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An Alternate Synthesis of 2-(4-Isobutylphenyl)-propionic Acid†

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Hydrochloric acid treatment of methyl 3-(4-isobutylphenyl)-3-methylglycidate and methyl 2-hydroxy-3-(4-isobutylphenyl)-3-butenoate, a rearrangement product of the former, in acetic acid gave 3-(4-isobutylphenyl)-3-methylpyruvic acid and 2-(4-isobutylphenyl)-propanal. The same treatment of 2-hydroxy-3-(4-isobutylphenyl)-3-butenoic acid gave 2-(4-isobutylphenyl)-propanal. Both 3-(4-isobutylphenyl)-3-methylpyruvic acid and 2-(4-isobutylphenyl)-propanal were oxidized to 2-(4-isobutylphenyl)-propionic acid.

We described in a previous paper[1] that the treatment of methyl 3-(4-isobutylphenyl)-3-methylglycidate (I) with boron trifluoride in dimethyl sulfoxide gave methyl 2-hydroxy-3-(4-isobutylphenyl)-3-butenoate (II). This paper presents an alternate synthesis of 2-(4-isobutylphenyl)-propionic acid (IV) *via* 2-(4-isobutylphenyl)-propanal (III).

Treatment of II with potassium hydroxide in methanol gave 2-hydroxy-3-(4-isobutylphenyl)-3-butenoic acid (V) in an excellent yield. V is stable at room temperature under an acidic condition, but when V was refluxed with 35% hydrochloric acid in acetic acid, it was easily decarboxylated to 2-(4-isobutylphenyl)-propanal (III), as is shown in formula (A) (Fig. 1).

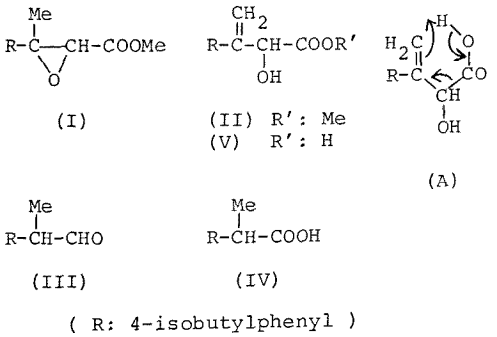
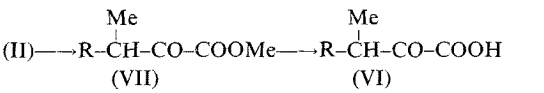


FIG. 1.

Refluxing of II with 35% hydrochloric acid in acetic acid for 1 hr gave III and 3-(4-isobutylphenyl)-3-methylpyruvic acid (VI). The same treatment of VI did not give III, but the unchanged starting material. Ketoester (VII), which was prepared by the previous method,[1] was easily hydrolysed to VI by refluxing with 35% hydrochloric acid in acetic acid. From these facts, it appears that III was formed *via* V, and VI was formed *via* VII which was probably formed by double bond migration of II to α,β-position from β,γ-position before hydrolysis of the ester (Fig. 2).



(R: 4-isobutylphenyl)

FIG. 2.

Dytham[2] reported that III had been obtained by the acid treatment of sodium 3-(4-isobutylphenyl)-3-methylglycidate which had been formed by hydrolysing I with sodium hydroxide in ethanol. The mechanism by which 2-phenylpropanal was formed from sodium β-methyl-β-phenylglycidate was elucidated by Shiner, Jr. and Martin.[3] Usually, hydrolysis of glycidic esters with base before acid treatment is performed in advance to obtain a carbonyl compound from the glycidic esters.[3,4] The direct acid treatment of glycidic esters under drastic conditions had not been reported as far as we know. So, much

† A Synthesis of 2-(Substituted phenyl)-propionic Acid. Part II. See Ref. 1). For the known methods of preparing IV by Nicholson *et al.*, see the Part I of this report.

interest was taken in the results of the direct acid treatment of I, without base hydrolysis. Refluxing of I with 35% hydrochloric acid in acetic acid for 1 hr gave an aldehyde (III) and a ketoacid (VI). Even though the ratio of *cis* to *trans* of I was changed, the ratio of III to VI was almost constant. From this fact, it appears that the stereochemistry of I does not influence the reaction course so much.

Experiments have been carried out to determine the intermediates of the above reaction with intent to elucidate the mechanism of the reaction. Treating of I (*trans* and *cis* mixtures) with 35% hydrochloric acid in acetic acid for 20 min at room temperature gave a diol ester (VIII), a diolester monoacetate (IX), II and chlorohydrin (X) and the starting material disappeared completely (Fig. 3). VIII was

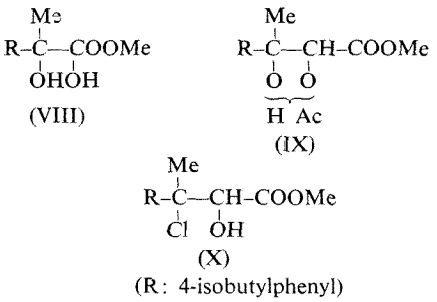


FIG. 3.

identified by comparing its IR and NMR spectra with those of an authentic sample which was prepared by treating I (*trans* and *cis* mixtures) with 10% aqueous sulfuric acid in tetrahydrofuran.[5] The structure of X was determined as follows. X was positive to the Beilstein test. Refluxing of X in pyridine for 30 min gave II and VII. Hydrogenation of X in the presence of palladium on carbon and sodium acetate in acetic acid gave a hydroxy ester (XI) (*erythro* and *threo* mixtures), which was identified by comparing its IR and NMR spectra with those of an authentic sample[1] prepared by hydrogenation of II. From these facts it was concluded that X was α-hydroxy-β-chloro ester (Fig. 4).

The structure of IX was determined as follows. The NMR spectrum of IX exhibited signals at δ 2.03 and 2.10 (3H, two s, -OAc, *erythro* and *threo* mixtures) and 3.3 (1H, broad s, -OH), and its IR spectrum exhibited a characteristic absorption peak at 3500 cm^{-1} (-OH). IX was transesterified in absolute methanol in the presence of sodium methoxide to give VIII. Further, IX was identified by comparing its IR and NMR spectra with those of the compound which was prepared by treating I with acetic acid. From these facts, it was concluded that IX was the monoacetate of VIII.

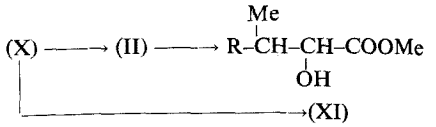


FIG. 4.

Refluxing of VIII, IX, II or X with 35% hydrochloric acid in acetic acid gave III and VI. VIII seems to be converted to III and VI *via* II, VII and *etc.* Also IX seems to be converted to III and VI *via* VIII and *etc.* X is unstable and easily dehydrochlorinated to II, while standing at room temperature. Therefore, X is probably converted to III and VI *via* II. III was oxidised with silver oxide in a aqueous alkaline solution to give 2-(4-isobutylphenyl)-propionic acid (IV).[2] VI was oxidized with hydrogen peroxide in a aqueous alkaline solution to afford IV.[1]

EXPERIMENTAL

All mps and bps were uncorrected. IR spectra refer to Nujol mulls for crystalline samples and films for oils and were determined on a JASCO IRA-1 spectrometer. NMR spectra were recorded at 60 MHz with TMS as an internal standard. GLC analyses were performed on a HITACHI 073 (FID) gas chromatograph.

2-Hydroxy-3-(4-isobutylphenyl)-3-butenoic acid (V)

Methyl 2-hydroxy-3-(4-isobutylphenyl)-3-butenoate (2.8 g) was stirred with KOH (2.0 g) in MeOH (20 ml) for 12 hr at room temperature. MeOH was removed *in vacuo* and water was added to the residue. The insoluble oil was extracted with ether and the resulting aqueous solution was acidified with hydrochloric acid. The product was extracted with ether. The ether extract was washed with water and brine, dried ($MgSO_4$)

and concentrated *in vacuo* to give crude crystals. Recrystallization from benzene-petroleum benzine gave V (1.8 g, 68%). mp 96.0~97.2°C. *Anal.* Found: C, 71.71; H, 7.92. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%. IR $\nu_{max}cm^{-1}$: 3380, 1738, 1300, 1204, 1109, 1071, 932, 720. NMR δ^{CDCl_3}: 0.89 (6H, d, $-C(Me_2)-$), 2.46 (2H, d, $-CH_2-$), 5.06 (1H, s, -CH-CO), 5.45, 5.52 (2H, two s, $H_2C=C$).

2-(4-Isobutylphenyl)-propanal (III)

2-Hydroxy-3-(4-isobutylphenyl)-3-butenoic acid(6.0g) was refluxed with 35% hydrochloric acid (20 ml) in acetic acid (30 ml) for 40 min. The reaction mixture was poured into water and extracted with ether. The ether extract was washed with water, aq.$NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give an oil, which was distilled to afford III (4.4 g, 90%). bp 64~65°C/0.2 mmHg. *Anal.* Found: C, 61.40; H, 5.96; N, 15.42. Calcd. for $C_{19}H_{22}O_4N_4$ (2,4-dinitrophenylhydrazone, mp 117.8~118.8°C): C, 61.61; H, 5.99; N, 15.13%. IR $\nu_{max}cm^{-1}$: 2720, 1721, 1388, 1369, 1021, 844, 798. NMR δ^{CDCl_3}: 0.87 (6H, d, $-C(Me_2)-$), 1.35 (3H, d, -C(Me)-CO), 2.41 (2H, d, $-CH_2-$), 3.48 (1H, m, -CH-CO), 7.14 (4H, s, Ph), 9.60 (1H, d, -CHO).

2-(4-Isobutylphenyl)-propanal (III) and 3-(4-isobutylphenyl)-3-methylpyruvic acid (VI)

Methyl 3-(4-isobutylphenyl)-3-methyl-3-butenoate (8.0 g) was refluxed with 35% hydrochloric acid (12 ml) in acetic acid (28 ml) for 1 hr. The reaction mixture was poured into water and extracted with ether. The ether extract was washed with water, aq. $NaHCO_3$, water and brine, dried ($MgSO_4$), concentrated *in vacuo* and distilled to give III (2.7 g, 44%), bp 62~64°C/0.2 mmHg.

The $NaHCO_3$ extract was acidified with hydrochloric acid and extracted with ether. The ether extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give crude crystals. Recrystallization from petroleum benzine gave VI (0.86 g, 11%), mp 60.6~61.4°C. *Anal.* Found: C, 71.54; H, 7.87. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%. IR ν_{max} cm^{-1}: 1720, 1380, 1261, 1133, 1118, 1023, 991, 938, 860, 724. NMR δ^{CDCl_3}: 0.88 (6H, d, $-C(Me_2)-$), 1.47 (3H, d, -C(Me)-CO), 2.45 (2H, d, $-CH_2-$), 4.67 (1H, q, -CH-CO).

2-(4-Isobutylphenyl)-propanal (III) and 3-(4-isobutylphenyl)-3-methylpyruvic acid (VI)

Methyl 3-(4-isobutylphenyl)-3-methylglycidate (10.0g, *trans*: *cis*=5: 2) was refluxed with 35% hydrochloric acid (15 ml) in acetic acid (35 ml) for 1 hr. The reaction mixture was poured into water and extracted with ether. The ether extract was washed with water, aq.$NaHCO_3$, water and brine, dried ($MgSO_4$), concentrated *in vacuo* and distilled to give III (4.0 g, 52%), bp 62~65°C/0.2 mmHg.

The $NaHCO_3$ extract was acidified with hydrochloric acid and extracted with ether. The ether extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give crude crystals. Recrystallization from petroleum benzine gave VI (1.55 g, 16.4%), mp 60.0~61.4°C.

The same procedure was applied to methyl 3-(4-isobutylphenyl)-3-methylglycidate (10.0 g, *trans*: *cis*= 5: 11). III (3.0 g, 39%) and VI (1.2 g, 13.9%) were obtained.

Methyl 2,3-dihydroxy-3-(4-isobutylphenyl)-butyrate(VIII)

To a stirred solution of methyl 3-(4-isobutylphenyl)-3-methylglycidate (10.0 g, *trans*: *cis*=5: 2) in THF (200 ml), was added 10% aq.H_2SO_4 (30 ml) over 10 min at 10~15°C. The reaction mixture was stirred for 12 hr at room temperature and concentrated *in vacuo* after neutralysing with $NaHCO_3$. The product was extracted with ether. The ether extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*, to give VIII (10.0 g, 94%, *erythro* and *threo* mixtures) as a colorless oil. This product was homogeneous on TLC. TLC: silica gel plate (0.25 mm), benzene-ethyl acetate (5: 1, v/v), *Rf*=0.24, detection by H_2SO_4. IR ν_{max} cm^{-1}: 3470, 1732, 1270, 1215, 1100. NMR δ^{CDCl_3}: 0.90 (6H, d, $-C(Me_2)-$), 1.57, 1.63 (3H, two s, Ph-C(Me)-), 2.43 (2H, d, $-CH_2-$), 3.07~3.37 (2H, m, -OH), 3.47, 3.65 (3H, two s, -COOMe), 4.23, 4.33 (1H, two d, -CH-CO). *Anal.* Found: C, 67.38; H, 8.20. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%.

Methyl 2,3-dihydroxy-3-(4-isobutylphenyl)-butyrate (VIII), methyl 2,3-dihydroxy-3-(4-isobutylphenyl)-butyrate monoacetate (IX), methyl 2-hydroxy-3-(4-isobutylphenyl)-3-butenoate (II) and methyl 3-chloro-2-hydroxy-3-(4-isobutylphenyl)-butyrate (X)

To a stirred solution of methyl 3-(4-isobutylphenyl)-3-methylglycidate (6.8 g, *trans*: *cis*=5: 2) in acetic acid (24 ml), was added 35% hydrochloric acid (10 ml) over 2 min below 20°C. The reaction mixture was stirred for 15 min at room temperature, poured into water and extracted with ether. The ether extract was washed with water, aq.$NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give an oil (7.6 g). This product showed four spots on TLC. TLC: silica gel plate (0.25 mm), benzene-ethyl acetate (5: 1, v/v), *Rf*=0.24, 0.33, 0.42, 0.53, detection by sulfuric acid. This material (7.6 g) was chromatographed over silica gel (Merck, 70 g). Elution with benzene-ethyl acetate (5: 1, v/v) gave X (2.3 g, *erythro* and *threo* mixtures) as a first elution component. IR ν_{max} cm^{-1}: 3480, 1735, 1272, 1210, 1104. NMR δ^{CDCl_3}: 0.90 (6H, d, $-C(Me_2)-$), 2.03, 2.06 (3H, two s, Ph-C(Me)-), 2.48 (2H, d, $-CH_2-$), 3.06 (1H, broad s, -OH), 3.53, 3.65 (3H, two s, -COOMe), 4.43, 4.53 (1H, two s, -CH-CO).

The second elution gave II (0.20 g) as a colorless oil. IR ν_{max} cm^{-1}: 3480, 1740, 1265, 1237, 1133, 1101, 937, 872. NMR δ^{CDCl_3}: 0.88 (6H, d, $-C(Me_2)-$), 2.44 (2H, d, $-CH_2-$), 3.61 (3H, s, –COOMe), 4.94 (1H, s, –CH–CO), 5.38, 5.33 (2H, two s, $H_2C=C$).

The third fraction gave IX (0.20 g, *erythro* and *threo* mixtures) as a colorless oil. IR ν_{max} cm^{-1}: 3500, 1743, 1382, 1242, 1219, 1090, 1062. NMR δ^{CDCl_3}: 0.90 (6H, d, $-C(Me_2)-$), 1.62, 1.63 (3H, two s, Ph–C(Me)–), 2.03, 2.10 (3H, two s, –OAc), 2.45 (2H, d, $-CH_2-$), 3.3 (1H, broad s, –OH), 3.52, 3.62 (3H, two s, –COOMe), 5.10, 5.23 (1H, two s, –CH–CO). *Anal.* Found: C, 66.36; H, 7.60. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85%.

The last fraction gave VIII (2.0 g, *erythro* and *threo* mixtures) as colorless oil.

Methyl 2-hydroxy-3-(4-isobutylphenyl)-3-butenoate (II)

Methyl 3-chloro-2-hydroxy-3-(4-isobutylphenyl)-butyrate (180 mg) was refluxed in dry pyridine (1 ml) for 1 hr. After cooling, the reaction mixture was poured into dil.hydrochloric acid and extracted with ether. The ether extract was washed with dil.hydrochloric acid, water, aq.$NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated *in vacuo*, to give II (138 mg). This product was almost homogeneous on TLC. TLC: silica gel plate (0.25 mm), benzene-ethyl acetate (5: 1, v/v), detection by sulfuric acid. This product contained 7.8% of VII, which was confirmed by GLC analysis. GLC: column; SE–30 (10 wt.%) on Chromosorb w AW, 1 m×0.3 cm, at 200°C. Carrier gas; N_2, 0.8 kg/cm^2. t_R (VII)=2 min 50 sec. t_R (II)=3 min 52 sec.

Methyl 2-hydroxy-3-(4-isobutylphenyl)-butyrate (XI)

Methyl 3-chloro-2-hydroxy-3-(4-isobutylphenyl)-butyrate (286 mg) in acetic acid (20 ml) was reduced by catalytic hydrogenation in the presence of sodium acetate (300 mg) and 10% palladium on carbon (200-mg). The reaction was carried out by stirring the mixture at room temperature for 30 min. After a theoretical amount of hydrogen had been absorbed, the reaction mixture was filtered to remove the catalyst. The filtrate was concentrated *in vacuo* and extracted with ether. The ether extract was washed with water, aq.$NaHCO_3$, water and brine, dried ($MgSO_4$), and concentrated *in vacuo*, to give XI (226 mg, *erythro* and *threo* mixtures) as a colorless oil. This product was negative for Beilstein test and homogeneous on TLC. TLC: silica gel plate (0.25 mm), benzene-ethyl acetate (5: 1, v/v), detection by sulfuric acid. GLC: column; SE–30 (10 wt.%) on Chromosorb w AW, 1 m×0.3 cm, at 200°C. Carrier gas; N_2, 0.8 kg/cm^2. t_R=3 min 20 sec and 3 min 40 sec (two peaks, *threo* and *erythro*). IR ν_{max} cm^{-1}: 3520, 1738, 1270, 1218, 1130, 1042, 850, 805. NMR δ^{CDCl_3}: 0.91 (6H, d, $-C(Me_2)-$), 1.23~1.47 (3H, two d, Ph–C(Me)–), 1.4~2.3 (1H, m, $-CH(Me_2)-$), 2.45 (2H, d, $-CH_2-$), 3.67, 3.71 (3H, two s, –COOMe), 4.30 (1H, m, –CH–CO), 2.9~3.6 (1H, m, Ph–CH–).

Methyl 3-chloro-2-hydroxy-3-(4-isobutylphenyl)-butyrate (X)

Into a stirred solution of methyl 3-(4-isobutylphenyl)-3-methylglycidate (9.1 g) in dry toluene (120 ml) was introduced dry hydrogen chloride gas over 1 hr below 5°C. The reaction mixture was poured into ice-water and extracted with toluene. The toluene extract was washed with water, aq.$NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated *in vacuo*, to give an oil (10.7 g). This product showed two spots on TLC. TLC: silica gel plate (0.25 mm), benzene-ethyl acetate (5: 1, v/v), detection by sulfuric acid. This product (10.7 g) was chromatographed on silica gel (Merk, 100 g). Elution with benzene-ethyl acetate (5: 1, v/v) gave X (4.9 g) as the first elution component.

Methyl 2,3-dihydroxy-3-(4-isobutylphenyl)-butyrate monoacetate (IX)

Methyl 3-(4-isobutylphenyl)-3-methylglycidate (7.0 g, *trans*: *cis*=5: 2) was refluxed with glacial acetic acid (15 ml) in dichloroethane (40 ml) for 4 hr. The reaction mixture was concentrated *in vacuo* and extracted with ether. The ether extract was washed with water, aq.$NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated *in vacuo*, to give an oil (7.8 g). This product showed two spots on TLC. TLC: silica gel plate (0.25 mm), benzene-ethyl acetate (5: 1, v/v), detection by sulfuric acid. This product was chromatographed on silica gel (80 g, Merck). Elution with benzene-ethyl acetate (5: 1, v/v) gave II (0.8 g) as the first elution component and IX (5.8 g) as the second elution component.

Methyl 2,3-dihydroxy-3-(4-isobutylphenyl)-butyrate (VIII)

Methyl 2,3-dihydroxy-3-(4-isobutylphenyl)-butyrate monoacetate (0.6 g) was stirred overnight in abs.MeOH (30 ml) in the presence of NaOMe (60 mg). After neutralysing with acetic acid, the reaction mixture was concentrated *in vacuo* and extracted with ether. The ether extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*, to give VIII (0.4 g) as a colorless oil. This product was homogeneous on TLC. TLC: silica gel plate (0.25 mm), benzene-ethyl acetate (5: 1, v/v), detection by sulfuric acid.

2-(4-Isobutylphenyl)-propanal (III) and 3-(4-isobutylphenyl)-3-methylpyruvic acid (VI)

1) From methyl 2,3-dihydroxy-3-(4-isobutylphenyl)-butyrate (VIII). VIII (10.0 g, *threo* and *erythro* mixtures) was refluxed with 35% hydrochloric acid (15 ml) in acetic acid (35 ml) for 1 hr. After cooling, the reaction mixture was poured into water and ex-

tracted with ether. The ether extract was washed with water five times and the acid portion was extracted with aq.$NaHCO_3$. The resulting ether extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*, to give an oil which was distilled to give III (4.6 g, 64%), bp 62~64°C/0.2 mmHg. The aq. $NaHCO_3$ extract was acidified with hydrochloric acid and extracted with ether. The ether extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*, to give crude crystals. Recrystallization from petroleum benzine gave VI (1.4 g, 14.8%), mp 60.0~61.4°C.

2) From methyl 2,3-dihydroxy-3-(4-isobutylphenyl)-butyrate monoacetate (IX). IX (5.0 g) was refluxed with 35% hydrochloric acid (8 ml) in acetic acid (18 ml) for 1 hr. The reaction mixture was then treated in the same manner as described in *1)*. III (1.5 g, 39%) and VI (0.65 g, 13.7%) were obtained.

3) From methyl 3-chloro-2-hydroxy-3-(4-isobutylphenyl)-butyrate (X). X (4.7 g) was refluxed with 35% hydrochloric acid (7 ml) in acetic acid (17 ml) for 1 hr. The reaction mixture was treated in the same manner as described in *1)*. III (1.5 g, 48%) and VI (0.66 g, 17%) were obtained.

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