(48.8%) of VI, a colorless water soluble liquid, b.p. 194.5–5.5° C./765 mm., n_D^{30} 1.43979. Anal. Calcd. for $C_6H_{10}N_2$: C, 65.41; H, 9.15; N, 25.43. Found: C, 65.37; H, 9.15; N, 25.44.

Reaction of Allyl Cyanide and Aziridine. Allyl cyanide (109.8 grams, 1.64 moles) and aziridine (70.5 grams, 1.64 moles) were placed in a flask and allowed to stand overnight. After the solution was heated on a steam bath for 6 hours, the product was vacuum distilled, yielding a fraction, of 62 grams, b.p. up to 76° C./10 mm.; a second fraction of 64.4 grams (35.7%), b.p. 76–7° C./10 mm.; and a viscous residue. The second fraction was redistilled to yield a product identical to VI, b.p. 193–4° C./760 mm., n_D^{30} 1.43980. The infrared spectrum was identical to that of VI.

2-(1-Aziridinylmethyl)glutaronitrile (VII). Compounds I (30.0 grams, 0.7 mole) and III (53.0 grams, 0.5 mole) were mixed in a flask and heated on a water bath at 80° C. for 9.5 hours. The product was distilled, yielding 66 grams (88.6%) of VII, a colorless water soluble liquid, b.p. 103–4° C./0.07 mm. Anal. Calcd. for $C_8H_{11}N_3$: C, 64.41; H, 7.43; N, 28.17. Found: C, 64.60; H, 7.60; N, 28.04.

3-(1-Aziridinyl)-3-phenylpropionitrile (VIII). Compounds I (12.9 grams, 0.3 mole) and IV (25.6 grams, 0.198 mole) were placed in a flask and heated on a water bath at 70° C. for 7 hours. The aziridine was recovered unreacted. Fresh aziridine (15 grams) was added to unchanged IV, and 0.4 gram of metallic sodium was added. The mixture was heated under a blanket of nitrogen gas for 1.25 hours at 65° C. After standing for 48 hours, 10 grams more of I and 0.1 gram of fresh sodium were added, and heating resumed for 2 hours at 70° C. The dark brown mixture was distilled, yielding 21.5 grams (63.0%) of VIII, a colorless water insoluble oil, b.p. 91° C./0.03 mm. The oil was redistilled for analysis. Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27; mol. wt., 172.2. Found: C, 76.88; H, 6.99; N, 16.34; mol. wt., 170. (Osmometer method).

3-(1-Aziridinyl)-2-methylpropionitrile (IX). Compounds I (53.0 grams, 1.23 moles), V (67.1 grams, 1.0 mole), and 0.5 gram of metallic sodium were placed in a flask and heated under reflux in a water bath at 60° C. for about 16 hours. After the first hour of heating, 10 ml. of fresh aziridine was added, and after 8 hours, an additional 10 ml. was added. The mixture turned a dark brown and upon distillation yielded 41 grams (41%) of IX, a colorless water soluble liquid, b.p. 68–70° C./11 mm. Anal. Calcd. for $C_6H_{10}N_2$: C, 65.41; H, 9.15; N, 25.43. Found: C, 65.30; H, 9.21; N, 25.44.

ACKNOWLEDGMENT

The authors thank Nancy M. Morris and Elizabeth R. McCall for the infrared analyses.

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RECEIVED for review October 18, 1967. Accepted December 19, 1967. The Southern Regional Research Laboratory is one of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U.S. Department of Agriculture.

New Procedure for the Preparation of Pure Optical Isomers of 2-Amino-5-phenyl-2-oxazolin-4-one

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Separation of diastereomeric 2-octyl mandelates by vapor-phase chromatography and reaction of the esters with guanidine provide a convenient economical route to enantiomers of 2-amino-5-phenyl-2-oxazolin-4-one.

THE central nervous system stimulating properties of 2-amino-5-phenyl-2-oxazolin-4-one (pemoline) have been described previously (*1*, *2*). There is also evidence that pemoline accelerates acquisition and enhances retention of a conditioned avoidance response in experimental animals (*3*). The enantiomers of pemoline have previously been prepared by reaction of guanidine with the enantiomers of methyl mandelate and only the D(+) isomer was reported to possess biological activity (*4*). Therefore, the author was interested in investigating more economical alternative routes to optically active pemoline.

Racemic mandelic acid was esterified with L-2-octanol and the diastereomeric esters separated using vapor-phase chromatography and identified by comparison with samples obtained from D- and L-mandelic acid. Reaction of each diastereomer with guanidine yielded optically active pemoline in yields comparable with those from methyl mandelate (*4*).

Resolution of organic compounds is generally a relatively expensive operation. In the procedure (*4*) previously described, the optically active mandelic acid is completely utilized, whereas in the procedure described above, racemic mandelic acid is used and the optically active 2-octanol can be readily recovered and recycled. Either enantiomer of 2-octanol could obviously be used.

EXPERIMENTAL

Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are corrected. Optical rotations were determined with a Hilger-Watts polarimeter using 0.5% solutions in dimethylformamide for 2-amino-5-phenyl-2-oxazolin-4-one samples and 1% solutions in acetone for all other samples.

Preparation of L-2-Octyl-DL-mandelate. DL-Mandelic acid (22.8 grams, 0.15 mole), L-2-octanol (19.5 grams, 0.15 mole,

$[\alpha]_D^{25}$ = −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*).

ACKNOWLEDGMENT

The author is grateful to Evelyn Baker of Abbott Laboratories for the chromatographic data.

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RECEIVED for review November 28, 1967. Accepted February 19, 1968.

New Route to Isogranatanine Derivatives

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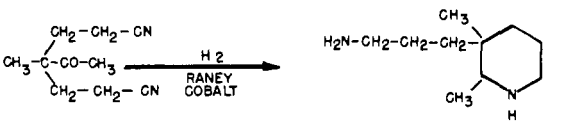
In the first step, 3,3-bis-(β-cyanoethyl)-butanone-2, the adduct of 2 moles of acrylonitrile to 1 mole of methyl ethyl ketone, is reduced in the presence of ammonia and Raney cobalt to 3-(γ-aminopropyl)-2,3-dimethylpiperidine giving a yield of 87 mole%. This piperidine compound is then cyclized over 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.