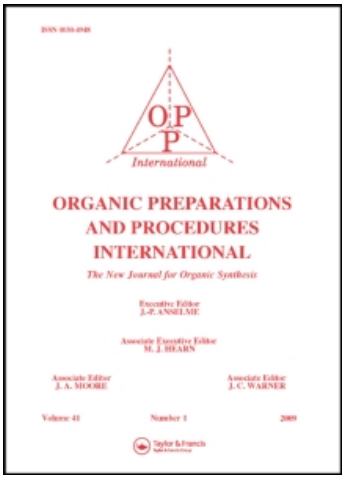

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PREPARATION OF 3-t-BUTYL-1,5-PENTANEDIOIC ACID AND OF 3-t-BUTYL-1,5-PENTANEDIOL DITOSYLATE

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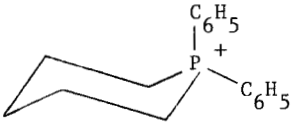
Six-membered heterocyclic systems possessing strategically located *t*-butyl substituents are of current interest with respect to conformational analysis.[1-6] Although a major portion of these investigations have dealt with heterocycles containing two heteroatoms, such as 1,3,2-dioxaphosphorinanes[4a,b] and trimethylene sulfites,[3] the use of the 4-*t*-butyl substituent to impart conformational stability to six-membered heterocycles with only one heteroatom has received scant attention.[5,6] The paucity of information in the latter case could be a result of a lack of synthetic procedures to obtain the desired *t*-butyl-substituted heterocycles.

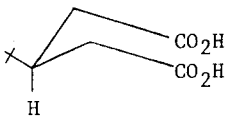
Although numerous methods exist for the introduction of a heteroatom, one major approach has involved an intramolecular cyclization of a 1,5-disubstituted pentane derivative with a selected heteroatom moiety. Two examples of this method have been reported in the preparations of diphenylphosphorinanium tosylate (I)[7] and the thiane 1-oxide (II).[8]



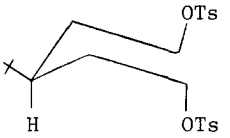
I

II

The introduction of a *t*-butyl substituent at the 4-position of a heterocyclic six-membered ring has usually been limited to the addition of *t*-butylmagnesium halide[9] or *t*-butyllithium[9] to a 4-keto functionality[10] or the conversion of 4-*t*-butylpyridine through a series of reactions to the desired heterocycle.[5a] In order to circumvent this necessity of a 4-keto moiety or the multistep conversion of 4-*t*-butylpyridine to a disubstituted pentane (a number of these steps proceed in yields of 50% or less), we have developed a simple, high-yield reaction sequence from readily available starting materials to prepare 3-*t*-butylpentanedioic acid (III) and subsequently 3-*t*-butyl-1,5-pentanediol ditosylate (IV).



III



IV

The first step in this sequence involved the LAH reduction of diethyl *t*-butylmalonate (V)[11] to 2-*t*-butyl-1,3-propanediol (VI).[2] By an increase in the time of reflux, the yield was raised to 92%. Conversion of the diol to ditosylate VII was also accomplished in high yield (98%) by utilizing an adaptation of the earlier procedure with *p*-toluenesulfonyl chloride in a large excess of pyridine at 0°.[1] This ditosylate VII was a crucial intermediate in the synthetic sequence for its conversion in one step to the dinitrile VIII. The one-step preparation of VIII (87%) involved the addition of VII to an excess of sodium cyanide in dimethylsulfoxide (DMSO) 90-95° for 3 hr. Although the conversion of halides or tosylates with sodium cyanide in DMSO in good yield has been known for some time,[12] its application to the simultaneous preparation of a dinitrile has received only sparse attention.[13]

3-t-BUTYL-1,5-PENTANEDIOIC ACID AND DIOL DITOSYLATE

$$(CH_3)_3CCH(CO_2Et)_2 \xrightarrow[Et_2O]{LAH} (CH_3)_3CCH(CH_2OH)_2 \xrightarrow[Pyridine]{TosCl,\,0^\circ}$$

V VI

$$(CH_3)_2CCH(CH_2OTos)_2 \xrightarrow[DMSO,\ 90\text{-}95^\circ]{NaCN} (CH_3)_3CCH(CH_2CN)_2$$

VII VIII

$$\xrightarrow[\Delta,\ H_2O]{NaOH} (CH_3)_3CCH(CH_2CO_2H)_2 \xrightarrow[H^+,\ \Delta]{EtOH} (CH_3)_3CCH(CH_2CO_2Et)_3$$

III IX

$$\xrightarrow[Et_2O]{LAH} (CH_3)_3CCH(CH_2CH_2OH)_2 \xrightarrow[Pyridine]{TosCl,\ 0^\circ} IV$$

X

Basic hydrolysis of VIII gave the previously unreported 3-*t*-butylpentanedioic acid (III) almost quantitatively. Esterification of III with ethanol afforded the desired diester IX (86%) which was reduced with LAH as previously to give 3-*t*-butyl-1,5-pentanediol (X) in 80% yield. This diol X itself could be utilized, for the intramolecular cyclizations with certain heteroatom moieties,[8] or converted in 69% to give the more reactive ditosylate IV.

With this synthetic sequence, the introduction of a heteroatom *via* intramolecular cyclization to a six-membered ring possessing a *t*-butyl substituent in the 4-position should be greatly facilitated or, at least, offer another approach to this type of heterocycle for future study.

EXPERIMENTAL[14]

2-t-Butyl-1,3-propanediol (VI) was prepared by an adaptation of an earlier literature procedure.[2] A slurry of lithium aluminum hydride (11.4 g, 0.30 mole) in 100 ml of anhydrous ether was treated (dropwise) with diethyl *t*-butylmalonate[11] (49.9 g, 0.23 mole) in 200 ml of ether at

room temperature. After complete addition (1 hr), the mixture was boiled for 5 hr, cooled to room temperature and hydrolyzed cautiously with 100 ml of a 20% NaOH solution. After filtration of the white precipitate, the filtrate layers were separated and the aqueous layer was extracted with ether (2 x 100 ml). The white precipitate was triturated with ether (2 x 100 ml). The combined ethereal extracts were dried ($MgSO_4$) and evaporated using a rotary evaporator; the residual oil was triturated with ligroin (bp 30-60°) whereupon solidification occured. Recrystallization of this solid from ligroin (bp 30-60°) gave 28.0 g (92%) of VI; mp 56-58°, lit.[1] mp 57-58°; IR (KBr) ν (cm^{-1}): 3242 (OH), 2809 and 2659 (CH), 1472, 1399, 1361, 1239, 1184, 1102, 1052, 1012 (CO), 985 and 954; pmr ($DCCl_3$) δ 0.92 (s, 9, $(CH_3)_3C$), 1.44-1.80 (m, 1, *CH*), 3.56-4.08 (m, 6, CH_2, *OH*).

2-t-Butyl-1,3-propanediol ditosylate (VII) was prepared by a modification of an earlier procedure.[1] 2-*t*-Butyl-1,3-propanediol (VI) (28.0 g, 0.21 mole) was dissolved in 100 ml of anhydrous pyridine and cooled to 0° in an ice bath. *p*-Toluenesulfonyl chloride (85.8 g, 0.45 mole) was then added in small portions with shaking. After complete addition, the mixture was stoppered, shaken at 0° for 30 min., and allowed to stand at 0° for 24 hr. The mixture was then warmed to room temperature and poured with stirring into 1 ℓ of ice water. After standing for 12 hr at room temperature, the aqueous solution was decanted from the white precipitate. The solid was dissolved in 200 ml of ether, dried ($MgSO_4$) and solvent was removed on a rotary evaporator to give a white solid. After recrystallization from cyclohexane and then the mixed solvent system hexane:ethyl acetate (4.1), 90.0 g (98%) of VII was obtained, mp 86.5-88.0°, lit.[1] mp 86.5-87.5°; IR (KBr) ν (cm^{-1}): 2908 (CH), 1590 (Ar), 1358, 1194, 1178, 1101, 970, 948, 858, 836, 817, 734, 676 and 668; pmr ($DCCl_3$) δ 0.85 (s, 9, $(CH_3)_3C$); 1.56-1.80 (m, 1, CH), 2.42 (s, 6, CH_3Ar), 3.92-4.62 (m, 4, CH_2), 7.32 (d, J_{HCCH} = 8 Hz, 4, ArH), 7.72 (d, J_{HCCH} = 8 Hz, 4, ArH).

3-t-Butylpentanedinitrile (VIII). 2-*t*-Butyl-1,3-propanediol ditosylate (VII) (90.0 g, 0.21 mole) was added to NaCN (35.0 g, 0.72 mole) in 200 ml of anhydrous dimethyl sulfoxide and the mixture was heated at 90-95° for 3 hr. The orange mixture was cooled to room temperature and extracted with ether (3 x 200 ml). The DMSO layer was diluted with distilled H_2O until the precipitate dissolved. This aqueous solution was also extracted with ether (3 x 200 ml). The combined extracts were dried ($MgSO_4$) and solvent was evaporated to afford an oil. Distillation of this residual oil *in vacuo* gave 26.8 g (87%) of VIII: bp 84-86°/1.0 mm; IR (film) ν (cm^{-1}), 2809 (CH), 2209 (CN), 1469, 1421, 1404, 1376, 1292, 1035, 932, 899; pmr ($DCCl_3$) δ 1.02 (s, 9, $(CH_3)_3C$), 1.78-2.08 (m, 1, CH), 2.52-2.68 (m, 4, CH_2CN).

3-t-Butylpentanedioic acid (III). 3-*t*-Butylpentanedinitrile (VIII) (26.8 g, 0.18 mole) was added to NaOH (20.0 g, 0.50 mole) in 250 ml of distilled H_2O. The solution was gently boiled (5 days) until the evolution of NH_3 ceased (vapors tested with litmus paper). The solution was cooled to room temperature and acidified with 10% H_2SO_4 (to a pH ~4) to give a white precipitate. This precipitate was collected, dried, and recrystallized twice (C_6H_6) to yield 33.8 g (99.7%) of III: mp 146-147.5°; IR (KBr) ν (cm^{-1}), 3550-2350 (broad, OH), 2915 (CH), 1691 (C=O), 1412, 1387, 1315, 1286, 1230, 1175, 1060, 900, 669; pmr ($DCCl_3$) δ 0.95 (s, 9, $(CH_3)_3C$), 1.98-2.80 (m, 5, $CH(CH_2)_2$, 11.34 (s, broad, 2, CO_2H).

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.45; H, 8.51. Found: C, 57.46; H, 8.46.

Diethyl 3-t-Butylpentanedioate (IX). 3-*t*-Butylpentanedioic acid (III) (39.0 g, 0.21 mole) was added to 200 ml of absolute ethanol containing 4 ml of conc. H_2SO_4. The solution was boiled vigorously for 48 hr, cooled at room temperature and poured onto K_2CO_3 (15 g, 0.11 mole). After standing at room temperature (24 hr), this mixture was filtered and solvent was distilled off at atmospheric pressure. Distillation of the residual oil *in vacuo* gave 43.5 g

(86%) or IX: bp 109-110° (2.5 mm); IR (film) ν (cm^{-1}), 2900, 1725 (C=O), 1450, 1370, 1305, 1255, 1195, 1160 (C-O), 1061, and 1935; pmr δ ($DCCl_3$) 0.90 (s, 9, $(CH_3)_3C$), 1.24 (t, J_{HCCH} = 8 Hz, 6, CH_3CH_2), 2.02-2.60 (m, 5, $CH(CH_2)_2$, 4.10 (q, J_{HCCH} = 8 Hz, 4, CH_3CH_2).

Anal. Calcd. for $C_{13}H_{24}O_4$: C, 63.93; H, 9.84. Found: C, 63.85; H, 9.87.

3-t-Butyl-1,5-pentanediol (X). Diethyl 3-*t*-butylpentanedioate (IX) (43.0 g, 0.17 mole) in 200 ml of anhydrous ether was added (dropwise) to a slurry of lithium aluminum hydride (7.6 g, 0.20 mole) in 150 ml of ether (1 hr). The resulting white slurry was stirred at room temperature for 24 hr, treated cautiously with 200 ml of 10% NaOH, and the layers separated. The aqueous solution was extracted with ether (3 x 200 ml). The combined ether extracts were dried ($MgSO_4$) and solvent was distilled at atmospheric pressure. The residual oil was distilled *in vacuo* to afford 22.0 g (80.4%) of X: bp 100° (0.4 mm) and 132° (4.5 mm); IR (film) ν (cm^{-1}), 3308 (OH), 2808 (CH), 1463, 1395, 1363, 1240, 1148, 1094, 1039, (C-O); pmr ($DCCl_3$) δ 0.83 (s, 9, $(CH_3)_3C$), 1.00-1.66 (m, 5, $CH(CH_2)_2$), 3.12-3.50 (m, 4, CH_2OH), 3.84-4.06 (m, 2, OH).

Anal. Calcd. for $C_9H_{20}O_2$: C, 67.45; H, 12.58. Found: C, 67.10; H, 12.86.

3-t-Butyl-1,5-pentanediol ditosylate (IV). 3-*t*-Butyl-1,5-pentanediol (X) (14.3 g, 0.09 mole) dissolved in 100 ml of anhydrous pyridine and cooled to 0° was treated (15 min) with *p*-toluenesulfonyl chloride (34.1 g, 0.18 mole) in small portions (4-5 g). After complete addition, the mixture was stoppered and maintained at 0° for 24 hr. The resultant white slurry was warmed to room temperature and poured into 300 ml of 20% HCl. This mixture was extracted with ether (3 x 300 ml). The ether extracts were washed with 100 ml of 10% $NaHCO_3$ and dried ($MgSO_4$). Removal of the solvent on a rotary evaporator afforded a white solid which was recrystallized from

hexane:ethyl acetate (5:1) to give 29.3 g (69%) of IV; mp 68-70°; IR (KBr) ν (cm^{-1}), 2900, 1584, 1340, 1185, 1167, 1092, 943, 892, 833, 815, 767, and 662; pmr ($DCCl_3$) δ 0.75 (s, 9, $(CH_3)_3C$), 0.84-2.06 (m, 5, $CH(CH_2)_2$), 2.43 (s, 6, CH_3Ar), 3.97 (t, J_{HCCH} = 7 Hz, 4, CH_2O), 7.34 (d, J_{HCCH} = 8 Hz, 4, ArH), 7.78 (d, J_{HCCH} = 8 Hz, 4, ArH).

Anal. Calcd. for $C_{23}H_{32}O_6S_2$: C, 58.97; H, 6.84; S, 13.68. Found: C, 58.94; H, 7.02; S, 13.87.

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10. If only the *t*-butyl group were required, this procedure would necessitate subsequent dehydration of the tertiary alcohol and reduction of the resulting alkene.

11. The diethyl *t*-butylmalonate was prepared by 1,4-addition of methylmagnesium iodide to diethyl isopropylidenemalonate (prepared in 50% yield by the method described by A. C. Cope and E. M. Hancock, *J. Am. Chem. Soc.*, 60, 2644 (1938) in a yield (65%) comparable to that previously reported (64%, G. M. Lampham, K. E. Apt, E. J. Martin, and L. E. Wangen, *J. Org. Chem.*, 32, 3950 (1967)). An improved yield for this 1,4-addition has also been reported with the utilization of cuprous chloride catalysis; see ref. 2.

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