Mercuric Salt Catalyzed Nitration of Toluene

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The mercuric acetate catalyzed nitration of toluene in acetic acid at 80 °C produces 36% 2-, 12% 3-, and 52% 4-nitrotoluene. Other soluble mercury compounds produce similar results. Under these conditions, toluene is 6.1-fold more reactive than benzene. The reaction of 4-deuteriotoluene proceeds with a primary kinetic isotope effect of 3.1. 4-Tolylmercuric acetate reacts with nitric acid under these conditions to yield 4-nitrotoluene rapidly and quantitatively. The addition of urea to the reaction mixture inhibits the catalyzed nitration reaction and the reaction of 4-tolylmercuric acetate with nitric acid. The mercuration of toluene is not inhibited by urea. 4-Tolylmercuric acetate reacts with nitrosation agents to yield 4-nitrosotoluene and with nitration reagents to yield 3-nitro-4-methylphenylmercuric acetate. These results indicate that the reaction occurs in three steps: mercuration, nitrosodemercuration (rather than nitrodemercuration), and oxidation of nitrosotoluene to nitrotoluene. The relative rate and product distribution are determined in the initial mercuration reaction.

The catalytic properties of mercury in the nitration reaction became apparent in 1908, when Wolffenstein and Boeters patented a procedure, later termed oxynitration, by which benzene was transformed into di- and trinitrophenols in the presence of mercuric nitrate in nitric acid.[1] In the decades that followed, the reaction was actively investigated and several mechanistic interpretations emerged.[2] Simultaneous reports by Westheimer, Segel, and Schramm,[3] and Titov and Laptev[4] in 1947 established the mechanism. They showed that the initial intermediate, phenylmercuric nitrate, was converted to nitrosobenzene in dilute nitric acid.[3,4] They also showed that nitrosobenzene could be converted to the observed products of the oxynitration reaction. Early workers reported that the yield of nitrobenzene approached 50% when the oxynitration reaction was carried out in concentrated nitric acid.[5] Tsutsumi and Iwata and Osawa and his co-workers studied the effects of other metal oxides and metal nitrates on nitration with nitric acid.[6–8] However, only mercuric oxide and mercuric nitrate accelerated the reaction importantly and altered the isomer distribution.[6,7,9] Komoto and his associates examined the mercuric acetate catalyzed nitration of toluene using concentrated nitric acid in acetic acid at 80 °C.[10] Under these conditions, the catalyzed reaction produced the isomeric nitrotoluenes in good yield.

Several investigators have proposed that electrophilic aromatic mercuration is the first step in this reaction.[7,10] The nature of the subsequent steps in the process remains unclear. Both nitrodemercuration and nitrosodemercuration followed

$$C_6H_5HgOAc + NO_2^+ \rightarrow C_6H_5NO_2 + HgOAc^+$$

$$C_6H_5HgOAc + NO^+ \rightarrow C_6H_5NO + HgOAc^+$$

$$C_6H_5NO + HNO_3 \rightarrow C_6H_5NO_2 + HNO_2$$

by oxidation have been suggested.[7,10] In addition, the available experimental evidence is in conflict with the proposal that mercuration is the key step in the reaction. To illustrate, the mercuration of toluene typically yields about 13% 3-tolylmercuric acetate.[11] Komoto and his associates[10] do not comment on the formation of the 3 isomer, Tsutsumi and Iwata[6] report only 3% of this isomer, and Osawa and his associates[7] report that the reaction yields 10% 3-nitrotoluene. Such uncertainty and the singular success of mercury compounds in the catalysis of the nitration reaction prompted us to undertake an investigation of the reaction mechanism prior to the study of other methods for the control of isomer distributions in nitration reactions.

Results and Discussion

Komoto and his associates report excellent material balances for the mercuric acetate catalyzed reaction of equimolar quantities of toluene with 90% nitric acid in acetic acid at 80 °C.[10] They also note that the reaction rate depends on the concentration of mercuric acetate.[10] We confirmed these observations in preliminary experiments. The use of anhydrous nitric acid rather than 90% nitric acid provides equivalent results. The catalyzed nitration reaction also occurs when nitrogen dioxide is used rather than nitric acid. However, the reaction is unsuccessful when sodium nitrate or sodium nitrite are used in place of nitric acid. Accordingly, we adopted the conditions used by Komoto and his associates for the investigation of the influence of mercury compounds on the reaction. The results are summarized in Table I.

The reaction proceeds readily in the presence of 1.6 mol % catalyst as shown by the major increase in the yield of nitrotoluenes in the initial experiments with mercuric acetate. The isomer distribution changes importantly with increased amounts of 3- and 4-nitrotoluene produced in the catalytic reaction. Other mercury compounds which are soluble in the reaction medium, mercuric oxide, mercuric nitrate, and 4-tolylmercuric acetate, also catalyze the reaction. Mercurous nitrate and mercury, which are oxidized to mercuric nitrate under the conditions of these experiments, are also effective catalysts. Mercuric sulfate, which is only partially soluble in the reaction medium, gives an intermediate result. Mercuric chloride, although soluble, does not catalyze the reaction. Indeed, the addition of sodium chloride, 3.2 mol %, inhibits the catalytic reaction with mercuric acetate whereas the addition of other salts, sodium nitrite, sodium nitrate, and sodium acetate, has no discernible influence on the yield and isomer distribution. The failure of the reaction with mercuric chloride and the inhibition of the catalytic reaction by sodium chloride are compatible with the viewpoint that mercuration is the key step in the process because it has long been known that mercuric chloride is ineffective as a mercuration reagent.[12]

At low catalyst concentration, the nitration reaction and the mercuric acetate catalyzed nitration reaction are competitive processes. This feature of the reaction is shown by the results presented in Table II.

These results indicate that the conventional nitration reaction and the catalyzed nitration reaction are both significant at short reaction times when the nitric acid to mercuric acetate ratio is large. The results presented in Table I indicate that, after 2 h, the uncatalyzed nitration reaction is responsible for only 7% of the observed nitration products. When the observed product distribution is adjusted for this result, the isomer distribution in the mercuric acetate catalyzed reaction is established as 33% 2-, 13% 3-, and 54% 4-nitrotoluene.

Mercuration. The intramolecular selectivity, the intermolecular selectivity, and the primary kinetic isotope effect

Table I. Catalytic Properties of Mercury Compounds for the Nitration of Toluene at 80 °C [a]

Registry no.	Catalyst	Isomer distribution 2	3	4	Conversion, %
	None	58	3	39	7
1600-27-7	$Hg(OAc)_2$	36	12	52	64
21908-53-2	HgO	36	13	51	62
10045-94-0	$Hg(NO_3)_2$	36	13	51	63
10415-75-5	$HgNO_3$	36	12	52	67
7439-97-6	Hg^b	36	12	52	46
2440-35-9	$4\text{-}H_3CC_6H_4HgOAc$	36	12	52	63
7783-35-9	$HgSO_4{}^c$	48	6	46	*d*
7487-94-7	$HgCl_2$	62	*d*	38	7

[a] The mole ratio is 1.0:1.0:0.016:5.0 for toluene–90% nitric acid–mercury compound–acetic acid. The reactions were carried out for 2 h. [b] Reaction becomes homogeneous after the addition of nitric acid. [c] Reaction is heterogeneous. [d] Quantity too small for accurate measurement.

Table II. Isomer Distribution for the Nitration of Toluene [a]

Conversion, %	Isomer distribution 2	3	4
1	45	*b*	55
3	48	4	48
6	53	*b*	47
11	47	4	49
21	38	11	51
60	36	12	52

[a] See Table I for reaction conditions. [b] Quantity insufficient for accurate measurement.

Table III. Isomer Distribution for the Mercuration of Toluene

Reaction conditions	Isomer distribution 2	3	4
$Hg(OAc)_2$, HOAc, 70 °C[a]	32	15	53
$Hg(OAc)_2$, HOAc, 90 °C[a]	32	16	52
$Hg(OAc)_2$, $HClO_4$, HOAc, 75 °C[b]	18	13	69
$Hg(OAc)_2$, 90% HNO_3, HOAc, 80 °C[c,d]			
30 s	26	14	61
3 min	30	15	55
6 min	29	16	55
15 min	31	15	55

[a] Reference 13. [b] Reference 14. [c] This study. [d] Urea present.

Table IV. Toluene to Benzene Relative Rates for Mercuration and Nitration

Reaction	Rel rate, k_T/k_B
Nitration, 90% HNO_3, HOAc, 80 °C[a]	20.5 ± 3.0
Nitration, NO_2, $Hg(OAc)_2$, HOAc, 80 °C[a]	4.8 ± 0.4
Nitration, 90% HNO_3, $Hg(OAc)_2$, HOAc, 80 °C[a]	
5% conversion	22.6 ± 3.0
20% conversion	9.9 ± 2.1
60% conversion	6.1 ± 1.5
Mercuration, $Hg(OAc)_2$, HOAc, 70 °C[b]	4.3
Mercuration, $Hg(OAc)_2$, HOAc, 90 °C[b]	3.6
Mercuration, $Hg(OAc)_2$, $HClO_4$, HOAc, 75 °C[c]	5.9
Mercuration, $Hg(OAc)_2$, 90% HNO_3, HOAc, 80 °C[a]	5.6 ± 0.4

[a] This study. [b] Reference 13. [c] Reference 14.

Table V. Primary Kinetic Isotope Effects in Nitration and Mercuration

Reaction, substrate, reagents	k_H/k_D
Nitration, C_6H_6[a]	1.00
Mercuration, C_6H_6, $Hg(OAc)_2$, HOAc[b]	3.2 (25 °C), 2.6 (50 °C), 1.9 (90 °C)
Mercuration, C_6H_6, $Hg(OAc)_2$, $HClO_4$, HOAc[b]	6.0 (25 °C)
Nitration, $4\text{-}CH_3C_6H_4D$ 90% HNO_3, $Hg(OAc)_2$, HOAc[c]	3.1 (80 °C)

[a] Reference 16a. [b] Reference 16. [c] This study.

in the mercuration of toluene are distinctive.[11,13,14] Accordingly, we compared the results for the catalyzed nitration of toluene with the results for the mercuration of toluene to establish the role of mercuration in the process.

The intramolecular selectivities of the two reactions were assessed by measurement of the isomer distribution for the nitric acid catalyzed mercuration of toluene in acetic acid at 80 °C for comparison with the isomer distribution in the nitration reaction. As discussed subsequently, the nitration reaction is efficiently inhibited by the addition of urea. The results are presented in Table III.

The isomer distribution in the mercuration of toluene in the presence of nitric acid is initially rich in the 4 isomer. This distribution is similar to the isomer distribution observed at short reaction time in the perchloric acid catalyzed mercuration reaction.[13] The product distribution observed after 3 min reaction time, 30% 2-, 15% 3-, and 55% 4-tolylmercuric acetate, closely resembles the product distribution found in the catalyzed nitration reaction, 33% 2-, 13% 3-, and 54% 4-nitrotoluene. These results indicate that the intramolecular selectivities in the two processes are virtually identical.

The intermolecular selectivities for the nitration and mercuration reactions were assessed by competition experiments with toluene and benzene. The results are summarized in Table IV.

The relative rate, $k_T/k_B = 20.5$, for the uncatalyzed nitration of toluene at 80 °C is comparable with other observations for the noncatalytic nitration of toluene.[11] The relative rate, $k_T/k_B = 6.1$, for the catalyzed nitration of toluene observed after 2 h reaction time (60% conversion) is virtually identical with the value, 5.6, for the nitric acid catalyzed mercuration of toluene and benzene under identical conditions. The relative rate, $k_T/k_B = 4.8$, for the catalyzed nitration of toluene with nitrogen dioxide is also near the value, 4.3, for the uncatalyzed mercuration in acetic acid at 70 °C. These results indicate that the intermolecular selectivities of the nitration and mercuration reactions are very similar.

Mercuration reactions generally exhibit a primary kinetic isotope effect.[16] In contrast, nitration proceeds without an isotope effect.[16a] This feature of the catalyzed nitration reaction was investigated by the study of the mercuric acetate catalyzed nitration of 4-deuteriotoluene. The reaction pro-

Table VI. The Influence of Urea on the Reactions of Toluene and Tolylmercuric Acetate with Nitric Acid[a]

Compd	Conditions	Isomer distribution 2	3	4	Conversion, %
Toluene	90% HNO_3, $Hg(OAc)_2$, HOAc, 80 °C	36	12	52	64
Toluene	Same with urea	61	*b*	39	8
4-Tolylmercuric acetate	90% HNO_3, HOAc, 80 °C			100	100
4-Tolylmercuric acetate	Same with urea	59	*b*	41	11

[a] See Table I for conditions. [b] Quantity too small for accurate measurement.

duces 55% 2-, 19% 3-, and 26% 4-nitrotoluene compared to 36% 2-, 12% 3-, and 52% 4-nitrotoluene in the reaction of unlabeled toluene. The isotope effect calculated from these results and the isotope effects for several related reactions are presented in Table V.

The observed k_H/k_D value, 3.1, for the mercuric acetate catalyzed nitration of toluene is quite comparable with prior observations of primary kinetic isotope effects in the mercuration reaction. Thus, the catalyzed nitration reaction shows all the distinctive features of the mercuration reaction with modest intra- and intermolecular selectivities and a kinetic isotope effect. These results establish that mercuration is the rate-determining and product-determining step in the catalyzed nitration reaction.

Nitrosodemercuration. The conclusion that mercuration is the key step requires that the isomeric tolylmercuric acetates formed in this step be rapidly converted to nitrotoluenes under the reaction conditions. To test this point, we studied the reactions of 4-tolylmercuric acetate. This compound is rapidly and quantitatively converted to 4-nitrotoluene by 90% nitric acid in acetic acid at 80 °C. Neither 2- nor 3-nitrotoluene is obtained in detectable (1%) amount. This nitrodemercuration reaction can be accomplished either by nitrodemercuration or by nitrosodemercuration followed by oxidation.

It is well known that nitrosation reactions are inhibited by urea and related compounds.[17] We, therefore, examined the catalytic nitration of toluene and the reactions of 4-tolylmercuric acetate in the presence and absence of urea. The results are summarized in Table VI.

The isomer distribution and conversion observed for the reaction in the presence of urea are indicative of the uncatalyzed nitration reaction. Both the catalyzed nitration reaction and the conversion of 4-tolylmercuric acetate to 4-nitrotoluene are inhibited by urea. These observations are compatible with interpretations which involve nitrosodemercuration and are incompatible with interpretations which center on nitrodemercuration. The nitro compounds obtained in the presence of urea are clearly formed from toluene produced in a protodemercuration reaction.

Further experimental evidence for nitrosodemercuration was obtained by study of the reactions of 4-tolylmercuric acetate with nitrosation and nitration reagents. The treatment of 4-tolylmercuric acetate with nitrosonium tetrafluoroborate in sulfolane at 25 °C provides 4-nitrosotoluene in 96% yield. Similar treatment of this acetate with nitronium tetrafluoroborate provides a more complex product distribution. The dominant product is 3-nitro-4-methylphenylmercuric acetate. Lesser amounts of 4-nitroso- and 4-nitrotoluene are produced in these reactions. For example, the reaction of purified nitronium tetrafluoroborate with 4-tolylmercuric acetate in sulfolane in a dry atmosphere yields 9% 4-nitrosotoluene, 29% 4-nitrotoluene, and 36% 3-nitro-4-methylphenylmercuric acetate. These products are also obtained in replicate experiments. However, they are formed in quite different relative amounts as described in the Experimental Section. These erratic results apparently originate from nitrosation reagents present in the starting material[18] and from the reactions of nitrogen oxides which are produced in the course of reaction. The freezing point of sulfolane prohibits the study of this reaction at low temperature.

Challenger and Rothstein report that phenylmercuric nitrate reacts with nitric acid at −20 °C to provide nitrophenylmercuric nitrates in 86% yield.[19] Accordingly, we adopted these conditions for the further study of the reaction of the arylmercuric acetates with nitration reagents. The reaction of phenylmercuric acetate with cold nitric acid which is free of nitrosation agents gives only nitrophenylmercuric acetates. Similarly, the heterogeneous reaction of 4-tolylmercuric acetate with this reagent yields only 3-nitro-4-methylphenylmercuric acetate. Under the conditions of these experiments the formation of cleavage products is completely suppressed.

These observations indicate that the arylmercury compounds react differently with nitrosation reagents than with nitration reagents. Nitrosation reagents, represented by the nitrosonium ion, clearly provide the nitrosodemercuration product.

$$4\text{-}CH_3C_6H_4HgOAc + NO^+ \rightarrow 4\text{-}CH_3C_6H_4NO + HgOAc^+$$

Nitrosodeprotonation apparently does not occur. On the other hand, nitration reagents, represented by nitronium ion, selectively yield the nitrodeprotonation product rather than the nitrodemercuration product.

$$4\text{-}CH_3C_6H_4HgOAc + NO_2^+ \rightarrow 3\text{-}NO_2\text{-}4\text{-}CH_3C_6H_3HgOAc + H^+$$

The experimental results offer strong support for the view that nitrosodemercuration rather than nitrodemercuration is the second reaction in the mercuric acetate catalyzed nitration reaction.

It is very surprising that the arylmercuric acetates react so differently with nitrosation reagents than with nitration reagents. However, many organometalloid compounds including arylthallium,[20] arylsilicon,[21] aryllead,[19] and aryltin[19] compounds selectively undergo nitrodeprotonation rather than nitrodemetalation. In contrast, many other electrophilic reagents including bromine, chlorine, proton acids, mercury salts, and nitrosation reagents very selectively cleave the carbon–metal bond. Eaborn and his students noted this anomaly.[21] They suggest that steric effects increase the energy requirements for nitrodetrimethylsilylation. Olah and Kuhn also suggest that steric effects have a major impact on the nitrodealkylation reactions of isopropylbenzene and *tert*-butylbenzene derivatives.[22] Indeed, the nitrodeisopropylation of 4-isopropyltoluene is at least 15-fold more rapid than the nitrode-*tert*-butylation of 4-*tert*-butyltoluene.[23] Clearly, steric interactions play an important role in these replacement reactions. The large steric effect may originate in the requirement that the central atom of the linear nitration reagent must interact with the aromatic carbon atom in the rate-determining step.[24]

Oxidation. Ogata and Tezuka studied the oxidation of nitrosobenzene to nitrobenzene by nitric acid in aqueous dioxane.[25] This complex reaction depends on the acidity of the reaction medium and on the concentration of nitric acid. The reaction is autocatalytic apparently because there is a progressive increase in the concentration of nitrous acid. Ogata and Tezuka propose that both nitrogen dioxide and protonated nitrogen dioxide are effective reagents for the oxidation reaction. We did not investigate this aspect of the catalyzed nitration reaction in detail. However, 2-nitrosotoluene is rapidly oxidized to 2-nitrotoluene under the conditions of the mercuric acetate catalyzed nitration reaction.

Conclusion

The relative rate measurements, the isomer distributions, the kinetic isotope effect, and the related findings establish that mercuration is the first step in the mercuric salt catalyzed nitration of toluene. The inhibition of the reaction by urea and the observations of facile reactions of nitrosation reagents with 4-tolylmercuric acetate indicate that nitrosodemercuration is the second step in the sequence. The information available in the literature and the work with 2-nitrosotoluene support the view that the nitroso compounds are oxidized to nitro compounds in the third step of the reaction. The product distributions are determined in the initial, rate-determining mercuration reaction.

Experimental Section

Materials. The starting materials and other reagents used in this work were analyzed reagents or were purified by well-known methods prior to use. The molecules used as reference compounds in analytical procedures were purified by fractionation or crystallization and shown to be free of isomeric contamination by suitable analytical methods.

4-Deuteriotoluene. This compound was prepared by the reaction of 4-tolylmagnesium bromide with deuterium oxide by the procedure of Turkevich et al.[26] The product was fractionated twice. Analysis by mass spectroscopy indicated that the compound was minimally 90% 4-deuteriotoluene.

4-Tolylmercuric Acetate. This compound was prepared by the perchloric acid catalyzed mercuration of toluene as described by Brown and McGary.[13] The initial product was recrystallized three times from ethanol to yield 4-tolylmercuric acetate (mp 150–151 °C, lit.[27] 153 °C) which was shown by nuclear magnetic resonance to contain less than 1% of the 2 isomer and no trace of the 3 isomer.

2-Nitro-4-bromotoluene. 4-Bromotoluene (4.4 g, 0.026 mol) was added to a mixture of nitric acid (70%, d = 1.42, 7.0 g) and sulfuric acid (9.0 g). The mixture was warmed on a steam bath for 30 min and then poured into cold water (25 mL). The product was collected by filtration and recrystallized from ethanol to give yellow crystals of 2-nitro-4-bromotoluene (mp 43–45 °C, lit.[28] 43 °C).

Nitration Reactions. All the reactions were carried out in flasks equipped with a reflux condenser, addition funnel, and Thermowatch temperature controller. In a typical experiment, toluene (10.0 g, 0.109 mol), mercuric acetate (0.50 g, 0.0016 mol), and acetic acid (30.0 g, 0.50 mol) was stirred and heated to 80 °C. Nitric acid (Fischer Certified Reagent, 90%, d = 1.5, 5.5 mL, 0.109 mol) was then added dropwise. The solution was heated at 80 °C for 2 h. The mixture was poured into water and then transferred to a separatory funnel containing ether and 1,2-dichlorobenzene (7.0 g). The organic materials were extracted into ether which was washed with water and dried (sodium sulfate) prior to concentration in vacuo.

The product distribution was established by gas chromatography on 5% QF-1 on Chromosorb G using a 2.5 m × 0.63 cm column. The relationship between peak area and composition was established by the analysis of known mixtures of 1,2-dichlorobenzene and the nitro compounds. These analytical experiments showed thatd acetic acid (30.0 g, 0.50 mol) was stirred and heated to 80 °C. Nitric acid (Fischer Certified Reagent, 90%, d = 1.5, 5.5 mL, 0.109 mol) was then added dropwise. The solution was heated at 80 °C for 2 h. The mixture was poured i the isomer distributions could be established within ±1%.

Nitration of 4-Deuteriotoluene. 4-Deuteriotoluene (2.00 g, 0.021 mol), mercuric acetate (0.10 g, 0.0003 mol), and acetic acid (6 mL) were heated to 80 °C. Nitric acid (90%, d = 1.5, 1.1 mL, 0.021 mol) was added dropwise. The reaction was allowed to proceed for 2 h. The reaction products were isolated and analyzed as described. The isomer distribution was 55% 2-, 19% 3-, and 26% 4-nitrotoluene. The isotope effect was calculated from the ratios, $(\text{para})_H/(\text{ortho})_H \times (\text{ortho})_D/(\text{para})_D$ and $(\text{para})_H/(\text{meta})_H \times (\text{meta})_D/(\text{para})_D$, obtained in three experiments to be 3.1 ± 0.2. A small correction (3%) for the presence of unlabeled toluene in the starting material was applied.

Nitration and Nitrosation of 4-Tolylmercuric Acetate. Nitronium and nitrosonium tetrafluoroborate were purified as described by Olah and Kuhn.[29] The compounds were manipulated in a nitrogen atmosphere in a drybox. A solution of the nitronium or nitrosonium salt (0.0015 mol) in sulfolane (10 mL) was added dropwise to a stirred solution of 4-tolylmercuric acetate (0.0015 mol) in sulfolane (10 mL). These reaction solutions became green during the initial stages of the reaction. The nitrosation reactions remained green. However, the nitration reactions turned brown. The mixture was poured into water. Ether and 1,2-dichlorobenzene were added and the layers were separated. The ether layer was examined by vapor phase chromatography. The aqueous layer was treated with sodium bromide to precipitate the organomercury compounds. These products, if any, were collected and dried in vacuo. The dry powder was suspended in chloroform and treated with bromine until the solution remained red. This mixture was allowed to stand overnight, then washed with aqueous sodium bisulfite and water prior to drying with sodium sulfate. The aryl bromides produced in these reactions were determined by gas chromatography.

No arylmercuric bromides were formed in the nitrosation reaction. Analysis of the ether layer indicated 96% 4-nitrosotoluene.

The results obtained in the reactions with nitronium tetrafluoroborate were erratic. The yields of 4-nitrosotoluene ranged from 4 to 24%, the yields of 4-nitrotoluene ranged from 6 to 29%, and the yields of 2-nitro-4-bromotoluene ranged from 11 to 41%. We believe that nitrosation reagents are present in the starting materials and that these reagents are responsible for the production of both 4-nitroso- and 4-nitrotoluene.

Nitration of Arylmercuric Acetates. Nitric acid (90%) was freed of nitrogen oxides by treatment with urea and nitrogen.[30] In separate experiments, phenylmercuric acetate (0.7 g, 0.002 mol) and 4-tolylmercuric acetate (0.5 g, 0.0015 mol) were slowly added over 1 h to nitric acid (4.5 mL) at −25 °C. The reactions were stirred for 1 or 2 days at −25 °C. The reactions with phenylmercuric acetate were homogeneous; the reactions with 4-tolylmercuric acetate were not homogeneous throughout the course of reaction.

The reaction mixtures were poured onto ice. The organomercury compounds were converted to bromo compounds by the procedure of Challenger and Rothstein.[19] The product distributions were assessed by vapor phase chromatography. 4-Tolylmercuric acetate provided only 3-nitro-4-methylbromobenzene. Phenylmercuric acetate gave 23% 2-, 51% 3-, and 19% 4-nitrobromobenzene. This product distribution is comparable with prior results.[19]

Competition Experiments. In a typical experiment, benzene (15.6 g, 0.20 mol), toluene (9.2 g, 0.10 mol), and mercuric acetate (1.5 g, 0.0047 mol) were dissolved in acetic acid (60 mL). The solution was heated to 80 °C and a solution of nitric acid (90%, d = 1.5, 0.30 mol) and acetic acid (30 mL) was added dropwise with vigorous stirring. Aliquots of the reaction mixture were taken at regular intervals and analyzed as described previously. The relative rates were assessed by measurement of the product ratios using the Ingold–Shaw expression.

Nitric Acid Catalyzed Mercuration. A solution of mercuric acetate (12.8 g, 0.040 mol), urea (2.0 g, 0.033 mol), acetic acid (120 g, 2.0 mol), and nitric acid (22 mL, 0.47 mol) was heated to 80 °C. A solution of toluene (40.0 g, 0.44 mol) in acetic acid (40 g, 0.67 mol) was added rapidly with stirring. Aliquots (20 mL) were taken from the reaction mixture at various intervals and quenched with an equal volume of water. The mixture was treated with sodium bromide (0.08 mol) to precipitate the tolylmercuric bromides. The precipitate was collected and dried in vacuo. This product mixture was converted to a mixture of bromotoluenes as described previously. The mixture was analyzed by NMR spectroscopy at 270 MHz using the intensity of the methyl resonances. This analytical approach was tested with known mixtures of the isomeric bromotoluenes.

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Registry No.—Toluene, 108-88-3; 4-deuteriotoluene, 4409-83-0.

References and Notes

(1) R. Wolffenstein and O. Boeters, German Patent 194 883; *Chem. Abstr.*, **2**, 1861 (1908).

(2) A concise review of the reaction is presented by A. V. Topchiev, "Nitration of Hydrocarbons and Other Organic Compounds", Pergamon Press, Elmsford, N.Y., 1959, p 43.

(3) F. H. Westheimer, E. Segel, and R. Schramm, *J. Am. Chem. Soc.*, **69**, 773

(1947).
(4) (a) A. I. Titov and A. N. Baryshnikova, *J. Gen. Chem. USSR*, **17**, 829 (1947); (b) A. I. Titov and N. G. Laptev, *ibid.*, **19**, 267 (1949).
(5) T. L. Davis, D. E. Worrall, N. L. Drake, R. W. Helmkamp, and A. M. Young, *J. Am. Chem. Soc.*, **43**, 594 (1921).
(6) S. Tsutsumi and E. Iwata, *J. Chem. Soc. Jpn., Pure Chem. Sect.*, **72**, 141 (1951); *Chem. Abstr.*, **46**, 6604*a* (1952).
(7) T. Osawa, T. Yoshida, and K. Namba, *Kogyo Kayaku Kyokaishi*, **27**, 162 (1966).
(8) The oxides of Ag, Cu, Pb, Pt, and W and the nitrates of Ag, Al, Ba, Bi, Ca, Cd, Co, Cr, Cu, Fe, K, Mg, Mn, Na, Ni, Pb, Sn, Sr, U, and Zn were examined.[6,7]
(9) R. O. C. Norman, W. J. E. Parr, and C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 369 (1974). These workers have achieved limited success using palladium salts and nitrogen dioxide in chloroacetic acid.
(10) H. Komoto, F. Hayano, T. Takami, and S. Yamato, *J. Polym. Sci., Part A-1*, **9**, 2983 (1971).
(11) A summary of the relative rates and isomer distributions for mercuration under several different conditions is found in L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, **1**, 35 (1963).
(12) F. C. Whitemore, "Organic Compounds of Mercury", Chemical Catalog Co., New York, N.Y., 1921, p 34.
(13) H. C. Brown and C. W. McGary, *J. Am. Chem. Soc.*, **77**, 2300 (1955).
(14) H. C. Brown and C. W. McGary, *J. Am. Chem. Soc.*, **77**, 2306 (1955).
(15) Perchloric acid catalyzes the isomerization of the arylmercuric acetates in acetic acid: ref 14.
(16) (a) H. Zollinger, *Adv. Phys. Org. Chem.*, **2**, 168 (1964); (b) W. Kitching, *Organomet. Chem. Rev., Sect. A*, **3**, 35 (1968).
(17) D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 655 (1975).
(18) (a) D. Cook, S. J. Kuhn, and G. A. Olah, *J. Chem. Phys.*, **33**, 1669 (1960). (b) R. W. Sprague, A. B. Garrett, and H. H. Sisler, *J. Am. Chem. Soc.*, **82**, 1059 (1960).
(19) F. Challenger and E. Rothstein, *J. Chem. Soc.*, 1258 (1934).
(20) (a) E. C. Taylor, R. H. Danforth, and A. McKillop, *J. Org. Chem.*, **38**, 2088 (1973); (b) B. Davies and C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 65 (1975); (c) E. C. Taylor, H. W. Altland, and A. McKillop, *J. Org. Chem.*, **40**, 3441 (1975).
(21) C. Eaborn, Z. S. Salih, and D. R. M. Walton, *J. Chem. Soc., Perkin Trans. 2*, 172 (1972).
(22) G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, **86**, 1067 (1964).
(23) The nitrode-*tert*-butylation of 4-*tert*-butyltoluene in acetic anhydride gives no more than 1.0% 4-nitrotoluene: M. Bishop, unpublished results.
(24) The steric requirements of nitration reagents are always greater than the steric requirements of comparable nitrosation reagents, e.g., the nitronium ion compared to the nitrosonium ion or acetyl nitrate compared to acetyl nitrite.
(25) Y. Ogata and H. Tezuka, *J. Am. Chem. Soc.*, **89**, 5428 (1967).
(26) J. Turkevich, H. A. McKenzie, L. Friedman, and R. Spurr, *J. Am. Chem. Soc.*, **71**, 4045 (1949).
(27) E. Dreher and R. Otto, *Justus Liebigs Ann. Chem.*, **154**, 174 (1870).
(28) E. Wroblevsky, *Justus Liebigs Ann. Chem.*, **168**, 176 (1873).
(29) G. A. Olah and S. J. Kuhn, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 480.
(30) J. P. Freeman and I. G. Shepard, *Org. Synth.*, **43**, 84 (1963).

Stereoselective Total Synthesis of Diterpene Resin Acids

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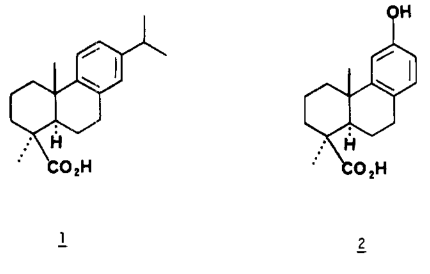
Stereoselective total syntheses of diterpene resin acids (±)-callitrisic acid (1) and (±)-podocarpic acid (2) are described. The synthetic approach to both natural products utilizes a highly stereoselective reductive elimination–alkylation reaction for establishing the axial stereochemistry of the carbomethoxyl functional group at position 1 in esters **12A** and **12B**. Thus treatment of vinyl esters **11A** or **11B** with lithium metal in liquid ammonia/DME followed by methyl iodide effects comcomitant reduction, deoxygenation, and stereoselective alkylation in a single step, therefore providing a general synthetic procedure for the construction of podocarpane type natural products.

The diterpene class of naturally occurring substances forms an enormous group of plant and fungal products derived, biogenetically, from four isoprene units via geranylgeranyl pyrophosphate.[1] Notable features of the diterpene natural products are the fascinating variation encountered in their structures and the wide range of their biological activities. Two diterpene molecules, which have common structure features in rings A and B, are resin acids callitrisic acid (1) and podocarpic acid (2). Callitrisic acid (1) was isolated from the Australian white cypress pine *Callitris columelaris* in 1967.[2] Several syntheses of callitrisic acid (1) have been reported.[3] Interestingly enough Haworth and Baker's synthesis,[3a] the first total synthesis of a diterpenoid natural product, occurred 28 years before callitrisic acid (1) was isolated. Podocarpic acid (2) was first isolated in 1873 from *Podocarpus cupressium*.[4] The structure and stereochemistry of podocarpic acid (2), however, were not characterized until 1940.[5] A number of syntheses of podocarpic acid (2) and deoxypodocarpic acid have been published.[6] The latter acid has been successfully converted to podocarpic acid (2); therefore, synthesis of it also constitutes a total synthesis of podocarpic acid (2). Both callitrisic acid (1) and podocarpic acid (2) have common structural features in rings A and B; namely, they both have a trans A,B ring fusion, an axially oriented carboxylic acid functional group at position 1, an axial methyl group at position 4a, and an equatorial methyl group at position 1. During the course of our investigations aimed at a total synthesis of the antifungal antibiotic LL-Z1271α we developed a new and highly stereoselective method for the construction of ring A of podocarpane type natural products. This new method has general applicability in the synthesis of podocarpane type naturally occurring substances as exemplified by our previously reported syntheses.[3g,6g,7] We wish to report, herein, the full details of our total syntheses of diterpene resin acids (±)-callitrisic acid (1) and (±)-podocarpic acid (2).

Chart I



1 2

Synthesis of (±)-Callitrisic Acid (1). The starting material chosen for our synthesis of (±)-callitrisic acid (1) is 6-isopropyl-1-methyl-2-tetralone (**8A**, Scheme I), which was previously prepared by Stork and Schulenberg[8] from cumene as well as 2-acetonaphthone by lengthy multistep sequences. We have developed a short and efficient alternate route to tetralone **8A** beginning with 4-isopropenylisopropylbenzene (3).[9] Epoxidation of alkene 3 with *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of disodium hydrogen phosphate