3α-Acetoxy-6,6-dimethylbicyclo[3.1.1]heptane-2-spiro-1′-cyclopropane from nopylamine deamination

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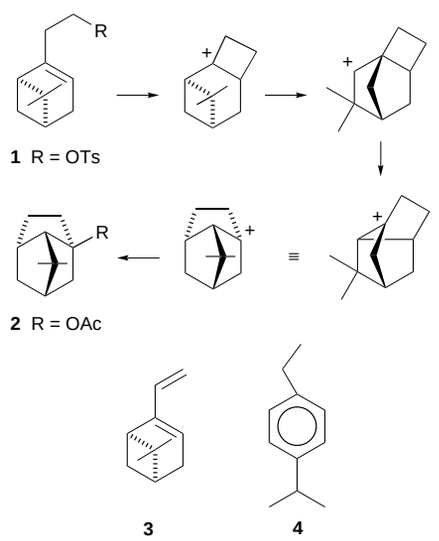
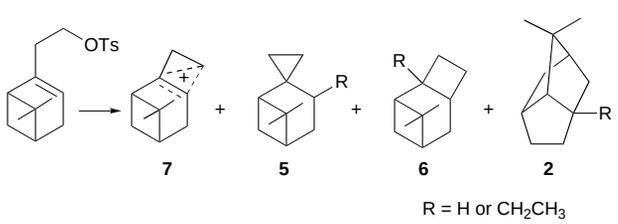
Deamination of nopylamine hydrochloride with sodium nitrite in acetic acid yields nopyl chloride 8, nopyl acetate 1 (R = OAc), 2-(1-acetoxyethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene 9 and 3α-acetoxy-6,6-dimethylbicyclo[3.1.1]heptane-2-spiro-1′-cyclopropane 12. The products are consistent with initial formation of a diazonium ion which reacts by nucleophilic attack, hydride shift or by shift of electrons of the double bond. The reaction is contrasted with the acetolysis of nopyl toluene-*p*-sulfonate, which yields 8,8-dimethyltricyclo[4.2.1.0^{3,7}]nonan-6-ol as the main product. The difference is suggested to result from the transition state being reached early (deamination) or late (toluene-*p*-sulfonate acetolysis) on the reaction coordinate.

Acetolysis[1] of the toluene-*p*-sulfonate ester of nopol {2-(2-hydroxyethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene, **1**, R = OH} yields 91% of the acetate of the tricyclic tertiary alcohol 8,8-dimethyltricyclo[4.2.1.0^{3,7}]nonan-6-ol **2** (R = OH) together with small amounts of the unrearranged diene **3** and 1-ethyl-4-isopropylbenzene **4**. The structure of **2** was eventually determined by an X-ray study[2] of a crystal of the 2-phenylpropionate ester. A probable mechanism[3] of the rearrangement is shown in Scheme 1.



Scheme 1

Formation of **2** (R = H), together with 6,6-dimethylnopinane-2-spiro-1′-cyclopropane **5** (R = H) and 8,8-dimethyltricyclo[5.1.1.0^{2,5}]nonane **6** (R = H) and their ethyl derivatives by treating nopyl toluene-*p*-sulfonate with triethylaluminium has been reported.[4] The authors suggest that all these structures arise from a common intermediate, **7**. The structure **2** is in fact a dimethyl derivative of brendane, first synthesised in 1965 by Nickon *et al*.[5] It is clear that acetolysis of nopyl toluene-*p*-sulfonate and its reaction with triethylaluminium do not proceed along the same pathways, though both are proposed to be carbocation reactions. To investigate this difference, we prepared nopylamine and deaminated it. Deamination provides another route to a carbocation, and proceeds very readily, since formation probably involves lower energy barriers than either of the above reactions.



Results and discussion

Nopylamine was prepared from nopol by conversion of the alcohol into the chloride, thence into the phthalimide, which was reacted with hydrazine hydrate, and then nopylamine was precipitated as its hydrochloride. Deamination of the hydrochloride in acetic acid with sodium nitrite gave a product which GLC examination showed to be a mixture of four major products plus traces (less than 1%) of minor products. Preparative GLC separated two of the products, but the other two were not resolvable on a preparative GLC column. The first two components were readily identified by spectroscopic techniques as nopyl chloride **8** and 2-(1-acetoxyethyl)-6,6-dimethylbicyclo-[3.1.1]hept-2-ene **9**. One component of the mixture had the same retention time as nopyl acetate **1** (R = OAc), and identification was confirmed by measuring the ^{13}C NMR spectrum of the mixture, which contained all the nopyl acetate peaks. The remaining peaks showed that the other component of the mixture was not **2** (R = OAc); it was a saturated secondary alcohol.

In an attempt to improve the yield of the unknown product, reaction conditions were varied,[6,7] as shown in Table 1. The reaction with acetyl nitrite in the presence of sodium acetate appeared promising, but a larger scale reaction produced very little volatile material. The main product of this reaction was the acetylated amine, *N*-nopylacetamide. Investigation showed the amide to be present in all our reaction products. The problem of obtaining a pure sample of the unknown product was solved when an attempted oxidation of nopol with chromic acid was found to oxidise the double bond as well as the hydroxy group.

We then carried out a deamination reaction of nopylamine hydrochloride in acetic acid with sodium nitrite. The products were reduced with lithium aluminium hydride, then oxidised with chromic acid. This should convert our unknown acetate into a secondary alcohol, and thence into a ketone. Isolation of

Table 1 Volatile products of nitrosation of nopylamine and nopylamine hydrochloride in acetic acid

Reagent	Substrate	*T*/°C	Products			
			8	**9**	**12**	**1**, R = OAc
Sodium nitrite	Amine	25	—	17	53	28
Nitric oxide			—	18	51	29
Acetyl nitrite			—	15	50	30
Sodium nitrite		80	—	22	36	36
Nitric oxide		80	—	17	34	30
Acetyl nitrite		80	—	19	38	36
Sodium nitrite	Amine HCl	25	19	14	37	27
Nitric oxide			0	27	45	11
Acetyl nitrite			54	5	14	14
Sodium nitrite + NaOAc*			4	13	61	22
Nitric oxide + NaOAc*			1	14	78	5
Acetyl nitrile + NaOAc*			0	0	95	5

* Sodium acetate was added at the rate of 3 equiv. per equiv. of the amine hydrochloride.

Table 2 ^{1}H Chemical shifts (δ/ppm) of **11** and its 2,4-dinitrophenylhydrazone compared to pinocarvone

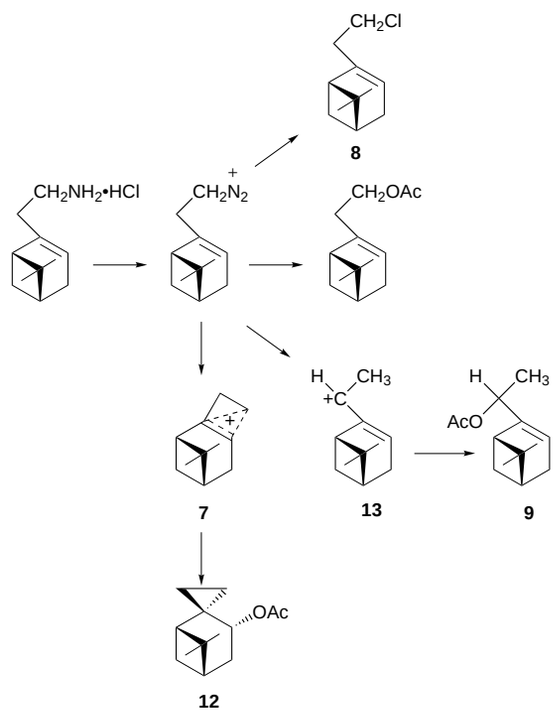
Compound	Solvent	Proton											
		1	4A	4B	5	7A	7B	8Me	9Me	10A	10B	11A	11B
11	$CDCl_3$	1.42	2.61	2.44	2.21	2.61	1.41	1.33	0.97	1.17	0.60	1.39	0.67
11	C_6D_6	1.05	2.48	2.31	1.82	2.38	1.20	1.08	0.78	1.24	0.32	1.44	0.36
DNPH of **11***	$CDCl_3$	1.38	2.78	2.70	2.27	2.57	1.39	1.31	0.99	1.24	0.72	1.40	0.82
DNPH of **11***	C_6D_6	0.94	2.28	2.13	1.68	2.18	1.04	1.09	0.73	1.21	0.48	1.34	0.55
Pinocarvone	$CDCl_3$	2.80	2.69	2.55	2.24	2.72	1.32	1.39	0.83	5.00	5.97	—	—
Pinocarvone	C_6D_6	2.44	2.53	2.34	1.76	2.35	0.98	1.06	0.60	4.67	6.08	—	—

* Aromatic protons are omitted.

Table 3 Proton–proton spin–spin coupling constants (*J*/Hz) for molecules **10** and **11**

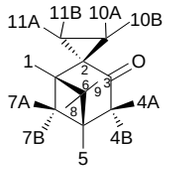
Coupling	**10**	**11**
$J_{1\text{-}5}$	6.0	6.5
$J_{1\text{-}7A}$	6.0	6.8
$J_{4A\text{-}4B}$	19.5	18.9
$J_{4A\text{-}5}$	3.2	2.7
$J_{4B\text{-}5}$	3.2	3.0
$J_{5\text{-}7A}$	5.5	4.3
$J_{7A\text{-}7B}$	10.5	10.3
$J_{4A\text{-}7A}$	2.5	2.7
$J_{10A\text{-}10B}$		3.2
$J_{10B\text{-}11B}$		9.4
$J_{10A\text{-}11A}$		9.3
$J_{10B\text{-}11A}$		6.3
$J_{10A\text{-}11B}$		6.3
$J_{11A\text{-}11B}$		3.0

the modified unknown product was then achieved by chromatography on a silica column using an eluent of 7% ethyl acetate and 93% light petroleum. This yielded the ketone in 96.3% purity, as tested by GLC. The ^{1}H NMR spectrum of the ketone was complex, and probably contained some peaks resulting from impurities. We thus converted the ketone into its 2,4-dinitrophenylhydrazone (DNPH), obtaining an orange solid, mp, 149–151 °C. This yielded a good ^{1}H NMR spectrum. The spectra were assigned by comparison with the published[8] spectrum of pinocarvone **10**, and showed that the unknown ketone was 3-oxo-6,6-dimethylbicyclo[3.1.1]heptane-2-spiro-1′-cyclopropane **11**. Assignments of peaks are listed in Table 2, and coupling constants are listed in Table 3. This leaves only the orientation of the hydroxy group on C-3 in the original unknown compound to assign. Reduction of the ketone with lithium aluminium hydride gave an alcohol which had a different retention time by GLC from the original alcohol; the original hydroxy group must therefore have an α orientation, that is, on the opposite side of the molecule from the *gem*-dimethyl bridge, as shown in **12**. The deamination reaction of nopylamine can be summarised by Scheme 2.

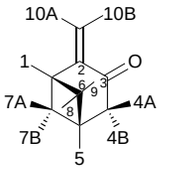


Scheme 2

The deamination of nopylamine would be expected to form the diazonium ion initially, by nitrosation of the amine group and dehydration. Attack of a nucleophile would displace the N_2, which is an excellent leaving group, so attack by Cl^- would give rise to nopyl chloride **8** and attack by acetate ion would give nopyl acetate **1** (R = OAc). Displacement of the diazo group by hydride shift of a hydrogen atom on C-10 would give the carbocation **13**, which could react with acetate ion to give **9**. Displacement of the diazo group by the double bond would give the ion **7**, which should give rise to **12**. A close parallel to the formation of **12** from nopylamine is in the



11



10

formation of 1-(cyclopropyl)ethanol by deamination of pent-3-enylamine.[9]

The interesting question is why the double bond assisting departure of a toluene-*p*-sulfonate group gives rise to a cyclobutyl system (which rapidly rearranges) while the double bond assisting departure of a diazo group gives rise to a spirocyclopropyl system. Hanack and Schneider[10] have shown that both reactions can give both systems; the spirocyclopropyl system is often produced on its own[10,11] but cyclobutyl systems are rarely the sole product, and then usually result from deamination rather than the toluene-*p*-sulfonate acetolysis. We are reluctant to propose a 'low energy' carbocation, and prefer the theory of Kirmse and Voigt,[12] who pointed out that heterolysis of a toluene-*p*-sulfonate to yield a carbocation involves an appreciable change in the geometry of the reactant; in other words, the transition date for the reaction is 'late' on the reaction coordinate. Decomposition of a diazonium ion, on the other hand, involves an excellent leaving group, and therefore passes its transition state early on the reaction coordinate and without significant distortion of the geometry of the substrate. Consequently, deamination can produce carbocations which are bypassed in solvolysis.

Our results provide an excellent illustration of this theory. Nitrogen is a very good leaving group, so deamination proceeds with loss of nitrogen at an early point on the reaction coordinate along the lines suggested in Scheme 2. The toluene-*p*-sulfonate group is an inferior leaving group, and leaves at a much later point on the reaction coordinate, not, in fact, until substantial electron shift has occurred, as a primary alkyl carbocation would be too unstable to be formed. Consequently, shift of the methylene bridge from C-1 to C-2 commences before separation of the leaving group is accomplished. Thus, the pinane cyclobutyl carbocation is not formed; the rearrangement sweeps through to yield the product **2**.

An alternative view of the situation is that nitrogen is a very good leaving group, so is easily displaced by shift of the electrons of the double bond. The toluene-*p*-sulfonate is much more difficult to displace with a nucleophile[1] and the electrons of the double bond are insufficient to accomplish this task until reinforced by the extra electrons supplied by the shift of the methylene bridge from C-1 to C-2.

Removal of the toluene-*p*-sulfonate group by a trialkyl aluminium compound would probably come between these two reactions, and would permit ion **7** to be formed without participation of a methylene bridge shift. Since the reactions took place in benzene or dichloromethane, the ion would probably have sufficient lifetime to equilibrate to yield all possible products, as was observed.

Experimental

NMR spectra were recorded on a Bruker AMX 400 spectrometer, the ^{1}H spectra at 400 MHz and the ^{13}C spectra at 100 MHz. Spectra were recorded in $CDCl_3$ or C_6D_6 with $SiMe_4$ as internal standard. COSY, DFTP and decoupling experiments were used to aid assignment.

Infrared spectra were recorded on a Perkin-Elmer 1320 spectrometer or a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Unless otherwise stated, solid samples were run as a Nujol mull, and liquid samples as neat liquid. Reaction mixtures were analysed on a Dani 3800 gas–liquid chromatograph with a flame ionisation detector using nitrogen as the carrier gas. The instrument used a 25 m capillary column with 0.3 mm internal diameter, coated with OV351 or with FFAP. Preparative separations were carried out on a Perkin-Elmer F21 chromatograph using a glass column of $\frac{1}{4}$ inch internal diameter containing Carbowax 20M coated on a Celite support. Mass spectra were measured on a Fisons Trio 1000 spectrometer, coupled to a Fisons 3800 gas–liquid chromatograph.

Preparation of materials

Samples of nopol and myrtenal were obtained from Aldrich, and were used without further purification.

Nopyl chloride 8

Nopol (49.8 g), triphenylphosphine (86.5 g) and carbon tetrachloride (175 ml) were refluxed together for 1 h.[13] In this time, a white solid precipitated out of solution. The flask was allowed to cool, and the solid filtered off. The solvent was removed to leave a colourless oil (45.7 g, 83%), which was purified by distillation at 59 °C at 0.8 Torr to give nopyl chloride (lit.,[14] bp 56–60 °C at 0.8 Torr), δ_H 0.92 and 1.36 (both 3H, s); ν_{max}/cm^{-1} 3000, 2900, 2810, 1645, 1460, 1440, 1425, 1375, 1360, 1285, 1260, 1235, 1225, 1195, 1175, 1130, 1110, 1090, 1075, 1035, 1020, 950, 900, 880, 800, 785, 770, 730 and 655; δ_C($CDCl_3$) 144.3 (s, C-2), 119.1 (d, C-3), 45.5 (d, C-1), 42.4 (t, C-11), 40.6 (d, C-5), 40.0 (t, C-10), 37.8 (s, C-6), 31.5 (t, C-4), 31.2 (t, C-7), 28.1 (q, C-8) and 21.0 (q, C-9). Assignments of C-4 and C-7 could be reversed.

N-Nopylphthalimide

Nopyl chloride (45 g) was converted into *N*-nopylphthalimide by the method of Cope and Burrows,[14] giving a dark oil (82.5 g), ν_{max}/cm^{-1} 3000, 2900, 2810, 1765, 1700, 1605, 1460, 1440, 1425, 1390, 1350, 1330, 1300, 1260, 1210, 1195, 1180, 1165, 1120, 1090, 1080, 1000, 950, 935, 880, 860, 785, 750, 710 and 655; δ_C($CDCl_3$) 166.2, 133.5, 131.9, 118.6, 144.3 (s, C-2), 122.8 (d, C-3), 45.3 (d, C-1), 40.4 (d, C-5), 37.6 (s, C-6), 36.0 (t, C-11), 35.1 (t, C-10), 31.4 (t, C-4), 31.0 (t, C-7), 25.9 (q, C-8) and 20.7 (q, C-9). Assignments of C-4 and C-7 could be reversed.

Nopylamine 1 (R = NH_2)

This was prepared from *N*-nopylphthalimide by the published route.[14] *N*-Nopylphthalimide (82.5 g) gave a yield of 27.2 g (55%) of nopylamine hydrochloride, mp 231–239 °C; δ_H 0.76 (3H, s), 1.20 (3H, s), 5.3 (1H, br) and 8.18 (3H, br); ν_{max}(KBr disc)/cm^{-1} 2900, 1570, 1465, 1375, 1355, 1255, 1210, 1195, 1135, 1120, 1085, 1070, 1035, 1005, 950, 940, 920, 880, 840, 800, 770, 700 and 600.

2-(1-Acetoxyethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene 9

Myrtenal (7.5 g) in anhydrous diethyl ether (20 ml) was added dropwise to an ethereal solution of methylmagnesium iodide made from magnesium (1.7 g) and methyl iodide (10 g). After refluxing for 1 h, the mixture was poured onto an ice–dilute sulfuric acid mixture, then extracted with diethyl ether. The diethyl ether extracts were washed with water, dried over magnesium sulfate, and the diethyl ether removed to give the alcohol as a yellow oil (7.9 g), ν_{max}/cm^{-1} 3350, 2900, 1460, 1440, 1375, 1360, 1200, 1060, 1040, 1000, 980, 905, 875 and 800. Acetylation with acetyl chloride in pyridine gave the acetate, ν_{max}/cm^{-1} 2980, 2810, 1720, 1440, 1360, 1230, 1035, 1010, 935 and 800.

Deamination with nitrous acid

The amine, or its hydrochloride, was dissolved in dry acetic acid, and to the stirred solution at room temperature was added sodium nitrite over a period of 30 min, and the solution stirred for 2 h. The solution was poured into water and extracted with diethyl ether. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate then water and dried over magnesium sulfate. The volume of solvent was reduced, and the products examined by GLC.

Deamination with acetyl nitrite

Acetyl nitrite was added to a solution of the amine or its hydrochloride in acetic acid,[7] then the products extracted as above.

Deamination with nitric oxide

Nitric oxide was bubbled through a sintered glass bubbler into a solution of the amine or its hydrochloride in acetic acid for a period of 30 min at room temperature, then the products extracted as above.

Analysis of reaction mixture

Two acetates were readily identified by preparative GLC followed by spectroscopic examination. The others were obtained as a mixture; the ^{13}C NMR spectrum was shown to consist of a mixture of nopyl acetate and an unknown product which had ^{13}C peaks at 168.9 (s), 73.5 (d), 50.6 (d), 40.6 (s), 39.8 (d), 34.1 (t), 27.7 (t), 26.3 (q), 25.5 (s), 21.7 (q), 21.2 (q), 16.0 (t) and 9.2 (t). To achieve separation of the unknown product, the acetate mixture was reduced with lithium aluminium hydride, then the alcohols oxidised by the method of Brown and Garg.[15] The chromic acid was prepared by addition of 1.6 g of sodium dichromate dihydrate to 2 ml of concentrated sulfuric acid, and the solution added to 16 ml of water. The solution was added over a period of 5 min to 0.5 g of alcohol mixture while cooling to maintain a temperature of 0 °C. The mixture was left for 2 h, then extracted with diethyl ether, washed, dried and concentrated. Analysis of the product on a silica column gave the ketone **11** with a purity of 96.3% by GLC, the ^{1}H NMR spectrum of **11** is given in Table 1; $\delta_C(CDCl_3)$ 213.0 (s, C-3), 47.8 (d, C-1), 43.9 (t, C-4), 41.2 (s, C-2), 39.7 (d, C-5), 35.3 (s, C-7), 33.4 (t, C-6), 26.7 (q, C-9), 21.6 (q, C-8), 19.7 (t, C-11) and 17.3 (t, C-12). Assignments of C-11 and C-12 could be reversed. *m*/*z* 164 (M^+, 1.3%), 121 (39), 95 (100), 93 (12), 91 (16), 79 (14), 77 (18), 67 (88), 55 (10), 53 (13), 41 (40), 39 (30) and 27 (15).

The ketone was then converted into its 2-4-dinitrophenylhydrazone by conventional methods.[16] Precipitation was slow. The product had mp 149–151 °C after recrystallisation from light petroleum (bp 60–80 °C), ν_{max}(KBr disc)/cm^{-1} 3412, 3307, 3107, 2920, 2851, 2365, 1700, 1619, 1590, 1538, 1518, 1503, 1465, 1417, 1384, 1335, 1310, 1263, 1219, 1137, 1078, 1055, 1029, 1020, 969, 954, 916, 902, 870, 833, 761, 743, 707, 642 and 564 (Found: M, 344.148 78. Calc. for $C_{17}H_{20}N_4O_4$: *M*, 344.148 44); the ^{1}H NMR spectrum is given in Table 1; $\delta_C(C_6D_6)$ 163.1, 144.9, 129.9, 123.6, 116.2, 48.4, 40.3, 38.4, 32.0, 31.9, 29.7, 28.2, 26.1, 21.1, 20.3 and 17.4; *m*/*z* 344 (16%), 163 (10), 162 (59), 160 (10), 147 (15), 146 (17), 134 (11), 133 (12), 132 (12), 121 (41), 120 (45), 119 (100), 118 (88), 117 (27), 107 (14), 106 (25), 105 (26), 103 (13), 95 (12), 94 (28), 93 (30), 92 (16), 91 (62), 80 (13), 79 (36), 78 (16), 77 (42), 75 (11), 69 (35), 67 (26), 65 (23), 63 (14), 55 (30), 53 (19), 43 (16) and 41 (37).

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