mg, 0.48 mmol) at 60 °C for 4 h followed by evaporation in vacuo to dryness. The residue was dissolved in ether and washed with 5% $NaHCO_3$, dried ($MgSO_4$), and evaporated to dryness. The crude material was purified by preparative TLC to yield the pure compound: 158 mg (88%); mp 114–116 °C (recrystallized from methanol); IR 1664 cm^{-1} (C(O)NH); ^1H NMR δ 0.66 (3 H, s, 18-Me), 0.97 (3 H, s, 19-Me), 3.73 (1 H, br s, 3α-H), 4.5 (2 H, s, benzylic protons), 5.27 (1 H, br s, 15-H), 6.53 1 H, d, J = 9 Hz, C_{23} H), 7.32 (7 H, m, aromatic protons, C_{21} H and C_{22} H).

3β-(Benzyloxy)-14β,15β-oxido-17β-(2-hydroxy-5-pyridyl)-5β-androstane (8). A mixture of the pyridone compound **7** (91.6 mg, 0.2 mmol) and water (0.3 mL) in acetone (3 mL) was stirred with *N*-bromoacetamide (34.5 mg, 0.25 mmol) at room temperature for a period of 15 min. The reaction mixture was diluted with CH_2Cl_2, washed with 5% Na_2SO_3, dried over anhydrous $MgSO_4$, and evaporated at room temperature in vacuo to dryness. The residue was redissolved in a 1:1 mixture of CH_2Cl_2 and MeOH (20 mL) and stirred at room temperature with aluminum oxide (180 mg) for 4 h. The filtrate was evaporated to dryness. The crude product was purified by TLC to yield pure epoxide **8** as a yellow liquid: 68 mg (72%); IR 1659 cm^{-1} (C(O)NH); ^1H NMR δ 0.68 (3 H, s, 18-Me), 0.96 (3 H, s, 19-Me), 3.5 (1 H, s, 15α-H), 3.7 (1 H, br s, 3α-H), 4.48 (2 H, s, benzylic protons), 6.5 (1 H, d, J = 9 Hz, C_{23} H), 7.4 (7 H, m, aromatic protons, C_{21} H and C_{22} H).

3β-(Benzyloxy)-14β,15β-oxido-17β-(1-benzyl-2-hydroxy-5-pyridyl)-5β-androstane (9). To a solution of compound **8** (95 mg, 0.2 mmol) in 1,2-dimethoxyethane were added potassium carbonate (85 mg, 0.61 mmol) and benzyl bromide (36 mg, 0.21 mmol). The reaction mixture was refluxed overnight and then filtered, and the filtrate was evaporated to dryness. The crude product was purified by preparative TLC to give pure *N*-benzyl pyridone **9**: 96 mg (85%); mp 104–106 °C (recrystallized from dichloromethane–ether); IR 1662 cm^{-1} (C(O)NH); ^1H NMR δ 0.7 (3 H, s, 18-Me), 0.98 (3 H, s, 19-Me), 3.48 (1 H, s, 15α-H), 3.75 (1 H, br s, 3α-H), 4.48 (2 H, s, benzylic protons), 5.12 (2 H, s, N-benzylic protons), 6.5 (1 H, d, J = 9 HZ, C_{23} H), 7.15 (1 H, d, J = 2 Hz, C_{21} H), 7.3 (10 aromatic ring protons), 7.53 (1 H, ABq, $J_{21,22}$ = 2 Hz, $J_{22,23}$ = 9 Hz, C_{22} H). Anal. Calcd for $C_{38}H_{45}O_3N$ (mol. wt 563): C, 80.95; H, 8.05; O, 8.51; N, 2.48. Found: C, 80.91; H, 8.16; O, 8.42; N, 2.4.

3β-(Benzyloxy)-14β-hydroxy-17β-(1-benzyl-2-hydroxy-5-pyridyl)-5β-androstane (10). The *N*-benzylpyridone compound **9** (113 mg, 0.2 mmole) was dissolved in dry THF (10 mL) and lithium aluminum hydride (228 mg, 0.6 mmol) was added under a nitrogen stream at −65 °C for 1 h, followed by filtration through Celite. The filtrate was evaporated to dryness. The crude product was purified by preparative TLC and yielded 90 mg (80%) of pure compound **10** (mp 256–257 °C) which was shown to be identical with a sample prepared earlier[2] as based on NMR, IR, and UV spectral evidence and melting point.

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Registry No. **1**, 81072-39-1; **2**, 73336-58-0; **3**, 83664-27-1; **4**, 83664-28-2; **5**, 83664-29-3; **6**, 83664-30-6; **7**, 83664-31-7; **8**, 83664-32-8; **9**, 83681-20-3; **10**, 81072-38-0; 2-(benzyloxy)-5-bromopyridine, 83664-33-9.

Use of Tellurium(IV) and Tellurium(VI) as Oxidants in Organic Synthesis[49]

Jan Bergman* and Lars Engman

Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden

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The oxidizing properties of TeO_2, $Te(OH)_6$, and TeO_3 in acetic acid solution containing LiBr have been explored. It was found that certain aromatic compounds were acetoxymethylated by the action of TeO_2 or, when especially activated, converted into diarylmethane derivatives. $Te(OH)_6$ and TeO_3, in contrast, mainly effected side-chain acetoxylation, as was also the case with SeO_2. In the acetoxymethylation reaction TeO_2 apparently slowly oxidized the solvent, HOAc, to a reactive species of some kind, e.g., acetoxycarbene, which attacked the aromatic compound. In the side-chain acetoxylations, Te(VI) oxidized bromide ions to Br_2, which caused benzylic bromination. The solvolysis of benzylic bromides to acetates was significantly enhanced by the presence of Te(IV) species. Both TeO_2 and TeO_3 effected more conventional oxidations like the transformation of deoxybenzil to benzil. Benzoin acetate is a probable intermediate in this oxidation.

The use of TeO_2 as an oxidant in organic synthesis was tentatively explored as early as the 1940's.[1] The results, however, were not especially encouraging due to the very low solubility of tellurium dioxide in almost all organic

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Scheme I

$$ArH \xrightarrow[LiBr,\ 120\ or\ 160\ °C]{TeO_2,\ HOAc} ArCH_2OAc$$

Table I. Acetoxymethylation of Alkyl Aromatic Compounds Using TeO_2

substrate	temp, °C	benzyl acetate (% yield)	diarylmethane derivatives (% yield)
benzene	160	benzyl acetate (5)	
toluene	118	methylbenzyl acetates (14)	
toluene	160	methylbenzyl acetates (9)	ditolylmethanes (23)
o-xylene	118	dimethylbenzyl acetates (27)	trace
p-xylene	118	2,5-dimethylbenzyl acetate (30)	trace
mesitylene	118	2,4,6-trimethylbenzyl acetate (16)	dimesitylmethane (17)

solvents. The interest was therefore first focused on the catalytic activity of TeO_2 in high-temperature vapor-phase oxidations, e.g., the oxidation of propylene to acrolein.[2] The selectivity of tellurium catalysts, the resulting favorable yields of the desired products, and the resistance of the catalysts to poisoning were noteworthy properties.[2] More recently catalytic systems containing TeO_2 and HOAc[3-5] or sulfolane[6] have attracted considerable attention. Ethylene, for example, was catalytically converted to ethylene glycol in high yield (95%):

$$C_2H_4 + 0.5O_2 + 2HOAc \xrightarrow[HBr]{TeO_2} AcOCH_2CH_2OAc + H_2O$$

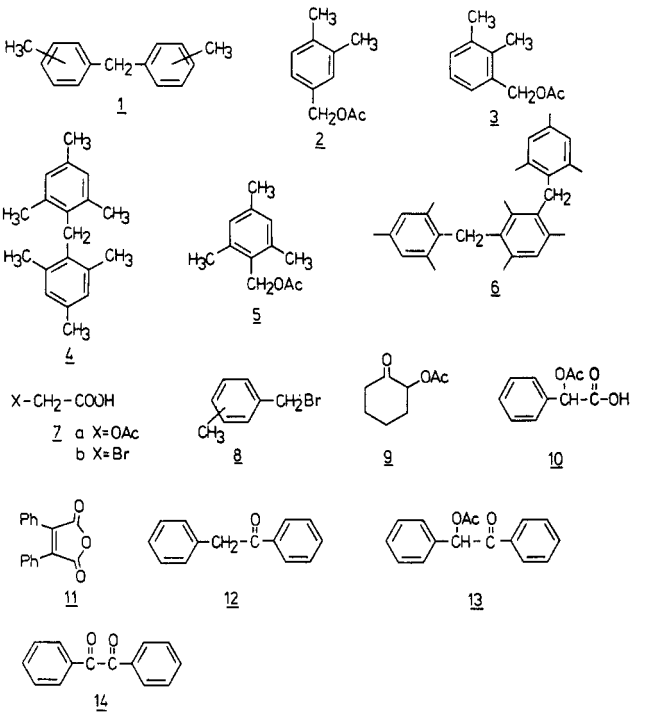
$$AcOCH_2CH_2OAc + 2H_2O \rightarrow HOCH_2CH_2OH + 2HOAc$$

$$C_2H_4 + 0.5O_2 + H_2O \rightarrow HOCH_2CH_2OH$$

Recently a group at Phillips Petroleum reported[7] that alkyl-substituted aromatic compounds, not unexpectedly,[8] could be catalytically oxidized by a similar procedure. Thus, toluene in one example (150 °C, O_2, 50 psig of O_2 initially at 24 °C, HOAc, TeO_2, LiBr, $LiNO_3$) gave benzyl acetate (76% yield) together with small amounts of benzaldehyde (7%) and bromo derivatives (8%) as well as other minor products (partly unspecified). A preparation of phenylacetic acid from benzene with catalytic amounts of Te(IV) in the presence of pressurized oxygen has also been reported.[9]

We have reported quite different results in a preliminary study[10] using similar systems, but without the introduction of pressurized oxygen. In the present study we present full experimental data for these reactions resulting in acetoxymethylation of certain aromatic compounds. In addition, we have studied the oxidizing properties of tellurium trioxide (TeO_3) and orthotelluric acid ($Te(OH)_6$) in organic systems, which to the best of our knowledge has not been done before.

Chart I



Results and Discussion

We have found that certain aromatic compounds were acetoxymethylated according to Scheme I, when heated at reflux in acetic acid containing tellurium dioxide and lithium bromide.

The yields were low (5–30%, Table I), and long reaction times were necessary (72 h), but the reactions were remarkably clean (only trace amounts of side-chain oxidation products were observed). The yields could be slightly improved by performing the reactions under an inert atmosphere, but generally no special precautions were carried out.

Benzene was very unreactive and yielded only a 5% yield of benzyl acetate even at elevated temperature (160 °C).

Toluene afforded a mixture of the three possible methylbenzyl acetates[11-13] in refluxing acetic acid. The relative yields (determined by NMR spectroscopy using a shift reagent) were 50:12:38 ortho/meta/para. At elevated temperature (160 °C, sealed tube) an isomeric mixture of ditolylmethanes (1, Chart I) was formed in addition to the methylbenzyl acetates.

o-Xylene was converted into a 1:1-mixture of the two possible dimethylbenzyl acetates **2** and **3**.[14]

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The formation of diarylmethane derivatives and other complex compounds was more pronounced with more reactive hydrocarbons, which seems to indicate that the diarylmethane derivatives are formed in a secondary process involving electrophilic attack on unreacted starting material. NMR analysis of the ditolylmethanes 1 revealed formation of the ortho–para and the para–para isomers as the main products in a 54:46 relationship. This result is in support of a secondary electrophilic reaction. Mesitylene afforded a mixture of dimesitylmethane (4)[15] and 2,4,6-trimethylbenzyl acetate (5),[16] after 48 h in refluxing HOAc. With a still longer reaction time, a small amount of the known[17] trimeric compound 6 was formed as indicated by mass spectral analysis.

Acetoxymethylations have previously been effected with reagents such as $Mn(OAc)_3$[18,19] and $Pb(OAc)_4$.[20] Heiba et al.[19] found evidence for a mechanism involving attack by the radical $\cdot CH_2COOH$ on an aromatic ring in the crucial step. The formation of several byproducts such as arylacetic acids and benzyl acetates resulting from side-chain oxidation further supported a radical mechanism.

We have isolated acetoxyacetic acid (**7a**) and bromoacetic acid (**7b**) in various amounts (1:1–2:1) as the only acidic byproducts in the TeO_2-induced acetoxymethylation reaction. Not even traces of phenylacetic acid derivatives could be detected in the oxidations of benzene and toluene. Our results are remarkable in view of the recent patent concerning the preparation of phenylacetic acid from benzene and a Te(IV) catalyst.[9] Attempts to increase the amount of LiBr to the specifications given in the patent also failed to give any trace of phenylacetic acid. The different results probably must be attributed to the fact that pressurized oxygen was employed in the patent procedure.

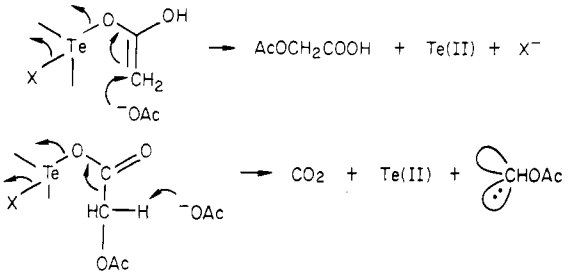
The absence of typical "radical products" in the TeO_2-induced acetoxymethylations prompted us look for other mechanistic alternatives. When the acetoxymethylation of toluene was carried out in a mixture of acetic anhydride (35 mL) and acetic acid (15 mL), methylene diacetate ($CH_2(OAc)_2$) was isolated in 7% yield in addition to methylbenzyl acetates (9%). This result inspired us to investigate possible electrophilic additions to aromatic compounds, resulting in acetoxymethylation. Methylene diacetate, however, failed to give any methylbenzyl acetates when heated with toluene and LiBr in acetic acid. This was also the case with CH_2Br_2. A related compound, bromomethyl acetate ($BrCH_2OAc$), on the other hand, gave a 52% yield of methylbenzyl bromides (8) in addition to ditolylmethanes (27%) when submitted to the same reaction conditions. The methylbenzyl bromides were readily acetolyzed to methylbenzyl acetates by the use of TeO_2 (vide infra) and the isomer distribution determined to be 52:2:46 ortho/meta/para. The small proportion of meta isomer is well in agreement with earlier studies of the chloro- and bromomethylation reactions[21] and far less than the 12% meta isomer obtained in the TeO_2-induced acetoxymethylation. The bromomethyl acetate was also ruled out as a possible intermediate by the fact that it was rapidly solvolyzed to methylene diacetate when heated in acetic acid containing TeO_2, LiBr, and toluene. No formation of methylbenzyl acetates was observed in this case.

We have previously suggested a carbene mechanism as more likely than an electrophilic or a radical one for the acetoxymethylation reaction. Acetoxy carbene (:CHOAc) was tentatively suggested as a possible alkylating agent.[10] Its formation from acetoxyacetic acid was also proposed. Any mechanistic suggestion is speculative in view of the absence of definite information about the structure of the solubilized tellurium species produced in the system TeO_2/LiBr/HOAc. However, the formation of a complex containing acetoxy or/and bromo ligands, as depicted in Scheme II, seems reasonable and consistent with previous results.[22]

Scheme II

$$TeO_2 \xrightarrow[LiBr]{HOAc} Te(OAc)_yBr_{4-y}$$

Scheme III



Scheme IV

$$Ar{-}CH_3 \xrightarrow[LiBr]{Te(OH)_6,\ HOAc} ArCH_2OAc$$

Scheme V

$$Te(VI) + 2Br^- \longrightarrow Te(IV) + Br_2$$

$$ArCH_3 + Br_2 \longrightarrow ArCH_2Br + HBr$$

$$ArCH_2Br \xrightarrow[HOAc]{Te(IV)} ArCH_2OAc + HBr$$

A possible mode of formation of acetoxycarbene via acetoxyacetic acid is shown in Scheme III. The reaction sequence involves an enolized carboxylate intermediate as well as an α elimination with loss of CO_2.

It should be noted, however, that the addition of acetoxyacetic acid as a reactant in a normal oxidation of toluene caused no increase in the product yield.

When tellurium dioxide was replaced by selenium dioxide (SeO_2) in the oxidation of toluene, only side-chain oxidation was observed, producing benzyl acetate (20%) and benzyl bromide (3%). Tellurium trioxide (TeO_3) and orthotelluric acid ($Te(OH)_6$), a less expensive and readily available Te(VI) reagent, could also be used to effect side-chain acetoxylation according to Scheme IV. When the Te(VI) acetoxylations were carried out for 24 h in refluxing acetic acid, only a very small amount of Te(0) was formed. Te(VI) seems to be mainly reduced to Te(IV), and only trace amounts of acetoxymethylated products could be detected. A number of representative examples are listed in Table II. Ring-brominated products and benzaldehyde derivatives were common byproducts. With activated aromatics such as 4-methoxytoluene and 2-methylnaphthalene, ring bromination became the predominating reaction. Deactivated aromatics such as 4-methylbenzoic acid failed to give any acetoxylated products.

The synthesis of benzylic acetates by using liquid-phase oxidation of hydrocarbons has recently been reviewed.[23] The list of reagents comprises metal ions such as Co(III),[24] Ce(IV),[25] Mn(III),[26] and Pd(II)[27] as well as other reagents such as peroxydisulfate.[28] Electrochemical methods have also been used.[29]

The formation of ring-brominated compounds in the Te(VI) acetoxylations and the fact that LiBr was required to give any oxidation products indicate that the benzyl acetates might be formed via benzylic bromination and subsequent solvolysis according to Scheme V. The for-

Table II. Side-Chain Acetoxylation of Alkyl Aromatic Compounds Using $Te(OH)_6$

substrate	benzyl acetates (%)	aldehyde (%)[b]	ring bromination product (%)
toluene	benzyl acetate (69)		bromotoluene (6)
o-xylene	2-methylbenzyl acetate (48)	2-methylbenzaldehyde (7)	bromo-*o*-xylene (6)
m-xylene	3-methylbenzyl acetate (27)	3-methylbenzaldehyde (3)	bromo-*m*-xylene (39)
p-xylene	4-methylbenzyl acetate (52)	4-methylbenzaldehyde (6)	bromo-*p*-xylene (5)
4-bromtoluene	4-bromobenzyl acetate (41)	4-bromobenzaldehyde (16)	
diphenylmethane	diphenylmethanol acetate (60)	benzophenone (7)[c]	
triphenylmethane	triphenylmethanol acetate (81)[a]		
4-methoxytoluene			2-bromo-4-methoxytoluene (68)
2-methylnaphthalene			1-bromo-2-methylnaphthalene (70)

[a] This acetate is very labile toward hydrolysis,[30] and only the alcohol was isolated; mp 163 °C (lit.[48] mp 162.4–162.5 °C). [b] It is assumed that 2 equiv of $Te(OH)_6$ are required to produce 1 equiv of aldehyde. [c] A ketone is formed in this case.

Scheme VI

$$TeO_2 + 4HBr \longrightarrow TeBr_4 + 2H_2O$$

mation of bromine could be visually observed, especially during the first 10 min of the reactions. GLC analysis during the reaction confirmed the formation of benzyl bromides as primary products that were slowly solvolyzed to benzyl acetates. After 24 h only traces of benzyl bromides remained. The solvolysis of benzyl bromide is usually slow in acetic acid. However, the addition of Te(IV) in the form of TeO_2 caused a large increase in the solvolysis rate. Benzyl bromide could be converted to benzyl acetate in 93% yield after 6 h in refluxing acetic acid containing TeO_2 and LiBr. When TeO_2 was omitted, only a 32% conversion to benzyl acetate was observed after 6 h (see Figure 1). Benzyl chloride was similarly solvolyzed to benzyl acetate in 88% yield under the influence of TeO_2. By varying the relative amounts of TeO_2 and benzyl bromide, it was concluded that 1 equiv of TeO_2 caused solvolysis of 4 equiv of benzyl bromide. A possible role of TeO_2 is to act as a recipient of HBr as shown in Scheme VI. Lead acetate, $Pb(OAc)_2$, was shown to function similarly in the acetolysis of various benzylic halides.[30]

The intermediacy of benzyl bromides has recently been proposed in several syntheses of benzyl acetates from toluenes by employing reagents like CuBr,[31] Co(II)–Cu(II)–NaBr,[32,33] or Mn(III)–KBr.[34]

The striking difference in the reactions of Te(IV) and Te(VI) with alkyl aromatic compounds is mainly due to the fact that Te(VI) oxidizes bromide ions to Br_2 while Te(IV) does not. Te(VI) gives products arising from side-chain oxidation whereas Te(IV) produces acetoxymethylated compounds.

A group at Phillips Petroleum[7] has reported the conversion of alkyl-substituted aromatics to benzyl acetates, benzaldehydes, and bromo derivatives—products that we isolated using Te(VI)—by employing reaction conditions where we exclusively obtained acetoxymethylated products. The only important difference seems to be the use of pressurized oxygen in their reactions. We therefore feel that Te(IV) can be oxidized to Te(VI) by using pressurized oxygen and that Te(VI) was the active catalyst in the Phillips Petroleum procedure. The O_2 oxidation of Te(IV) has been briefly mentioned by Brownstein.[5]

Both tellurium dioxide and tellurium trioxide could be used in acetic acid solution containing LiBr to effect more conventional oxidation reactions (Table III). Thus, cyclohexanone was converted into 2-acetoxycyclohexanone (9) by the action of TeO_2 or TeO_3. In contrast, it is known that cyclohexanone is oxidized all the way to 1,2-cyclohexanedione with SeO_2 in dioxane.[35] Phenylacetic acid was α acetoxylated to afford α-*O*-acetyl-mandelic acid (10). Oxidation of phenylacetic acid in a mixture of acetic acid and acetic anhydride afforded diphenylmaleic anhydride (11) in low yield (5%), probably via the primary oxidation product phenylglyoxalic acid that underwent further condensation with phenylacetic acid.[36]

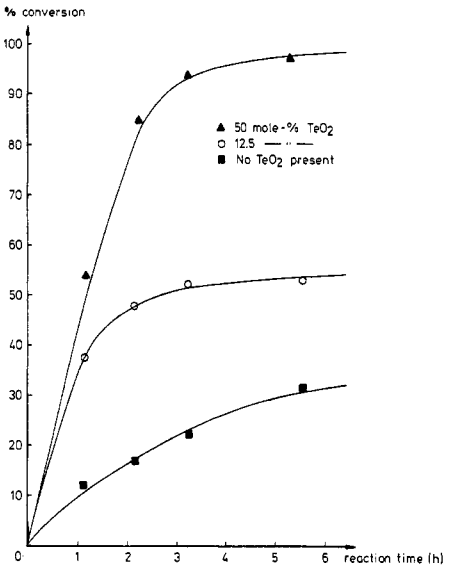


Figure 1. Solvolysis of benzyl bromide in acetic acid containing LiBr and various amounts of TeO_2.

Table III. Oxidation of Carbonyl Compounds Using TeO_2 and TeO_3

substrate	oxidant	products (% yield)
phenylacetic acid	TeO_2	α-*O*-acetylmandelic acid (36)
cyclohexanone	TeO_2	2-acetoxycyclohexanone (38)
cyclohexanone	TeO_3	2-acetoxycyclohexanone (47)
deoxybenzil	TeO_2	benzil (36) + benzoin acetate (8)
deoxybenzil	TeO_3	benzil (63) + benzoin acetate (17)
benzoin acetate	TeO_2	benzil (76)

Deoxybenzil (12) gave a mixture of benzoin acetate (13) and benzil (14) with TeO_2 as well as TeO_3. Benzoin acetate is a likely intermediate in these oxidations since a good yield of benzil was obtained when this compound was oxidized with TeO_2.

Experimental Section

All melting points were uncorrected. Infrared spectra were obtained by using a Perkin-Elmer 257 instrument. Mass spectra were recorded by using an LKB 9000 mass spectrometer, and NMR spectra were obtained by using a Varian EM-360 instrument and a Bruker WP-200 instrument. TeO_2 was obtained from PCR Research Chemicals Inc., TeO_3 from Cerac Pure Inc., and $Te(OH)_6$ from Merck. Acetoxyacetic acid,[37] methylene diacetate,[38] benzoin acetate,[39] bromomethyl acetate,[40] diphenylmaleic anhydride,[36] and *p,p'*-ditolylmethane[41] were synthesized according to literature methods. The products in Tables I–III were usually compared with commercial samples or samples synthesized according to literature methods: 2-acetoxycyclohexanone,[42] 2-bromo-4-methoxytoluene.[43] The three methylbenzyl acetates were synthesized

by lithium aluminium hydride reduction of the corresponding methylbenzoic acids,[44] followed by acetylation in refluxing acetic anhydride.[13] 1-Bromo-2-methylnaphthalene was prepared from 2-methylnaphthalene and bromine in refluxing HOAc. α-O-Acetylmandelic acid was synthesized from mandelic acid in refluxing acetic anhydride.

o,p-Ditolylmethane was obtained from *p*-tolylmagnesium bromide and *o*-methylbenzaldehyde followed by lithium aluminium hydride reduction of the resulting benzhydrol as described for similar compounds.[41]

The acetoxymethylations of toluene and *p*-xylene were performed under N_2 as well as under a normal atmosphere. The product distribution was unaffected by the presence of N_2, but the yields were slightly improved (14% compared to 9% for toluene, 30% compared to 24% for *p*-xylene). The other acetoxymethylations presented in Table I were carried out under a normal atmosphere.[45]

General Procedure. Acetoxymethylation of *p*-Xylene. TeO_2 (4.0 g, 0.025 mol), LiBr(3.0 g, 0.035 mol), and 0.075–0.100 mol of the aromatic compound (8.0 g of *p*-xylene, 0.075 mol) were heated at reflux in acetic acid (50 mL) for 72 h. The cooled reaction mixture was then poured into ethyl ether (200 mL) and neutralized with $NaHCO_3$ (5% aqueous solution). Drying ($CaCl_2$) and evaporation of the organic phase, including excess *p*-xylene, yielded 1.36 g (30%) of 2,5-dimethylbenzyl acetate, bp 112–114 °C (10 mm) [lit.[46] bp 138–41 °C (28 mm)].

Mixtures of acetoxymethylated compounds and diarylmethane derivatives were separated by column chromatography.

In the experiments carried out at elevated temperature the reactants were heated to 160 °C in a sealed tube for 72 h. After cooling to −78 °C the tube was opened, releasing considerable pressure of CO_2. The workup was continued as described above.

The isomeric mixture of ditolylmethanes from the high-temperature oxidation of toluene was analyzed by ^1H NMR. The ortho–para and the para–para isomers were identified as the main products in a 54:46 relationship.

The isomer distribution in the acetoxymethylation of toluene was determined by ^1H NMR spectroscopy. Addition of $Eu(fod)_3$ to a chloroform solution resolved all signals completely and the relative amounts were determined to be as follows: ortho, 50%; meta, 12%; para, 38%.

The acetoxymethylation of *o*-xylene yielded a 1:1-mixture of 2,3-dimethylbenzyl acetate and 3,4-dimethylbenzyl acetate as revealed by ^1H and ^{13}C NMR spectroscopy and mass spectral analysis.

In the acetoxymethylation of mesitylene, TeO_2 (2.0 g, 0.013 mol), mesitylene (1.0 g, 0.008 mol), and LiBr (2.0 g, 0.023 mol) were heated at reflux in acetic acid (40 mL) for 48 h. The usual workup and chromatography (hexane/CH_2Cl_2, 4:1) afforded 0.18 g of dimesitylmethane [mp 131–2 °C (lit.[15] mp 129–30 °C)] and 0.26 g of 2,4,6-trimethylbenzyl acetate, bp 126–127 °C (8 mm) [lit.[16] bp 97–98 °C (1.5 mm)].

The acidic reaction products formed in the acetoxymethylation reaction were isolated in the following way. The acetic acid solutions from the reactions of benzene and toluene, respectively, were evaporated and dissolved in $NaHCO_3$ (5% aqueous solution). After several washings with ethyl ether, the aqueous phases were acidified (HCl) and extracted with ether. Drying and evaporation yielded 0.12 and 0.29 g of material, respectively, from the reactions of benzene and toluene, in both cases a mixture of acetoxyacetic acid and bromoacetic acid. The relative amounts of $AcOCH_2COOH/BrCH_2COOH$ were determined by ^1H NMR to be 19:17 (benzene) and 16:9 (toluene). Both acids were compared with authentic samples.

A fourfold increase of the amount of LiBr used in the general procedure for the acetoxymethylation of toluene caused no change in the products. No arylacetic acid derivatives could be detected.

The addition of 2.0 g of acetoxyacetic acid as a reactant in the acetoxymethylation of toluene caused no change in the product yield.

When the acetoxymethylation of toluene was carried out according to the general procedure, but in a mixture of acetic anhydride (35 mL) and acetic acid (15 mL), methylene diacetate (7%) was isolated in addition to methylbenzyl acetates (9%). However, no formation of methylbenzyl acetates was detected when toluene (6.5 g), LiBr (3.0 g), and methylene diacetate (1.5 g) were refluxed in acetic acid (50 mL) for 72 h.

The same result was obtained with CH_2Br_2. When toluene (8.0 g), bromomethyl acetate (2.0 g), and LiBr (3.0 g) were heated in acetic acid (40 mL) for 16 h, methylbenzyl bromides (1.27 g, 52%) and ditolylmethanes (0.64 g, 27%) could be isolated after the usual workup. The methylbenzyl bromides from 1.40 g of crude product were solvolyzed to methylbenzyl acetates by heating at reflux for 16 h in acetic acid (35 mL) containing TeO_2 (0.60 g) and LiBr (1.50 g). ^1H NMR analysis of this product (1.28 g) showed a complete conversion to methylbenzyl acetates. After chromatographic separation from the ditolylmethanes, the isomer distribution was determined to be 52:2:46 ortho/meta/para.

Oxidation of Toluene with SeO_2. SeO_2 (1.22 g, 0.011 mol), LiBr (3.0 g, 0.035 mol), and toluene (6.5 g, 0.071 mol) were heated at reflux in HOAc (40 mL) for 24 h. A workup according to the general procedure for acetoxymethylation afforded benzyl acetate (0.65 g, 20%) and benzyl bromide (0.10 g, 3%).

The acetoxylation of toluene with $Te(OH)_6$ was performed under N_2 as well as under a normal atmosphere. There was no significant difference in yields or in product distribution in the two experiments. The acetoxylations reported in Table II were all carried out under a normal atmosphere.

General Procedure. Acetoxylation of *p*-Xylene. $Te(OH)_6$ (2.53 g, 0.011 mol), LiBr (3.0 g, 0.035 mol), and *p*-xylene (1.20 g, 0.011 mol) were heated at reflux in HOAc (40 mL) for 24 h. The workup followed the procedure described for the acetoxymethylation reactions. Chromatography of the crude reaction mixture afforded 0.96 g of 4-methylbenzyl acetate, 0.04 g of 4-methylbenzaldehyde, and 0.11 g of bromo-*p*-xylene. The acetate and the aldehyde were usually inseparable on a column, and their relative amounts were determined by GLC.

The acetoxylation of toluene was carried out by using a large excess of substrate (6.5 g, 0.071 mol).

The acetoxylation of 4-bromotoluene was performed with the following amounts of reactants: $Te(OH)_6$ (5.0 g, 0.022 mol), LiBr (5.0 g, 0.058 mol), 4-bromotoluene (1.60 g, 0.009 mol).

When $Te(OH)_6$ was replaced by TeO_3 (2.0 g, 0.011 mol) in the acetoxylation of toluene, benzyl acetate (0.95 g, 56%) and bromotoluene (0.12 g, 6%) were isolated.

During the acetoxylation of toluene with $Te(OH)_6$, aliquots were withdrawn periodically to study the conversion of benzyl bromide to benzyl acetate. The samples were neutralized with Na_2CO_3 (5% aqueous solution), extracted with ethyl ether and analyzed by GLC. After 13 min only benzyl bromide and a trace of bromotoluene was present. The molar relationship of benzyl acetate to benzyl bromide was determined as a function of time (minutes to be 0.11 (45), 0.50 (145), and 2.13 (194). After 24 h only trace amounts of benzyl bromide remained.

The solvolysis of benzyl bromide in acetic acid was studied in the presence of TeO_2: TeO_2 (1.0 g, 0.006 mol), benzyl bromide (2.0 g, 0.012 mol), and LiBr (2.0 g, 0.023 mol) were heated at reflux in HOAc (40 ml) for 6 h. A workup according to the general procedure for acetoxymethylation afforded benzyl acetate (1.62 g, 93%). When TeO_2 was omitted in the above-mentioned procedure, a 32% conversion to benzyl acetate was obtained after 6 h, according to GLC analysis. The amount of TeO_2 could be lowered to 25 mol % with a high conversion (95%) after 6 h. However, with 12.5 mol % of TeO_2, the conversion dropped to 50% after 6 h.

When the acetoxylation of toluene was carried out in the absence of LiBr, no oxidation took place.

Oxidation of Carbonyl Compounds. The various carbonyl compounds in Table III were heated at reflux with the oxidant (TeO_2 or TeO_3) in acetic acid (40 mL) containing LiBr. The workup followed the procedure described for the acetoxymethylations. The products were usually purified by chromatography.

Cyclohexanone (1.0 g, 0.010 mol), TeO_3 (1.5 g, 0.009 mol), and LiBr (2.0 g, 0.023 mol) gave, after 16 h, 0.75 g of 2-acetoxycyclohexanone. With TeO_2 (2.0 g, 0.0125 mol), 0.60 g of 2-acetoxycyclohexanone was obtained.

Deoxybenzil (1.0 g, 0.005 mol), TeO_2 (2.0 g, 0.0125 mol), and LiBr (2.0 g, 0.023 mol) gave, after 23 h, benzil [0.38 g; mp 93–94 °C (lit.[47] mp 94–95 °C)], benzoin acetate [0.10 g; mp 81–82 °C (lit.[39] mp 80–82 °C)], and deoxybenzil (0.50 g).

Deoxybenzil (0.50 g, 0.0025 mol), TeO_3 (1.2 g, 0.0068 mol), and LiBr (1.2 g, 0.0138 mol) similarly afforded benzil (0.34 g) and benzoin acetate (0.11 g).

Benzoin acetate (1.0 g, 0.0039 mol), TeO_2 (1.5 g, 0.0094 mol), and LiBr (2.0 g, 0.023 mol) gave, after 24 h, benzil (0.63 g) and benzoin acetate (0.20 g).

Phenylacetic acid (1.0 g, 0.0074 mol), TeO_2 (1.5 g, 0.0094 mol), and LiBr (2.0 g, 0.023 mol) were heated at reflux for 29 h. The residue obtained after solvent evaporation was dissolved in $NaHCO_3$ (5% aqueous solution) and extracted with ether. Acidification (HCl) of the aqueous layer afforded the free acidic products which were extracted into ethyl ether. Methylation with diazomethane and chromatography afforded methyl mandelate acetate (0.55 g) and methyl phenylacetate (0.50 g). Both compounds were compared with authentic samples. When the experiment was carried out in a mixture of acetic anhydride (35 mL) and acetic acid (15 mL), diphenylmaleic anhydride (11) could be isolated in 5% yield from the first ether extract.

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Registry No. 1, 1335-47-3; 4, 733-07-3; 5, 63548-92-5; 9, 17472-04-7; 10, 5438-68-6; 12, 451-40-1; 13, 574-06-1; 14, 134-81-6; TeO_2, 7446-07-3; $Te(OH)_6$, 7803-68-1; TeO_3, 13451-18-8; LiBr, 7550-35-8; SeO_2, 7446-08-4; acetic acid, 64-19-7; acetoxycarbene, 83585-70-0; bromide anion, 24959-67-9; benzene, 71-43-2; toluene, 108-88-3; *o*-xylene, 95-47-6; *p*-xylene, 106-42-3; mesitylene, 108-67-8; benzyl acetate, 140-11-4; methylbenzyl acetate, 30676-70-1; dimethylbenzyl acetate, 83585-71-1; 2,5-dimethylbenzyl acetate, 22184-23-2; *m*-xylene, 108-38-3; 4-bromotoluene, 106-38-7; diphenylmethane, 101-81-5; triphenylmethane, 519-73-3; 4-methoxytoluene, 104-93-8; 2-methylnaphthalene, 91-57-6; 2-methylbenzyl acetate, 17373-93-2; 2-methylbenzaldehyde, 529-20-4; bromotoluene, 28807-97-8; 3-methylbenzyl acetate, 17369-57-2; 3-methylbenzaldehyde, 620-23-5; bromo-*m*-xylene, 42715-80-0; bromo-*o*-xylene, 51317-35-2; 4-methylbenzyl acetate, 2216-45-7; 4-methylbenzaldehyde, 104-87-0; bromo-*p*-xylene, 553-94-6; 4-bromobenzyl acetate, 21388-92-1; 4-bromobenzaldehyde, 1122-91-4; diphenylmethanol acetate, 954-67-6; benzophenone, 119-61-9; triphenylmethanol, 76-84-6; phenylacetic acid, 103-82-2; cyclohexanone, 108-94-1; *o*-methylbenzoic acid, 118-90-1; *o,p*-ditolylmethane, 21895-17-0; *p*-tolylmagnesium bromide, 4294-57-9; *o*-methylbenzaldehyde, 529-20-4; *o,p*-ditolylmethanol, 21945-70-0; acetic anhydride, 108-24-7; methylene diacetate, 628-51-3; bromomethyl acetate, 590-97-6; *m*-methylbenzoic acid, 99-04-7; *p*-methylbenzoic acid, 99-94-5.

Notes

Epoxidation of an Unsaturated Tertiary Amine. Application to the Synthesis of Two Pirprofen Metabolites

Naba K. Chaudhuri* and Thomas J. Ball

Research Department, Pharmaceuticals Division
CIBA-GEIGY Corporation, Ardsley, New York 10502

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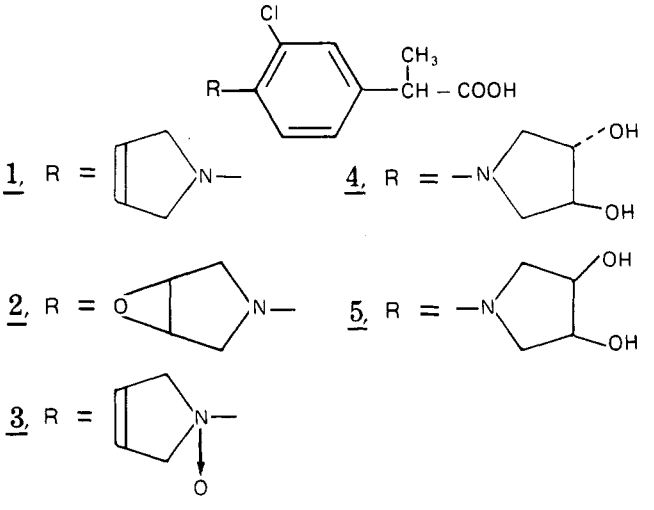
Pirprofen, 2-[3-chloro-4-(3-pyrrolin-1-yl)phenyl]-propionic acid (1, Chart I) is a new antiinflammatory agent.[1-3] Egger et al.[4] studied its in vivo metabolism and isolated several metabolites. One of the metabolites, A, was assigned the epoxide structure 2 and another metabolite, B, a dihydrodiol structure based on ^1H NMR and mass spectral characteristics. We undertook the unequivocal synthesis of these two metabolites to confirm their assigned structures, establish the stereochemistry of B, and also to prepare them on a larger scale for further biological studies. We report in this article that we have now synthesized the epoxide 2 by a novel method and found it to be identical with the isolated metabolite A. We have also synthesized two diols, 4 and 5 by unequivocal methods and found that the *trans*-diol 4 was identical with the metabolite B.

Epoxides are usually prepared by the electrophilic addition of an oxygen atom derived from an organic peracid to an olefinic double bond. The nucleophilic nitrogen of

Chart I



pirprofen posed a problem in the synthesis of the epoxide 2 by this method. Reaction of pirprofen with 1 mol equiv of peroxyacetic, peroxyformic, or 3-chloroperoxybenzoic acid gave a solid (mp 146–48 °C) which analyzed for a monooxide of pirprofen; its ^1H NMR spectrum showed bands due to olefinic protons. We therefore assigned the *N*-oxide structure 3 to this compound based on its ^1H NMR and mass spectral characteristics (Table I). In agreement with the structure 3, the ^1H NMR spectrum of the peracid oxidation product exhibited a peak at 5.97 ppm due to the olefinic protons. The methylene protons adjacent to the *N*-oxide moiety were shifted downfield to 4.97–5.09 ppm compared to the methylene protons of pirprofen, which appeared as a singlet at 4.3 ppm. One of the aromatic protons that is in close proximity to the *N*-oxide moiety was also shifted downfield to 8.5 ppm compared to the corresponding proton of pirprofen, which

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