[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GIVAUDAN CORPORATION]

NITRO MUSKS. I. ISOMERS, HOMOLOGS, AND ANALOGS OF MUSK AMBRETTE

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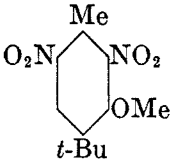
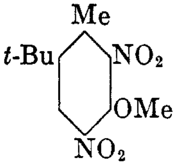
Among the synthetic nitro musks, Musk Ambrette holds a dominant position because of the fineness and strength of its odor. Numerous attempts have been made to synthesize similar products of equal or greater value, but none have been successful. The problem remains, however, a challenge to workers in the field of aromatics. The present paper describes the preparation of a number of isomers, homologs, and analogs of Musk Ambrette and discusses the relationship between structure and odor which is revealed by a comparative study of the various compounds synthesized. At the outset of the project only a few of the more obvious possibilities were contemplated, but as the work expanded it soon became apparent that some of the compounds had little in common with Musk Ambrette other than a benzene nucleus, an alkoxy, a *tert*-alkyl, and a nitro group (in two cases, even the nitro group was missing). Yet it was felt that all could be included under the selected heading if for no other reason than that Musk Ambrette is the only one of the commercial musks which contains an alkoxy group.

In spite of the conclusive work of Zeide and Dubinin (1) which established the structure of Musk Ambrette as I, occasional references are to be found in the subsequent literature (2, 3, for example) which adhere to the former Darzens and Lévy structure XVI (4):



I

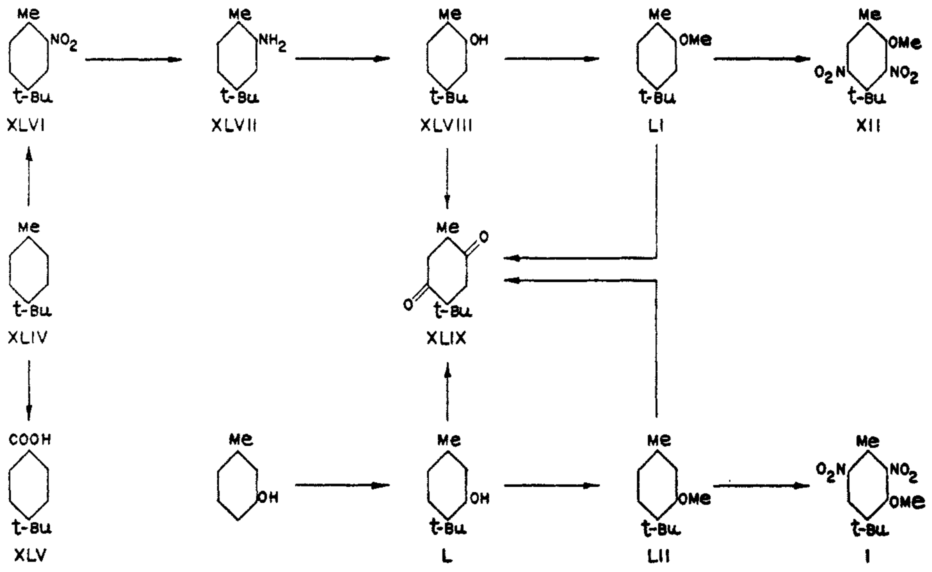


XVI

In the course of the present work, further confirmation of structure I has been obtained, as outlined in Flow Sheet A. *p*-*tert*-Butyltoluene, XLIV, whose constitution was established by oxidation to *p*-*tert*-butylbenzoic acid, XLV, was nitrated to 2-nitro-4-*tert*-butyltoluene, XLVI, the constitution of which has been established (5). Reduction to the amine, XLVII, followed by diazotization, led to 2-methyl-5-*tert*-butylphenol, XLVIII. Oxidation of the latter with chromic anhydride gave 5-*tert*-butyltoluquinone, XLIX, melting at 96–97°, and undepressed upon mixture with the quinone obtained by oxidation of 3-methyl-6-*tert*-butylphenol, L, obtained by *tert*-butylation of *m*-cresol. The quinone was also obtained as a by-product from the nitration of the methyl ethers LI and LII. The quinone was also prepared from L by way of the *p*-nitroso- and *p*-aminophenol, using the method described (6) for the preparation of thymoquinone. The latter method was not successful when applied to the isomeric phenol

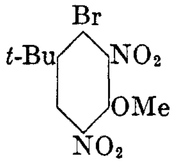
XLVIII, as it was not possible to prepare the nitroso compound. The methyl ethers, LI and LII, yielded upon nitration the isomeric dinitro derivatives XII (odorless) and I (Musk Ambrette).

FLOW SHEET A



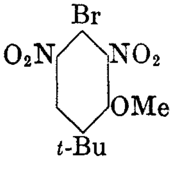
In Table I are listed the compounds prepared in the course of the investigation.

An examination of the table reveals several significant facts with respect to the relation between chemical structure and the musk odor. In no case but one is the musk odor observed when the *tert*-alkyl group is in other than the *ortho* position with respect to the alkoxy group. This observation has led us to postulate what will be referred to throughout this paper as the "*ortho* rule", which can be stated as follows: The most important requisite for musk odor in the aromatic nitro alkoxy series is the presence of a *tert*-alkyl group *ortho* to the alkoxy group. Obviously, not all compounds in which this requisite is fulfilled will be musks, but conversely, only a single musk is known in which it is not fulfilled. This curious anomaly is presented by the isomeric pair XX and XXI:



XX

M. P. 101–102°
Musk

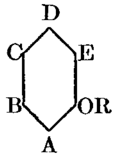


XXI

M. P. 107–108°
Odorless

TABLE I

ISOMERS, HOMOLOGS, AND ANALOGS OF MUSK AMBRETTE



NO.	R	A	B	C	D	E	FLOW SHEET	M.P., °C.	ODOR
I	Me	*tert*-Bu	H	NO_2	Me	NO_2	A	85	Musk Ambrette
II	Me	*tert*-Bu	H	NO_2	H	NO_2	B	82	Musk
III	Et	*tert*-Bu	H	NO_2	H	NO_2	B	79.5	Musk
IV	Me	NO_2	H	*tert*-Bu	H	NO_2	K	101–102.5	Odorless
V	Et	*tert*-Bu	H	NO_2	Me	NO_2	A	68.5	Musk
VI	Me	*tert*-Bu	H	NO_2	Et	NO_2	A	78.5	Strong Musk
VII	Et	*tert*-Bu	H	NO_2	Et	NO_2	A	62.5	Strong Musk
VIII	iso-Pr	*tert*-Bu	H	NO_2	Me	NO_2	A	Oil	Musk
IX	*n*-Bu	*tert*-Bu	H	NO_2	Me	NO_2	A	Oil	Non Musk
X	Me	*tert*-Bu	H	NO_2	iso-Pr	NO_2	C	86	Weak Musk
XI	Me	*tert*-Bu	H	NO_2	*tert*-Bu	NO_2	D	127	None
XII	Me	Me	H	NO_2	*tert*-Bu	NO_2	A	63	None
XIII	Me	NO_2	H	NO_2	*tert*-Bu	H	D	81	None
XIV	Me	NO_2	H	NO_2	*tert*-Bu	NO_2	D	100	None
XV	Me	NO_2	H	CHO	*tert*-Bu	NO_2	D	125–126	None
XVI	Me	NO_2	H	*tert*-Bu	Me	NO_2	E	112–113	None
XVII	Me	*sec*-Bu	H	NO_2	Me	NO_2	F	Oil	None
XVIII	Me	iso-Bu	H	NO_2	Me	NO_2	F	Oil	None
XIX	Me	iso-Bu	H	NO_2	CF_3	NO_2	F	Oil	None
XX	Me	NO_2	H	*tert*-Bu	Br	NO_2	G-3	101–102	Musk
XXI	Me	*tert*-Bu	H	NO_2	Br	NO_2	G-3	107–108	None
XXII	Me	*tert*-Bu	H	NO_2	MeO	NO_2	G-3	98–99	Strong Musk
XXIII	Me	*tert*-Am	H	NO_2	Me	NO_2	A	43–44	Strong Musk

XXIV	Me	*tert*-Am	H	NO_2	Et	NO_2	A	41.5–42.5	Strong Musk
XXV	Me	*tert*-Hex	H	NO_2	Me	NO_2	A	Oil	None
XXVI	Me	*tert*-Hep	H	NO_2	Me	NO_2	A	75–76	None
XXVII	Me	*tert*-Oct	H	NO_2	Me	NO_2	A	75–76	None
XXVIII	Me	*tert*-Oct	H	NO_2	Et	NO_2	A	Oil	None
XXIX	Me	*tert*-Bu	H	CHO	H	NO_2	B	58–59	Musk
XXX	Et	*tert*-Bu	H	CHO	H	NO_2	B	59–60	Musk
XXXI	Me	*tert*-Bu	H	CH_3CO	H	NO_2	B	Oil	None
XXXII	Me	*tert*-Bu	H	*tert*-Bu	H	NO_2	B	53–54	Weak Musk
XXXIII	Me	*tert*-Bu	H	NO_2	Me	H	H	82–83	Non Musk
XXXIV	Me	*tert*-Bu	H	NO_2	*tert*-Bu	H	D	Oil	None
XXXV	Me	*tert*-Bu	H	*tert*-Bu	Me	NO_2	J	139–140	None
XXXVI	Me	NO_2	H	CHO	*tert*-Bu	H	D	Oil	None
XXXVII	Me	iso-Pr	H	iso-Pr	H	NO_2	K	Oil	None
XXXVIII	Me	*tert*-Bu	H	Me	Me	NO_2	H	Oil	None
XXXIX	Me	*tert*-Bu	H	*tert*-Bu	CHO	H	J	68–69	Musk
XL	Me	*tert*-Bu	H	*tert*-Bu	H	CHO	J	Oil	None
XLI	Me	*tert*-Bu	NO_2	*tert*-Bu	CHO	H	J	112–113	None
XLII	Me	CHO	H	*tert*-Bu	H	NO_2	K	68.5–70	None
XLIII	Me	NO_2	H	MeO	*tert*-Bu	H	K	96–97	None

XXI, in which the methyl group of Musk Ambrette has been replaced by bromine, fulfills the *ortho* rule. Such a replacement in Musk Xylene (2,4,6-trinitro-*tert*-butyl-*m*-xylene) (7) does not result in loss of musk odor, but in the present case it does. XXI has a faint, non-descript odor which cannot possibly be characterized as musk. XX, with the *tert*-butyl and methoxy groups in *para* relationship, has, surprisingly, a strong musk odor and constitutes the only exception to the "*ortho* rule" within our ken. If the bromine in either compound be replaced by methoxy a strong musk, XXII, is produced.

Another case in which the *tert*-butyl:methoxy relationship is *para* is XVI, an isomer of Musk Ambrette. Zeide and Dubinin (1) reported this compound to have a faint musk odor, but our preparation was quite odorless.

Five compounds, XII, XIII, XIV, XV, and XXXVI, in which the *tert*-butyl: methoxy relationship is *meta*, are all odorless. In the early stages of our work, before the general validity of the "*ortho* rule" was appreciated, it seemed somewhat surprising that XIII was odorless, when compared with II, and more surprising when the introduction of a third nitro group, XIV, failed to produce odor. Baur's original musk (8) was 2,4,6-trinitro-*m*-*tert*-butyltoluene. It was not to be expected that replacement of the methyl group by the usually strongly osmophoric methoxy group would totally extinguish odor.

Other factors, such as increasing molecular weight, affect the musk odor, as is demonstrated in the series I, VI,[1] VII, X, XI, in all of which the above-mentioned *ortho* relationship is preserved. The odor of Musk Ambrette is enhanced when the methyl group is replaced by ethyl (VI and VII), diminished when it is replaced by isopropyl (X), and extinguished when it is replaced by *tert*-butyl (XI).

There is no significant change in odor when methoxy is replaced by ethoxy (II, III, V, VI, VII, XXIX, XXX). When replaced by isopropoxy (VIII) the musk odor is retained, but with loss of both quality and strength. When replaced by *n*-butoxy (IX), the musk odor is lost.

The presence of a *tert*-alkyl group seems to be essential for musk odor. When the *tert*-butyl group is replaced by *sec*- or iso-butyl (XVII or XVIII), the musk odor disappears. Isolated instances have been noted (9, 10) where an *n*- or iso-alkyl group has contributed to musk odor, but it is felt that these should be reviewed critically. The *tert*-butyl group may be replaced by *tert*-amyl without loss of musk odor (XXIII & XXIV) (11), but when *tert*-hexyl, *tert*-heptyl, or *tert*-octyl are substituted, the odor disappears (XXV, XXVI, XXVII, XXVIII). This effect is possibly attributable to excessive molecular weight rather than to any intrinsic osmophoric factor inherent in the alkyl groups themselves.

An interesting case is presented by XXIX,[2] XXX,[2] and XXXII. These are, with the possible exception of the chloro- and bromo-nitro cymenes (12) the only known mononitro compounds having a musk odor. Replacement of the aldehyde group in XXIX by acetyl (XXXI) extinguishes the odor. Several more mononitro compounds, XXXIII–XXXVIII and XLI–XLIII, were prepared in the hope of extending the series of mononitro musks but, although most

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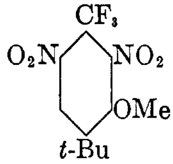
[1] U. S. Patent 2,493,797 (Jan. 10, 1950).

[2] U. S. Patent 2,450,878 (Oct. 12, 1948).

of them adhered to the *ortho* rule, all were either odorless or non-musky. The most unexpected result encountered during the the entire investigation was occasioned upon the preparation of XXXIX.[3] This compound, containing no nitro groups, has a fine, persistent musk odor, with a nuance more toward the multi-membered cyclic type (such as muscone, exaltone, or exaltolide) rather than the nitro type musk. The mononitro derivative of this musk, XLI, is odorless. An isomer, XL, of XXXIX, proved to be odorless. Both, it will be noted, adhere to the *ortho* rule. Further work in this direction is contemplated.

Impressed by the considerable odor strength of *m*-trifluoromethyl anisole compared to that of *m*-cresol methyl ether, we attempted to prepare the compound



in the anticipation that it might prove to be a powerful musk. All attempts to introduce a *tert*-butyl group into *m*-trifluoromethylphenol or its methyl ether by a variety of alkylation methods failed, however. XIX, the existence of which is uncertain, represents the nearest approach which could be realized. That it was odorless was to be expected in consideration of the lack of odor of XVIII.

The preparation of compounds II,[4] III,[4] XXIX, XXX, XXXI, and XXXII, their interrelationships and proof of structure are outlined in Flow Sheet B. As indicated, II (or the corresponding ethyl ether III) can be prepared by several routes. LIII, prepared (13) by *tert*-butylation of *p*-cresol methyl ether, yielded upon oxidation with manganese dioxide and sulfuric acid the aldehyde LIV and, concurrently, the acid LV. Nitration of LIV or LV with mixed acid led to II. Nitration of LIV in the presence of acetic acid-acetic anhydride led to the mononitro aldehyde diacetate, LVI which, odorless itself, became the musk XXIX (XXX being the corresponding ethyl ether). The existence of LVII is inferred from the circumstance that the oily mother liquor from the crystallization of LVI yielded upon further nitration II. Both LVI and XXIX yielded II upon nitration. *o*-*tert*-Butylanisole (LVIII) yielded II upon moderate nitration. Vigorous nitration of II, XXIX, or LVIII led to methyl picrate, LIX.

By a series of reactions analogous to those of *p*-cresol methyl ether, *p*-ethylanisole (LX) was *tert*-butylated to LXI, oxidized to the ketone LXII, and nitrated to the odorless ketonic analogue XXXI of the musk XXIX. Further nitration eliminated the acetyl group and yielded II.

Similarly, 2,4-di-*tert*-butylphenol (LXIII) yielded the methyl ether LXIV and the mononitro derivative XXXII (having a faint musk odor) which, upon further nitration led to II by elimination of a *tert*-butyl group.

Thus, we have instances of the replacement by nitro of the following groups: CHO, COOH, $(CH_3COO)_2CH$, $COCH_3$, and *tert*-Bu. The methyl radical is

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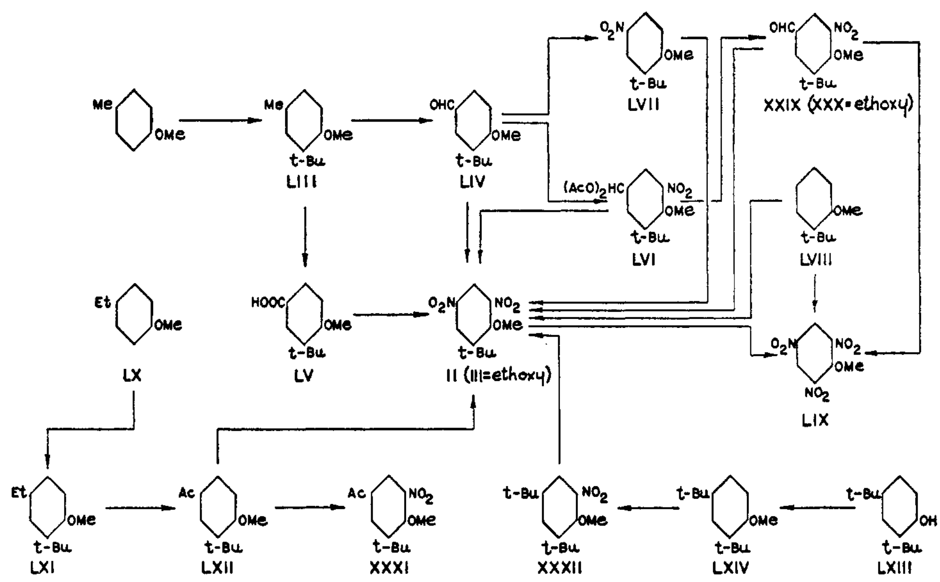
[3] U. S. Patent 2,450,879 (Oct. 12, 1948).

[4] U. S. Patent 2,476,815 (July 19, 1949).

apparently more difficult to eliminate. Dubinin found (13; see also 32) that nitration of LIII led first to 2-nitro-4-methyl-6-*tert*-butylanisole and that further nitration eliminated the *tert*-butyl group rather than the methyl group with formation of 2,6-dinitro-4-methylanisole. (See also 3, 14, and 15).

FLOW SHEET B

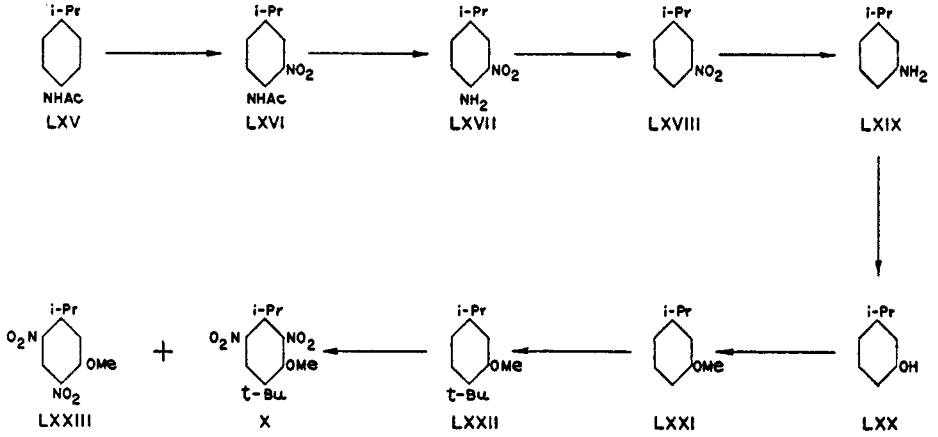


Hanai reported (16) a dinitro *tert*-butylanisole of m.p. 100°, but with no statement as to its structure, and claimed it had a "strong odor like Musk Ambrette". We have prepared dinitro derivatives of the three *tert*-butylanisoles. The *o*-derivative (II, m.p. 82°) has been discussed above. The *m*-derivatives, XIII and XV, m.p. 81° and 72–73° respectively, will be discussed later. The *p*-derivative (IV, m.p. 101–102°) has been prepared by nitration of *p*-*tert*-butylanisole (Flow Sheet K). Of the four, only II has a musk odor, the others are odorless. Thus if Hanai actually had in hand a dinitro *tert*-butylanisole, the presumption is that it must have been the *p*-derivative, contaminated with some *ortho*. It is known that *tert*-butylation of phenol leads predominantly to *p*-substitution, with a small admixture of *ortho* (17). Even if this hypothesis were correct it would be surprising if enough *o*-derivative could have been present to impart a "strong odor like Musk Ambrette" and at the same time to depress the m.p. by not more than 2°.

Compounds V to IX and XXIII to XXVIII were prepared by the method outlined in Flow Sheet A for the preparation of Musk Ambrette, with obvious substitutions.

X was prepared according to the sequence of reactions in Flow Sheet C. *p*-Acetcumidide (LXV) (18) led, by the indicated sequence, to *m*-isopropylphenol (LXX), the methyl ether of which was *tert*-butylated to LXXII. Nitration gave the weak musk X, together with a small proportion of LXXIII, formed by elimination of the *tert*-butyl group in a manner analogous to the formation of 4,6-dinitro-*m*-cresol methyl ether (XCII, Flow Sheet E), a by-product in the manufacture of Musk Ambrette.

FLOW SHEET C



Compounds XI, XIII, XIV, XV, XXXIV, and XXXVI were prepared according to Flow Sheet D. 2,5-Di-*tert*-butylnitrobenzene (LXXIV) led, by the indicated sequence, to 2,5-di-*tert*-butylanisole (LXXVII) and gentle nitration gave the mononitro compound, XXXIV; more vigorous nitration gave XI and, as a by-product formed by elimination of a *tert*-butyl group, XIII. *p*-*tert*-Butylacetanilide (LXXVIII) (19) led, by the indicated sequence, to *m*-*tert*-butylphenol (LXXXIII). This compound is mentioned but once in the literature (20) and no indication is given as to its synthesis. The methyl ether LXXXIV gave, upon nitration in the presence of acetic anhydride, XIII, or with mixed acid the trinitro derivative XIV. Chloromethylation of LXXXIV gave LXXXV and the latter gave, by the Sommelet reaction, the corresponding aldehyde LXXXVI. Mononitration gave an odorless oil, XXXVI. Nitration of the latter with mixed acid gave a mixture of XIII (thereby establishing the structure of XXXVI) and the odorless dinitro aldehyde XV.

XVI was first prepared by Zeide and Dubinin (1; see also 4). Their statement that it had a very faint musk odor seemed to be in conflict with our "*ortho* rule", the general validity of which had been established in a number of instances, and we deemed it important to repeat the preparation. We used a somewhat different, but equally unequivocal, synthesis which is outlined in Flow Sheet E. Zeide and Dubinin used 4-bromo-*m*-cresol as a point of departure, whereas we

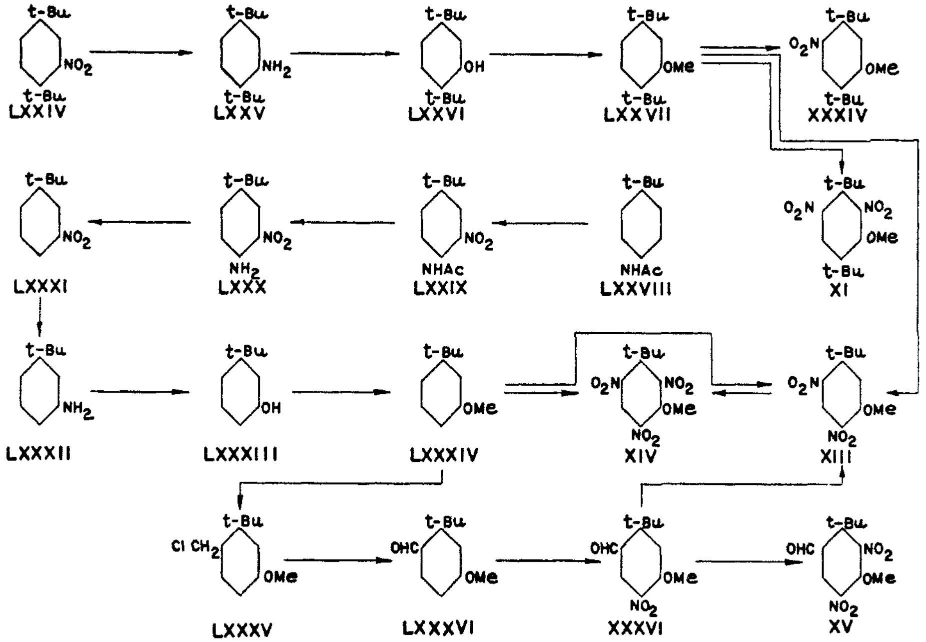
TABLE II
Cresyl Ethers and Derivatives

COMPOUND	CRESYL ETHER			ALKYL CRESYL ETHER				M.P., °C.	ANALYSES		ODOR	NOTES
	B.P., °C./MM.	d_{25}^{25}	n_D^{20}	B.P., °C./MM.	M.P., °C.	d_{25}^{25}	n_D^{20}		Calc'd	Found		
V	*m*-Cresol Et ether			2-*tert*-Bu 5-Me phenetole				68–68.5	$C_{13}H_{18}N_2O_5$			
	53/3	0.9458	1.5052	86/3.5	—	0.9158	1.4987		C 55.29 H 6.43 N 9.93	55.34 6.44 10.05	Like I, but milder	*A*
VI	*m*-Et anisole			2-*tert*-Bu 5-Et anisole				78.5	$C_{13}H_{18}N_2O_5$			
	85/20			87/4	−16	0.9248	1.5030		C 55.29 H 6.43 N 9.93	55.31 6.50 9.43	Like I, but stronger	*B* *C* *D*
VII	*m*-Et phenetole			2-*tert*-Bu 5-Et phenetole				61.5–62.5	$C_{14}H_{20}N_2O_5$			
	67/4	0.9348	1.5028	99/3.5		0.9097	1.4982		C 56.72 H 6.80 N 9.46	56.70 6.77 9.41	Like VI, but weaker	*B* *E*
VIII	*m*-Cresol iso-Pr ether			3-iso-PrO 4-*tert*-Bu toluene								
	54/2	0.9257	1.4948	88/2		0.9079	1.4950	Oil			Like I, but much weaker	
IX	*m*-Cresol *n*-Bu ether			3-*n*-BuO 4-*tert*-Bu toluene								
	88/3	0.9232	1.4970	119/2		0.9115	1.4965	Oil			Non-musk	
XXIII	*m*-Cresol Me ether			2-*tert*-Am 5-Me anisole				43–44	$C_{13}H_{18}N_2O_5$			
				86/3	16				C 55.29 H 6.43 N 9.93	55.24 6.56 9.94	Like I	*F*

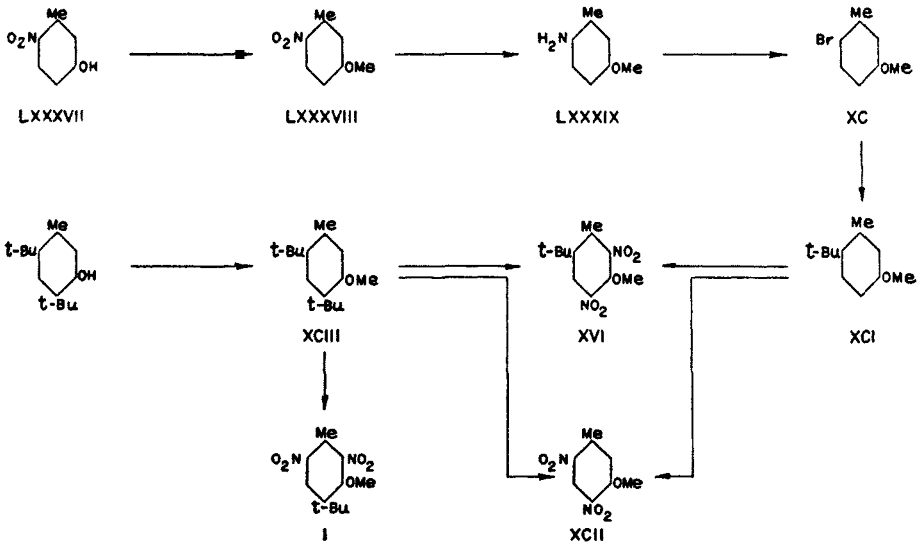
XXIV	*m*-Et anisole	|	|	2-*tert*-Am 5-Et anisole 93/3	8	|	|	41.5–42.5	$C_{14}H_{20}N_2O_5$ C 56.72 H 6.80 N 9.46	 56.93 6.83 9.46	Like I	*B* *G*
XXV	*m*-Cresol Me ether	|	|	2-*tert*-Hex 5-Me anisole 93–94/1	34	|	|	Oil			Odorless	*H*
XXVI	*m*-Cresol Me ether	|	|	2-*tert*-Hep 5-Me anisole 101–102/1	19	|	|	75–76	$C_{15}H_{22}N_2O_5$ C 58.04 H 7.15 N 9.03	 57.22 7.02 9.00	Odorless	*J*
XXVII	*m*-Cresol Me ether	|	|	2-*tert*-Oct 5-Me anisole 109–110/1.5	33	|	|	75–76	$C_{16}H_{24}N_2O_5$ C 59.24 H 7.46 N 8.64	 59.22 7.47 8.71	Odorless	*K* *L*
XXVIII	*m*-Et anisole	|	|	2-*tert*-Oct 5-Et anisole 97/0.5	|	|	|	Oil			Odorless	*B* *K*

A. 2,4-Dinitro-5-methylphenetole, m.p. 98–99°, obtained as a by-product. *B*. *m*-Ethylphenol obtained from Reilly Tar & Chemical Corp. *C*. Oxidation of 2-*tert*-butyl-5-ethylanisole with aqueous permanganate gave 3-methoxy-4-*tert*-butylbenzoic acid, m.p. 150–151°; Neut. equiv., 210 (Calc'd for $C_{12}H_{16}O_3$, 208) identical with that obtained upon oxidation of LII. *D*. 2-Ethyl-5-*tert*-butylbenzoquinone, bright yellow crystals, m.p. 60°, and 2,4-dinitro-5-ethylanisole, pale yellow crystals, m.p. 88–89°, obtained as by-products. *E*. 2,4-Dinitro-5-ethylphenetole, m.p. 69–70.5°, obtained as a by-product. *F*. 2,4-Dinitro-5-methylanisole (XCII), m.p. 101–102°, obtained as a by-product. *G*. 2,4-Dinitro-5-ethylanisole, m.p. 88–89°, obtained as a by-product, identical with that obtained from VI (note *D*). *H*. 3-Methyl-3-pentene, prepared by dehydration of diethyl methyl carbinol with iodine, used as olefin. *J*. 3-Ethyl-3-pentene, prepared by dehydration of triethyl carbinol with odine, used as olefin. *K*. Commercial diisobutylene used as olefin. *L*. A mixture of XXVII and XXVI melted at 40–60°.

FLOW SHEET D



FLOW SHEET E



started with 4-nitro-*m*-cresol (LXXXVII) arriving by the indicated sequence at XCI, nitration of which gave XVI, m.p. 112–113° (Z. and D. reported 111°). The pale yellow crystals were quite odorless after two crystallizations. Zeide and Dubinin reported as a by-product crystals of m.p. 82–83°, which were probably 3-methyl-4-*tert*-butyl-6-nitroanisole. Our only by-product was a trace of XCII, which is always obtained in the manufacture of Musk Ambrette.

FLOW SHEET F

No.	X	R
XCIV	Me	Crotyl
XCVIII	Me	Methallyl
CII	CF_3	Methallyl

No.	X	R
XCV	Me	sec-Butenyl
XCVI	Me	sec-Butyl
XCIX	Me	Methallyl
C	Me	i-Butyl
CIII	CF_3	Methallyl
CIV	CF_3	i-Butyl

No.	X	R
XCVII	Me	sec-Bu
CI	Me	i-Bu
CV	CF_3	i-Bu

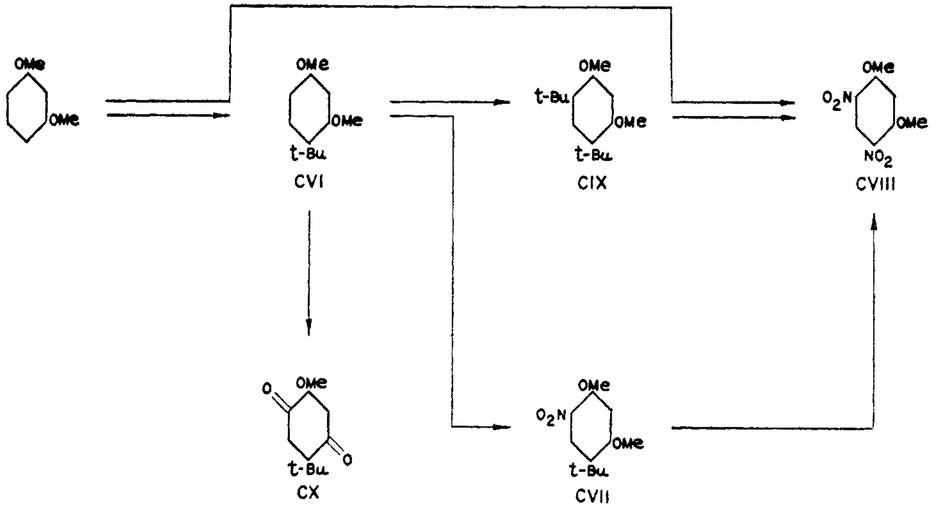
No.	X	R
XVII	Me	sec-Bu
XVIII	Me	i-Bu
XIX	CF_3	i-Bu

Borman claimed (21) that upon nitration of 2,4-di-*tert*-butyl-5-methylanisole, XCIII, (Flow Sheet E) with nitric acid he obtained a musk of m.p. 111.8–113.2° "which in fineness of odor and strength is intermediate between Musk Ketone and Musk Ambrette", and to which he assigned the highly unorthodox structure 1-methyl-3-methoxy-4,6-di-*tert*-butyl-2,5-dinitrobenzene. This assumption is an error, as an elementary analysis would have revealed. We have repeated the nitration and obtained odorless crystals of m.p. 112–113° identical in every respect with those obtained from XCI. We have found that if XCIII be nitrated in the presence of acetic anhydride rather than with nitric acid alone a mixture of nitration products was formed, from which Musk Ambrette (I) could be isolated in indifferent yield, but no XVI. It is thus conceivable that Borman's product may have contained some I, but how enough can have been present, in view of the stated melting point, to merit the claim that the product had odor value comparable to that of Musk Ambrette is not easy to imagine.

Compounds XVII, XVIII, and XIX were prepared according to Flow Sheet F. The crotyl or methallyl ethers XCIV, XCVIII, and CII were rearranged to the corresponding *o*-crotyl- or *o*-methallyl-phenols, then hydrogenated to the *sec*- or iso-butylphenols (22), the latter converted to the methyl ethers, and nitrated. All three nitration products were odorless, yellow to amber oils which were not further investigated or characterized. It is thus questionable whether the dinitro compounds as postulated were actually realized; however, the crude yields obtained, the lack of evidence of extensive decomposition and the general similarity of the reaction to that of many other analogous nitrations successfully accomplished by us—all indicate that probably the dinitro derivatives were present in the crude mixtures to some extent.

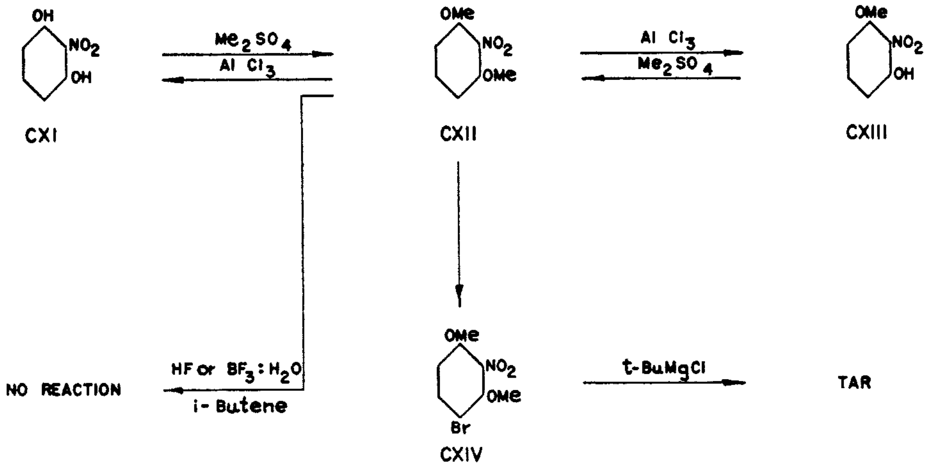
Many attempts were made to prepare the *tert*-butyl analog of CV from *m*-hydroxybenzotrifluoride or its methyl ether by alkylation with isobutene in the presence of sulfuric, phosphoric, or hydrofluoric acids, boron trifluoride or aluminum chloride, and from 3-methoxy-4-bromobenzotrifluoride by the Grignard reaction. In no case was any alkylation effected. CV was the closest approximation to the desired compound that could be realized, and the fact that it produced no musk odor upon nitration was not unexpected in view of the odorless XVIII.

FLOW SHEET G-1



Having in mind the frequently strongly osmophoric character of the methoxy group, it was felt that replacement of the methyl group in Musk Ambrette by a methoxy group might produce a strong musk. The preparation of this product, XXII (Flow Sheet G-3) proved to be a more arduous undertaking than had been anticipated, and a number of routes were explored before success was attained (Flow Sheets G-1, G-2, and G-3). The obvious starting point seemed to be 4-*tert*-butylresorcinol dimethyl ether (CVI) and the nitration of this product was investigated (Flow Sheet G-1) before the similar work of Dubinin (13) was discovered. It is possible that this investigator was seeking the same product. We found, as did he, that it was possible to prepare only a mononitro derivative, CVII, and that introduction of a second nitro group eliminated the *tert*-butyl group and produced 4,6-dinitroresorcinol dimethyl ether (CVIII). It was observed, however, that the mother liquors from the crystallization of these nitration products always had a musky odor, which led us to presume that the desired product had been formed to a limited extent. The only crystalline product which could be isolated from these mother liquors was the quinone CX, analogous to the 5-*tert*-butyltoluquinone XLIX (Flow Sheet A) obtained as a by-product in the preparation of Musk Ambrette.

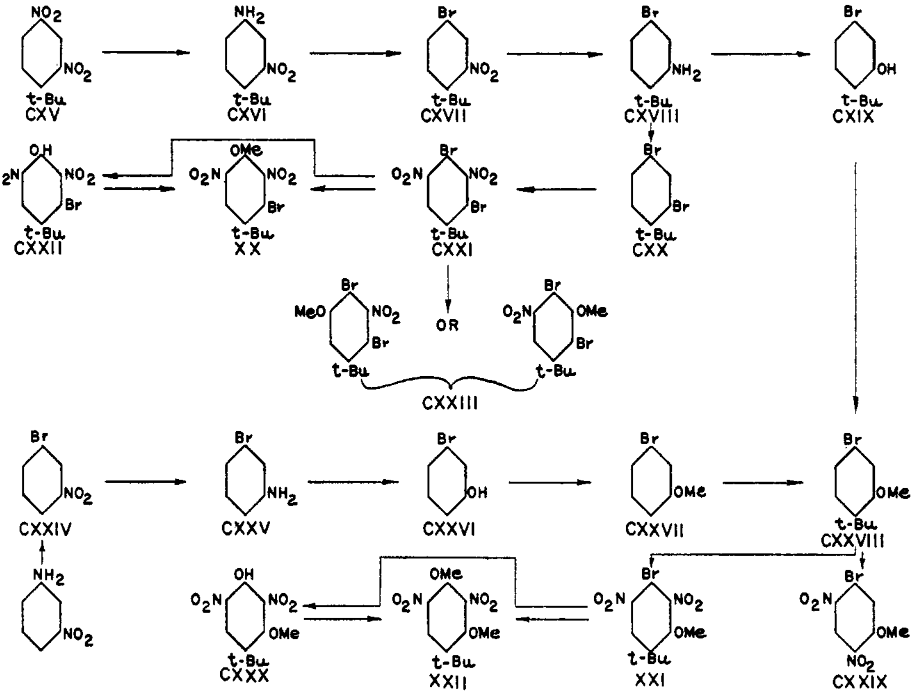
FLOW SHEET G-2



The next approach (Flow Sheet G-2) was to introduce a nitro group in the 2-position of resorcinol (CXI) (23) and attempt to alkylate the methyl ether CXII. Reaction with aluminum chloride and *tert*-butyl chloride served only to hydrolyze either one or both of the methoxy groups, depending upon the amount of aluminum chloride used and to produce, respectively, CXIII or CXI. CXII could not be alkylated with isobutene in the presence of hydrogen fluoride, a method which has been used successfully in the case of *o*-nitroanisole (24). A Grignard reaction was attempted with 2-nitro-4-bromoresorcinol dimethyl ether (CXIV) (25) and *tert*-butyl magnesium chloride, but only tar was produced.

The third approach started with 2,4-dinitro-*tert*-butylbenzene (CXV) (Flow Sheet G-3) which was carried through the indicated sequence to 2,4-dibromo-*tert*-butylbenzene (CXX), nitration of which led to CXXI. This devious course was necessitated by the circumstance that direct bromination of *tert*-butylbenzene gave a product which, although it analyzed well for a dibromo derivative, was evidently a mixture of isomers since upon nitration no crystalline product could be isolated (CXXI has m.p. 167–168°). Treatment of CXXI with sodium methoxide effected the replacement of but one bromine by methoxy, XX, (with concurrent formation of the free phenol CXXII). CXXIII was obtained as a side product, a nitro group rather than a bromo having been replaced by methoxy. It should be noted that at this stage the orientation of XX, which had a musk odor and melted at 101–102°, was not certain, although it was to be presumed that the bromine between the two nitro groups would be the more readily replaced.

FLOW SHEET G-3

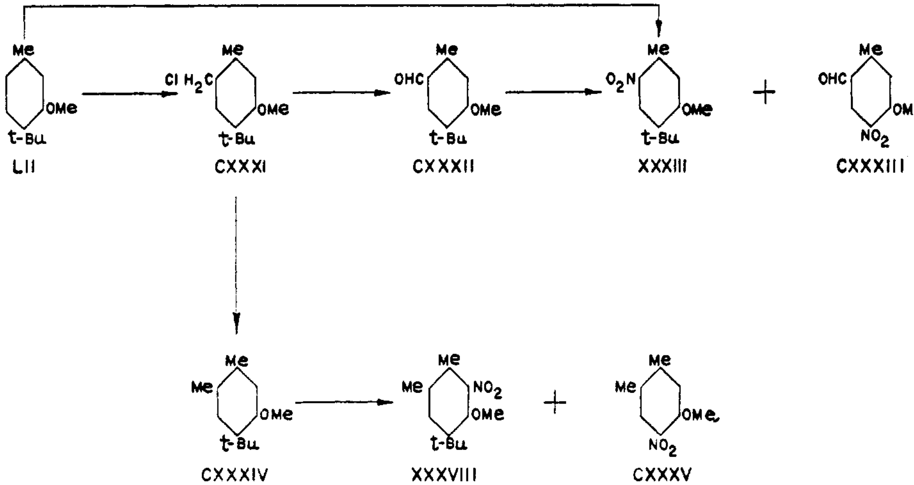


The next series of reactions led to the desired compound XXII, and at the same time provided the solution to the orientation problem. *m*-Nitrobromobenzene (CXXIV) led through the indicated sequence to *m*-bromoanisole (CXXVII) which, upon *tert*-butylation gave a product CXXVIII identical with that obtained by methylation of CXIX. This connecting link established the orientation of XX and its odorless isomer (XXI, m.p. 107–108°), formed, together with CXXIX, by nitration of CXXVIII. A mixture of XX and XXI melted at 90–99°. Treatment of XXI with sodium methoxide readily yielded the desired compound XXII, pale yellow prisms of m.p. 98–99°, having a strong musk odor. A small proportion of the phenol CXXX was concurrently produced.

Compounds XXXIII and XXXVIII were prepared according to Flow Sheet H. LII (Flow Sheet A), which is the intermediate for Musk Ambrette, and commonly designated Ambrogene, was chloromethylated to CXXXI and the latter converted to the corresponding aldehyde CXXXII by the Sommelet reaction.

Our hope was to prepare a mononitro derivative of the aldehyde, one free *meta* position being available. However, upon gentle nitration a mixture of two products was obtained, in one of which, XXXIII, the aldehyde group was eliminated and in the other, CXXXIII, the *tert*-butyl group was replaced. XXXIII had a mild odor similar to that of LII, and CXXXIII was odorless. Treatment of CXXXI with zinc dust and water gave CXXXIV. Nitration of the latter gave an odorless oil which, from the weight yield, probably consisted of a mixture of the desired product XXXVIII and CXXXV, the latter formed by elimination of the *tert*-butyl group.

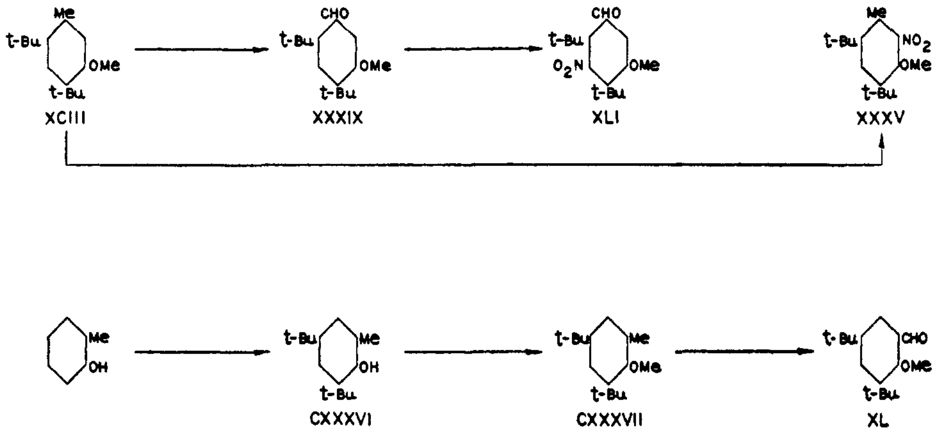
FLOW SHEET H



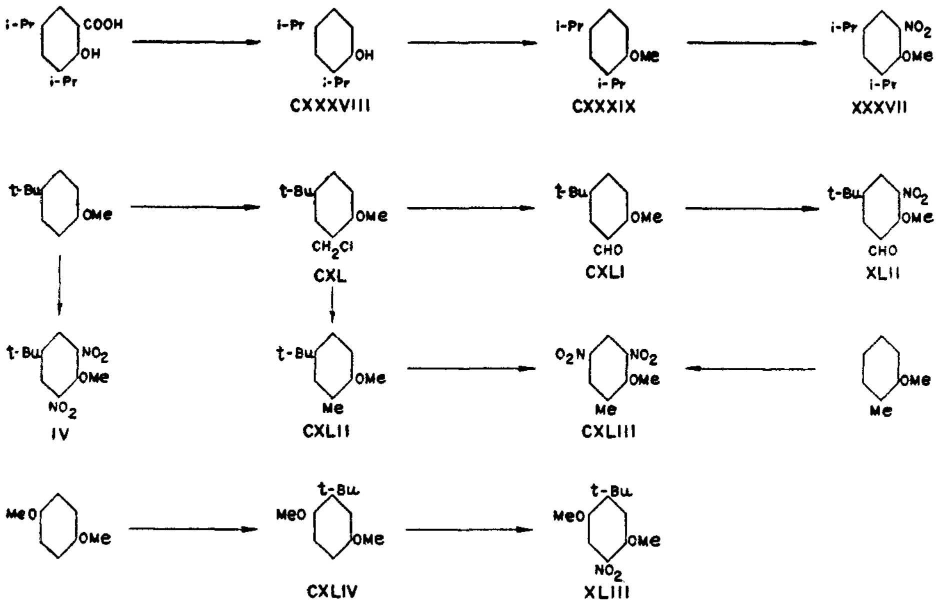
Compounds XXXV, XXXIX, XL, and XLI were prepared as outlined in Flow Sheet J. 4,6-Di-*tert*-butyl-*m*-cresol methyl ether (XCIII) (Flow Sheet E) was nitrated to the odorless XXXV. This was previously prepared by Lur'e (32), but no mention was made of its odor. XCIII yielded, upon oxidation with manganese dioxide and sulfuric acid, the musk-like aldehyde XXXIX, and the latter gave upon nitration the odorless mononitro derivative XLI. *o*-Cresol gave, with isobutene and sulfuric acid, the di-*tert*-butyl derivative CXXXVI, the methyl ether of which, CXXXVII, was oxidized with manganese dioxide and sulfuric acid to the odorless aldehyde XL.

Compounds XXXVII, XLII, and XLIII were prepared as indicated in Flow Sheet K. 3,5-Diisopropylsalicylic acid (31) was decarboxylated to 2,4-diisopropylphenol (CXXXVIII), the methyl ether of which, CXXXIX, was nitrated to the odorless oil, XXXVII. The chloromethyl derivative CXL of *p*-*tert*-butylanisole was converted to the corresponding aldehyde CXLI, an isomer of LIV (Flow Sheet B) and nitrated to XLII, an odorless isomer of the musk

FLOW SHEET J



FLOW SHEET K



XXIX (Flow Sheet B). CXL was converted to 2-methyl-4-*tert*-butylanisole (CXLII) and the latter nitrated to 2,4-dinitro-6-methylanisole (CXLIII), identical with that prepared by the nitration of *o*-cresol methyl ether, and thus confirming the structure of CXL and CXLI. CXLIII was first prepared by

Baur (30) by nitration of a *tert*-butyl-*o*-cresol methyl ether, but he considered it to be a trinitro *tert*-butyl-*o*-cresol methyl ether (by coincidence the nitrogen contents of the two formulations are practically identical). It remained for Dubinin (31) to point out that the product prepared by Baur's method was identical with that prepared from *o*-cresol methyl ether.

Nitration of *p*-*tert*-butylanisole led to the odorless IV. Hydroquinone dimethyl ether was converted to the *tert*-butyl derivative CXLIV, and the latter nitrated to the odorless mononitro compound XLIII. This had been prepared previously by Lur'e (32) but no mention was made of its odor.

EXPERIMENTAL

NITRATIONS

Most of the nitrations performed in this work were carried out according to one of the three following procedures, which will be described here and, for the sake of brevity, thereafter referred to by type designation.

Type A. This usually led to dinitration. Nitric acid (5 moles, 98%) was added with agitation to 3.5 moles of acetic anhydride, keeping the temperature below 20°. One mole of the compound to be nitrated was added to this solution at temperatures between −10° and +20° depending upon the case. Where the compound was solid, part of the acetic anhydride might be used to dissolve it and the rest mixed with the nitric acid. The nitration mixture was quenched on ice, and the product taken up in benzene, washed with water, then with 5% sodium hydroxide until the washes were free of color, then with water to neutrality, and the solvent removed. The crude product was then crystallized from an appropriate solvent.

Type B. This usually led to dinitration or, in some cases, to trinitration. One mole of the compound was added with agitation and cooling to a mixed acid composed of 6 moles of 98% nitric acid and 9.5 moles of 93% sulfuric acid. In some cases, ethylene dichloride was added to the mixed acid and the compound added in ethylene dichloride solution. Temperature varied between −10° and +20°. Quenching and washing were as in *Type A.*

Type C. This practically always led to mononitration, in some cases in almost quantitative yields. Nitric acid (2.5 moles, 98%) was added to a solution of 8 moles of acetic acid and 4 moles of acetic anhydride, keeping the temperature below 20°. The compound, either alone or dissolved in part of the acetic acid, was added at temperatures varying from −10° to +20°. Quenching and washing were as in *Type A.*

FLOW SHEET A

Toluene (2 kg.) was chilled to −10° and 500 g. of 93% sulfuric acid was added, keeping the temperature below 0°; 350 liters of isobutene was passed in with vigorous agitation at a rate of 90 liters per hour, keeping the temperature between −5° and 0°. The toluene layer was washed to neutrality and distilled, yielding 1,895 g. of *p*-*tert*-butyltoluene (XLIV), b.p. 65–68°/10 mm. Oxidation with alkaline permanganate gave *p*-*tert*-butylbenzoic acid (XLV) melting, alone or admixed with an authentic specimen, at 164°. A mixed acid composed of 140 g. of 98% nitric acid and 230 g. of 80% sulfuric acid was added with agitation to a mixture of 296 g. of XLIV and 330 g. of 85% sulfuric acid at 20°. After warming 15 min. at 60°, the oil layer was separated, washed to neutrality and distilled; 339 g. of 2-nitro-4-*tert*-butyltoluene (XLVI) was collected at 103°/2 mm.; d_{25}^{25} 1.050, n_D^{20} 1.525. XLVI (310 g.) was refluxed 15 hours with a mixture of 540 g. of water, 32 g. of 31% hydrochloric acid, and 323 g. of 40-mesh iron filings. Steam-distillation followed by vacuum-distillation yielded 244 g. of 2-amino-4-*tert*-butyltoluene (XLVII), b.p. 90–92°/2 mm., d_{25}^{25} 0.9394, n_D^{20} 1.536.

Anal. Calc'd for $C_{11}H_{17}N$: N, 8.59. Found: N, 8.64.

A solution of 38 g. of sodium nitrite in 500 g. of water was added during one-half hour to a refluxing solution of 81 g. of XLVII in 3,250 g. of 14% sulfuric acid. After cooling, the oil was separated, washed, and distilled, yielding 65 g. of 2-methyl-5-*tert*-butylphenol (XLVIII), b.p. 92–94°/2 mm., c.p. 32°. A solution of 19.5 g. of chromic anhydride in 200 g. of acetic acid was added, with agitation, to a solution of 20.5 g. of XLVIII in 200 g. of acetic acid at 35°. After 2 hours, the mixture was diluted with 2 liters of water and steam-distilled. The bright yellow-orange crystals were recrystallized from naphtha, yielding 11 g. of 5-*tert*-butyltoluquinone (XLIX) m.p. 97–98°.

A suspension of the sodium salt of XLVIII in toluene, treated with methyl sulfate, gave 2-methyl-5-*tert*-butylanisole (LI), b.p. 74–75°/0.7 mm., c.p. −13°, m.p. −12°. *Type A* nitration of 55 g. of LI at 10° gave an oil which was distilled. Fraction 1, 94–100°/1 mm. (10 g.) proved to be the quinone XLIX; Fraction 2, 155–160°/1 mm. (50 g.) partially crystallized on standing. Three crystallizations from ethanol yielded 28 g. of 2,4-dinitro-3-*tert*-butyl-6-methylanisole (XII) as pale yellow, odorless crystals, m.p. 62.5–63.5°.

Anal. Calc'd for $C_{12}H_{16}N_2O_5$: C, 53.8; H, 5.97; N, 10.44.
Found: C, 54.0; H, 6.1; N, 10.4.

2-*tert*-Butyl-5-methylphenol (L) (from Koppers Co.) (20 g.) was oxidized with chromic anhydride as for XLVIII (above), giving 5 g. of the quinone XLIX, identical in all respects with that obtained from the isomeric XLVIII.

A suspension of the sodium salt of L in hot toluene, treated with methyl sulfate, yielded the methyl ether, LII, b.p. 69°/1.5 mm., d_{25}^{25} 0.930, n_D^{20} 1.504, m.p. 22°. *Type A* nitration of 100 g. of LII at 10° gave a crude product which was digested with 1 kg. of naphtha and filtered, removing 25 g. of 2,4-dinitro-5-methylanisole (XCII, Flow Sheet E), m.p. 101–102° after crystallization from methanol. The naphtha was distilled off and the residue twice crystallized from ethanol, yielding 90 g. of Musk Ambrette (I), pale yellow, m.p. 85°. Reworking of the mother liquors yielded, aside from a further amount of I, 1 g. of the quinone XLIX.

The quinone XLIX was prepared in 70% over-all yield from the phenol L by the method described (6) for the preparation of thymoquinone. It was identical in all respects with that obtained by the above routes.

Compounds V–IX and XXIII–XXVIII were prepared by the same general method outlined above for I. The cresyl-type ethers were prepared in the customary manner with the alkyl sulfates or, in the case of VIII and IX, with the alkyl chlorides. The alkylcresyl ethers were prepared by adding the appropriate olefin to the cresyl ether containing a catalytic amount of either aluminum chloride or 93% sulfuric acid at room temperature. *Type A* nitrations were employed. In Table II are listed the physical constants and analytical data, together with explanatory and supplemental notes.

FLOW SHEET B

Isobutene (330 liters) was added, with vigorous agitation, to a mixture of 1,464 g. of *p*-cresol methyl ether and 75 g. of 93% sulfuric acid during 3 hours, maintaining the temperature at 25° by cooling. The oil layer was washed with 5% sodium hydroxide, then with water to neutrality, and distilled; 2,105 g. of 2-*tert*-butyl-4-methylanisole (LIII) was obtained as a colorless oil of mild odor, b.p. 78°/3 mm., c.p. 15.5°, m.p. 16.5°, d_{25}^{25} 0.9287, n_D^{20} 1.5039. A mixture of 400 g. of LIII, 221 g. of manganese dioxide, and 2,000 g. of 30% sulfuric acid was agitated vigorously for 28 hours at 62–65°. After cooling, the mixture was filtered, the oil layer separated, washed with 10% sodium carbonate solution, then to neutrality with water, and distilled. After recovering 226 g. of unreacted LIII there was obtained 187 g. of 3-*tert*-butyl-4-methoxybenzaldehyde (LIV) as a colorless crystalline mass, b.p. 122°/3 mm. Crystallization from half its weight of naphtha yielded 170 g. of pure aldehyde, m.p. 55°, having a somewhat empyreumatic, licorice-type odor.

Anal. Calc'd for $C_{12}H_{16}O_2$: C, 74.95; H, 8.39.
Found: C, 74.45; H, 8.48.

The *semicarbazone* had m.p. 181–182°. Acidification of the carbonate wash of the crude aldehyde yielded 6 g. of 3-*tert*-butyl-4-methoxybenzoic acid (LV), m.p. 193–194° after crystallization from a mixture of naphtha and benzene. The acid was also prepared by dilute nitric acid oxidation of LIII.

Type B nitration of 48 g. of LIV in ethylene dichloride at −5° gave a crude product which, after two crystallizations from ethanol, yielded 42 g. of 2,4-dinitro-6-*tert*-butylanisole (II), pale yellow prisms of m.p. 81–82°, having a musk-like odor.

Anal. Calc'd for $C_{11}H_{14}N_2O_5$: C, 51.95; H, 5.55; N, 11.02.
Found: C, 51.63; H, 5.52; N, 10.88.

Type B nitration of 41 g. of the acid LV in ethylene dichloride at −5° yielded 32 g. of II, m.p. 81–82°.

Type C nitration of 48 g. of LIV at 0–15° gave, after crystallization from naphtha, 50 g. of the diacetyl derivative of 3-*tert*-butyl-4-methoxy-5-nitrobenzaldehyde (LVI), pale yellow odorless prisms, m.p. 97–98°.

Anal. Calc'd for $C_{16}H_{21}NO_7$: C, 56.61; H, 6.23; N, 4.13.
Found: C, 56.61; H, 6.25; N, 3.95.

LVI (50 g.) was refluxed with vigorous agitation for 1 hour with a solution of 25 g. of ethanol in 500 g. of 15% hydrochloric acid. After cooling, the crystals were washed with water and crystallized from ethanol, yielding 32 g. of 3-*tert*-butyl-4-methoxy-5-nitrobenzaldehyde (XXIX) as pale yellow prisms, m.p. 58–59°, having a Musk Ambrette-like odor.

Anal. Calc'd for $C_{12}H_{15}NO_4$: C, 60.74; H, 6.37; N, 5.90.
Found: C, 60.68; H, 6.37; N, 5.87.

The mother liquor from the crystallization of LVI was evaporated and the remaining oil, LVII, was nitrated in the same manner as for LIV. II was obtained in good yield, m.p. 81–82°. Using the same *Type B* nitration, both LVI and XXIX gave II in good yield.

o-*tert*-Butylphenol (sample by courtesy of Dow Chemical Company) was methylated to *o*-*tert*-butylanisole (LVIII), b.p. 66°/4.5 mm., d_{25}^{25} 0.9426, n_D^{20} 1.5078. *Type B* nitration of 36 g. of LVIII in ethylene dichloride at −5° gave 32 g. of II.

XXIX (9 g.) was nitrated with a mixture of 30 g. of 20% oleum, 15 g. of 93% sulfuric acid, and 15 g. of 98% nitric acid at 30–70°, yielding 7 g. of methyl picrate (LIX), m.p. 67–68°, undepressed upon admixture with an authentic specimen. II and LVIII, nitrated in the same manner, likewise yielded LIX.

2,4-Di-*tert*-butylphenol (LXIII), m.p. 55°, was prepared from phenol and *tert*-butyl chloride in the presence of aluminum chloride. The sodium salt, suspended in hot toluene and treated with methyl sulfate, yielded the methyl ether, LXIV, m.p. 36–37°, b.p. 114°/4 mm.

Anal. Calc'd for $C_{15}H_{24}O$: C, 81.75; H, 10.98.
Found: C, 81.85; H, 10.98.

Type C nitration of 55 g. of LXIV at −5° gave, after three crystallizations from ethanol, 38 g. of 2,4-di-*tert*-butyl-6-nitroanisole (XXXII) as practically colorless, microscopic needles, m.p. 53–54°, having a very faint musk odor.

Anal. Calc'd for $C_{15}H_{23}NO_3$: C, 67.7; H, 8.68; N, 5.27.
Found: C, 68.2; H, 8.7; N, 5.3.

Type B nitration of XXXII in ethylene dichloride at −5° yielded II, m.p. 81–82°.

p-Ethylphenol (from Reilly Tar & Chemical Corp.) was methylated to *p*-ethylanisole (LX), b.p. 59°/4 mm. Isobutene (120 liters) was passed, with vigorous agitation, into a mixture of 544 g. of LX and 25 g. of 93% sulfuric acid at 30°. After washing to neutrality and distilling there was obtained in addition to 223 g. of recovered LX, 453 g. of 2-*tert*-butyl-4-ethylanisole (LXI), b.p. 90°/4 mm., d_{25}^{25} 0.9242, n_D^{20} 1.5008.

A mixture of 288 g. of LXI, 700 g. of 40% sulfuric acid, and 150 g. of manganese dioxide was agitated vigorously at 60° for 24 hours. The oil layer, after washing and distilling, yielded 190 g. of unchanged LXI and 96 g. of 3-*tert*-butyl-4-methoxyacetophenone (LXII), b.p. 128°/2.5 mm. as colorless crystals which, after crystallization from naphtha, melted at 70–70.5°. Its odor was similar to that of the corresponding aldehyde, LIV, but much weaker.

Anal. Calc'd for $C_{13}H_{18}O_2$: C, 75.7; H, 8.74.
Found: C, 75.7; H, 8.80.

Type C nitration of 51.5 g. of LXII at −5° to 15° gave an oil which, after hydrolysis with dilute sulfuric acid and methanol, gave 56 g. of 3-nitro-4-methoxy-5-*tert*-butylacetophenone (XXXI) as an odorless oil.

Addition of LXII to 98% nitric acid at 10° gave II, m.p. 81–82°.

III and XXX, the ethoxy homologues of II and XXIX, respectively, were prepared in the same manner. *p*-Cresyl ethyl ether, b.p. 59°/3 mm., d_{25}^{25} 0.9447, n_D^{20} 1.5041, yielded upon butylation 3-*tert*-butyl-4-ethoxytoluene, b.p. 84°/3 mm., m.p. 22°, d_{25}^{25} 0.9153, n_D^{22} 1.4991. The latter, upon oxidation with manganese dioxide and sulfuric acid, gave 3-*tert*-butyl-4-ethoxybenzaldehyde, colorless crystals, m.p. 69–70°, b.p. 133°/3.5 mm., having an empyreumatic odor similar to that of LIV but somewhat milder.

Anal. Calc'd for $C_{13}H_{18}O_2$: C, 75.68; H, 8.79.
Found: C, 75.83; H, 8.98.

The corresponding acid, 3-*tert*-butyl-4-ethoxybenzoic acid, had m.p. 215–216°.

Type B nitration of the aldehyde in ethylene dichloride at −5° gave 2,4-dinitro-6-*tert*-butylphenetole (III) as pale yellow plates exhibiting two melting points, 71° and 79.5°, and having a musk odor similar to that of II.

Anal. Calc'd for $C_{12}H_{16}N_2O_5$: C, 53.79; H, 5.95; N, 10.46.
Found: C, 53.67; H, 5.86; N, 10.59.

Type C nitration of the aldehyde at 0° to 15° gave the diacetate of 3-*tert*-butyl-4-ethoxy-5-nitrobenzaldehyde, as odorless crystals, m.p. 129.5–130°. Hydrolysis of the latter gave 3-*tert*-butyl-4-ethoxy-5-nitrobenzaldehyde (XXX) as pale yellow prisms, m.p. 59–60°, having a musk odor similar to that of XXIX.

Anal. Calc'd for $C_{13}H_{17}NO_4$: C, 62.20; H, 6.82; N, 5.57.
Found: C, 62.09; H, 6.83; N, 5.67.

FLOW SHEET C

Acetic anhydride (165 g.) was added gradually to 220 g. of *p*-cumidine, the solution refluxed 1 hour, cooled, 400 ml. of benzene added, and the solution washed free of acid. The resulting solution was added to 200 ml. of 28% ammonium hydroxide and agitated for 1 hour during which time the temperature was raised to 55°. The benzene layer was removed, washed to neutrality, and the solvent distilled off, leaving 283 g. of *p*-acetcumidide (LXV) as waxy plates, m.p. 103–106°. After crystallization from naphtha, m.p. 105–106° [Literature (18) m.p. 102–102.5°]. *Type C* nitration of 295 g. of LXV at 0–10° gave a crude product which was digested with 1 liter of benzene. Filtration removed 10 g. of powder which, after crystallization from methanol, had m.p. 215–216°, and was probably 3,5-dinitro-4-acetaminocumene. Treatment with alkali gave bright yellow needles, m.p. 149–149.5°, which were probably the corresponding free amine. The benzene was distilled from the solution, leaving 349 g. of crude product which, after crystallization from 70% ethanol, gave 297 g. of 3-nitro-4-acetaminocumene (LXVI), m.p. 80–81°.

Potassium hydroxide (115 g. of 50%) was added to a refluxing solution of 196 g. of LXVI in 175 g. of ethanol. After 15 minutes' refluxing the solution was poured into 2 liters of water and the dark oil layer removed; 159 g. of 3-nitro-4-aminocumene (LXVII) was obtained (100% yield). It was dissolved in 800 ml. of ethanol and 345 g. of 31% hydrochloric acid, refluxed, and a solution of 122 g. of sodium nitrite in 190 g. of water was added during 35 minutes. The mixture was steam-distilled, the oil taken up in benzene, washed with 5% sodium carbonate, and distilled; 86 g. of *m*-nitrocumene (LXVIII) was obtained, b.p. 92°/3.5 mm., d_{25}^{25} 1.0830, n_D^{20} 1.5301.

LXVIII (285 g.) was added during 1 hour to a refluxing mixture of 570 g. of water, 34g of 31% hydrochloric acid, and 342 g. of 40-mesh iron filings. Refluxing and agitation were continued for 16 hrs., the mixture steam-distilled, and the oil distilled *in vacuo*; 223 g. of *m*-cumidine (LXIX) was obtained, b.p. 79–80°/3 mm., d_{25}^{25} 0.9534, n_D^{20} 1.5445. Acetylation gave *m*-acetcumidide, feathery needles from naphtha, m.p. 77.5–78°.

LXIX (147 g.) in 3 kg. of 21% sulfuric acid was diazotized at −5° with 79 g. of sodium nitrite, and a few grams of urea were added to destroy excess nitrous acid. A vigorous current of steam was passed into 700 g. of 15% sulfuric acid and the cold diazonium solution gradually was added and the steaming continued until no more oil passed over. After redistillation there was obtained 127 g. (85% yield) of *m*-isopropylphenol (LXX), b.p. 81°/2.5 mm., c.p. 25.5°, m.p. 26°. *m*-Isopropylanisole (LXXI), prepared with methyl sulfate, had b.p. 59°/3 mm., d_{25}^{25} 0.9405, n_D^{20} 1.5042. Isobutene (19 liters) was added with vigorous agitation to a mixture of 172 g. of LXXI and 7 g. of 93% sulfuric acid at 25°. After washing and distilling in the presence of a few flakes of potassium hydroxide there was obtained 78 g. of 2-*tert*-butyl-5-isopropylanisole (LXXII), b.p. 89–90°/3 mm., d_{25}^{25} 0.9170, n_D^{20} 1.5000.

Type A nitration of 58 g. of LXXII at −10° gave, after crystallization from ethanol, 30 g. of 2,4-dinitro-3-isopropyl-6-*tert*-butylanisole (X) as pale yellow prisms, m.p. 85.5–86°, having a weak, Musk Ambrette-like odor. From the mother liquor there was isolated 13 g. of 2,4-dinitro-5-isopropylanisole (LXXIII) as pale yellow, odorless rhombs, m.p. 71.5–72.5°.

Anal. Calc'd for (X) $C_{14}H_{20}N_2O_5$: C, 56.7; H, 6.75; N, 9.45.

Found: C, 56.9; H, 6.70; N, 9.30.

Calc'd for (LXXIII) $C_{10}H_{12}N_2O_5$: C, 50.0; H, 5.0; N, 11.68.

Found: C, 50.3; H, 4.90; N, 11.20.

FLOW SHEET D

Type C nitration of 237 g. of *p*-di-*tert*-butylbenzene, m.p. 78–78.5°, at 20° yielded, after crystallization from ethanol, 220 g. of 2,5-di-*tert*-butylnitrobenzene (LXXIV) as pale yellow plates, m.p. 87–88°.

Anal. Calc'd for $C_{14}H_{21}NO_2$: C, 71.3; H, 8.98; N, 5.96.

Found: C, 71.4; H, 8.80; N, 5.92.

A mixture of 235 g. of LXXIV, 200 g. of 40-mesh iron filings, 400 g. of 50% ethanol, and 20 g. of 31% hydrochloric acid was refluxed with vigorous agitation for 24 hours, then steam-distilled. The crystals filtered from the distillate yielded, after crystallization from ethanol, 200 g. of 2,5-di-*tert*-butylaniline (LXXV) as colorless, odorless crystals, m.p. 103–104°.

Anal. Calc'd for $C_{14}H_{23}N$: N, 6.82. Found: N, 6.67.

LXXV (100 g.) was added to 3,250 g. of 14% sulfuric acid and the thick slurry refluxed for 10 min. A solution of 35 g. of sodium nitrite in 500 g. of water was dropped in during 30 min. while maintaining reflux. The thin mixture was cooled, extracted with benzene, the extract washed with 5% sodium hydroxide and then steam-distilled; 80 g. of crude phenol was obtained which, after crystallization from naphtha, gave 64 g. of 2,5-di-*tert*-butylphenol (LXXVI) as colorless, odorless crystals, m.p. 118–119°. Sodium hydroxide (56 g., 50%) was added gradually to a refluxing solution of 103 g. of LXXVI in 400 g. of toluene and refluxing continued under a water separator until all water was removed. Methyl sulfate (63 g.) was then added during one-half hour, refluxing continued 3 hrs., the solution cooled, washed to neutrality and distilled; 101 g. of 2,5-di-*tert*-butylanisole (LXXVII) was obtained as a practically odorless oil, b.p. 128°/11 mm., c.p. 23°, m.p. 24°.

Type A nitration of 30 g. of LXXVII at −12° gave 37 g. of crude product which was taken up in 370 g. of naphtha and filtered, removing 12 g. of powder which, recrystallized from ethanol, gave 11 g. of 2,4-dinitro-5-*tert*-butylanisole (XIII) as bright yellow odorless needles, m.p. 80–81°.

Anal. Calc'd for $C_{11}H_{14}N_2O_5$: C, 51.9; H, 5.55; N, 11.02.

Found: C, 51.6; H, 5.70; N, 10.80.

The solvent was distilled from the filtered naphtha solution and the remainder crystallized from ethanol to yield 10 g. of 2,4-dinitro-3,6-di-*tert*-butylanisole (XI) as pale yellow, odorless needles, m.p. 126–127°.

Anal. Calc'd for $C_{15}H_{22}N_2O_5$: C, 58.0; H, 7.1; N, 9.03.

Found: C, 58.6; H, 7.1; N, 8.90.

Type C nitration of 27 g. of LXXVII at 0–15° gave 32 g. of 2,5-di-*tert*-butyl-4-nitroanisole (XXXIV) as an odorless oil which could not be crystallized.

Poor yields having been obtained by the published procedure (19) for preparation of *p*-*tert*-butylacetanilide (LXXVIII) the following modified procedure was adopted: 80 g.

of aluminum chloride was suspended in 500 g. of ethylene dichloride and 68 g. of acetanilide was added at −15° to −12°; 51 g. of *tert*-butyl chloride was then added at −12°. The solution was quenched on ice, washed to neutrality, and the solvent distilled. The crude residue, 95 g., m.p. 158–164°, was dissolved in the minimum of hot benzene (250 g.), the solution poured into 400 g. of naphtha, allowed to crystallize and the crystals washed with 250 g. of naphtha; 78 g. of LXXVIII was obtained as colorless plates, m.p. 170–171°.

Type C nitration of 48 g. of LXXVIII at 0–10° gave, upon quenching, 59 g. (100% yield) of 2-nitro-4-*tert*-butylacetanilide (LXXIX) as bright yellow crystals, m.p. 103–106°. Then 162 g. of LXXIX was dissolved in 150 g. of boiling ethanol, 84 g. of 50% potassium hydroxide added, the solution refluxed 15 min., poured into 1,500 ml. of ice-water, and the orange-red crystals filtered and washed with water; 133 g. (100% yield) of 2-nitro-4-*tert*-butylaniline (LXXX) was obtained, m.p. 102.5–105.5°.

A solution of 200 g. of LXXX in 1 liter of ethanol and 400 g. of 31% hydrochloric acid was refluxed and a solution of 142 g. of sodium nitrite in 220 g. of water was added as rapidly as the heat of reaction would permit. The mixture was steam-distilled, the oil separated, washed with 5% sodium hydroxide then to neutrality and distilled, yielding 122 g. of *m*-nitro-*tert*-butylbenzene (LXXXI), b.p. 97–99°/2.5 mm., d_{25}^{25} 1.0645, n_D^{20} 1.5271. Reduction with iron and hydrochloric acid as for LXIX (Flow Sheet C) gave a 95% yield of *m*-*tert*-butylaniline (LXXXII), b.p. 83–84°/2 mm. LXXXII (75 g.) in 1,400 g. of 20% sulfuric acid was diazotized at −5° and the cold solution added during 20 min. to 325 g. of 14% sulfuric acid through which a current of steam was passed. The distillate was extracted with benzene and the extract distilled, yielding 65 g. of *m*-*tert*-butylphenol (LXXXIII), b.p. 98°/3 mm., c.p. 40.5°, m.p. 41°. The methyl ether, LXXXIV, prepared from the sodium salt in toluene with methyl sulfate, had b.p. 65°/2.5 mm., d_{25}^{25} 0.9372, n_D^{20} 1.5033.

Type A nitration of 46 g. of LXXXIV at −10° gave, after crystallization from methanol, 20 g. of 2,4-dinitro-5-*tert*-butylanisole (XIII), identical with that previously obtained by nitration of LXXVII.

LXXXIV (25 g.) was added to a mixture of 85 g. of 93% sulfuric acid and 50 g. of 98% nitric acid at 10–25°, the mixture quenched on ice, and the crude taken up in benzene and washed with 5% sodium hydroxide. Acidification of the wash yielded crystals which, after crystallization from ethanol, gave pale yellow needles of 2,4,6-trinitro-3-*tert*-butylphenol, m.p. 172°.

Anal. Calc'd for $C_{10}H_{11}N_3O_7$: C, 42.1; H, 3.86; N, 14.7.
Found: C, 42.5; H, 4.0; N, 14.5.

The solvent was distilled from the washed solution and the residue crystallized from methanol. There was obtained, in addition to a little XIII, 24 g. of 2,4,6-trinitro-3-*tert*-butylanisole (XIV) as pale yellow, odorless needles, m.p. 99.5–100°.

Anal. Calc'd for $C_{11}H_{13}N_3O_7$: C, 44.1; H, 4.34; N, 14.0.
Found: C, 44.6; H, 4.4; N, 13.7.

A mixture of 128 g. of LXXXIV, 11 g. of paraformaldehyde, and 156 g. of 31% hydrochloric acid was agitated for 24 hours at room temperature, the oil layer separated, washed with 10% sodium carbonate, dried over sodium carbonate, and distilled. There was obtained, in addition to 84 g. of recovered LXXXIV, 48 g. of 3-*tert*-butyl-4-chloromethylanisole (LXXXV), b.p. 112°/2 mm. A mixture of 132 g. of LXXXV, 87 g. of hexamethylenetetramine, and 53 g. of water was agitated and warmed to 85°, whereupon the heat of reaction carried the temperature to the reflux point, 118°. Refluxing was continued for 3 hours and the mixture steam-distilled, carrying the pot temperature up to 165° at the end. The oily distillate was taken up in benzene, washed with 10% sulfuric acid, then to neutrality, and distilled, yielding 75 g. of 2-*tert*-butyl-4-methoxybenzaldehyde (LXXXVI), (isomer of LIV, Flow Sheet B), b.p. 127°/3.5 mm., n_D^{20} 1.5387, practically odorless; *semicarbazone*, m.p. 230–231°.

Type C nitration of 35 g. of LXXXVI at −5 to 15° gave 54 g. of a pale yellow oil, the diacetate of XXXVI. It was hydrolyzed with 15% sulfuric acid in methanol as for LVI (Flow Sheet B) yielding 39 g. of 2-*tert*-butyl-4-methoxy-5-nitrobenzaldehyde (XXXVI) as a pale yellow, odorless oil which refused to congeal.

Type B nitration of 16 g. of LXXXVI at −10° gave, after three crystallizations from ethanol, 4.5 g. of pale yellow odorless crystals, m.p. 72–73°.

Anal. Calc'd for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.55; N, 11.02.

Found: C, 52.48; H, 5.55; N, 11.04.

This product was assumed to be an isomer of XIII, but a mixture of the two melted at 80–81°. The 72–73° crystals were recrystallized from ethanol, seeding with XIII, whereupon they melted at 80–81° and were thus XIII.

Type B nitration of 30 g. of XXXVI in the presence of ethylene dichloride at 0° gave a mixture of two crystalline products, resolved by successive crystallization from naphtha and ethanol into 10 g. of XIII, m.p. 80–81°, and 7.5 g. of dark yellow, odorless plates of 2-*tert*-butyl-3,5-dinitro-4-methoxybenzaldehyde, XV.

Anal. Calc'd for $C_{12}H_{14}N_2O_6$: C, 51.01; H, 5.00; N, 9.93.

Found: C, 52.49; H, 5.43; N, 10.26.

FLOW SHEET E

p-Nitro-*m*-cresol (LXXXVII), m.p. 128–129°, was methylated in the usual manner to 2-nitro-5-methoxytoluene, (LXXXVIII), m.p. 52°, having an odor remarkably similar to that of anisaldehyde. Reduction with iron filings and dilute hydrochloric acid gave 2-amino-5-methoxytoluene (LXXXIX), b.p. 110–112°/4 mm., c.p. 13°, m.p. 13.5°, 175 g. of which, diazotized and treated with cuprous bromide according to the Sandmeyer reaction, gave 189 g. of 2-bromo-5-methoxytoluene (XC), b.p. 81–83°/4 mm., c.p. 16°, m.p. 16.5°. A Grignard reagent was prepared from 180 g. of XC and 22 g. of magnesium turnings in 520 ml. of ether. Several hours were required to activate the magnesium. *tert*-Butyl chloride (84 g.) was added to the solution and, after the vigorous reaction had subsided, the mixture was refluxed 4 hours, quenched in acidified ice-water, and the ethereal solution washed and distilled; 66 g. of *m*-cresol methyl ether was collected, followed by 21 g. of 3-methyl-4-*tert*-butylanisole (XCI), b.p. 83–84°/2 mm., c.p. 9°, m.p. 11° [Zeide and Dubinin (1) reported m.p. 6°].

Type A nitration of 21 g. of XCI at −10° gave, after three crystallizations from ethanol, 21 g. of 2,6-dinitro-3-methyl-4-*tert*-butylanisole (XVI) as pale yellow prisms, odorless, m.p. 112–113°.

Anal. Calc'd for $C_{12}H_{16}N_2O_5$: C, 53.7; H, 6.01; N, 10.43.

Found: C, 53.82; H, 5.86; N, 10.57.

From the mother liquors, there was isolated 0.5 g. of 2,4-dinitro-5-methylanisole (XCII), m.p. (alone or admixed with an authentic specimen) 101–102°.

4,6-Di-*tert*-butyl-m-cresol (from Koppers Co.) gave, upon treatment of a toluene suspension of its sodium salt with methyl sulfate, the ether, 2,4-di-*tert*-butyl-5-methylanisole (XCIII), b.p. 110°/3 mm., m.p. 60°. The latter (30 g.) was nitrated according to the method of Borman (21) by adding it to 300 g. of 98% nitric acid at −5°. The crude oily nitration product was resolved, after alternate crystallizations from ethanol and naphtha, into three crystalline fractions: (a) 7 g. of XVI, m.p. 112–113°, identical in all respects with that obtained above from XCI; (b) 1 g. of Musk Ambrette (I); and (c) 3 g. of XCII.

Type A nitration of XCIII led to a mixture of products from which only Musk Ambrette (I) was isolated in poor yield, but no XVI.

FLOW SHEET F

Crotyl *m*-cresyl ether (XCIV) prepared from *m*-cresol, crotyl chloride (26), and potassium carbonate in acetone solution (b.p. 88–90°/3.5 mm., d_{25}^{25} 0.9502, n_D^{20} 1.5170) was isomerized in boiling diethylaniline to 2-*sec*-butenyl-5-methylphenol (XCV), b.p. 97–98°/4 mm., d_{25}^{25} 0.9843, n_D^{20} 1.5350. Hydrogenation (22) of XCV in methanol with Raney nickel at atmospheric pressure and 40° gave 2-*sec*-butyl-5-methylphenol (XCVI), b.p. 89–90°/2 mm., d_{25}^{25} 0.9640, n_D^{20} 1.5188, having an odor somewhat like thymol. The methyl ether, XCVII, prepared in the usual manner, had b.p. 74–75°/2 mm., d_{25}^{25} 0.9278, n_D^{20} 1.5048. *Type A* nitration of 50 g. of XCVII at −12° gave 58 g. of crude XVII as an odorless yellow oil which could not be induced to crystallize.

2-Isobutyl-5-methylphenol (C) prepared as above (22), was converted to the methyl ether, CI, b.p. 98°/8 mm., d_{25}^{25} 0.9418, n_D^{20} 1.5118. *Type A* nitration of 38 g. of CI, gave 41 g. of crude XVIII as a dark colored odorless oil which could not be induced to crystallize.

m-Hydroxybenzotrifluoride was prepared in 95% yield by decomposition of the diazonium sulfate of *m*-aminobenzotrifluoride (Hooker Electrochemical Co.); pale yellow oil, b.p. 57°/3 mm., d_{25}^{25} 1.3458, n_D^{20} 1.4570, having a powerful odor like chlorophenol. By the same sequence of reactions as above, there were prepared: the methallyl ether, CII, b.p. 63°/3 mm., d_{25}^{25} 1.1462, n_D^{20} 1.4578; 3-hydroxy-4-methallylbenzotrifluoride, CIII, b.p. 82°/4.5 mm.; 3-hydroxy-4-isobutylbenzotrifluoride, CIV, b.p. 86°/5 mm.; and 3-methoxy-4-isobutylbenzotrifluoride, CV, b.p. 65°/3 mm. *Type A* nitration of 26 g. of CV at −12° gave 28 g. of crude XIX, as an odorless, light yellow oil which could not be induced to crystallize.

Attempts to *tert*-butylate *m*-hydroxybenzotrifluoride with isobutene in the presence of sulfuric acid, boron trifluoride, or hydrogen fluoride were unsuccessful. *m*-Methoxybenzotrifluoride, prepared from the free phenol, was a colorless oil, b.p. 67°/27 mm., d_{25}^{25} 1.2342, n_D^{20} 1.4418, having an odor somewhat like *m*-cresol methyl ether, but much more powerful. Attempts to *tert*-butylate the ether with isobutene in the presence of sulphuric acid or boron trifluoride hydrate, or with *tert*-butyl chloride in the presence of aluminum chloride, were likewise unsuccessful.

Bromine (127 g.) in 150 g. of carbon tetrachloride was added to a refluxing solution of 122 g. of *m*-hydroxybenzotrifluoride in 300 g. of carbon tetrachloride.

After cooling, washing and distilling, there was collected 144 g. of 3-hydroxy-4-bromobenzotrifluoride, b.p. 49–50°/3.5 mm., c.p. 5°, m.p. 15°.

Anal. Calc'd for $C_7H_4BrF_3O$: Br, 33.16. Found: Br, 33.1.

Methylation gave 3-methoxy-4-bromobenzotrifluoride, b.p. 103°/18 mm., c.p. 26°, m.p. 27.5°.

Anal. Calc'd for $C_8H_6BrF_3O$: Br, 31.34. Found: Br, 31.2.

A small end fraction was collected, consisting of 3-methoxy-6-bromobenzotrifluoride, b.p. 118°/18 mm., c.p. 34°, m.p. 36.5°; Br, 31.0.

3-Methoxy-4-bromobenzotrifluoride did not react with magnesium in boiling diethyl or di-*n*-butyl ether, or with *tert*-butyl magnesium chloride.

FLOW SHEET G-1

Isobutene (83 g.) was passed, with vigorous agitation, into a mixture of 204 g. of resorcinol dimethyl ether and 150 g. of 85% phosphoric acid at 30–55°. The temperature was raised to 70° for 10 min., the mixture cooled, the oil layer removed, washed with 5% sodium carbonate, and distilled, yielding 215 g. of 4-*tert*-butylresorcinol dimethyl ether (CVI), b.p. 93°/2 mm., d_{25}^{25} 0.9928, n_D^{20} 1.5114, and 11 g. of 4,6-di-*tert*-butylresorcinol dimethyl ether (CIX), b.p. 113°/2 mm., m.p. 75–76° (after crystallization from methanol).

Type A nitration of 54.5 g. of CVI at −12° gave, after crystallization from benzene, 42 g. of 4,6-dinitroresorcinol dimethyl ether (CVIII) as pale yellow, odorless needles, m.p. 157°.

Anal. Calc'd for $C_8H_8N_2O_6$: C, 42.1; H, 3.51; N, 12.3.
Found: C, 42.5; H, 3.8; N, 12.3.

The mother liquor had a pronounced musk odor. It was evaporated and the residue crystallized repeatedly from benzene: ethanol and 80% ethanol. The only crystalline product which could be isolated was 1 g. of 2-methoxy-5-*tert*-butylbenzoquinone (CX), brilliant, chrome yellow, odorless plates, m.p. 162–163°.

Anal. Calc'd for $C_{11}H_{14}O_3$: C, 68.00; H, 7.26.
Found: C, 67.6; H, 7.2.

Type C nitration of 48.5 g. of CVI at −10° gave a crude product which was resolved, after repeated crystallizations from ethanol and naphtha, into 9 g. of CVIII, a trace of CX, and 24 g. of 4-nitro-6-*tert*-butylresorcinol dimethyl ether (CVII), pale yellow, odorless crystals, m.p. 101–102°.

Anal. Calc'd for $C_{12}H_{17}NO_4$: C, 60.2; H, 7.11; N, 5.85.
Found: C, 60.2; H, 7.1; N, 6.0.

A musk odor remained in the final mother liquors.

Type A nitration of 10 g. of CIX gave 6 g. of CVIII. Again the musk odor was apparent in the mother liquors.

Type A nitration of 22 g. of resorcinol dimethyl ether gave 14 g. of CVIII. There was no musk odor in the mother liquors.

FLOW SHEET G-2

2-Nitroresorcinol (CXI) was prepared by a modification of the method of Kauffman and de Pay (23): 176 g. of resorcinol in fine crystals was stirred into 1,200 g. of 20% oleum at 30–70°. The paste was cooled to 0° and a mixture of 120 g. of 98% nitric acid and 320 g. of 20% oleum was added with agitation and cooling. Stirring was continued 1 hour at 0° after completion of the addition; 1,080 g. of water was then added carefully, keeping the temperature below 50°. The mixture was finally steam-distilled, the crystals separated, and the water extracted with benzene. The 128 g. of crude thus obtained yielded, after crystallization from ethylene dichloride and reworking the mother liquors, 124 g. of CXI as orange-red crystals, m.p. 84°, having an odor like *o*-nitrophenol. The dimethyl ether, CXII, was prepared in the usual manner; pale yellow rods from ethanol, m.p. 130–130.5°, having a faint, characteristic odor.

One mole of CXII in ethylene dichloride, treated with 1.1 moles of aluminum chloride and 1 mole of *tert*-butyl chloride gave bright yellow-orange crystals of 2-nitroresorcinol monomethyl ether (CXIII), m.p. 53°, having a powerful maple-black walnut odor.

Anal. Calc'd for $C_7H_7NO_4$: C, 49.7; H, 4.15; N, 8.28.
Found: C, 49.4; H, 4.1; N, 7.5.

Upon treatment with methyl sulfate and alkali, it was converted to CXII.

When the above experiment was repeated with 3.3 moles of aluminum chloride, CXI was formed.

Isobutene was passed into a solution of CXII in ethylene dichloride to which had been added boron trifluoride:water (1:1.5 moles). No alkylation took place. Anhydrous boron trifluoride failed to absorb in an ethylene dichloride solution of CXII. One equivalent of isobutene was passed into a solution of 92 g. of CXII in 200 g. of anhydrous hydrogen fluoride at 10°. No alkylation took place and the starting material was recovered unchanged.

Bromination of CXII in acetic acid gave 2-nitro-4-bromoresorcinol dimethyl ether (CXIV), m.p. 60–60.5° (25). Reaction of CXIV with *tert*-butyl magnesium chloride yielded nothing but tar.

FLOW SHEET G-3

tert-Butylbenzene, nitrated with mixed acid at 25–55°, gave a 79% yield of 2,4-dinitro-*tert*-butylbenzene (CXV), m.p. 62.5–63.5° [literature, m.p. 61–62° (27)]. Reduction with sodium sulfide and sodium carbonate gave 2-nitro-4-amino-*tert*-butylbenzene (CXVI) in 83% yield. An interesting case of polymorphism was here observed. The crude product, m.p. 46–48°, was recrystallized from 70% ethanol to give lemon-yellow crystals, a sample of which was quickly dried and had m.p. 47–48°. The batch, consisting of about 100 g., was spread in a thin layer on paper to dry. Six hours later, a small spot of orange-colored crystals was observed in the center of the mass. This was disturbed with a spatula and in the course of about 3 min. the orange color had spread throughout the entire batch. The orange-colored crystals then melted at 58–59°. Recrystallization from naphtha-benzene failed to raise the m.p. [literature (28), m.p. 55°]. From the crude mother liquor there was isolated a small amount of yellowish-tan plates of m.p. 169.5°, which is possibly the corresponding hydrazo compound. Treatment of the diazonium bromide of CXVI with cuprous bromide gave 2-nitro-4-bromo-*tert*-butylbenzene (CXVII) in 65% yield, b.p. 115–116°/4 mm., d^{25}_{25} 1.3867, n^{20}_{D} 1.4993. Reduction of the latter with iron and dilute hydrochloric acid gave a 91% yield of 2-amino-4-bromo-*tert*-butylbenzene (CXVIII), b.p. 124–126°/4 mm., d^{25}_{25} 1.1193, n^{20}_{D} 1.5781. The diazonium bromide of CXVIII, treated with cuprous bromide, gave an oil which was partially soluble in Claisen's solution. The insoluble portion was washed to neutrality and distilled to give an impure 2,4-dibromo-*tert*-butylbenzene (CXX), b.p. 112–116°/4 mm., d_{25}^{25} 1.4642, n_D^{20} 1.5774.

Anal. Calc'd for $C_{10}H_{12}Br_2$: C, 41.1; H, 4.1; Br, 54.8.

Found: C, 46.3; H, 5.0; Br, 45.4.

The Claisen's solution extracts, after washing with benzene, acidifying, and distilling, yielded 2-*tert*-butyl-5-bromophenol (CXIX), b.p. 107–108°/4 mm., d_{25}^{25} 1.3490, n_D^{20} 1.5565.

Anal. Calc'd for $C_{10}H_{13}BrO$: C, 52.4; H, 5.68; Br, 34.9.

Found: C, 52.3; H, 5.7; Br, 34.5.

The impure CXX (20 g.) was added with agitation to 400 g. of 98% nitric acid at 30°. The clear solution was quenched on ice, the crystals filtered, taken up in benzene, washed with 5% sodium hydroxide, then to neutrality, and the solvent removed and the crystals twice crystallized from ethanol, yielding 11 g. of 2,4-dibromo-3,5-dinitro-*tert*-butylbenzene (CXXI) as pale yellow needles, m.p. 167–168°.

Anal. Calc'd for $C_{10}H_{10}Br_2N_2O_4$: C, 31.4; H, 2.6; N, 7.3; Br, 41.8.

Found: C, 31.7; H, 3.0; N, 7.6; Br, 41.2.

Thus, the impurities in the CXX were apparently eliminated in the nitration.

In an attempt to shorten the above devious route to CXXI, *tert*-butylbenzene was brominated directly in the presence of iron to a dibromo compound having b.p. 112°/1.5 mm., d_{25}^{25} 1.5937, n_D^{20} 1.5718, Br, 56.0 (Calc'd, 54.8). Nitration of this product with either nitric acid or mixed acid yielded only an oil and, in the case of mixed acid, a small percentage of crystals, m.p. 120–121°. This result was not surprising since it is known that dibromination of similar hydrocarbons, such as toluene, produces a variety of isomers.

Preliminary experiments indicated that upon treatment of CXXI with a hot solution of sodium in methanol, only one bromine was attacked, and that higher temperature (sodium methoxide in boiling xylene) caused extensive decomposition. CXXI (26 g.) was dissolved in 260 g. of methanol, 29 g. of a 6% solution of sodium in methanol (1.1 equivalents sodium) was added, and the mixture was refluxed 1 hour. The amber solution was poured into 500 ml. of water, acidified, and the mixture twice extracted with benzene. The extracts were washed with warm 5% sodium hydroxide, then to neutrality, and the solvent removed. Repeated crystallization of the residue from ethanol gave 10 g. of 2,6-dinitro-3-bromo-4-*tert*-butylanisole (XX) as pale yellow needles, m.p. 101–102°, having a musk odor.

Anal. Calc'd for $C_{11}H_{13}BrN_2O_5$: C, 39.65; H, 3.93; N, 8.41; Br, 24.0.

Found: C, 39.99; H, 4.03; N, 8.41; Br, 22.4.

The alkaline washes, upon cooling, precipitated the sparingly soluble, orange-colored sodium salt of the corresponding 2,6-dinitro-3-bromo-4-*tert*-butylphenol (CXXII). Acidification and crystallization from 90% ethanol yielded 3 g. of CXXII, as yellow, odorless needles, m.p. 161–162°.

Anal. Calc'd for $C_{10}H_{11}BrN_2O_5$: C, 37.64; H, 3.47; N, 8.78; Br, 25.05.

Found: C, 37.50; H, 3.66; N, 8.83; Br, 25.1.

Methylation of CXXII by conventional methods was not successful, but was readily accomplished by heating the anhydrous sodium salt directly with methyl sulfate; XX was produced quantitatively.

The ethanol mother liquors from the recrystallization of XX were reworked and yielded 2 g. of practically colorless, odorless needles exhibiting a double melting point: they first melted at 119°, then on slight cooling re-solidified and finally melted at 128–128.5°. This product was probably CXXIII, although the analysis is not altogether concordant.

Anal. Calc'd for $C_{11}H_{13}Br_2NO_3$: C, 35.95; H, 3.54; N, 3.81; Br, 43.6.

Found: C, 37.69; H, 3.68; N, 3.86; Br, 40.6.

After several fruitless attempts to brominate nitrobenzene according to *Organic Syntheses*,[5] *m*-bromonitrobenzene (CXXIV) was prepared in 68% yield from *m*-nitroaniline by the Sandmeyer reaction; m.p. 53.5–55.5°. Reduction with iron filings and dilute hydro-

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[5] *Org. Syntheses*, Coll. Vol. I, 2nd Ed., 123 (1941).

chloric acid gave *m*-bromoaniline (CXXV), b.p. 90–92°/5 mm., c.p. 16°, in 81% yield. The diazonium sulfate yielded *m*-bromophenol (CXXVI), b.p. 88–89°/3 mm., c.p. 31°, in 63% yield. *m*-Bromoanisole (CXXVII), b.p. 74°/5 mm., was prepared from the phenol in 97% yield. A mixture of 206 g. of CXXVII and 2 g. of aluminum chloride, treated with 94 g. of *tert*-butyl chloride at 25°, gave, in addition to 120 g. of recovered CXXVII, 106 g. of 2-*tert*-butyl-5-bromoanisole (CXXVIII), b.p. 91°/2.5 mm., d_{25}^{25} 1.2629, n_D^{20} 1.5378.

Type A nitration of 69 g. of CXXVIII at −10° gave 86 g. of crude product which was resolved, by systematic crystallizations, alternating between naphtha and ethanol, into 14 g. of 2,4-dinitro-5-bromoanisole (CXXIX), pale yellow, odorless crystals, m.p. 109.5–110.5° [literature (29) m.p. 110°],

Anal. Calc'd for $C_7H_5BrN_2O_5$: C, 30.32; H, 1.82; N, 10.11; Br, 28.86.
Found: C, 31.0; H, 2.8; N, 10.2; Br, 24.1.

and 34 g. of 2,4-dinitro-3-bromo-6-*tert*-butylanisole (XXI), pale yellow, odorless crystals, m.p. 107–108°.

Anal. Calc'd for $C_{11}H_{13}BrN_2O_5$: C, 39.65; H, 3.93; N, 8.41; Br, 24.0.
Found: C, 39.8; H, 4.1; N, 8.4; Br, 24.1.

A suspension of the sodium salt of CXIX in boiling toluene was treated with methyl sulfate and the ether thus obtained yielded, upon *Type A* nitration, CXXIX and XXI, identical in all respects with the products previously prepared, thus establishing the orientation of XX and XXI. A mixture of XX and XXI melted at 90–99°.

XXI (20 g.) was dissolved in 150 g. of methanol, 10 g. of a 4% solution of sodium in methanol was added and the whole was refluxed 3 hours. The solution was poured into 1 liter of water, neutralized with hydrochloric acid, and extracted with benzene. The extract was washed with warm 5% sodium hydroxide, then to neutrality, and the solvent removed. Two crystallizations of the crude product from ethanol gave 14 g. of 2,4-dimethoxy-3,5-dinitro-*tert*-butylbenzene (XXII) as pale yellow, brilliant prisms, m.p. 98–99°, having a strong musk odor.

Anal. Calc'd for $C_{12}H_{16}N_2O_6$: C, 50.69; H, 5.67; N, 9.85.
Found: C, 50.83; H, 5.61; N, 9.86.

Acidification of the alkaline wash yielded crystals which, after crystallization from 70% ethanol, gave 2 g. of 2,6-dinitro-3-methoxy-4-*tert*-butylphenol (CXXX) as lemon yellow, odorless needles, m.p. 109–110°.

Anal. Calc'd for $C_{11}H_{14}N_2O_6$: C, 48.8; H, 5.22; N, 10.37.
Found: C, 48.51; H, 5.17; N, 10.32.

FLOW SHEET H

A mixture of 534 g. of LII (Flow Sheet A), 30 g. of paraformaldehyde, and 468 g. of 31% hydrochloric acid was agitated vigorously for 16 hours at 25°. The oil layer was separated, washed once with 5% sodium carbonate, dried over sodium carbonate, and fractionated: 400 g. of LII was recovered, followed by 120 g. of 2-methyl-4-methoxy-5-*tert*-butylbenzyl chloride (CXXXI), b.p. 128°/3 mm., m.p. 69–70°. The 40 g. of crystalline residue yielded, after crystallization from naphtha, 20 g. of crystals, m.p. 101–102° which were probably 2,2′-dimethyl-4,4′-dimethoxy-5,5′-di-*tert*-butyldiphenylmethane.

A mixture of 300 g. of CXXXI, 186 g. of hexamethylenetetramine, and 105 g. of water was agitated vigorously and warmed to 85°. The heat of reaction carried the temperature to the reflux point. After about 5 min. heat was again applied and the mixture refluxed 3 hours. It was then distilled with super-heated steam, carrying the pot temperature to a final 165°. The distillate was taken up in benzene, washed with 5% sulfuric acid, then to neutrality, and distilled: 180 g. of 2-methyl-4-methoxy-5-*tert*-butylbenzaldehyde (CXXXII) was obtained as colorless, practically odorless crystals, b.p. 118°/1.5 mm., m.p. (after crystallization from naphtha) 84–85°.

Anal. Calc'd for $C_{13}H_{18}O_2$: C, 75.7; H, 8.79.
Found: C, 75.6; H, 8.80.

Type C nitration of 51.5 g. of CXXXII at −5 to 15° gave 73 g. of crude product which was refluxed 1 hour with a mixture of 550 g. of 15% sulfuric acid and 80 g. of methanol. The methyl acetate was distilled off, 80 g. of fresh methanol added, refluxing continued 1 hour, and the methyl acetate-methanol distilled off. After cooling, the crystals were washed with water, leaving 59 g. They were digested with 590 g. of naphtha at 25° and the suspension filtered, removing 11 g. of powdery crystals which, crystallized from ethanol, gave 9 g. of 2-methyl-4-methoxy-5-nitrobenzaldehyde (CXXXIII) as practically colorless, odorless needles, m.p. 138–139°.

Anal. Calc'd $C_9H_9NO_4$: C, 55.3; H, 4.61; N, 7.18.

Found: C, 55.3; H, 4.50; N, 7.3.

The solvent was removed from the naphtha solution and the residue twice crystallized from ethanol, giving 9 g. of 2-*tert*-butyl-4-nitro-5-methylanisole (XXXIII) as pale yellow crystals, m.p. 82–83° (unchanged upon admixture with an authentic specimen prepared by gentle nitration of LII [Zeide and Dubinin (1) give m.p. 81–82°].

Anal. Calc'd for $C_{12}H_{17}NO_3$: C, 64.5; H, 7.61; N, 6.27.

Found: C, 64.23; H, 7.91; N, 6.27.

A mixture of 180 g. of CXXXI, 200 g. of benzene, 160 g. of water, and 60 g. of zinc dust was agitated at 30° for 20 hours. The mixture was filtered and the halogen-free benzene solution washed and distilled: 42 g. of 2-*tert*-butyl-4,5-dimethylanisole (CXXXIV) was collected as colorless crystals, b.p. 95°/3 mm., m.p. 72–73° (after crystallization from ethanol), having a mild odor similar to that of LII.

Anal. Calc'd for $C_{13}H_{20}O$: C, 81.19; H, 10.48.

Found: C, 80.8; H, 10.3.

Type C nitration of 24 g. of CXXXIV at −5° to 15° gave 25 g. of dark red oil which was taken up in benzene and washed repeatedly with 5% sodium hydroxide. Considerable tar was formed. After washing to neutrality and removing the solvent 16 g. of dark, odorless oil remained which could not be induced to congeal. From the weight of the original crude, it seemed probable that a mixture of XXXVIII and CXXXV was produced.

FLOW SHEET J

A mixture of 940 g. of XCIII (Flow Sheet E), 400 g. of manganese dioxide, and 2,940 g. of 40% sulfuric acid was agitated vigorously for 24 hours at 65–70°, cooled, thinned by the addition of 1,000 g. of benzene, filtered, and the benzene solution washed with 5% sodium carbonate, then to neutrality, and distilled. In the fore-run was collected a small amount of XLIX (Flow Sheet A), followed by 647 g. of recovered XCIII, and finally 212 g. of 2,4-di-*tert*-butyl-5-methoxybenzaldehyde (XXXIX), b.p. 134°/3.5 mm. Crystallization from methanol gave colorless prisms, m.p. 68–69°, having a mild but very persistent musk odor.

Anal. Calc'd for $C_{16}H_{24}O_2$: C, 77.36; H, 9.74.

Found: C, 77.31; H, 9.81.

The *semicarbazone* had m.p. 188–189°.

XXXIX (52 g.) was nitrated by the *Type C* method at −10° to −5°. It was necessary to add 150 ml. of chloroform to thin the pasty reaction mixture. Working up in the usual manner gave, after two crystallizations from ethanol, 50 g. of 2,4-di-*tert*-butyl-3-nitro-5-methoxybenzaldehyde (XLI) as pale yellow odorless crystals, m.p. 112–113°.

Anal. Calc'd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.88; N, 4.77.

Found: C, 65.49; H, 7.95; N, 4.79.

Type C nitration of XCIII in the same manner as for XXXIX gave a crude product which smelled of Musk Ambrette, and probably contained some. Two crystallizations from ethanol gave 2,4-di-*tert*-butyl-5-methyl-6-nitroanisole (XXXV), pale yellow, odorless crystals, m.p. 139–140°.

Anal. Calc'd for $C_{16}H_{25}NO_3$: C, 68.74; H, 9.02; N, 5.02.

Found: C, 68.41; H, 9.01; N, 5.65.

2,4-Di-*tert*-butyl-*o*-cresol (CXXXVI), prepared from *o*-cresol and isobutene in the presence of sulfuric acid, b.p. 113°/2.5 mm., m.p. 50–52° (20), was converted by way of the sodium salt in toluene to the methyl ether, CXXXVII, b.p. 114°/4 mm., c.p. 14°, m.p. 16°.

Oxidation of the latter with manganese dioxide and sulfuric acid as for XCIII gave 2-methoxy-3,5-di-*tert*-butylbenzaldehyde (XL) as a practically odorless oil, b.p. 128°/2.5 mm., which refused to congeal.

Anal. Found for $C_{16}H_{24}O_2$: Aldehyde, 97%.

FLOW SHEET K

3,5-Diisopropylsalicylic acid (33) (420 g.) was gradually heated to 250° until carbon dioxide evolution ceased, cooled partially, and distilled *in vacuo*: 259 g. of 2,4-diisopropylphenol (CXXXVIII) was collected (79% yield) as a colorless oil of mild, phenolic odor, b.p. 97°/2 mm., c.p. 22°, m.p. 23°, d_{25}^{25} 0.9474, n_D^{20} 1.5122. Reaction of the sodium salt in toluene with methyl sulfate gave the methyl ether, CXXXIX, b.p. 85°/2 mm., d_{25}^{25} 0.9172, n_D^{20} 1.4992, liquid at −50°. *Type C* nitration of 48 g. of CXXXIX at 15° gave 57 g. of yellow oil having no musk odor, which could not be induced to crystallize. It probably consisted essentially of 2-nitro-4,6-diisopropylanisole (XXXVII) (59 g., theoretical yield).

A mixture of 328 g. of *p*-*tert*-butylanisole (c.p. 18.5°, m.p. 19.5°), 20 g. of paraformaldehyde, and 312 g. of 31% hydrochloric acid was agitated vigorously for 7 hours at 55°, cooled, thinned with benzene, the benzene solution washed once with 10% sodium carbonate solution, dried over sodium carbonate, and distilled to yield, in addition to 217 g. of recovered *p*-*tert*-butylanisole, 130 g. of 2-chloromethyl-4-*tert*-butylanisole (CXL), b.p. 110°/3 mm., c.p. 27°, m.p. 29°. A mixture of 375 g. of CXL, 247 g. of hexamethylenetetramine, and 150 g. of water was agitated vigorously and warmed to 85°, whereupon the heat of reaction carried the temperature to the reflux point. Refluxing was continued for 3 hours and the mixture distilled with super-heated steam, carrying the pot temperature up to 160° at the end. The oily distillate was taken up in benzene, washed with 10% sulfuric acid to remove amines, then to neutrality, and distilled: 200 g. of 2-methoxy-5-*tert*-butylbenzaldehyde (CXLI) was obtained, b.p. 128°/3.5 mm., c.p. 28°, m.p. 32°, having a very weak odor by comparison with its isomer, LIV, (Flow Sheet B).

Anal. Calc'd for $C_{12}H_{16}O_2$: C, 74.95; H, 8.39.

Found: C, 74.80; H, 8.41.

Type C nitration of 48 g. of CXLI at −5° to 15° gave 73 g. of crude nitration product, which was hydrolyzed by refluxing 1 hour with 550 g. of 15% sulfuric acid and 80 g. of methanol, distilling off the methyl acetate, adding fresh methanol and again refluxing, distilling, etc. The 53 g. of crude crystals thus obtained yielded, after two crystallizations from ethanol, 30 g. of 2-methoxy-3-nitro-5-*tert*-butylbenzaldehyde (XLII), pale yellow, m.p. 68.5–70°, and odorless in contrast to its musk-like isomer, XXIX (Flow Sheet B).

Anal. Calc'd for $C_{12}H_{15}NO_4$: C, 60.74; H, 6.37; N, 5.90.

Found: C, 60.76; H, 6.35; N, 5.91.

CXL (254 g.) was added with vigorous agitation, during 3 hours to a refluxing mixture of 93 g. of zinc dust and 240 g. of water. Agitation and heating were continued 16 hours further and the oil layer, which was free of chlorine, was washed and distilled: 161 g. of CXLII was collected as a colorless, mildly odorous oil, b.p. 82°/2.5 mm., d_{25}^{25} 0.9335, n_D^{20} 1.5098.

Type B nitration of 43 g. of CXLII in ethylene dichloride at −5° gave 46 g. of crude crystals which, after two crystallizations from ethanol, yielded 24 g. of CXLIII as pale yellow, practically odorless needles, m.p. 69–70°. *Type B* nitration of 30 g. of *o*-cresol methyl ether at 0° gave 34 g. of CXLIII, melting at 69–70° and undepressed upon admixture with the product obtained from CXLII.

Type B nitration of 41 g. of *p*-*tert*-butylanisole in ethylene dichloride at −5° yielded 55 g. of crude crystals which, twice crystallized from ethanol, gave 41 g. of 2,6-dinitro-4-*tert*-butylanisole (IV) as pale yellow, odorless plates, m.p. 101–102.5°.

Anal. Calc'd for $C_{11}H_{14}N_2O_5$: C, 51.95; H, 5.55; N, 11.02.

Found: C, 52.22; H, 5.60; N, 10.58.

tert-Butyl chloride (100 g.) was added to a solution of 138 g. of hydroquinone dimethyl ether and 1 g. of aluminum chloride in 330 g. of ethylene dichloride at 25°, the solution warmed to 70° to complete gas evolution, cooled, washed to neutrality, and distilled. In addition to 48 g. of recovered hydroquinone dimethyl ether, there was obtained 104 g. of *tert*-butylhydroquinone dimethyl ether (CXLIV), b.p. 121°/10 mm., n_D^{20} 1.5110.

Anal. Calc'd for $C_{12}H_{18}O_2$: C, 74.2; H, 9.34.

Found: C, 74.0; H, 9.40.

The distillation residue yielded 16 g. of 2,5-di-*tert*-butylhydroquinone dimethyl ether, m.p. 103–104° after crystallization from naphtha.

Type A nitration of 40.5 g. of CXLIV at −15° gave 32 g. of crude crystals which, after three crystallizations from ethanol, yielded 17 g. of 2-nitro-5-*tert*-butylhydroquinone dimethyl ether (XLIII) as bright yellow, odorless needles, m.p. 96–97°.

Anal. Calc'd for $C_{12}H_{17}NO_4$: C, 60.1; H, 7.16; N, 5.85.

Found: C, 59.5; H, 7.10; N, 5.80.

All analyses were performed by Mr. D. Johnston and the staff of the Analytical Laboratory.

SUMMARY

1. The structure of Musk Ambrette has been further confirmed to be 2,4-dinitro-3-methyl-6-*tert*-butylanisole.

2. Examination of a considerable number of isomers, homologs, and analogs of Musk Ambrette has indicated that, with a single exception, the only ones which have a musk odor have a *tert*-alkyl group *ortho* to the alkoxy group.

3. Various other aspects of the relationship between musk odor and chemical constitution have been discussed.

4. A new type of musk has been discovered in the aromatic series, containing no nitro groups: 2,4-di-*tert*-butyl-5-methoxybenzaldehyde.

5. Three musks containing but a single nitro group have been discovered.

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