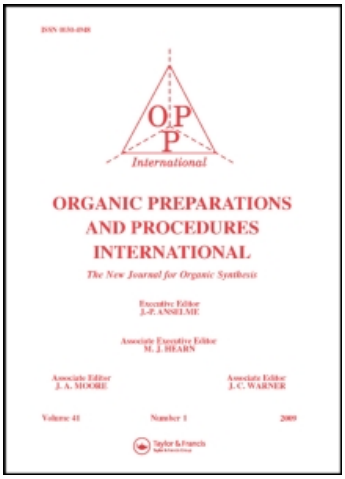

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THE RESOLUTION OF (±)-3-METHYLCYCLOHEXANONE AND (±)-3-tert-BUTYLCYCLOHEXANONE

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THE RESOLUTION OF (±)-3-METHYLCYCLOHEXANONE AND (±)-3-tert-BUTYLCYCLOHEXANONE

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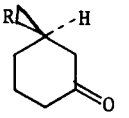
(+)-(3*R*)-Methylcyclohexanone (1) and its derivatives are frequently cited in stereochemical literature and studies based on them are a firm part of the foundation of optical rotatory dispersion, circular dichroism, conformational analysis, and absolute configuration.[2] This is partly due to the ready availability of (+)1 in optically active form from (+)-pulegone.[2f]

(-)-(3*S*)-Methylcyclohexanone (1) and (+)-3-*tert*-butylcyclohexanone (8) or (-)8 are not available except through resolution of the racemic ketones. Resolution of (±)1 has been accomplished through the use of (-)-menthyl N-aminocarbamate [(-)-menthylsemicarbazide],[3] (-)-α-phenethylamine bisulfite,[4] 5-(α-phenethyl)semioxamazide,[5] and 4-(4-carboxyphenyl)-semicarbazide.[6] The recently described resolution method[7a] using iminium salts appears promising. Ketones may also be indirectly resolved as derivatives of the corresponding alcohols,[7b] e.g. 3β-acetoxy-Δ^5-etienic acid proved effective in resolving (±)-*trans*-3-*tert*-butylcyclohexanol to the (+) isomer which was subsequently oxidized to (+)8.[7c]



(+)1, R = CH_3
(+)8, R = $C(CH_3)_3$

We recently required substantial quantities of (-)1 to continue our synthesis of optically active 3-methylcyclopentane-1,2-dicarboxylic acids[8a] and 3-methyl-1-cyclopentene-1,2-dicarboxylic acids[8b] and considered all of the above methods for resolution of (±)1. Each method except the amine bisulfite procedure[4] requires the prior preparation of resolving agent or derivative. The previously used α-phenethylamines[4] were considered too expensive for use and consequently the homolog, (+)-(2*S*)-α-methylphenethylamine (2), was tried instead.[9] An optically active, crystalline, amine bisulfite addition compound, (+)4b, was obtained with (±)1. Three recrystallizations of this compound and regeneration of the ketone gave a 48% yield of (-)1. That resolution was accomplished was shown by comparison of circular dichroism (CD) and optical rotatory dispersion (ORD) data from resolved (-)1 and from (+)1 obtained from (+)-pulegone. In addition, the 2,6-dibenzylidene derivatives of these samples of (-)1 and (+)1 were prepared and their optical activity also showed that resolution of (±)1 had been achieved. The ease of amine bisulfite addition compound preparation and the high yield of resolved ketone, (-)1, prompted us to extend the study to the preparation and investigation of the properties of the amine bisulfite addition compounds from (+)1, (-)1, (±)1, (+)2, (-)2, and (±)2 and to the resolution of (±)8. An illustration of the reaction using (-)1 and (+)2 is given in Scheme I, and some properties and analytical data for the amine bisulfite compounds are listed in Table I.

SCHEME I

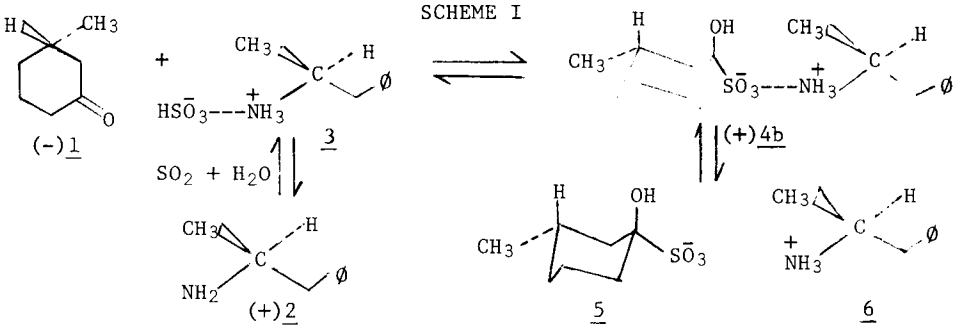


TABLE I

AMINE BISULFITE ADDITION COMPOUNDS OF THE 3-METHYLCYCLOHEXANONES

Compound	Mp, °C (dec)	Found,[a] % C	H	N	[α]D	% Solubility in 95% ethanol 0°	25°	40°
(+)4a[b]	136-138	58.31	8.15	4.42	+12.5°	4.8	9.3	17.4
(-)4a[c]	145-148	58.35	8.19	4.23	-12.1°	0.9	1.7	5.1
(+)4b[d]	146-149	58.56	8.22	4.28	+12.5°	1.0	2.0	5.5
(-)4b[e]	135-137	58.27	8.15	4.39	-13.5°	4.5	8.9	16.2
(±)4[f]	132-135	58.18	8.19	4.38	---	4.4	6.5	11.5

[a]Calcd for $C_{16}H_{27}NO_4S$: C, 58.33; H, 8.26; N, 4.25. Prepared from: [b](+)1 and (+)2; [c](+)1 and (-)2; [d](-)1 and (+)2; [e](-)1 and (-)2; [f](±)1 and (±)2.

The interaction of (±)1 and (+)2 creates a new asymmetric center and hence a pair of diastereoisomers of which a probable structure for the less soluble one, (+)4b, is shown in Scheme I. The solid state infrared spectrum (KBr pellets and hydrocarbon mulls) of the amine bisulfite addition compound (+)4a is the same as that of (-)4b, and the spectra of (-)4a and (+)4b are identical. These spectra show transparency in the carbonyl region (1705 cm^{-1}) and the amine bisulfite region (900 cm^{-1}, but show absorption in the same regions (891, 950, 963, 1022, 1052, 1100, 1273 cm^{-1}) as have been observed for the sodium bisulfite addition complex of (±)1.

The ir spectra of the amine bisulfite addition compounds in solution are distinctly different from the solid state spectra. In time, the individual differences in the spectra of dissolved amine bisulfite addition compounds disappear; this suggests that (+)4b is rapidly dissociating in solution into 5 and 6 as shown in Scheme I. The nmr spectra of the compounds of Table I support this concept since all the spectra in hexadeuterodimethyl sulfoxide are essentially identical. A slower dissociation of

(+)4b to (-)1 and (+)2 also takes place since ORD,[10a] CD,[10a] and uv and ir spectroscopy studies show absorption changes with time which are attributed to a gradual increase in ketone concentration. After a sample has been in dilute solution in 95% ethanol at room temperature for 24 hrs, the dissociation to ketone and amine bisulfite is nearly complete, since the concentration of (-)1 as shown by uv spectroscopy studies levels off at about 80% of the theoretical value.

The foregoing data suggest that the resolution of ketone (±)1 is likely due to the relative stability and solubility of a given amine bisulfite addition compound, e.g. (-)4b as compared to the more soluble (±)4, (+)4a, or (-)4b.

The resolution of (±)8 with (+)2 to (-)8 and (-)2 to (+)8 in 38% yield was straightforward. We have been advised that the method fails with (±)camphor, since an amine bisulfite addition compound could not be isolated.[10b] It has also been reported that α-phenethylamine bisulfite and camphor do not react.[4b] The resolution of (±)2 with (+)1 was attempted but was found to be impractical.

EXPERIMENTAL

Preparation of Amine Bisulfite Addition Compounds.[4a]

a. Compound (+)4a from (+)1 and (+)2.— A 27-g sample of (+)-α-methylphenylethylamine (2) was added to a mixture of 60 ml of 95% ethanol, 50 ml of ether, and 2 ml of water. Sulfur dioxide was bubbled through this solution for about 1.5 hrs until all of the initially formed precipitate had dissolved. (+)-3-Methylcyclohexanone (1) (30 g, 0.27 mole) was added slowly with stirring and cooling (reaction temperature not exceeding 30°). After a few minutes, SO_2 was evolved and the reaction mixture solidified. Two hours later more ether was added, the slurry was filtered, and the crystals were washed with ether to give 60 g (95%) of crude amine

bisulfite compound. A sample twice recrystallized from 95% ethanol at <50° gave (+)4a: mp 136-138° dec; $[\alpha]^{24}D$ +12.5° (*c* 1.85, H_2O); ir (KBr or hydrocarbon mull) 641, 698, 738, 838, 890, 950, 963, 995, 1022, 1052, 1100, 1127, 1156, 1205, 1275, 1290, 1400, 1420, 1445, 1520, 1610, 2945, and 3320 cm^{-1}.

b. Compound (-)4a from (+)1 and (-)2.— The procedure and quantities described above were used to prepare 59.4 g (90.3%) of (-)4a: mp 145-148° dec; $[\alpha]^{25}D$ -12.1° (*c* 1.85, H_2O); ir (KBr or hydrocarbon mull) 641, 703, 745, 844, 892, 902, 954, 968, 996, 1020, 1050, 1065, 1108, 1130, 1163, 1205, 1270, 1372, 1400, 1455, 1520, 1595, 1645, 2950, and 3190 cm^{-1}.

c. Compound (+)4b from (±)1 and (+)2.— The amine bisulfite addition compound (+)4b was obtained by combining 86 g (0.75 mole) of (±)1 with 68.5 g (0.5 mole) of (+)2 in 250 ml of 95% ethanol, 250 ml of ether and 10 ml of water and then fractionally crystallizing the 145 g of salt which formed from 95% ethanol to give 46.5 g (65%) of (+)4b: mp 146-149° dec, $[\alpha]^{24}D$ +12.5° (*c* 1.8, H_2O); ir (KBr) identical to that of (-)4a.

d. Compound (-)4b from (-)1 and (-)2.—This salt, 3 g (85%), was prepared from 1.5 g (-)2 and 2 g (-)1 in 10 ml of 95% ethanol, 10 ml ether and 0.5 ml water: mp 135-137° dec, $[\alpha]^{24}D$ -13.5° (*c* 2.0, H_2O); ir (KBr or hydrocarbon mull) identical to that of (+)4a.

e. Compound (+)4 from (±)1 and (±)2.— This salt, mp 132-135°, was prepared as described under "a".

(-)-(3*S*)-Methylcyclohexanone (1).— The resolved amine bisulfite compound (+)4b (30 g) was decomposed by adding 200 ml of 20% HCl. The solution was extracted 5 times with benzene and the combined benzene layers were dried ($MgSO_4$) and distilled to give 7.4 g (74%) of (-)1: bp 70-71° (20 mm); $[\alpha]^{24}D$ -11.8° (neat) [lit.[2] -11.5°]; ORD (*c* 0.137 g/100 ml, (CH_3OH) $[\alpha]^{25}_{589}$ -7.6°, $[\alpha]_{308}$ -912°, $[\alpha]_{266}$ +1532°; CD $[\theta]_{290}$ (*c* 0.14, CH_3OH) -2069.[10a] A sample of (+)1 prepared from (+)-pulegone[2] showed ORD

(*c* 0.157, CH_3OH) $[\alpha]_{589}^{25}$ +9.6°, $[\alpha]_{308}$ +1000°, $[\alpha]_{266}$ -1410°; CD (*c* 0.157, CH_3OH) $[\theta]_{290}^{25}$ +1912.[10a]

(+)-2,6-Dibenzylidene-(3*S*)-methylcyclohexanone (7).— A 0.56-g sample of (-)1 was converted to (+)7:[2] mp 126-127°, $[\alpha]^{22}\underline{D}$ +41.5° (*c* 3.2, $CHCl_3$); ir (KBr) 693, 771, 794, 939, 995, 1008, 1033, 1075, 1113, 1162, 1270, 1312, 1445, 1485, 1575, 1610, 1660, and 2905 cm^{-1}.

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.50; H, 6.94. Found: C, 87.65; H, 7.05.

A sample of the (-) isomer[2] of 7 was prepared from (+)1 and its mp and ir spectrum were identical with those of (+)7. The optical rotation at 589 nm was equal and opposite in sign.

Resolution of (±)-3-*tert*-Butylcyclohexanone (8).— A 23-g sample of (+)8 was converted to the amine bisulfite compound using 13.7 g of (+)2 as previously described to give 34.6 g (93.3%) of derivative. After 3 recrystallizations from 95% ethanol, there was obtained 7.1 g (38%) of the amine bisulfite salt: 138-142° dec, $[\alpha]^{23}\underline{D}$ 0° (*c* 0.4, H_2O).

Anal. Calcd for $C_{19}H_{33}NO_4S$: C, 61.42; H, 8.95; N, 3.76. Found, C, 61.28; H, 9.02; N, 3.68.

The amine bisulfite salt was decomposed with aqueous hydrochloric acid and the resolved ketone was extracted with benzene, dried ($MgSO_4$) and evaporatively distilled to give (-)8: $[\alpha]^{22}\underline{D}$ -25.2° (*c* 3.1, $CHCl_3$); CD (*c* 0.713, hexane) $[\theta]_{340}$ 0, $[\theta]_{316}$ -1204, $[\theta]_{304}$ -2228, $[\theta]_{296}$ -2488, $[\theta]_{289}$ -2145, $[\theta]_{240}$ 0.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 78.03; H, 11.77.

In a similar manner, (-)2 was used to prepare (+)8: $[\alpha]^{23}\underline{D}$ +27.5° (*c* 0.5, $CHCl_3$) [lit.[7b] $[\alpha]^{24.5}\underline{D}$ +25° (*c* 0.49, $CHCl_3$)]; CD (*c* 0.759, hexane) $[\theta]_{340}$ 0, $[\theta]_{316}$ +1234, $[\theta]_{306}$ +2227, $[\theta]_{296}$ +2442, $[\theta]_{289}$ +2145, $[\theta]_{240}$ 0.

(±)-3-METHYLCYCLOHEXANONE AND (±)-3-*tert*-BUTYLCYCLOHEXANONE

An Attempted Resolution of (±)2 with (±)1.— A 27-g sample of (±)2 was treated with 30 g of (+)1 in 100 ml ether, 100 ml 95% ethanol and 5 ml H_2O in the presence of sulfur dioxide in a manner analogous to the resolution of (±)1 to yield 64 g (97%) of crude amine bisulfite compound. After three recrystallizations from 95% ethanol, a sample was decomposed with HCl and the amine recovered. Optical rotation of this amine indicated a resolution of about 10%.

An alternate procedure to prepare the amine bisulfite addition compound was explored. This procedure involved separate preparation of amine hydrochloride of (-)2 and the sodium bisulfite addition compound of ketone (+)1. These products were combined and found to form the expected amine bisulfite addition compound in essentially the same yield as experienced with the Adams procedure.[7a]

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