling reaction between tri-*t*-butylphenoxyl (**2**) and various phenoxy radicals (**4**),[3,4,7] it may be concluded that at low temperatures the equilibrium shown in eq 5 is displaced toward the left, while with an increase in temperature **5** dissociates more and more into **2** and **4** (displacement of the equilibrium toward the right). The unstable *o*-quinol ether (**7**) thus formed undergoes de-*t*-butylation, as shown in eq 6, to form the corresponding *o*-hydroxydiphenyl ether (**8**).[10] In general, 2,4-cyclohexadienones having a *t*-butyl group in addition to another substituent at position 6 are known to be quite unstable.[8] For instance, the reaction between various phenols and a 2,6-di-*t*-butylphenoxyl (**11**) bearing an electron-withdrawing group (R = $COOCH_3$, $COCH_3$, CN, etc.) at position 4 results in the formation of an *o*-hydroxydiphenyl ether (**13**), *via* an unstable *o*-quinol ether intermediate (**12**), which usually is so unstable that it cannot be isolated (eq 7).[11,12] It has previously pointed out that with an increase in temperature *p*-quinol ethers (**5**) dissociate more and more into free radicals (**2** and **4**).[3]



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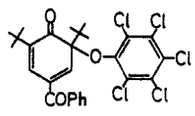
11 12 13



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To the best of our knowledge, the *o*-quinol ether **14** obtained by the oxidation of 4-benzoyl-2,6-di-*t*-butylphenol and pentachlorophenol is the only example of the *o*-quinol ether isolated so far.[11] In this case the phenoxyl radical has an electron-withdrawing group (which promotes *o*-quinol ether formation) at position 4.

When 2,4,6-tri-*t*-butylphenoxyl (**2**) was treated with methyl *p*-hydroxybenzoate (**3**, R_1 = H, R_2 = $COOCH_3$), we were surprised to find that the *o*-quinol ether **7i** (R_1 = H, R_2 = $COOCH_3$) could be isolated together with the *p*-quinol ether **5i** in an *ortho/para* ratio of 1:3. Both quinol ethers are quite stable and can be easily separated without interconversion by column chromatography on neutralized alumina. Although they could not be distinguished by uv and ir spectroscopy since their uv and ir spectra are very similar, their structure could be determined on the basis of their nmr spectra. The spectrum of **5i** is quite analogous to those of other *p*-quinol ethers of type **5** (Table I). On the other hand, in the case of **7i** signals of three *t*-butyl groups appear as three nonequivalent singlets at δ 1.00, 1.17, and 1.25 and two olefinic protons appear as a pair of doublets at δ 5.98 and 6.92 with J = 2.5 Hz. These results clearly show that this compound has an *o*-quinol ether structure. Reaction of *p*-hydroxybenzoic acid (**3j**, R_1 = H, R_2 = COOH) with 2,4,6-tri-*t*-butylphenoxyl (**2**) also gave a mixture of the *p*- (**5j**) and *o*-quinol ethers (**7j**, R_1 = H, R_2 = COOH). The structure of these compounds was confirmed by methylation with diazomethane which led to the corresponding methyl esters **5i** and **7i**. The free acids **5j** and **7j** are also stable and are not interconvertible, even in boiling ethanol.

Recently Da Rooge and Mahoney[13] have investigated the kinetics of the reaction of 2,4,6-tri-*t*-butylphenoxyl with 3- and 4-substituted phenols. They found that a linear relationship exists between the reaction rate and

(8) B. Miller and H. Margulies, *J. Org. Chem.*, **30**, 3895 (1965).

(9) T. Matsuura and K. Ogura, *Tetrahedron*, in press.

(10) Another pathway, by which *o*-hydroxydiphenyl ether (**8**) is formed through simple de-*t*-butylation of compounds of type **5**, cannot be neglected. The authors thank a referee who called our attention on this point.

(11) T. Matsuura, A. Nishinaga, and H. J. Cahnmann, *J. Org. Chem.*, **27**, 3620 (1962).

(12) A. Rieker, *Chem. Ber.*, **98**, 715 (1965).

(13) M. A. DaRooge and L. R. Mahoney, *J. Org. Chem.*, **32**, 1 (1967).

the Hammett σ or Brown σ^+ parameters of the substituents; the reaction rate increases with an increased σ constant. We also observed in a qualitative fashion that reactions of 2,4,6-tri-*t*-butylphenoxyl with methyl *p*-hydroxybenzoate, *p*-hydroxybenzoic acid, *p*-hydroxyacetophenone, *p*-nitrophenol, and 3,5-dinitrophloretic acid proceed more slowly than those with phenols bearing an alkyl group at position 4. Considering the formation of the *o*-quinol ethers (**7**) from *p*-hydroxybenzoic acid and its methyl ester, these results suggest that, in the reaction of 2,4,6-tri-*t*-butylphenoxyl (**2**) with phenols bearing electron-withdrawing groups such as NO_2 and $COCH_3$ at position 4, an *o*-quinol ether (**7**) is formed in detectable amounts together with a *p*-quinol ether (**5**). Therefore we investigated this free-radical coupling reaction using *p*-hydroxyacetophenone and *p*-nitrophenol. Although no *o*-quinol ether could be isolated in either case, the corresponding *o*-hydroxydiphenyl ethers **8k** and **8l** were obtained in 16 and 19% yields, respectively, together with the *p*-quinol ethers **5k** and **5l** (78.5 and 65%, respectively). The structures of these products were deduced from their nmr spectral data (Tables I and II). Since the *p*-quinol ethers **5k** and **5l** did not give the corresponding *o*-hydroxydiphenyl ethers **8k** and **8l**, respectively, under conditions employed in the course of the product separation (column chromatography and recrystallization), it may be concluded that the *o*-hydroxydiphenyl ethers are formed from the *o*-quinol ethers **7k** (R_1 = H, R_2 = $COCH_3$) and **7l** (R_1 = H, R_2 = NO_2) which are unstable under these conditions and undergo de-*t*-butylation.

The reaction of 2,4,6-tri-*t*-butylphenoxyl (**2**) with 3,5-dinitrophloretic acid was also investigated. In this case, the only isolable product was a *p*-quinol ether **5m** (R_1 = NO_2, R_2 = CH_2CH_2COOH).

Although it is of interest that, in the coupling reaction between 2,4,6-tri-*t*-butylphenoxyl and phenols (eq 5), a slow reaction causes the formation of the *o*-quinol ether **7** to some extent, there is no reasonable explanation for the *o*-quinol ether formation from phenols bearing an electron-withdrawing group at position 4, as well as for the unusual stability of the *o*-quinol ethers **5i** and **5j**.

Reactions of the *o*-Quinol Ether 7i.—As expected from its structure, the *o*-quinol ether **7i** easily undergoes de-*t*-butylation by pyrolysis or by acid catalysis to give the corresponding *o*-hydroxydiphenyl ether **8i** in good yield, while the *p*-quinol ether **5i** gives **8i** by pyrolysis but 2,4,6-tri-*t*-butylphenol (**1**) and methyl *p*-hydroxybenzoate as only isolable products by acid catalysis. The photochemical reaction of **7i** will be reported in a separate paper.

Experimental Section

Melting points were determined in capillary tubes and are uncorrected. Nmr spectra were taken with a JMN-3H-60 recording spectrometer, using tetramethylsilane as an internal reference. Infrared spectra (Nujol mulls) were recorded with a Nihon Bunko Model IR-S instrument. The elemental analyses were done by the Analytical Service Center of this university.

Treatment of *p*-Quinol Ether 5c with Boron Trifluoride.—A solution of 1.00 g of **5c**[3] dissolved in 15 ml of 47% boron trifluoride etherate in ether was allowed to stand at room temperature for 6 days. The mixture was shaken with 30 ml of ether and 50 ml of water. The ethereal layer was separated and extracted twice with 40 ml of 1 *N* NaOH solution. The alkaline extract was acidified with dilute HCl and extracted with ether (two 100-ml portions). The ethereal layer was washed with water, dried, and evaporated. The brown oily residue (385 mg) was chromatographed on a column of silica gel (15 g). Elution with 25 ml of chloroform gave 132 mg of an oil. Successive elution with 250 ml of chloroform yielded 95 mg of crystals, identified as phloretic acid (ir). The oil was heated for 4 hr under reflux with a mixture of 5 ml of hydrobromic acid (sp gr 1.48) and 5 ml of acetic acid. After dilution with 30 ml of water, the reaction mixture was extracted with ether (three 50-ml portions). The ethereal extract was washed with water, dried, and evaporated. The crystalline residue gave on recrystallization from benzene 70 mg (12%) of crystals, mp 156–158°, identified as thyropropionic acid (mixture melting point and ir) (lit. 162–163°,[14] 161°,[15] and 175°[16]).

Treatment of 5c with Hydrobromic Acid.—A solution of 300 mg of **5c** dissolved in 20 ml of a mixture of acetic acid and hydrobromic acid (sp gr 1.48) (1:1) was stirred at room temperature for 1 hr. After addition of 20 ml of water, the mixture was allowed to stand for several hours whereupon fine crystals formed which were collected by filtration (138 mg, 75%, mp 125–128°). They were identified by mixture melting point and ir as 2,4,6-tri-*t*-butylphenol. The aqueous filtrate, after addition of 60 ml of H_2O, was extracted with ether (three 50-ml portions). The ether extract was washed with water (four 100-ml portions), dried, and evaporated. The resulting residue gave on drying over NaOH in a desiccator 144 mg of a yellow oil, which slowly crystallized. Recrystallization from benzene gave 84 mg (49%) of colorless prisms, mp 87–89°, which were identical with 3-bromophloretic acid prepared as described below (mixture melting point and ir). Tlc analysis (silica gel; benzene–methanol–acetic acid, 8:1:1) showed that this material was contaminated with a small amount of phloretic acid. Further recrystallization from methanol–water gave colorless crystals, mp 90–91°.

3-Bromophloretic Acid.—To a stirred solution of 1.00 g (6 mmol) of phloretic acid and 1.6 g of potassium bromide in 20 ml of ethanol and water (1:1) was added 1.0 g (12 matoms) of bromine in 14 ml of ethanol–water (1:1) at room temperature. After the addition of 50 ml of water, the reaction mixture was concentrated to 50 ml and then was extracted with ether (three 50-ml portions). The ether extract was washed with water, dried, and evaporated to give 1.42 g of a yellow oil, which crystallized on standing. Recrystallization from benzene gave 1.03 g of straw-colored crystals. Tlc showed that they consisted of three components, phloretic acid, 3-bromophloretic acid, and 3,5-dibromophloretic acid. Preparative tlc (silica gel G_{F234}, Merck & Co; benzene–methanol–acetic acid, 8:1:1) gave 83 mg of 3-bromophloretic acid, mp 87–89° (lit.[17] 90°).

Acid Treatment of 4-Methoxy-2,4,6-tri-*t*-butylcyclohexa-2,5-dien-1-one.—A solution of 4-methoxy-2,4,6-tri-*t*-butylcyclohexa-2,5-dien-1-one dissolved in 25 ml of acetic acid–hydrobromic acid (4:1) was stirred at room temperature for 2 hr. The mixture, after the addition of 25 ml of water, deposited 60 mg (74%) of a crystalline solid, mp 78–81°, which was identical with an authentic sample[18] of 2,6-di-*t*-butyl-4-methoxyphenol (mixture melting point and ir).

3-[4-(2-Methoxyphenoxy)phenyl]propionic Acid. A. De-*t*-butylation of 8a.—A solution of 200 mg of **8a**[3] in 15 ml of acetic acid–hydrobromic acid (1:1) was refluxed for 10 hr. The reaction mixture, after the addition of 50 ml of water, was extracted with ether (three 50-ml portions). The ether extract was washed with water (four 100-ml portions), dried, and evaporated *in vacuo* to yield 97 mg of a crystalline residue. Recrystallization from methanol–water gave colorless crystals, mp 150–157°, identical with 3-[4-(2-hydroxyphenoxy)phenyl]-propionic acid synthesized as described below (mixture melting point and ir).

B. From *o*-Iodoanisole.—A mixture of 1.8 g of methyl *p*-hydroxyhydrocinnamate[19] and 0.5 g of potassium in 25 ml of absolute benzene was refluxed for 1 hr. After evaporation of

(14) A. Nishinaga and T. Matsuura, *J. Org. Chem.*, **29**, 1812 (1964).
(15) J. Walker, *J. Chem. Soc.*, 347 (1942).
(16) R. I. Meltzer, S. Farber, E. Merrill, and A. Caro, *J. Org. Chem.*, **26**, 1413 (1961).
(17) K. Misaki, *J. Biochem.* (Tokyo), **5**, 1 (1925); *Chem. Abstr.*, **20**, 422 (1926).
(18) E. Müller and K. Ley, *Chem. Ber.*, **88**, 601 (1955).
(19) E. Fisher and O. Nonri, *ibid.*, **50**, 614 (1917).

the solvent, 2 g of *o*-iodoanisole[20] and 1 g of active copper[21] was added and the mixture was heated at 150–170° for 6 hr. The reaction mixture was triturated with ether (two 100-ml portions) and filtered. The filtrate was washed with 2 *N* KOH (two 5-ml portions) and with water, dried, and evaporated. The yellow oily residue was dissolved in 100 ml of 0.5 *N* ethanolic KOH and heated at 60° for 3 hr. The reaction mixture was concentrated to 10 ml and extracted with 2 *N* aqueous NaOH (100 ml). The aqueous solution was acidified with dilute HCl, then extracted with ether (two 150-ml portions). The ether extract was dried and evaporated to give a crystalline residue (703 mg, 26%). Recrystallization from benzene gave 3-[4-(2-methoxyphenoxy)phenyl]propionic acid as colorless crystals, mp 112–113°. *Anal.* Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.33; H, 6.13.

A solution of 90 mg of the acid in 12 ml of acetic acid–hydrobromic acid (1:1) was refluxed for 4 hr. The reaction mixture, after adding 30 ml of water, was extracted with ether (three 50-ml portions). The ether extract was washed with water (three 50-ml portions), dried, and evaporated to give 65 mg of crude crystals. Recrystallization from methanol–water gave as straw-colored crystals of 3-[4-(2-hydroxyphenoxy)phenyl]propionic acid, mp 159–162°. *Anal.* Calcd for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.13; H, 5.84.

Reaction of 2,4,6-Tri-*t*-butylphenoxyl (2) with Methyl *p*-Hydroxybenzoate.—2,4,6-Tri-*t*-butylphenoxyl was prepared by oxidation of 15.72 g of 2,4,6-tri-*t*-butylphenol dissolved in 150 ml of benzene with a solution of 66 g of potassium ferricyanide and 30 g of potassium hydroxide in 500 ml of water under nitrogen as described previously.[3,4] The stirred radical solution was diluted with 200 ml of benzene. Then 6.2 g of methyl *p*-hydroxybenzoate dissolved in 50 ml of ethyl acetate was added in one portion, and the mixture was stirred for 2 hr. The greenish solution was allowed to stand overnight under nitrogen. After washing with 2 *N* KOH to remove the excess of methyl *p*-hydroxybenzoate, the reaction mixture was stirred with a solution of 20 g potassium ferricyanide and 9 g of potassium hydroxide in 150 ml of water. The aqueous layer was removed and the blue organic layer containing 2,4,6-tri-*t*-butylphenoxyl was washed with water. After the addition of a solution of 2.05 g of methyl *p*-hydroxybenzoate in 50 ml of ethyl acetate to the organic solution, the mixture was stirred for 1 hr and the resulting greenish solution was allowed to stand overnight. It was then washed with 4 *N* KOH (100 ml), again oxidized with a solution of 20 g of potassium ferricyanide and 9 g of potassium hydroxide in 150 ml of water, and then allowed to react with 1.14 g of methyl *p*-hydroxybenzoate in 20 ml of ethyl acetate. The reaction mixture was washed with 4 *N* KOH then water, dried, and evaporated *in vacuo*. The residue was crystallized from petroleum ether (bp 40–60°) to give 2.37 g of crystals, mp 140° dec, which were identified as bis(1,3,5-tri-*t*-butyl-2,5-cyclohexadien-4-one) peroxide[4] (mixture melting point and ir). The mother liquor was chromatographed on a neutralized alumina (activity I) column (400 g). Elution with petroleum ether (400 ml) gave an additional 4.47 g of the peroxide. Subsequent elution with petroleum ether (3150 ml) followed by benzene (75 ml) gave 7.78 g (31%) of yellow crystals. Recrystallization from petroleum ether gave 6.77 g of *p*-quinol ether **5i** as pale yellow crystals: mp 85–87°; ir (CS_2), no OH band, 1716 (ester), 1665 and 1645 cm^{-1} (C=O, cross-conjugated dienone); uv (C_2H_5OH), 250 mμ (ε 20,000). *Anal.* Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80. Found: C, 75.42; H, 8.85.

Further elution with benzene (900 ml) gave 2.31 g (9.3%) of *o*-quinol ether **7i** as yellow crystals which were recrystallized from petroleum ether: mp 108–109°, ir (CS_2), no OH band, 1718 (ester), 1677 and 1653 cm^{-1} (shoulder) (dienone); uv (C_2H_5OH), 308 mμ (ε 1310) and 255 (19,800). *Anal.* Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80. Found: C, 75.48; H, 8.74.

Reaction of 2,4,6-Tri-*t*-butylphenoxyl with *p*-Hydroxybenzoic Acid.—A blue free-radical solution was prepared from 21.0 g (80 mmol) of 2,4,6-tri-*t*-butylphenol as described above. A solution of 11.0 g (80 mmol) of *p*-hydroxybenzoic acid in 200 ml of ethyl acetate was then added and the mixture was stirred for 3 hr in an atmosphere of nitrogen. The resulting greenish yellow solution was evaporated *in vacuo*. To the residue was added 200 ml of petroleum ether. The pale yellow crystals which formed were dissolved in 200 ml of hot benzene, and the resulting solution was filtered. The filtrate was concentrated to 30 ml to give 6.6 g of crude crystals. Recrystallization from benzene gave the *p*-quinol ether **5j** as pale yellow needles (1.5 g), mp 178–179° dec. *Anal.* Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.55; H, 8.80.

The *p*-quinol ether (**5j**, 0.5 g) was methylated with diazomethane in ether. The methyl ester obtained was crystallized from CS_2. Recrystallization from petroleum ether gave 0.154 g of 2,4,6-tri-*t*-butyl-4-(*p*-carbomethoxyphenoxy)-2,5-cyclohexadien-1-one as pale yellow plates, mp 87–88.5°, identical with the *p*-quinol ether **5i** described above (mixture melting point and ir).

The mother liquor from the *p*-quinol ether **5j** was evaporated *in vacuo*. Repeated recrystallizations of the residue from benzene or ethyl acetate failed to give pure crystals. The crude crystals were methylated with diazomethane in ether. The methylated product was recrystallized twice from petroleum ether to give pure 2,4,6-tri-*t*-butyl-6-(*p*-carbomethoxyphenoxy)-2,4-cyclohexadien-1-one (**7i**) as yellow crystals, mp 108.5–109°, identical with the *o*-quinol ether **7i** described above (mixture melting point and ir).

Acid Treatment of *o*-Quinol Ether 7i.—A solution of 200 mg of **7i** in a mixture of 20 ml of acetic acid and 5 ml of hydrobromic acid (sp gr 1.48) was stirred at room temperature for 2 hr. The mixture, upon standing after adding 20 ml of water, deposited the *o*-hydroxydiphenyl ether **8i** as colorless crystals, which were collected by filtration to give 166 mg (97%); mp 130°; uv (C_2H_5OH), 255 mμ (log ε 4.29); ir (KBr), 1710 cm^{-1} (ester). *Anal.* Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.35; H, 8.11.

Pyrolysis of *o*-Quinol Ether 7i.—In a test tube 175 mg of **7i** was heated at 140° for 10 min, then temperature was raised up to 170° over a period of 15 min. The pyrolysate was crystallized from petroleum ether to give 80 mg (53%) of a colorless semicrystalline solid identified as **8i** (ir).

Pyrolysis of *p*-Quinol Ether 5i. A.—Quinol ether **5i** (500 mg) was heated at 155–165° for 15 min, then at 185° for 20 min. The product was crystallized from petroleum ether to give 218 mg (51%) of colorless needles. Recrystallization from petroleum ether gave colorless needles, mp 127–129°, identified as the *o*-hydroxydiphenyl ether **8i** (mixture melting point and ir).

B.—A solution of 505 mg of **5i** in 15 ml of *m*-xylene was refluxed for 5.5 hr. The reaction mixture was chromatographed on a column of silica gel (15 g). Elution with a mixture of benzene and petroleum ether (1:1) (500 ml) gave 193 mg of crude crystals, which were found by tlc to be a mixture of 2,4,6-tri-*t*-butylphenol (**1**) and bis(1,3,5-tri-*t*-butyl-2,5-cyclohexadien-4-one) peroxide. Elution with mixture of $CHCl_3$ (100 ml) and acetone (50 ml) gave 128 mg of crystals identified as methyl *p*-hydroxybenzoate (ir).

Acid Treatment of *p*-Quinol Ether 5i.—A suspension of 500 mg of **5i** in a mixture of 20 ml of acetic acid and 5 ml of hydrobromic acid (sp gr 1.48) was stirred at room temperature for 2.3 hr. The mixture became clear after 20 min. The reaction mixture was diluted with 25 ml of water and allowed to stand in a refrigerator overnight. The yellow crystals which deposited (96 mg, 30%) were collected by filtration and recrystallized from methanol to give 20 mg of 2,4,6-tri-*t*-butylphenol (**1**) as colorless plates, mp 125–127°, identified with an authentic sample (mixture melting point and ir). The aqueous filtrate was extracted with ether, and the ether extract was washed with water, dried, and evaporated *in vacuo* to give a semicrystalline residue (265 mg). Crystallization from petroleum ether gave 146 mg (79%) of methyl *p*-hydroxybenzoate as colorless crystals, mp 113–118°, identified with an authentic sample (mixture melting point and ir).

Reaction of 2,4,6-Tri-*t*-butylphenoxyl with 3,5-Dinitro-4-hydroxyhydrocinnamic Acid.—A blue free-radical solution was prepared from 1.0 g (4 mmoles) of 2,4,6-tri-*t*-butylphenol as already described. A solution of 2.0 g (8 mmoles) of 3,5-dinitro-4-hydroxyhydrocinnamic acid[22] in 10 ml of ethyl acetate was then added and the mixture was allowed to stand at room temperature in an atmosphere of nitrogen until the blue color dis-

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(22) R. K. Callow, J. M. Gulland, and R. D. Haworth, *J. Chem. Soc.*, 1452 (1929).

appeared (3 days). The greenish yellow reaction mixture was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to yield a crystalline residue. The residue was shaken with ether and with a solution of $NaHCO_3$. From the aqueous layer 1.3 g of 3,5-dinitro-4-hydroxyhydrocinnamic acid was recovered. The ether layer was washed with water, dried, and evaporated to give 1.3 g of a semisolid residue. Upon trituration of this with petroleum ether, the *p*-quinol ether **5m** was obtained as yellow crystals, mp 147–149°, yield 0.52 g (51%). Tlc showed a single spot; ir (Nujol), no OH band, 1705 (COOH), 1667, 1645, and 1542 cm^{-1}. *Anal.* Calcd for $C_{27}H_{36}N_2O_8$: C, 62.77; H, 7.02; N, 5.42. Found: C, 62.88; H, 7.02; N, 5.44.

Reaction of 2,4,6-Tri-*t*-butylphenoxyl with *p*-Hydroxyacetophenone.—To a blue free-radical solution, prepared from 1.05 g (4 mmoles) of 2,4,6-tri-*t*-butylphenol in the usual manner, was added 0.27 g (2 mmoles) of *p*-hydroxyacetophenone dissolved in 20 ml of ether. The mixture was allowed to stand under nitrogen at room temperature. After 2 days,[23] the solution became greenish yellow. The reaction mixture was evaporated *in vacuo* and the residue (1.33 g) was chromatographed on silica gel (20 g). Elution with petroleum ether–benzene (1:1) gave 0.48 g of 2,4,6-tri-*t*-butylphenol as colorless crystals. Elution with benzene–ether (99:1) gave 0.623 g (78.5%) of *p*-quinol ether **5k** as yellow crystals. Recrystallization from methanol gave pale yellow prisms, mp 115–116°. *Anal.* Calcd for $C_{26}H_{36}O_3$: C, 78.74; H, 9.15. Found: C, 78.66; H, 9.05.

Further elution with benzene–ether (99:1) gave 0.112 g of a yellow crystalline solid, whose tlc showed one main spot with a minor spot of *p*-quinol ether **5k**. Recrystallization from petroleum ether gave 0.1 g (16%) of *o*-hydroxydiphenyl ether **8k** as colorless needles: mp 131–132°; ir (Nujol), 3400 (OH) and 1670 cm^{-1} (=CO). *Anal.* Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.37; H, 8.11.

Reaction of 2,4,6-Tri-*t*-butylphenoxyl with *p*-Nitrophenol.—To a blue free-radical solution, prepared from 1.05 g (4 mmol) of 2,4,6-tri-*t*-butylphenol, was added 0.28 g (2 mmol) of *p*-nitrophenol dissolved in 10 ml of benzene. The mixture was allowed to stand at room temperature under N_2 atmosphere. After 2 days the blue color of the solution still persisted. An additional 3 g of *p*-nitrophenol was therefore added to the mixture, which turned greenish yellow after 3 hr. The reaction mixture was evaporated *in vacuo* and the residue (4.65 g) was triturated with petroleum ether and filtered to remove *p*-nitrophenol. The filtrate was chromatographed on a silica gel column (20 g). Elution with petroleum ether gave 0.5 g of 2,4,6-tri-*t*-butylphenol as colorless crystals. Elution with petroleum ether–ether (98:2) gave 0.534 g (65%) of *p*-quinol ether (**5l**) as yellow crystals. Recrystallization from methanol gave yellow prisms, mp 136–138°. *Anal.* Calcd for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; N, 3.51. Found: C, 72.23; H, 8.38; N, 3.77.

Further elution with petroleum ether–ether (98:2) gave 0.134 g (19%) of crude *o*-hydroxydiphenyl ether (**8l**) as a yellow crystalline solid. Recrystallization from petroleum ether gave colorless prisms, mp 128–129°. *Anal.* Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.33; N, 4.08. Found: C, 69.83; H, 7.48; N, 4.31.

Registry No.—**5a**, 18826-70-5; **5b**, 18826-71-6; **5c**, 18826-72-7; **5d**, 18826-73-8; **5e**, 18826-74-9; **5f**, 18826-75-0; **5g**, 18826-76-1; **5h**, 18826-77-2; **5i**, 18826-78-3; **5j**, 18826-79-4; **5k**, 18826-80-7; **5l**, 18826-81-8; **5m**, 18826-82-9; **7i**, 18826-83-0; **8a**, 18826-84-1; **8e**, 18826-85-2; **8f**, 18826-86-3; **8i**, 18826-87-4; **8k**, 18826-88-5; **8l**, 18826-89-6; **3-[4-(2-methoxyphenoxy)phenyl]propionic acid**, 18826-90-9; **10**, 18826-91-0.

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(23) When 2.7 g (20 mmoles) of the phenol was used the reaction was completed within 3 hr.

Alkaloids of the *Papaveraceae*. X. New Alkaloids From *Argemone gracilenta* Greene[1]

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The alkaloid content of the poppy *Argemone gracilenta* Greene has been investigated. Of the total alkaloid content, over 90% was argemonine. Other known alkaloids found were (+)-laudanidine, (−)-munitagine, muramine, protopine, (+)-reticuline, and (−)-platycerine. The structure of (−)-platycerine was unequivocally established. New natural alkaloids isolated were (−)-argemonine N-oxide, (−)-argemonine methohydroxide, and (−)-isonorargemonine.

As part of our continuing investigation of the poppy genus *Argemone*, we collected for analysis plants of *A. gracilenta* Greene, whose habitat and distribution is described[2] as being in desert terrain mainly below 1000 ft from west-central Arizona southward in the Sonoran Desert to Baja California del Sur. In a preliminary report[3] we indicated the taxonomic closeness of *A. gracilenta* to *A. munita* and *A. hispida*, using both morphological and chemical criteria. In the present report, we describe the complete alkaloid analysis of *A. gracilenta*.

Results

A. gracilenta proved to have a relatively rich (0.33% of the dried plant) total alkaloid content and would be a prime source of (−)-argemonine (Ia) since this alkaloid represented over 90% of the total. The alkaloids (−)-munitagine (IIa), protopine, muramine, and (+)-reticuline (IIIa) were easily identified. Five additional alkaloids were also isolated and their structures were proven as indicated below (with complete details in the Experimental Section).

(1) Previous paper: F. R. Stermitz and R. M. Coomes, *Phytochemistry*, in press. The present work was supported by Grant GM-15424 from the U. S. Public Health Service.

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