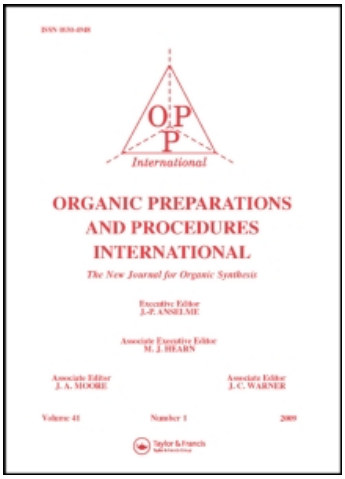

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SYNTHESIS OF 1,1-DIMETHYLINDANE DERIVATIVES HAVING SYNTHETICALLY USEFUL SUBSTITUENTS AT THE 5- AND 6-POSITIONS

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SYNTHESIS OF 1,1-DIMETHYLINDANE DERIVATIVES HAVING SYNTHETICALLY USEFUL SUBSTITUENTS AT THE 5- AND 6-POSITIONS

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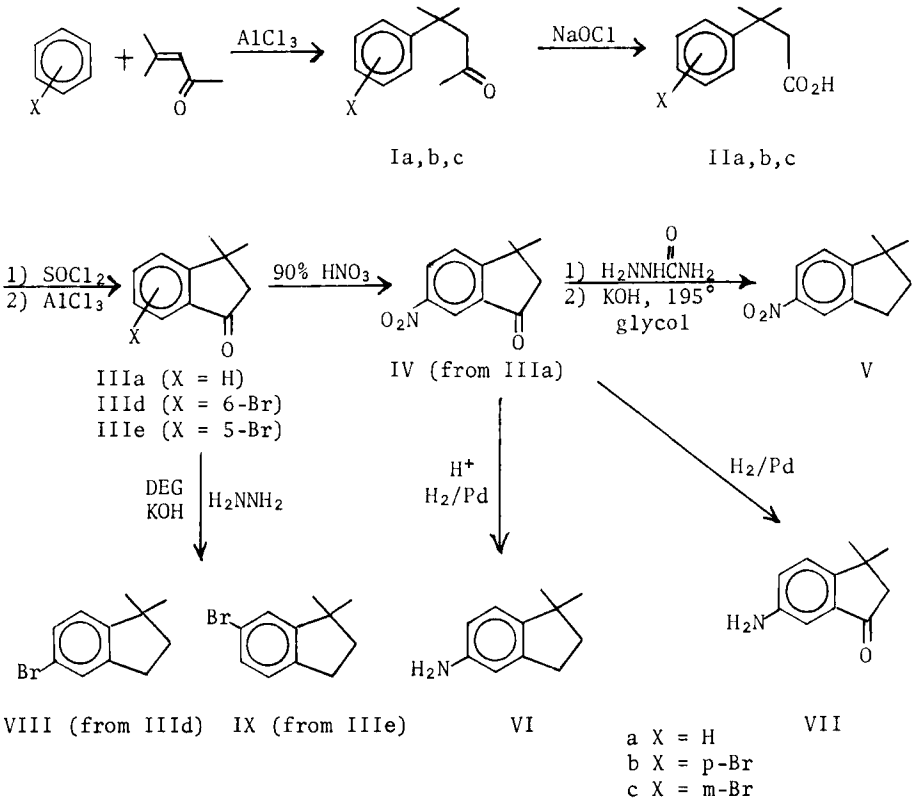
Surprisingly few 1,1-dimethylindanes substituted in the 5-position with a synthetically useful functional group (e.g. -Br, $-NH_2$) are available. This communication describes our preparation of 5-amino-, 5-bromo- and 6-bromo-1,1-dimethylindane (VI, VIII and IX). The most useful compound reported was 5-nitro-1,1-dimethylindane prepared[2,3] as shown in Scheme 1. Hydrogenation of the final nitroindane to 5-amino-1,1-dimethylindane has been described[1]; functional group transformation via the diazonium salt is an obvious means of elaborating the 5-position.

The most serious flaw of this synthesis is the Wolff-Kishner reduction of IV to V which utilized[3] the semicarbazone of IV and provided a low yield (~25%) of V. It was found that IV could be hydrogenated directly to VI under acidic conditions. Under neutral conditions only the nitro group was hydrogenated giving VII. Two other improvements were made in the synthetic sequence. The hypochlorite oxidation was reported[2,3] to be incomplete; the use of hypobromite[4] eliminated this problem. Purification of the crude acid was most conveniently effected by distillation of the acid chloride (75% yield overall). The nitration of IIIa was accompanied by oxidation of IV to the nitro-α,α-dimethylhomophthalic acid. This oxidation presumably proceeded by initial

nitrosation[2] of IV caused by nitrous acid impurities in the nitric acid and was thus autocatalytic. The procedure described in the experimental section minimized this problem.



Scheme 1

In a second approach to the problem, this synthetic sequence commenced with bromobenzene in expectation of obtaining the series Ib, IIb and IIId. Unfortunately, the initially formed alkylation product isomerizes with ease to a 2:1 meta:para mixture. Careful control of the temperature and duration of the alkylation reaction provided usable yields of the para-ketone Ib which was converted to 6-bromo-3,3-dimethyl-

1-indanone, IIId. While the meta-ketone Ic can be separated from the Ib:Ic equilibrium mixture by fractional distillation through a spinning band column, it was more convenient to oxidize the ketone mixture and separate the meta-acid IIc by crystallization. Cyclization of the acid chloride gave a mixture of 5- and 7-bromo-3,3-dimethyl-1-indanone in which the former (IIIe) predominated and was easily separated by crystallization.

Both IIId and IIIe were reduced to the corresponding indanes by a Wolff-Kishner reduction. Hydrogenation and Clemmensen reduction were tried as well; the former reaction failed while the latter produced considerable non-volatile by-products.

EXPERIMENTAL

Melting points were measured in a Mel-temp apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-10 spectrometer and nmr spectra were recorded on a Perkin-Elmer R12 spectrometer in deuterochloroform (unless otherwise specified) with chemical shifts reported in δ units downfield from internal tetramethylsilane. Vapor phase chromatography (vpc) was performed on a Varian 1520 instrument with flame ionization detectors. Column chromatography of the crude products was accomplished on 0.05 - 0.20 mm silica gel (E. Merck). A VG70-77 high resolution mass spectrometer was used to obtain the mass spectral data.

6-Nitro-3,3-dimethyl-1-indanone, (IV). Urea (0.2 g) was added to 40 ml of 90% nitric acid and the solution agitated with an air stream until it became colorless (ca. 20 min). The acid was cooled to -15° and 10 g (0.062 m) of 3,3-dimethyl-1-indanone added dropwise with stirring at such a rate that the temperature did not exceed -10°. After completing the addition, stirring was continued at -10 ± 5° for thirty min. and then the solution was poured onto ice. The solid (11.7 g) was filtered off, washed with water, dried and recrystallized from methanol (100 ml) giving 8.9 g (70%) of IV, mp 130-133°.

If the nitration reaction mixture was allowed to warm to +10° and the reaction time extended an additional 60 min., brown fumes of nitrogen

oxides were evolved and the yield of once recrystallized product fell to 54%. The methanol filtrate was diluted with water, made basic with sodium carbonate and filtered. The filtrate was acidified, and the precipitate (an oily solid) boiled with 200 ml of water and the hot solution filtered through filter cell to remove some insoluble oil. On cooling 2.4 g of 5-nitro-α,α-dimethylhomophthalic acid separated, mp 141-144°d, (and 160-162° on remelting); IR (nujol) 3300 (broad, OH), 1740 and 1700 (C=O), 1530 and 1350 (NO_2), 1240, 1220, 1060 cm^{-1}. Recrystallization from acetic acid containing a few drops of sulfuric acid converted the acid to its anhydride, mp 164-166°, lit.[2] mp 163-165°; IR (nujol) 1800 and 1760 (anhydride), 1530 and 1360 (NO_2), 1260, 1080, 1040, 690 cm^{-1}; nmr 1.70 (s, 6, CH_3), 7.75 (d, 1, J = 8 Hz, H_3), 8.68 (double d, $J_{3,4}$ = 8 Hz, $J_{4,6}$ = 2.5 Hz, 1, H_4), 9.08 (d, 1, J = 2.5 Hz, H_6).

6-Amino-3,3-dimethyl-1-indanone, (VII). 6-Nitro-3,3-dimethyl-1-indanone (IV, 2.0 g) in 100 ml methanol was hydrogenated at 20° and 50 psi over 100 mg of 5% Pd on charcoal for 8 hr. The mixture was filtered, the solvent evaporated whereupon the residue solidified, 1.5 g of VII (87%), mp 75-80°. An analytical sample was obtained by dissolving VII in a small amount of isopropanol, adding 30-60° pet. ether and cooling to 10°, mp 80-82°; IR (CCl_4) 3500 and 3400 (NH_2), 2960, 1710 (C=O), 1630, 1500, 1310 cm^{-1}; nmr 1.38 (s, 6, CH_3), 2.58 (s, 2, CH_2), 3.80 (broad s, 2, NH_2), 6.8-7.4 (m, 3, aromatic H).

5-Amino-1,1-dimethylindane, VI. 6-Nitro-3,3-dimethyl-1-indanone (IV, 2.0 g) was dissolved in 75 ml of glacial acetic acid containing 3 ml of 70% perchloric acid and the solution hydrogenated over 400 mg of 5% Pd on charcoal at 55 psi for 6 hr. After filtering, the filtrate was diluted with 200 ml water containing 4 g of sodium hydroxide. The aqueous solution was extracted three times with benzene, and the benzene extract

washed with water, dil. aqu. sodium carbonate solution, dried and evaporated to give 1.32 g (87%) of VI as a brown oil. Distillation gave 1.15 g, bp 75-76° at 0.2 mm of a pale yellow oil whose spectral properties were identical to those reported[1], (benzamide mp 140-141.5°).

4-(Bromophenyl)-4-methyl-2-pentanone

(a) para isomer, (Ib). A suspension of 101 g (0.8 m) of aluminum chloride in 300 ml of carbon disulfide and 84 ml (0.96 m) of bromobenzene was cooled to 10° in an ice bath and 69 ml (0.64 m) of mesityl oxide added over a 45 min. period so that the temperature did not exceed 15°. After an additional 20 min. stirring, the ice bath was removed and the reaction mixture monitored by vpc using a 6 ft by 1/8 inch column containing 4% OV-101 and 6% OV-210 on 80-100 mesh HP Chromosorb at 130° (relative retention time Ic:Ib = 0.85:1.0). When the content of Ic reached[6] 10% (2-3 hr) of the total alkylation product, the reaction mixture was poured onto ice and conc. HCl, the organic phase separated, washed with water and dil. aqu. sodium bicarbonate, dried and distilled giving 54.1 g (33%) of Ib, bp 102-120° at 0.2 mm, containing 5% of Ic. Redistillation gave Ib , bp 100-104° at 0.2 mm; IR (neat) 2970, 1725 and 1710 (C=O), 1500, 1360, 1005, 820 (para sub.) cm^{-1}; nmr (CCl_4) 1.38 (s, 6, $C(CH_3)_2$), 1.80 (s, 3, $CH_3C=O$), 2.65 (s, 2, $CH_2C=O$), 7.22 and 7.40 (ABq, J = 9 Hz, 4, aromatic H).

(b) meta isomer, (Ic). The above reaction was repeated using 126 g (1.0 m) aluminum chloride, 158 g (1.2 m) bromobenzene in 300 ml of carbon disulfide and 73.6 g (0.8 m) of mesityl oxide. The reacting mixture was allowed to reflux during the addition of mesityl oxide and the mixture was stirred an additional 12 hrs.

The organic product, isolated as in (a), was distilled giving 159 g (78%), bp 100-110° at 0.3 mm which, analyzed by vpc, was found to

be 66% meta- and 35% para-bromoketone. Separation can be effected by careful vacuum fractionation through a spinning band column. Redistillation gave Ic , bp 95-97° at 0.3 mm, 97% Ic by vpc; IR (neat) 2970, 1725 and 1710 (C=O), 1600, 1570, 1480, 1360, 780 and 690 (meta sub.) cm^{-1}; nmr (CCl_4) 1.38 (s, 6, $C(CH_3)_2$), 1.81 (s, 3, $CH_3C=O$), 2.64 (s, 2, $CH_2C=O$), 7.1-7.5 (m, 3, aromatic H).

3-(Bromophenyl)-3-methylbutanoic acid

(a) para, (IIb). The ketone Ib (54.1 g, 0.21 m) was oxidized with sodium hypobromite using the literature procedure[4] to give 56.5 g IIb as a gummy solid. An analytical sample was obtained by repeated recrystallisations from 80-100° pet. ether, mp 67-69°; IR (nujol) 3000 (broad, OH), 1700 (C=O), 1470, 1320, 1000, 820 (para sub.), 710 cm^{-1}; nmr 1.45 (s, 6, CH_3), 1.62 (s, 2, CH_2), 7.23 and 7.43 (ABq, J = 9 Hz, 4, aromatic H), 10.7 (s, 1, CO_2H).

Generally, the crude acid was converted to its acid chloride with thionyl chloride and distilled, bp 103-110° @ 0.2 mm, 44.3 g (73%).

(b) meta, (IIc). The meta/para ketone mixture was oxidized by sodium hypobromite to give a brown gummy solid (125 g from 128 g of the ketone mixture). This solid was stirred with 250 ml of 30-60° pet. ether overnight, after breaking up the lumps manually. The insoluble material was filtered off (86.5 g, mp 74-90°) and recrystallized twice from 200 ml of 80-100° pet. ether to yield 41.2 g (32%) of IIc, mp 102-104°, sufficiently pure for further use. An additional 10 g of less pure IIc can be obtained by concentrating the filtrates from the recrystallisations of half volume.

An analytical sample obtained by two additional recrystallisations from benzene had a mp 105-107°; IR (nujol) 3100 (broad, CO_2H), 1690(C=O), 1470, 1320, 1270, 980, 790 and 690 (meta sub.) cm^{-1}; nmr 1.40 (s, 6,

CH_3), 2.60 (s, 2, CH_2), 7.1-7.5 (m, 4, aromatic H).

The acid chloride was prepared using thionyl chloride and purified by distillation, bp 101-110° at 0.2 mm, 39.3 g (89%).

Bromo-3,3-dimethyl-1-indanone

(a) 6-bromo, (IIId). The acid chloride of IIb (44.4 g, 0.16 m) was added dropwise with stirring to a suspension of 29.6 g (0.22 m) of aluminum chloride in 100 ml of carbon disulfide at such a rate that the solvent refluxed. After addition was complete, the mixture was refluxed for one hr. then stirred at 20° for an additional 6 hr. The reaction mixture was poured onto ice and conc. hydrochloric acid and the hydrolyzed mixture extracted with ether. The ether layer was washed with water, dilute base, dried ($MgSO_4$) and evaporated giving 36.1 g of crude product mp 90-115°. Two recrystallisations from ethanol gave IIId, 22.2 g (60%) mp 115-118° as a yellow solid. An analytical sample was obtained by sublimation at 75° and 0.1 mm (to remove the persistent color) followed by recrystallisation from ethanol, mp 117-119°; IR (nujol) 1710 (C=O), 1470, 1240, 870, 830 cm^{-1}; nmr 1.45 (s, 6, CH_3), 2.61 (s, 2, CH_2), 7.38 (d of d, $J_{4,5}$ = 9 Hz, $J_{4,7}$ = 1 Hz, 1, H_4), 7.70 (d of d, $J_{5,7}$ = 1.8 Hz, 1, H_5), 7.79 (d, 1, H_7).

(b) 5-bromo, IIIe. The same procedure using 19.2 g (0.07 m) 3-(m-bromopheny1)-3-methylbutanoyl chloride gave 16.2 g of crude product mp 93-113° which consisted of 87% IIIe and 13% 7-bromo-3,3-dimethyl-1-indanone (analyzed on a 5 ft by 1/8 inch column containing 3% SE-52 on 80/100 mesh Chromosorb W operated at 115°; relative retention times IIIe:IIId:7-bromo = 1.0:1.07:1.47). One recrystallisation from ethanol gave 10.1 g (61%) of IIIe mp 122-124°. Two additional recrystallisations from ethanol gave an analytical sample mp 123-125°; IR (nujol) 1710 (C=O), 1600, 1580, 1410, 1310, 1285, 1250, 800 cm^{-1}; nmr 1.41 (s, 6,

CH_3), 2.58 (s, 2, CH_2), 7.57 and 7.67 (broad s, 3, aromatic H).

The filtrate from the recrystallisation of IIIe gave an additional 1.0 g of IIIe, mp 118-122°, on concentration to half volume. Complete evaporation of this filtrate gave 5.1 g of a mixture of IIIe (45%) and 7-bromo-3,3-dimethyl-1-indanone (55%). These two isomers can be separated by chromatography on silica gel using benzene as eluant with the 7-bromo isomer eluting first. This minor product was purified by vacuum sublimation and recrystallisation from methanol, mp 108-109°; IR (nujol) 1710 (C=O), 1590, 1465, 1310, 1230, 1030, 785, 735 cm^{-1}; nmr 1.40 (s, 6, CH_3), 2.62 (s, 2, CH_2), 7.45 (broad s, 3, aromatic H).

Bromo-1,1-dimethylindane. The bromo-1,1-dimethylindanes were obtained by Wolff-Kishner reduction (Huang-Minlon procedure[5]) of the corresponding bromo-3,3-dimethyl-1-indanone; 5-bromo-1,1-dimethylindane , VIII, from IIId in 88% yield, bp 65-68° at 0.2 mm; IR (neat) 2950, 1470, 1080, 870, 850, 810, 715 cm^{-1}; nmr 1.22 (s, 6, CH_3), 1.87 (t, J = 7 Hz, 2, CH_2), 2.86 (t, J = 7 Hz, 2, CH_2), 6.97 (d, J = 10 Hz, 1, H_7), 7.1-7.4 (m, 2, H_4 and H_6); 6-bromo-1,1-dimethylindane , IX, from IIIe in 76% yield, bp 62-68° at 0.2 mm; IR (neat) 2950, 1470, 1450, 1440, 1255, 1155, 870, 840, 805 cm^{-1}; nmr 1.26 (s, 6, CH_3), 1.93 (t, J = 7 Hz, 2, CH_2), 2.86 (t, J = 7 Hz, 2, CH_2), 6.9-7.3 (m, 3, aromatic H).

Table 1. Analytical Data for New Compounds

Compound	Analyses Calc. %			Found %			Mass spectral data Calc.	Found
	C	H	Br	C	H	Br		
Ib	56.48	5.94	31.32	56.55	5.90	31.08	254.0306	254.0304
Ic	"	"	"	56.40	5.84	31.11	"	254.0303
IIb	51.37	5.11	31.08	51.47	5.02	31.00	256.0098	256.0100
IIc	"	"	"	51.50	5.15	31.19	"	256.0106
IIId	55.24	4.65	33.42	55.42	4.70	33.29	237.9993	237.9995
IIIe	"	"	"	55.30	4.50	33.33	"	237.9993
*	"	"	"	55.32	4.62	33.45	"	237.9995
VII	75.38	7.49	7.99†	75.40	7.25	8.08†	175.0997	175.1000
VIII	58.67	5.83	35.49	58.75	5.89	35.22	224.0200	224.0203
IX	"	"	"	58.80	5.95	35.30	"	224.0201

* 7-bromo-3,3-dimethyl-1-indanone † %N

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6. This reaction was variable and dependent on the quality of the aluminum chloride. Occasionally, mild exothermic reaction occurred when the temperature reached 20° and rapid isomerization was observed.

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