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The Beckmann Rearrangement of Some Terpene Ketone Oximes

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For pharmacological purposes some terpenoid oximes have been prepared and transformed into aza-compounds *via* Beckmann rearrangement and subsequent reduction of the resulting lactams.

For comparative pharmacological studies bases containing head to tail arranged isopentane units were needed and we wish to report the preparation of some compounds of this type. The method of choice was to subject suitable terpene oximes to a Beckmann rearrangement and to reduce the resulting lactams to the corresponding secondary amines.

3-Bornanone ("epicamphor") was prepared according to a new method [1] and its oxime (*1*) was rearranged with TsCl in pyridine [2,3] to give a lactam and a product which according to IR and GLC was a complex mixture of unsaturated nitriles.

The latter was not investigated further. The structure of the lactam (*2a*) follows from its non-identity with the known [4] structural isomer *3a* and was corroborated by spectral data. Reduction of *2a* with lithium aluminium hydride gave a crystalline amine (*2b*) in good yield. The hydrochloride of *2b* melted at 214–215°, whereas 288–290° is reported for that of *3b*.[5] The NMR spectrum of *2b* showed only three protons α to the nitrogen atom. The fact that the nitrogen atom is next to the bridgehead indicates that the hydroxyl group of the oxime *1* should be oriented *anti* to the bridgehead at C_4. The amine *2b* was *N*-methylated with formic acid and formaldehyde [6] and further methylated with methyl iodide to the quaternary ammonium salt.

4-Pinanone [7] ("verbanone") was prepared from (−)α-pinene.[8–10] The oxime had an unsharp melting point (64–69°. Lit. 77–78°,[11] 88°[10]). Repeated crystallizations from light petroleum did not improve its purity. The NMR spectrum showed two slightly broadened doublets at 2.86 and 3.28 ppm with J = 11 Hz in a ratio of *ca.* 3:1. These four signals integrate for one proton

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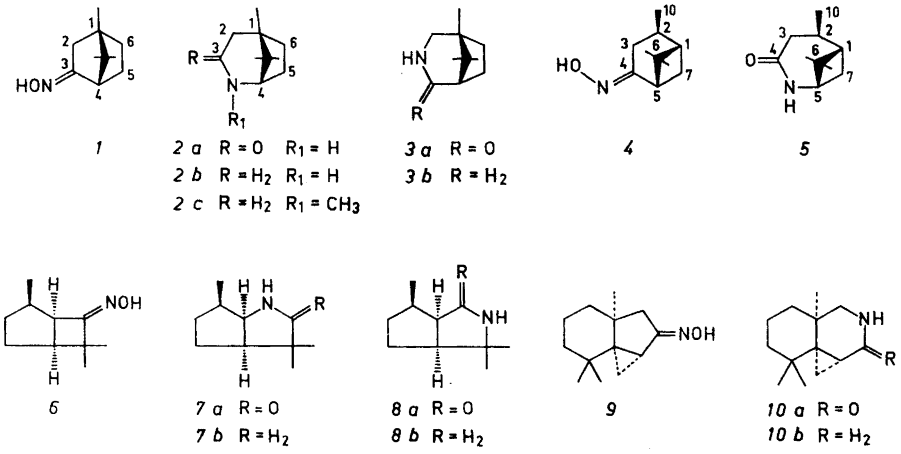

Fig. 1.

only and are interpreted as originating, respectively, from the H_{3e} proton of the *syn*-form (75 %) and the corresponding proton of the *anti*-form (*4*) (25 %). The shift difference between *anti*- and *syn*-forms (0.42 ppm) is in good agreement with previous observations for oxime isomers.[12,13]

The Beckmann rearrangement of the impure 4-pinanone oxime gave a single lactam (*5*) in poor yield. The structure of *5* was established with the help of double resonance techniques (100 MHz-spectrum). A first order analysis of the 1.50—3.20 ppm region is presented in Fig. 2. The magnitude of the coupling constants $J_{H_{3a}\text{-}H_2}$ and $J_{H_{3e}\text{-}H_2}$ together with an inspection of a Dreiding model of *5* strongly suggest the C_{10}-methyl group to be *cis* to the *gem*-dimethyl group. The axial C_3 proton then appears at lower field than the corresponding equatorial proton, a phenomenon which might be explained by a 1—3 diaxial interaction with the nitrogen.

The racemic oxime *6*, prepared from citral,[14,15] was rearranged to give largely nitriles (52 %) but also a lactam (18 %). NMR did not permit unequivocal differentiation between lactam isomers *7a* and *8a*, although a one-proton triplet at 3.90 ppm is more likely to be due to a proton α to nitrogen than α to carbonyl. Reduction of the lactam with lithium aluminium hydride afforded an amine. The mass spectrum of the hydrochloride had a prominent peak at $m/e=110$ (rel. abund. 52 %) representing the loss of C_3H_7, which makes structure *7b* more likely than *8b*.[16] The NMR spectrum of the hydrochloride in D_2O showed a triplet at 0.52 (1H; $J=6$ Hz: CH—N) and a singlet (2H; $N-CH_2$) at 1.61 ppm upfield from the HOD signal, thus establishing the amine and lactam structures as *7b* and *7a*, respectively.

The tricyclic oxime *9*[17] was rearranged in $SOCl_2$/dioxan[18] to the lactam *10a*, which was reduced to the amine *10b*. The structures of these compounds were demonstrated by NMR.

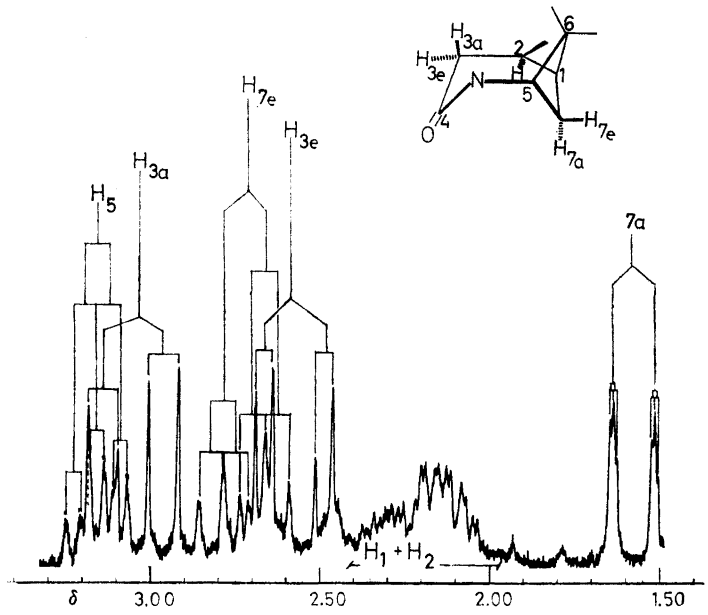

Fig. 2.

EXPERIMENTAL

Melting points are uncorrected. IR spectra: oils neat, solids in KBr. The rotations were taken in chloroform (*c* 1.5 unless otherwise stated). Unless otherwise stated the NMR spectra were recorded on a Varian A-60 instrument (60 Mc/s) in $CDCl_3$ with TMS as internal standard. The chemical shifts are given in δ-units.

(+)*3-Bornanone oxime* (*1*). (−)3-Bornanone,[1] on treatment with $NH_2OH \cdot HCl$ in abs. EtOH-pyridine, gave the *oxime* (*1*), m.p. 103−104°, $[\alpha]_D = +97°$ (C_6H_6). Lit.[19] m.p. 103−104° $[\alpha]_D = +99°$ (C_6H_6).

4-Pinanone oxime (*4*). (−)α-Pinene, $[\alpha]_D^{20} = -44.5°$, was oxidized with $Pb(OAc)_4$ in dry benzene to pin-2-en-4-ol acetate which was hydrolyzed with NaOH in aqueous MeOH to the alcohol,[8] which was further oxidized with $Na_2Cr_2O_7/H_2SO_4$ in a two phase (ether-water) system [9] to the α,β-unsaturated ketone. Catalytic hydrogenation (Pd/C) in methanol [10] afforded 4-pinanone [7] ("verbanone") in 25 % total yield.

B.p.$_{10}$ = 84−86°, $n_D^{23} = 1.4777$, IR ν_{max} cm^{-1}: 1712 (C=O). (Lit.[10] b.p.$_{20}$ 104−105° $n_D^{20} = 1.4752$.) The *oxime* (*4*) had m.p. 64−69°. (Lit.[11,10] m.p. 77−78°, 88°.) $[\alpha]_D = -7.7°$. NMR suggests about 25 % *syn* (*4*) and 75 % *anti* form. (See discussion in the text.).

2,6,6-Trimethylbicyclo[3.2.0]heptan-7-one oxime (*6*). Citral was oxidized with Ag_2O in aqueous alkali [14] to geranic acid, which was further cyclized and hydrogenated according to Beereboom [15] to give the parent racemic ketone from which the *oxime* (*6*) was prepared. M.p. 123−125° (sealed tube). IR ν_{max} cm^{-1}: 3290, 3170 (broad, OH), 1692 (C=N), 922 (N−O). NMR δ: 3.34 (1H, triplet, $J = 7$ Hz, H_1), 2.28 (1H, broadened triplet, $J = 7$ Hz, H_5), 1.35, 1.20 (3H each, singlets, *gem* CH_3), 1.12 (3H, doublet; $J = 6$ Hz; CH_3-C_2). (Found: C 71.8; H 10.2; N 8.4. $C_{10}H_{17}NO$ requires: C 71.8; H 10.2; N 8.4).

1,7,7-Trimethyltricyclo[4.4.0.0^{4,8}]decan-3-one oxime (*9*). The parent ketone was prepared from thujopsene as described by Norin.[17]

The *oxime* had m.p. 106−107°; $[\alpha]_D = -39.2°$ (*c* 2.2); IR (CS_2) ν_{max} cm^{-1}: 3610, 3265 (broad, OH), 1675 (C=N), 960 (N−O); UV λ_{max} (EtOH): 208 nm (ε 8210). NMR δ:

2.90—1.80 (4H multiplets, 3 protons α to C=N, one proton on the cyclopropane ring), 1.18, 1.06 (6H, singlets, *gem* CH_3), 0.90 (1H, multiplet, H on cyclopropane ring), 0.60 (3H doublet, $J_{long-range}=2.5$ Hz; angular CH_3). (Found: C 74.7; H 10.2; N 6.9. $C_{13}H_{21}NO$ requires: C 75.3; H 10.2; N 6.8).

Beckmann rearrangements with *p*-toluenesulfonyl chloride in pyridine

The process is in essence that described by Morita and Suzuki.[3] However, the reaction times and the work-up were slightly different.

"Epicamphorlactam" (2a). *p*-Toluenesulfonyl chloride (6.76 g) in dry pyridine (15 ml) was added dropwise to a stirred solution of 3-bornanone oxime (*1*) (4.48 g) in dry pyridine (10 ml). After 6 h at room temperature the reaction mixture was warmed at 50° for 3 h and after cooling the dark red reaction mixture was poured into 20 ml conc. H_2SO_4 in 150 g ice and stirred for 30 min. The water phase was extracted with hexane (2×50 ml) and chloroform (4×50 ml). The two organic phases were washed with saturated NaCl solution, dried over Na_2SO_4 and the solvents evaporated. The residue from the hexane phase (1.15 g) was chromatographed on alumina and eluted with hexane, which afforded a mixture of nitriles, 0.88 g (22 %). The residue from the chloroform phase, 3.05 g, was recrystallized from hexane-benzene and yielded the *lactam* (*2a*), 1.91 g (43 %). An analytical sample was obtained by sublimation *in vacuo* and had m.p. 232—234° (sealed tube); $[\alpha]_D=+112°$ (*c* 1.8), +119.5° (*c* 10; C_6H_6). IR ν_{max} cm^{-1}: 3190, 3080 (NH), 1665 (C=O), 1550, 1410, 1320, 1308. NMR δ: 3.14 (1H, multiplet; H_4), 2.35 (1H, broadened doublet with $J_{gem}=18$ Hz, $J_{long-range}=1$ Hz; H_{2exo}); 2.12 (1H doublet $J_{gem}=18$ Hz; H_{2endo}), 1.04 (3H singlet, $-CH_3$), 0.94 (6H, CH_3, CH_3). [Found: C 71.9; H 10.2; N 8.4; MS: $m/e=167$ (M^+). $C_{10}H_{17}NO$ requires: C 71.8; H 10.2; N 8.4]. Lit. data [4] for the structural isomer (*3a*); m.p. 227—228°; $[\alpha]_D^{20}=+66.5°$ (*c* 10; C_6H_6).

"Verbanonelactam" (5). The oxime *4* (5.00 g) was rearranged as described above for (*1*), for 5 h at 50°. The acidic water phase was extracted with chloroform (5×100 ml) and the organic phase was washed with saturated bicarbonate solution and saturated NaCl solution, dried and evaporated. The residue, 6.50 g, was chromatographed on SiO_2. Elution with hexane gave 0.40 g of nitriles + unchanged oxime (TLC), and elution with benzene:ether (9:1) gave 1.52 g of essentially pure starting material (TLC). The lactam fraction, a brownish oil (2.79 g), was eluted with EtOAc:MeOH (9:1). The lactam phase was rechromatographed on alumina and ether elution afforded a brownish oil, 1.85 g, which was crystallized from hexane to give the pure *lactam* (*5*), 0.95 g, (27 % based on reacted oxime). An analytical sample was prepared by sublimation *in vacuo*. M.p. 88—90°, $[\alpha]_D=-7.9°$; IR ν_{max} cm^{-1}: 3180, 3200, 3265 (NH), 1650 (C=O), 1415 (CH_2-CO), 1328, 1315, 1160, 1150. NMR (100 Mc/s) δ: 1.09, 1.31 (6H, singlets, *gem* CH_3), 1.14 (3H doublet, $J=7$ Hz, C_2-CH_3), 1.58 (1H doublet of triplets, $J=12$ Hz, $J=1$ Hz, H_{7a}), 1.99—2.41 (2H, multiplets, H_1 and H_3), 2.58 (doublet of doublets, $J=18$ Hz, $J=5$ Hz, H_{3e}), 2.72 (doublet of triplets, $J=12$ Hz, $J=7$ Hz, H_{7e}), 3.03 (doublet of doublets, $J=18$ Hz, $J=9$ H_{3a}), 3.15 (triplet of broadened doublets, $J=7$ Hz, $J=4$, $J=1$ Hz; H_5). [Found: C 71.8; H 10.1; N 8.3; MS: $m/e=167$ (M^+). $C_{10}H_{17}NO$ requires: C 71.8; H 10.2; N 8.4].

4,4,8-Trimethyl-2-azabicyclo[3.3.0]octan-3-one (7a). The oxime (*6*), 2.20 g, was rearranged as described for (*1*), and after heating 30 h at 50°, 20 h at 70°, and 8 h at 100° the reaction mixture was worked up. The chloroform phase afforded 0.17 g of a crystalline residue which was recrystallized from hexane to give the *lactam* (*7a*). The hexane phase, together with the mother liquor from the recrystallization, was chromatographed on SiO_2 and gave a mixture of nitriles, 1.12 g, 52 % (hexane); unreacted oxime (benzene: ether [9:1]) 0.40 g, 18 % (TLC, IR); and lactam (EtOAc:MeOH [9:1]) in a total yield of 0.40 g, 18 %. The lactam was sublimed *in vacuo*. M.p. 127—129° (sealed tube) IR ν_{max} cm^{-1}: 3195, 3085 (NH), 1680 (C=O) 1400, 1325, 1265. NMR δ: 3.90 (1H, broad triplet, $J=6$ Hz; proton α to nitrogen), 2.40 (1H broad triplet, proton at bridgehead C_5), 1.17, 1.08 (6H singlets, *gem* CH_3), 1.00 (3H, doublet, $J=5.5$ Hz; C_8-CH_3). [Found: C 71.8; H 10.3; N 8.4. MS: $m/e=167$ (M^+). $C_{10}H_{17}NO$ requires: C 71.8; H 10.2; N 8.4].

Beckmann rearrangement with thionyl chloride

1,8,8-Trimethyl-3-azatricyclo[5.4.0.0^{5,7}]undecane-4-one (*10a*). Purified thionyl chloride (4 ml) was added dropwise to a stirred solution of the oxime *9* (2.00 g) in dry dioxan [18] (80 ml) at 40°. After stirring for 48 h at room temperature aqueous bicarbonate solution was added to alkaline reaction. The reaction mixture was extracted with ether (3×50 ml), and the organic phase was dried over Na_2SO_4 and evaporated to give a crystalline residue, which was recrystallized from petroleum ether:chloroform to give the *lactam 10a*, 1.49 g (74 %). An analytical sample was obtained by sublimation *in vacuo* and had m.p. 143.5–144.5°; $[\alpha]_D = +11.0°$; IR ν_{max}: 3350, 3190, 3080 (NH), 3020 (cyclopropane CH_2), 1670 (C=O, free), 1630 (C=O ass.), 1497, 1327, 1130, 1095, 1085. NMR δ: 2.91 (2H doublet of doublets $J_{gem} = 13.5$ Hz, $J_{CHNH} = 1.5$ Hz; axial proton α to nitrogen), 2.48 (1H, doublet of doublets which collapses to a doublet on shaking with D_2O, $J_{gem} = 15.5$ Hz, $J_{CHNH} = 6$ Hz; equatorial proton α to nitrogen), 1.12 (6H, singlet *gem*-dimethyl), 0.97 (1H, quartet $J = 10$ Hz, $J = 5$ Hz, a methylene proton on the cyclopropane ring), 0.64 (3H, singlet; angular methyl group). (Found: C 75.2; H 10.2; N 7.1. $C_{13}H_{21}NO$ requires: C 75.3; H 10.2; N 6.8).

Lithium aluminium hydride reduction of the lactams

"Epicamphoramine" (*2b*). A solution of the lactam *2a* (0.016 moles) in 40 ml dioxan was added dropwise under nitrogen to a stirred suspension of 1.22 g (0.032 moles) $LiAlH_4$ in 100 ml dioxan. After 2 h at room temperature the reaction mixture was refluxed for 22 h. After cooling the excess lithium aluminium hydride was decomposed by adding $Na_2SO_4 \cdot 10\ H_2O$ until a white precipitate was formed. To the filtrate was added 3 g oxalic acid and the solvent was largely removed by distillation through a Vigreux column at reduced pressure. The residue was diluted with water (200 ml) and extracted twice with ether (150 ml). After drying over Na_2SO_4 and evaporation, the ether phase gave 0.10 g of neutral compounds consisting mostly of unreacted lactam (TLC). The water phase above was made strongly alkaline with NaOH and extracted with ether (4×50 ml). The combined ether phases were washed with saturated NaCl solution, dried over Na_2SO_4 and evaporated. The residue, 2.36 g, was almost pure *amine* (*2b*). Sublimation at 10 mm Hg and 90° to a cold finger afforded 2.04 g amine (83 %) with m.p. 186–187° (sealed tube), $[\alpha]_D = +40.0°$ (*c* 1.0). No characteristic infrared bands; *v* H–N very weak. NMR δ; 2.71–3.34 (3H, multiplet, protons α to nitrogen), 1.02, 0.85, 0.82 (methyl singlets). MS: $m/e = 153$ (M^+) ($C_{10}H_{19}N$). *Hydrochloride*, m.p. 207–208°; 214–215° (dimorphous) (sealed tube). IR ν_{max} cm^{-1}: 2700–2400, broad (NH_2^+), 1585 (NH_2^+), 1400 ($-CH_2-N^+$). Lit.[4,5] data for the structural isomer *3b:* m.p. 188–190°. Hydrochloride, m.p. 288–290° (decomp.).

4,4,8-Trimethyl-2-azabicyclo[3.3.0]octane (*7b*). $LiAlH_4$ reduction of the lactam *7a* (0.60 g) in dioxan (*vide supra*), and distillation of the crude alkaline fraction gave the *amine* (*7b*), as an oil, 0.50 g (91 %). No characteristic absorptions in IR except NH at 3320 cm^{-1}. *Hydrochloride*, m.p. 193–195° (sealed tube). IR ν_{max}: 2720–2500 (broad, NH_2^+), 1405 (CH_2 α to N^+). NMR δ_{D_2O}: Shifts are given in ppm units upfield from the HOD signal. *c* = *ca.* 5 mg in 25 μl D_2O: 0.52 (1H; triplet $J = 6$ Hz, angular proton α to nitrogen), 1.61 (2H singlet, CH_2 α to nitrogen), 2.27 (1H broadened doublet, $J = 6$ Hz, proton at C_5), 3.54 (3H doublet, $J = 7$ Hz, methyl at C_8): *geminal* methyls as singlets at 3.54, 3.57. (Found: N 7.3. $C_{10}H_{20}ClN$ requires: N 7.4.). MS: $m/e = 153$ (P)($C_{10}H_{20}ClN - HCl$); P+1 = 11.75 %; P+2 = 0.63 %. Calc. for $C_{10}H_{19}N$: P+1 = 11.49 %; P+2 = 0.60 %. $m/e = 110$ ($P - C_3H_7$).

1,8,8-Trimethyl-3-azatricyclo[5.4.0.0^{5,7}]undecane (*10b*). Reduction of the lactam *10a*, 0.68 g (*vide supra*), gave an oil. When distilled *in vacuo* (80°C) the oil afforded white crystals of *10b*, 0.48 g (80 %) m.p. 56–57°; $[\alpha]_D = +28.0°$ (*c* 1.8); IR ν_{max}: 3060 (cyclopropane–CH_2–), 1540, 1410, 1307, 1262. NMR δ: 3.33 (1H doublet of doublets, $J_{gem} = 13.5$ Hz; $J_{vic} = 7.5$ Hz: equatorial proton at C_4), 2.76 (1H, a broadened doublet $J_{gem} = 13.5$ Hz, $J_{vic} = 2$ Hz, C_4 axial proton), 2.06 (2H singlet, C_2 protons), 1.60 broad (NH). Three methyl singlets at 1.02, 0.97, 0.53. Cyclopropane CH_2 at 0.51 (1H, doublet of doublets $J_{gem} = 5$ Hz, $J_{vic,cis} = 10.5$ Hz, *exo* C_6) and 0.21 (1H, triplet $J_{gem} = J_{vic} = 5$

Hz, *endo* C_6). *Hydrochloride:* m.p. 235–238°. *Picrate:* m.p. 201–203°; 226–227.5° (dimorphous). (Found: N 13.0. $C_{19}H_{26}N_4O_7$ requires: N 13.3).

"N-*Methyl-epicamphoramine*" (*2c*). The secondary amine *2b* (0.210 g) was methylated with HCOOH (0.205 g) and HCHO (0.225 g).[6] It was necessary to warm the reaction mixture to 65° to start the evolution of CO_2. Work-up of the reaction mixture gave a brownish oil from which the *tertiary amine* was isolated as the hydrochloride. Recrystallization twice from tetrahydrofuran gave pure *hydrochloride of 2c*, 0.065 g (25 %), m.p. 240–241°; $[\alpha]_D = +42.8°$ (*c* 1.3, D_2O). IR ν_{max} cm^{-1}: 2800–2400 broad (NH^+), 1490, 1402, 1390. NMR δ_{D_2O}(DSS) 3.55–2.86 (3H, multiplet, –CH–N), 2.75 (3H, singlet N–CH_3), 1.11 (3H, singlet, –CH_3), 0.93 (6H singlet, –CH_3, –CH_3). (Found: C 64.1; H 10.8, N 6.7. $C_{11}H_{22}ClN$ requires C 64.8; H 10.9; N 6.9).

The mother liquor from the recrystallization of the *N*-methylamine (*2c*) was evaporated and the residue methylated with CH_3I in diisopropyl ether to give the *quaternary dimethylammonium iodide* which had m.p. 331–333° (sealed tube), $[\alpha]_D = +20.1°$ (*c* 1.0, EtOH). IR ν_{max} cm^{-1}: 2810, 2680, 1400, 1390. (Found: C 46.6; H 7.8; N 4.4. $C_{12}H_{24}IN$ requires C 46.6; H 7.8; N 4.5).

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