$[\alpha]_D^{25}$ = −9.7°) and *p*-toluene sulfonic acid (75 mg.) were refluxed in benzene (150 ml.) for 24 hours. The water liberated (2.3 ml., 85.2% theory) was collected using a Dean-Stark trap. The benzene solution was cooled, washed with 10% sodium carbonate (50 ml.) and water (2 × 50 ml.), dried ($MgSO_4$), and concentrated to a clear liquid (38.4 grams) which on distillation yielded L-2-octanol (2.8 grams, b.p./2.5 mm. 53–55° C.) and L-2-octyl-DL-mandelate (32.0 grams, 80.7% yield, b.p./1.5 mm. 146–148° C., $[\alpha]_D^{25}$ = −28.5°).

L-2-Octyl-D-mandelate (76.1% yield, b.p./1.5 mm. 150–152° C., m.p. 50–51° C., $[\alpha]_D^{25}$ = −77.2°) and L-2-octyl-L-mandelate (76.1% yield, b.p./0.5 mm. 128–130° C., n_D^{25} 1.4851, $[\alpha]_D^{25}$ = +19.9°) were prepared in the same manner from D-mandelic acid and L-mandelic acid, respectively.

All of the esters gave satisfactory elemental analyses (C, H) and had identical infrared spectra (5% chloroform solutions) with strong bands at 3500 $cm.^{-1}$ (OH) and 1710 $cm.^{-1}$ (C=O).

Separation of Diastereomeric Octyl Mandelates. L-2-Octyl-DL-mandelate was separated into its component diastereoisomers by vapor-phase chromatography using a Barber-Coleman Model 10 gas chromatograph and an 8-foot × ¼-inch column with a liquid phase of 1.5% neopentylglycolsuccinate on Chromosorb W at 160° C. The retention time for L-2-octyl-D-mandelate was 20.2 minutes and that for L-2-octyl-L-mandelate 24.4 minutes. The esters thus obtained were identical to the samples prepared from D- and L-mandelic acid as described above.

Preparation of D(+)-2-Amino-5-phenyl-2-oxazolin-4-one. Sodium (1.15 grams, 0.05 gram atom) was dissolved in ethanol (23 ml.) and the solution added to a solution of guanidine hydrochloride (6.37 grams, 0.67 mole) in ethanol (45 ml.). The mixture was filtered and the filtrate added to a solution of L-2-octyl-D-mandelate (13.2 grams, 0.05 mole) in ethanol (16 ml.). The solution was allowed to stand at 24° C. for 68 hours, and the white crystals, which were deposited, were filtered, washed with ethanol until the washings were no longer basic, and dried at 24° C. and 1 mm. pressure (5.28 grams, 60.0% yield, m.p. 252–255° C., $[\alpha]_D^{23}$ = +138.5°; after two recrystallizations from ethanol m.p. 270–272° C., $[\alpha]_D^{23}$ = +163°). The combined filtrate and ethanol washings were concentrated, the residue was distilled, and L-2-octanol was recovered (5.51 grams, 85% recovery, b.p./1.5 mm. 49–51° C., $[\alpha]_D^{25}$ = −9.7°).

In the same manner, L-2-octyl-L-mandelate yielded L(−)-2-amino-5-phenyl-2-oxazolin-4-one (59.2% yield, m.p. 252–255° C., $[\alpha]_D^{25}$ = −142.2°, after two recrystallizations from ethanol m.p. 270–272° C., $[\alpha]_D^{25}$ = −163°). In this case, an 88% recovery of L-2-octanol was obtained.

Satisfactory elemental analyses (C, H, N) were obtained for both enantiomers and their infrared spectra were identical and as previously described (*5*).

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New Route to Isogranatanine Derivatives

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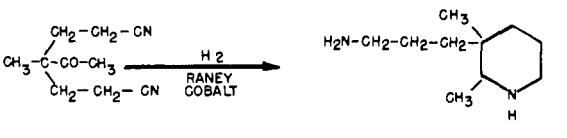
In the first step, 3,3-bis-(β-cyanoethyl)-butanone-2, the adduct of 2 moles of acrylonitrile to 1 mole of methyl ethyl ketone, is reduced in the presence of ammonia and Raney cobalt to 3-(γ-aminopropyl)-2,3-dimethylpiperidine giving a yield of 87 mole%. This piperidine compound is then cyclized over Houdry kaolin cracking catalyst at 370° C. yielding 5,9-dimethyl-1-azabicyclo(3.3.1)nonane (5,9-dimethyl-1-isogranatanine) and the corresponding nonene. Mass, NMR, and infrared spectra were used to elucidate the structure of the intermediate and the products.

THE first synthesis of a derivative of 1-isogranatanine [1-azabicyclo(3.3.1)nonane] was reported by McElvain and Adams (*10*) in 1923. This and most of the other routes to these bicyclic compounds are multistep procedures or involve difficultly accessible intermediates (*3, 5-7, 9, 11*). A simpler procedure was reported by Badger, Cook, and Walker (*3*) in which 5-phenyl-1-azabicyclo(3.3.1)nonane was prepared by reduction of a trinitrile or a diester nitrile with a copper chromite catalyst.

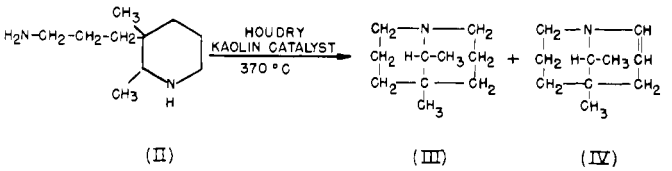
The authors report another simple procedure that led not only to a saturated 1-isogranatanine [a 1-azabicyclo-(3.3.1)nonane] but also unexpectedly to an unsaturated 1-isogranatanine [a 1-azabicyclo(3.3.1)non-2-ene].

In the first stage of the process, a Michael additional product, γ-acetyl-γ-methyl-pimelonitrile, (I), was reduced to 3-(γ-aminopropyl)-2,3-dimethylpiperidine, (II), in a yield of 87 mole %.



(I) (II)

In the second stage, compound (II) was cyclized by passing over Houdry kaolin cracking catalyst.



(II) (III) (IV)

Two major products were obtained, one with a mass of 153 in 10.6 mole % yield (III) and another with a mass of 151 in a molar yield of 26.6% (IV). The mass spectra suggested that two products had the same skeletal structure, differing only by the presence of two more hydrogens in (III) than in (IV). Compounds (III) and (IV) could not be separated by distillation but were isolated in high purity by gas chromatography. A large number of other products (over 30) were also obtained in this reaction.

The carbon, hydrogen, and nitrogen analyses for compounds (III) and (IV) as well as the neutralization equivalents supported the structures shown for these compounds. The infrared spectrum of compound (IV) indicated it to have a cis-double bond with absorption bands at 3028, 1640, and 682 cm.$^{-1}$. These bands were absent in the infrared spectrum of the saturated compound.

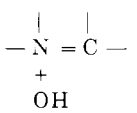
NMR substantiated the assigned structures (III) and (IV) and indicated the α,β-unsaturation of compound (IV).

As the first step in the cyclization mechanism leading to the isogranatanine (III), the authors propose the protonation of the primary amine group of the aminopropylpiperidine (II) on the surface of the acidic cracking catalyst. This step is then followed by an attack of the secondary amine group, resulting in the release of ammonia and in the formation of the bicyclic amine (III) adsorbed on the catalyst in its protonated form. Desorption of (III) completes the cycle and regenerates the catalyst.

The formation of the unsaturated cyclization product (IV) is the consequence of the definite dehydrogenation activity of cracking catalyst observed in the interaction of cycloparaffins with this type of catalyst (*8*).

Compound (III) is more basic than (IV) (pK_a values in Table I), contrary to the usual observation that α,β-unsaturated tertiary amines are more basic than the corresponding saturated amines.

Adams and Mahan (*1*) have accounted for the increased basicity of vinyl tertiary amines by suggesting that these amines in aqueous solution are in equilibrium with a quaternary ammonium hydroxide having the following structure:



The unsaturated amine (IV) cannot form a similar quaternary hydroxide since the latter would have a double bond at a bridgehead nitrogen.

Table I. Elemental Analyses and Neutralization Equivalents of Compounds (III) and (IV)

	(III)	($C_{10}H_{19}N$)	(IV)	($C_{10}H_{17}N$)
	Found	Calcd.	Found	Calcd.
C, %	77.86	78.4	79.22	79.40
H, %	12.33	12.4	11.22	11.33
N, %	9.09	9.15	9.13	9.26
Neut. equiv.	166	153	154	151
pK_a (1 acetone: 1 water	10.09		7.63	
pK_a (water)			8.74	

EXPERIMENTAL

NMR spectra were measured on a Varian Associates Model A-60A instrument, and the chemical shifts are reported in parts per million (δ values) downfield from tetramethylsilane. Infrared spectra were obtained with a Perkin-Elmer Infracord Model 137. Mass spectra were obtained on a Consolidated Electrodynamics Corp. Model MS 21-103. Melting points were taken on a Fisher-Johns melting point apparatus.

3-(γ-Aminopropyl)-2,3-dimethylpiperidine (II). REDUCTION WITH RANEY COBALT. γ-Acetyl-γ-methylpimelonitrile (*4*) (17.8 grams) was hydrogenated with approximately 2 grams of Raney cobalt in 80 cc. of ethanol in the presence of 27.2 cc. of liquid ammonia and 0.28 gram of ammonium chloride at 2200 p.s.i.g. hydrogen pressure and 125° C. for 3 hours in a 300-ml. autoclave. The catalyst was filtered off and the solvent removed on a rotary evaporator leaving a liquid residue of 17.5 grams. This liquid was transferred to a distillation flask and distilled under reduced pressure. The first cut (2.06 grams) boiled at 90° C./4 mm. and a second cut (12.41 grams) at 90–95° C./4 mm. Anal. calcd. for $C_{10}H_{22}N_2$: C, 71.15; H, 12.21; N, 16.36. Found: C, 70.6; H, 12.96; N, 16.45. Molecular weight calcd. for $C_{12}H_{22}N_2$: 170. Found: ~182.

Picrate (melting point, 159–162° C.), reported melting point (*2*): 194–195° C. Calcd. for mono-picrate: N, 17.52. Found: N, 18.01.

Phenylthiourea adduct (melting point, 133.5–135° C.), calcd. for mono-adduct: S, 9.53. Found: S, 10.49.

Hydrochloride (melting point, 258–260° C.), reported (*2*) 243–246° C. n_D^{25} Found: 1.5056.

REDUCTION WITH RANEY NICKEL. Because of the discrepancy in the found and reported (*2*) melting points of the picrate and hydrochloride of (II), the procedure of Albertson (*2*) for the preparation of (II) was repeated using a Raney nickel catalyst. γ-Acetyl-γ-methylpimelonitrile (*4*) (15 grams) was reduced with approximately 2 grams of Raney nickel in 50 ml. of absolute ethanol at 500 p.s.i.g. of hydrogen and at temperatures up to 105° C. during a period of 1 hour and 40 minutes. The product was distilled, yielding 11.8 grams of product which boiled over a range of 84.5° to 90° C. at 2.5 mm. vacuum. The infrared and NMR spectra of this product and that obtained from the Raney cobalt reduction were identical. This product gave a picrate, melting at 161–163° C. In the NMR spectra, the doublet expected for the methyl on the carbon α to the nitrogen was not apparent, although there is a possibility that one peak of this doublet is being masked by the singlet of the other methyl group. The NMR spectra have been used primarily to indicate that the products obtained by Albertson's procedure and by the present one are identical.

Cyclization of 3-(γ-Aminopropyl)-2,3-dimethylpiperidine. 3-(γ-Aminopropyl)-2,3-dimethylpiperidine (37.5 grams) was passed over 50 cc. of Houdry cracking catalyst in the form of pellets in a vapor reactor at 370° C. over a period of 101 minutes. The recovered effluent (22.6 grams) was shown to contain 14.4% by mass spectrometry or 17.4% by vapor fractometry of a compound with mass 153, (III), and 36.9% (MS) or 41.6% (VF) of a compound of mass 151, (IV), in addition to a number of minor products. A distillation cut (11.3 grams) boiling from 42° to 48° C. at 1 mm. was collected and pure samples of compounds (III) and (IV) were prepared from this fraction by employing a preparative gas chromatographic column (15% Ucon on alkaline chromosorb). Attempts to separate the two products with a spinning band column at a 40 theoretical plate efficiency were unsuccessful.

The NMR spectra of compounds (III) and (IV) shown in Figures 1 and 2 support the assigned structures.

The carbon, hydrogen, and nitrogen analyses for com-

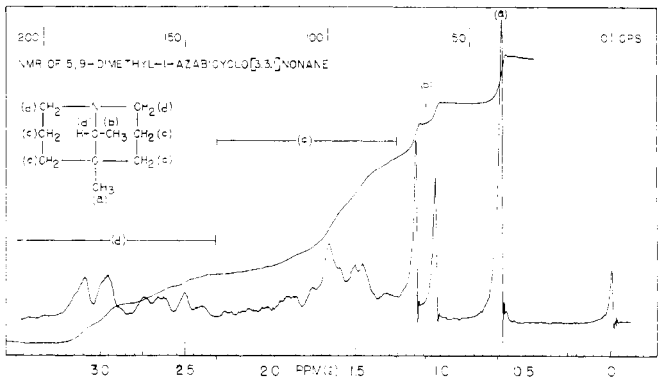


Figure 1. NMR spectrum of 5,9-dimethyl-1-azabicyclo(3.3.1)nonane

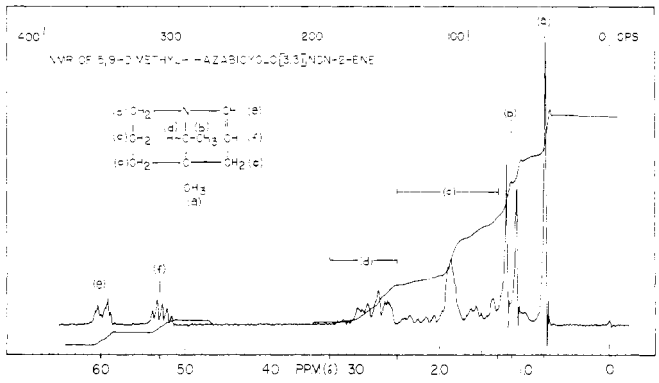


Figure 2. NMR spectrum of 5,9-dimethyl-1-azabicyclo(3.3.1)non-2-ene

pounds (III) and (IV), their neutralization equivalents and pK values are summarized in Table I.

Compound (III) δ Values. NMR (neat), singlet at 0.68 (3H in $CH_3-\overset{|}{C}-$); doublet at 1.08 (3H in $CH_3-\underset{|}{C}-H$); complex of medium size peaks at 1.27 to 2.32 (8H in $-CH_2-CH_2-\overset{|}{\underset{|}{C}}-CH_2CH_2-$); complex of short peaks at 2.32 to 3.5 [5H in $(CH_2)_2N-\underset{|}{CH}$].

Compound (IV) δ Values. (neat), singlet at 0.77 (3H in $CH_3-\overset{|}{C}-$); doublet at 1.13 (3H in the methyl groups of $CH_3-\underset{|}{C}-H$); complex of peaks at 1.31 to 2.41 (6H in $-CH_2-CH_2-\overset{|}{\underset{|}{C}}-CH_2-C=$); complex of short peaks at 2.41 to 3.3 (3H in $-CH_2-\underset{|}{N}-\underset{|}{CH}-$); complex of short peaks at 5.3 and 6.0 (2H in $-CH=CH-N$).

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