A DERIVATIVE OF AZEPINE AND ITS APPLICATION AS A SPECIFIC OPTICAL RESOLUTION AGENT

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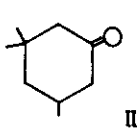
Abstract - The synthesis of (-)-(2S,trans)-perhydro-2-isopropyl-5-methylazepin-1-amine (I) and its use as a specific optical resolution agent of ketones is described. A method for the resolution of ketones and its application to three ketones is described. This method also involves the synthesis and separation of the pairs of hydrazones diastereomers followed by removal of hydrazines by hydrolysis to give the individual enantiomers of II, III and IV with high chiral purities.

Resolution of racemic ketones and aldehydes, although it has the frequent interest in mechanism studies and synthesis, remains a difficult problem. Several approaches to this problem have been suggested, prominent among which are optically active carbonyl reagents such as hydrazines[1], semicarbazides[2], diols[3], dithiols[4], semioxamazides[5], acid hydrazides[6], carbamates[7], aminebisulfites[8], amines[9], and second-order methods such as reduction to the alcohol (which introduces another chiral center) followed by resolution and reoxidation. These methods all suffer from one or more the following difficulties: stringent hydrolysis conditions for regeneration of the carbonyl component which may cause rearrangement or other undesirable reaction, production of a new chiral center and in general, no one of them is of a wide use, being limited our employ to a limited number of substrates.

The selection of the chiral N,N-disubstituted hydrazines as specific optical resolution agents, was made on account of the easy formation of the hydrazone, the major stability of these hydrazines, and the easy recuperation of starting carbonyl compounds.

Resolution of ketones has traditionally been accomplished by crystallization of diastereomeric salts. These derivatives offer potential advantages such as chromatographic separability.

We report here the development of such method involving the synthesis of the hydrazine (I) and the preparation and separation of diastereomeric hydrazones, followed by removal of this hydrazine by hydrolysis. The method is illustrated by the resolution of II, III and IV.



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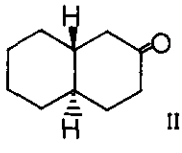

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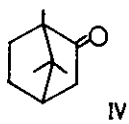
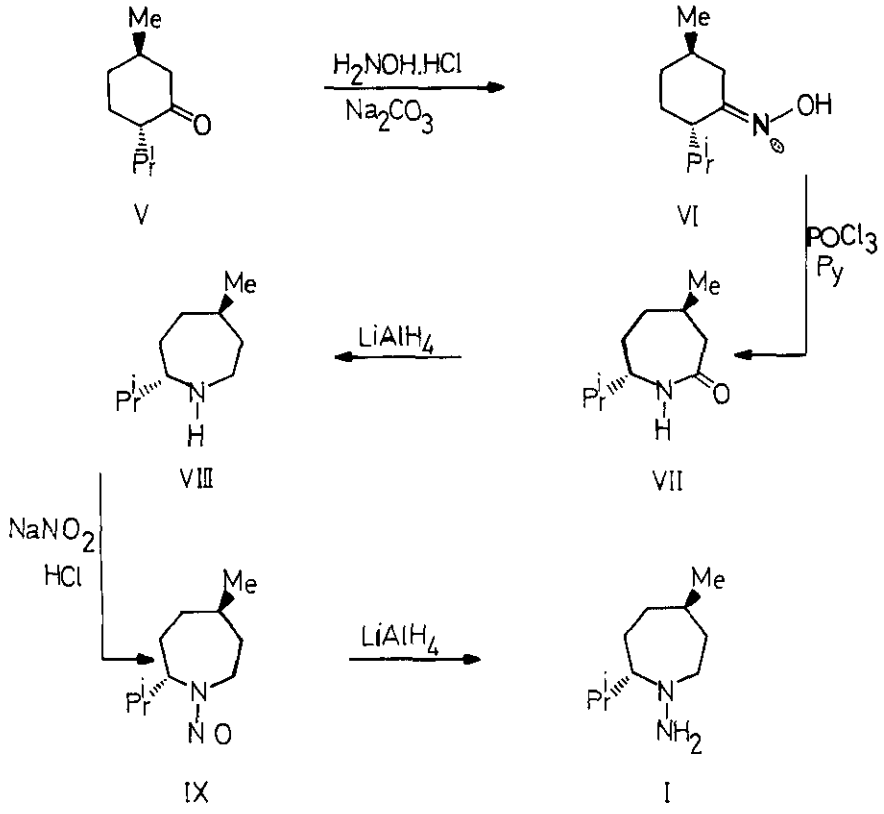


IV

One of these specific agents is the hydrazine derivative of (2S,trans)-perhydro--2-isopropyl-5-methylazepine (VIII). The heterocyclic hydrazine (I) was synthesized according to the reactions of the Scheme I.



Scheme I

(-)-E-Menthone oxime (VI), which was obtained by a conventional method, with a *practically quantitative yield*, by Beckmann rearrangement, using $POCl_3$ as a non--protic acid agent, afforded the lactam (VII) in 93% yield, by means of a highly stereoselective reaction, as expected.

The amine (VIII), which was obtained by reduction wiht LAH of the lactam (VII), afforded the corresponding N-nitrosoamine (IX) by nitrosation in acidic medium. The reduction of N-NO group is very sensitive to the experimental conditions. Because of the hydrogenolysis of the N-N bond, the secondary amine is the major product in the most of cases (LAH ether and LAH/THF in different reaction conditions; $Zn/(NH_4)_2CO_3/NH_3$; Zn/AcOH, Zn/AcOH/Ac_2O; Al(Hg)/ether; $Na_2S_2O_4/OH^-$/EtOH) and only when the reaction is carried out with LAH in ether at 25°C in molar ratio substrate: reagent 1:2, during 17 h, the yield of hydrazine is satisfactory

(79%). On more vigorous treatment (higher temperature and/or higher molar ratio) the N-nitrosamine suffers the reductive cleavage and in mild conditions ($NaBH_4$)/EtOH; $Sx(NH_4)_2$/EtOH-H_2O; H_2/Pd-C) we recuperated the starting N-nitrosamine unchanged.

The hydrazine is a colorless liquid, which may be stored as a salt (hydrochloride, sulfate, pricate and tetrafluoroborate) and as an acetylated derivative. The formation of the corresponding hydrazones was made through two general procedures, according to the facility of their formation. Carbonyl compounds, which react easily, were heated under reflux in benzene of xylene, with the hydrazine catalyzed by p-toluensulfonic acid, during several hours (Procedure A). Because the formation of hydrazone required a long reaction time in some cases, and the ketone reacts only slowly or not at all, we tried another procedure, in order to get a better yield and decrease the reaction time (Procedure B). In this procedure the mixture of ketone and hydrazine is heated with stirring in ethanol with acetic acid and sodium acetate, affording the hydrazone in a short reaction time. But in this case, the acetylated derivative of hydrazine was found, decreasing the yield in hydrazone. The separation of the diastereoisomeric hydrazones was achieved by consecutive column chromatographies, until the values of the optical rotation observed for these were practically constant.

The posterior acidic hydrolysis of separated diastereoisomers led to the corresponding enantiomeric ketones. The optical purity of these compounds, estimated from D-line optical rotations, is in general good, better than 90% (see Table I) being practically quantitative in (+)-3,3,5-trimethylcyclohexanone (II) and in (-)-trans-2-decalone (III).

hydrazone	solvent	reflux time (h)	$\nu_{C=N}(cm^{-1})$	optical purity(%) ketone	(+)	(-)
X	xylene	48	1630	II	96	92
XI	toluene	48	1625	III	93	97
XII	xylene	72	1625	IV	92	90

Table I

EXPERIMENTAL

Melting points were determined in a Reichert microscopy and in a Büchi melting point apparatus in open capillary and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 257 spectrophotometer in potassium bromide pellets. The ^1H-nmr spectra were obtained on a Varian T-60A spectrometer in the solvents as indicated. Chemical shifts are quoted in δ values, using TMS as an internal standart. Mass spectra were recorded on a Varian MAT-711 at 100 ev. Analytical tlc was performed on silica gel plates, using n-hexane/diethyl ether as the eluent. Specific rotations, (α), were determined on a Perkin-Elmer Model 141 polarimeter. Microanalyses were performed by "Centro Nacional de Química Orgánica" de Madrid.

E-(-)-(1R,trans)-3-p-Menthanonoxime (VI). This compound was prepared in 93% yield

according to the reported method[10]; mp 58-59°C (from methanol-water) (lit.[11] mp 57-59°C); bp 85°C (0.1 mmHg), 251°C (760 mmHg); $(\alpha)_D^{23}$-40.3° (c 0.95, EtOH); ir (KBr) (ν, cm^{-1}): 3280 (O-H), 1660 (C=N), 930 (N-O); ^1H nmr (Cl_3CD) (δ, ppm): 8.48 (br s, 1H, =N-OH); ms m/z (relative intensity): 169(M^+,11), 154(17), 137(21); 127(100), 81(26). Anal. Calcd. for $C_{10}H_{19}NO$: C,70.95; H,11.31; N,8.27. Found C, 70.96; H,11.57; N,8.40.

(-)-(4R,trans)-4,5,6,7-Tetrahydro-7-isopropyl-4-methylazepin-2(3H)-one (VII). Procedure a): Compound VII was obtained in 96% yield from VI according to the Schmidt[12] method, using $POCl_3$ in pyridine as a non-protic acid agent of the Beckmann rearrangement which undergoes without geometric isomerization, and with a retention of the configuration as expected. White needles, mp 119-121°C (from water) (lit.[13] mp 118-119°C) bp 295°C (760 mmHg); $(\alpha)_D^{23}$-56.5° (c 1,EtOH); ir (KBr) (ν, cm^{-1}): 3220 (N-H), 1660 (C=O), ^1H nmr (Cl_3CD) (δ, ppm): 5.63 (br s, 1H, -NH-CO), 3.2 (m, 1H, -CH-N<), 2.4 (d, 2H, $-CH_2$-CON-); ms m/z (relative intensity): 169 (M^+, 10), 154(4), 126(100), 81(27), 72(40). Anal. Calcd. for $C_{10}H_{19}NO$: C,70.95; H,11.31; N,8.27. Found: C,70.77; H,11.53; N,8.11. Procedure b): This compound *was also obtained in 21% yield according* to the Eck[14] and Marvel method, using H_2SO_4 as a protic acid agent of this rearrangement which undergoes with geometrical isomerization leading to a mixture of the two isomeric lactams, where lactam VII was the minor compound.

(-)-(2S,trans)-Perhydro-2-isopropyl-5-methylazepine (VIII). To a stirred solution of the lactam (VII) (10.4 g, 61.6 mmole) in 200 ml of dry ether was added a suspension of 5.8 g (153 mmole) of lithium aluminum hydride in 70 ml of dry ether dropwise at a rate to maintain gentle refluxing. The mixture was refluxed for 90 h and the excess hydride destroyed by the dropwise addition of 20 ml of wet ether followed by about 20 ml of water until phase separation occurred. The combined extracts were dried (sodium sulfate), the ether was removed and the residual liquid was distilled, bp 84°C (18 mmHg), yield 79%; $(\alpha)_D^{23}$7.4° (c 0.55, EtOH); ir (film) (ν,cm^{-1}): 3300 (N-H), 2940, 2900, 2860, 1544, 1155 (C-N), 1110; ^1H nmr (CCl_4) (δ ppm): 2.9-2.6 (t not resolute, 2H, $-CH_2$-N<); 2.5-2.1 (m, 1H,-CH-N<), 1.8(s, 1H,>NH, δ: 6.7 in TFA), 1.7-1.1 (m, 8H,$-CH_2$- and -CH<), 1.0-0.8 (3d, 9H, $-CH_3$); ms m/z (relative intensity): 155 (M^+,2), 112(74), 83(22), 79(29), 78(100), 77(91), 76(23).

The hydrochloride of VII, crystallized from ether mp 149°C, $(\alpha)_D^{23}$-0.8° (c 4, MeOH); Anal. Calcd. for $C_{10}H_{22}NCl$: C,62.66; H,11.48; N,7.31; Cl,18.53. Found: C,62.82; H,11.70; N,7.18; Cl,18.58.

The picrate derivate of VIII, prepared in the usual manner, crystallized from benzene as small yellow needles, mp 134°C. Anal. Calcd. for $C_{16}H_{24}N_4O_7$: C,50.00; H,6.25; N,14.58. Found: C,49.76; H,6.59; N,14.47.

(-)-(2S,trans)-Perhydro-2-isopropyl-5-methyl-1-nitrosoazepine(IX). A solution of sodium nitrite (5 g, 72.4 mmole) in 15 ml of water was added, with swirling and protecting the flask with an ice bath, to a solution of the amine (VIII) (4.8 g, 31 mmole) in 12 ml of water. After the addition, concentrated hydrochloric acid (10 ml) and 25 g of ice were added, keeping the mixture swirling for 2 h. After the usual treatment, 4.9 g of a yellow liquid of bp 100°C (0.7 mmHg), pure according to glc, were obtained. Yield 87% $(\alpha)_D^{23}$-120° (c 0.5, EtOH); ir (film) (ν,cm^{-1}):

2960, 2870, 1450 (N=O), 1360, 1340, 1320, 1240, 1210, 1165, 1145, 1100 (N-N), 970 (N-O), 920, 880, 680 (N-NO); ^{1}H nmr (Cl_3CD) (δ,ppm): 4.4 (m, 1H, H-CH-NNO pseudo ecuatorial); 4.3 (m, 1H, Pr^1-CH-NNO pseudo axial), 2.7 (t, 1H, H-CH-NNO pseudo axial); 2.0-1.1 (m, 8H, $-CH_2-$ and -CH<), 1.0-0.6 (3d, 9H, $-CH_3$); ms m/z (relative intensity): 184 (M^+,10), 167(29), 154(6), 141(47), 111(100), 82(48). Anal. Calcd. for $C_{10}H_{20}N_2O_3$: C, 65.21; H,10.86; N,15.21. Found: C,65.02; H,10.97; N,14.85.

(-)-(2S,trans)-Perhydro-2-isopropyl-5-methylazepin-1-amine (I). Lithium aluminum hydride (0.82 g, 21.7 mmole) was stirred for several minutes with sodium-dried ether (45 ml) and a solution of N-nitrosoamine (IX) (2 g, 10.8 mmole) in anhydrous ether (20 ml) was then added dropwise, with stirring, at a rate which was adjusted so as to keep the reaction under control (this reduction often is accompanied by a dangerous induction period). The mixture, monitored by means of analytical glc and tlc, was stirred for 17 h at room temperature. Water (20 ml) was then added very cautiously with vigorous stirring; the solution was filtered to remove the aluminum salts, and the residue was washed with ether. The combined filtrate and washings were dried. Concentration followed by distillation afforded the hydrazine (50°C (0.5 mmHg), 106°C (0.9 mmHg)). Yield 68%, $(\alpha)_D^{23}$ 21.4° (c 5.7, benzene), ir (film) (ν,cm^{-1}): 3210 and 3200 ($-NH_2$), 2960, 2875, 1600, 1460, 1370, 1120, 1100, 990, 940, 890, 850, 790; ^{1}H nmr (CCl_4) (δ,ppm): 3.3 (br s, 2H, >N-NH_2, δ: 5.0 in TFA), 3.1-2.9 (2H, m, $-CH_2-N<$), 2.4-1.0 (m, 9H, $-CH_2-$ and -CH<); 1.0-0.7 (3d, 9H, CH_3), ms m/z (relative intensity): 169(M^+-1, 2), 155(4), 153(11), 112(100), 83(18). Anal. Calcd. for $C_{10}H_{22}N_2$: C, 70.58; H, 12.94; N, 16.47. Found: C, 71.11; H, 13.06; N, 15.74.

The Tetrafluoroborate Derivative: To a solution of tetrafluoroboric acid in water was added, with stirring, the hydrazine dissolved in ethanol. When the addition was complete, stirring was continued for 30 min more. The oily residue solidified on standing for several days. This is a white solid, mp 138°C (fom n-hexane) ir (KBr) (ν,cm^{-1}): 3080, 2980, 2960, 1620 ($-NH_3^+$), 1200-920 (B-F). Anal. Calcd. for $C_{10}H_{23}N_2BF_4$: C,46.54; H,8.92; N,10.86. Found: C,45.96; H,9.02; N,11.02.

Hydrazones (X-XII). General Procedures.

A) This procedure is exemplified by the formation of the hydrazone derivative of II.

3,3,5-Trimethylcyclohexanone Hydrazones (X). A solution of racemic ketone II (1.4 g, 10 mmole), hydrazine I (1.7 g, 10 mmole) and a catalytic amount of p-toluenesulfonic acid in dry xylene (50 ml) was heated under reflux for 48 h. The reaction was monitored by tlc and by ir spectrum. The solvent was removed in vacuo and the residue taken up with 5% hydrochloric acid and ether. The organic extracts were dried over sodium sulfate and the solvent was evaporated to give a crude mixture (2.82 g) of hydrazone diastereomers (ν: 1620 cm^{-1}) and the ketone (ν: 1710 cm^{-1}).

trans-2-Decalone Hydrazones (XI). These were obtained in 78% yield by method A.

B) This procedure is exemplified by the formation of the camphor hydrazones.

Camphor Hydrazones (XII). (±)-Camphor (0.01 mole) and hydrazine I (0.01 mole) were dissolved in just sufficient cold ethanolic solution (prpared by addition of 2 g of sodium acetate and 1 ml of acetic acid to 100 ml of 95% ethanol) for com-

plete solution. The reaction mixture was boiled for 50 h. After usual work-up, the mixture of hydrazone diastereomers (1.52 g, yield 50%) was isolated. These hydrazones were obtained in 69% yield by method A.

Separation of Diastereomeric Hydrazones. General Procedure.

The crude mixture (2.82 g) of hydrazones (X) and ketones (II) were chromatographed on a silica gel column (75 g) eluting first with n-heptane and then with n-heptane-benzene (5-40%). This procedure allowed us to eliminate the unreacted starting materials and a high Rf hydrazone; the fractions containing mixtures of the two diastereomeric hydrazones were combined and chromatographed again on a second silica gel column. It was necessary three chromatographies more in order to isolate significant amount of the two isomers. These consecutive chromatographies afforded 0.61 g of X-a, Rf 0.76(n-heptane-diethyl ether 95.5) and 0.67 g of X-b, Rf 0.62.

trans-2-Decalone Hydrazones (XI): This mixture (1.62 g) was separated affording 0.47 g (XI-a) of a high Rf (0.72) and 0.39 g (XI-b) of a low Rf (0.61) components.

Camphor Hydrazones (XII): The mixtrure (1.52 g) was separated affording 0.31 g (XII-a) of a high Rf (0.69) and 0.45 g (XII-b) of a low Rf (0.59) components.

Hydrolysis of Hydrazones. General Procedure.

The hydrazone X-a (0.61 g) was hydrolyzed boiling with 10% sulfuric acid (2 ml) in 10 ml of water and 10 ml of ethanol until complete solution had taken place, and then for 2 h longer. The solution was then steam-distilled until about 25 ml of liquid had passed over, and the ketone was extracted with three 10 ml portions of ether. The etherea solution was dried, and the solvent was removed yielding (0.20 g, 70%) the 5S enantiomeric ketone. The ketone was purified by distillation (bp 60°C (8mmHg)), the ir spectrum was identical with that of the racemic ketone, $(\alpha)_D^{23}$+25.9° (c 1, $CHCl_3$) (96% optically pure)*. The lower diastereomeric hydrazone (X-b) provided the 5R enantiomer (II-b) (0.23 g, 72% yield), $(\alpha)_D^{23}$-24.8°(c 1, $CHCl_3$) (lit.[16] $(\alpha)_D^{23}$-27.0° (c 0.9, $CHCl_3$)).

trans-2-Decalones (III-a y b). The higher hydrazone diastereomer (XI-a) gave the 9S isomer (III-a) (0.16 g, 71% yield) $(\alpha)_D^{23}$+50.2° (c 0.5, MeOH); while the lower diastereomer provided the 3R enantiomeric ketone (III-b) (0.13 g, 67% yield), $(\alpha)_D^{23}$-48.6° (c 0.85,$CHCl_3$) (lit.[17] $(\alpha)_D^{23}$-50.1° (c 0.85, $CHCl_3$)). Both isomers were oils which were purified by chromatography (SiO_2, CH_2Cl_2).

Camphor (IV-a y b). The higher diastereomer (XII-a) gave the (-)-ketone (IV-a) (0.10 g, 69% yield) mp 170-172°C (ethanol-petroleum ether), $(\alpha)_D^{23}$-39.1° (c 10, EtOH); while the lower diastereomer provided the (+)-camphor (0.15 g, 67% yield), *which was purified by crystallization, mp* 177-178°C (ethanol-petroleum ether), $(\alpha)_D^{23}$+40.0° (c 10, EtOH) (commercial camphor (Fluka AG) $(\alpha)_D^{23}$+43.5° (c 10, EtOH)).

(*) The optical purity was determined by comparision with the reported value.

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