# Synthesis of (*R*)-5-(2′-Pentyl)barbituric Acid Derivatives of High Optical Purity (1)

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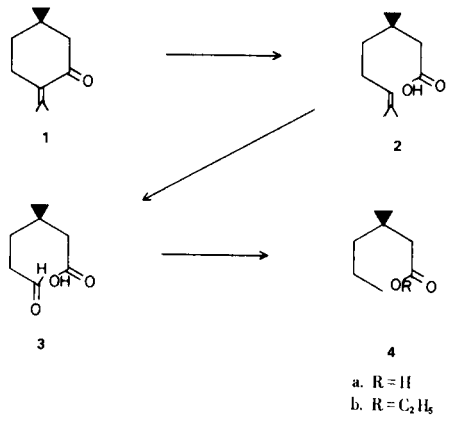
Natural (*R*)-(+)-pulegone (**1**) was converted to 3-methylhexanoic acid (**4**) by a sequence which precluded racemization. Conversion of this to malonic esters **8**, **5**, and **11** permitted the synthesis of pentobarbital (**6**) secobarbital (**12**), thiopental (**9**), **thiamylal** (**10**), and 5-(2′-pentyl)barbituric acid (**7**),all having the (*R*)-configuration in the side chain.

The known propensity of biological systems for interacting in different ways with enantiomeric compounds requires in many cases that the pure enantiomers be studied separately. For this reason we have investigated synthetic routes to barbiturates such as pentobarbital [5-ethyl-5-(2′-pentyl)barbituric acid (**6**)] which could lead to the pure *R* and *S* forms.

In 1934 Kleiderer and Shonle synthesized (+)- and (-)-pentobarbital by a route involving resolution of 2-pentanol, conversion to 2-bromopentane, alkylation of ethyl malonic ester with the latter, and finally condensation with urea. The isomers had rotations of +4.93° and -4.73° (2). This may be compared with resolution results of +3.2° and -3.5° (3). The synthetic method cited suffers theoretically from the involvement of the asymmetric center in reactions subsequent to resolution of 2-pentanol, which could have resulted in partial racemization. In addition, for studies of enzyme fit and specificity in activity and metabolism, it is of interest to know the absolute configurations of the isomers.

FIGURE 1




Both goals (high optical purity and determination of absolute configuration) could be achieved by synthesis from a pure compound of known configuration if the synthetic steps did not permit any racemization. Dissection of one synthetic route to pentobarbital suggested that 3-methylhexanoic acid (**4a**) would be a suitable starting material if it could be obtained in optically active form. Resolution of this acid has been reported (4) and the absolute configurations of its enantiomers established by correlation with those of methyl hydrogen β-methyl glutarate (5), which in turn were related to methylsuccinic acid (6). Fredga has correlated this compound with glyceraldehyde by application of the quasiracemate method (7). For a check on optically purity, it was still desirable to start with a natural compound of high optical purity. Fortunately a synthesis of **4a** from natural (*R*)-(+)-pulegone (**1**) could be devised. The absolute configuration of pulegone has been determined by relating it to methylsuccinic acid (8), and is supported by application of the octant rule to (+)-3-methylcyclohexanone derived from pulegone (9). The compound is readily available in high optical purity (10). Since the asymmetric center is isolated from the reactive centers during the course of the synthesis to be described, no possibility of racemization or inversion exists.

(*R*)-(+)-pulegone (**1**) was converted to citronellic acid (**2**) (10, 11). Ozonization of **2** gave crude 3-methyl-6-oxohexanoic acid (**3**) (10). Reduction of the ozonide with dimethylsulfide (12) proved convenient but did not appear to greatly increase the yield over that reported for zinc-acetic acid reduction (10). The crude aldehyde (**3**) was reduced by a Wolff-Kishner reaction to 3-methylhexanoic acid (**4a**) which was esterified to **4b**. Hydrolysis gave back acid **4a**, $[\alpha]_D^{22}$ + 2.55° (neat). This rotation agrees with that reported for **4a** by resolution (+2.49°) (4).

TABLE

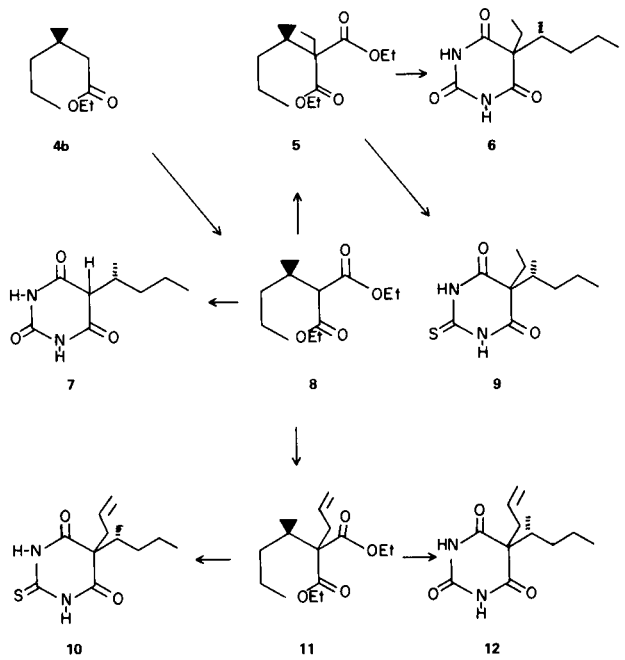
| Compound | $[\alpha]_D^{22}$ (EtOH, C ≈ 2) (a) | M.P. (b) | |
|---|---|---|---|
| | | (*R*) | (Racemic) |
| Pentobarbital (**6**) | +13.12° | 122-122.5° | 128-129° (c) |
| Secobarbital (**12**) | + 9.23° | 103-106° | 98-100° (c) |
| | | | 99-100° (d) |
| Thiopental (**9**) | +10.66° | 151-151.5° | 158-159° (e) |
| Thiamylal (**10**) | + 6.68° | 117-118° | 127-129° (e) |
| 5-(2′-pentyl)barbituric acid (**7**) | - 4.80° | 182.5-183° | 165.6-166.5° (d) |

(a) Optical rotations were determined on a photoelectric Perkin-Elmer Model 141 polarimeter. We thank Dr. George Wahl of North Carolina State University for the use of this instrument. (b) All melting points on a Kofler hot-stage apparatus except for pentobarbital, which was obtained by the capillary tube method. (c) D. L. Tabern and E. H. Volwiler, *J. Am. Chem. Soc.*, 56, 1139 (1934). (d) H. A. Shonle, *ibid.*, 56, 2490 (1934). (e) Reference 20.

Ethyl ester **4b** was converted to malonic ester **8** by a modification of the procedure of Floyd and Miller (13). Alkylation of **8** with ethyl iodide yielded **5** which condensed with urea to yield (*R*)-(+)-pentobarbital (**6**), $[\alpha]_D$ +13.1°. This value is much higher than those previously reported (2,3). Comparison with the data of Kleiderer and Shonle (2) would indicate an optical purity of 35-40% for their barbiturate. However, their malonic ester **5**, $[\alpha]_D$ + 11.62°, was 77% optically pure when compared with our **5**, $[\alpha]_D$ + 14.95°. Our rotations have been independently confirmed in this laboratory by exhaustive resolution of *RS*-pentobarbital and by synthesis of the (-) isomers (14a). Nmr and mass spectra were consistent with our assigned structures (see Experimental) and tlc and glc confirmed their purity. Since racemization in the last step seems impossible, we are unable to explain the discrepancy.

The availability of malonic esters **5** and **8** permitted the preparation of some other pharmacologically useful barbiturates. Allylation of **8** gave malonic ester **11**, which condensed with urea to yield (*R*)-(+)-secobarbital (**12**). Substitution of thiourea for urea gave (*R*)-(+)-thiopental (**9**) from **5** and (*R*)-(+)-thiamylal (**10**) from **11**. Finally ester **8** reacted with urea to yield (*R*)-(-)-5-(2′-pentyl)-barbituric acid (**7**). Optical rotations and melting points are given in the Table. The four 5,5-disubstituted derivatives all showed positive rotations at the D-line and **6** a positive Cotton effect (14b). The monosubstituted compound, however, showed negative rotation at the D-line and a negative Cotton effect. It should also be noted that in malonic esters **8**, **5**, and **11**, alkylation exerts a marked effect on the rotation. Thus monosubstituted ester **8** has only a small positive rotation, (+0.62°) whereas **5** and **11** have considerably higher rotations (+14.95° and +16.45°). Melting points of the pure isomers differed from those reported for the racemates. Therefore, the identity of each compound was established by nmr, mass spectrum, and analysis. Purity was established by tlc. The isolated position of the asymmetric center during the reaction sequence leads to confidence in the optical purity of the products. Although more emphasis was placed on obtaining pure compounds than on yields, overall yields by this sequence were acceptable.

FIGURE 2



## EXPERIMENTAL

Optical rotations of liquids were determined on a Rudolph Model 80 polarimeter; those of solids in ethanol (C~2) on a Perkin-Elmer Model 141 polarimeter. Nmr spectra were determined with tetramethylsilane as internal standard on a Varian A-60 spectrometer. Mass spectra were obtained on an MS-902 under the direction of Dr. David Rosenthal of the Research Triangle Center for Mass Spectrometry. Tlc was carried out on silica gel HF using acetone-chloroform (1:9) as solvent.

(*R*)-(+)-Citronellic Acid (**2**).

Distilled (*R*)-(+)-pulegone [Aldrich Chem. Co., b.p. 109° at 5.1 mm, 95% pure by glc on 2% OV-17] was converted (10, 11) to (*R*)-(+)-citronellic acid [48% yield, b.p. 152-153° (22 mm.) $[\alpha]_D^{23}$ +8.35° (neat); lit. (10) b.p. 80.5-81° (0.07 mm), $[\alpha]_D^{25}$ + 8.48° (neat)].

Ethyl (*R*)-(+)-3-Methylhexanoate (**4b**).

Treatment of acid **4a** (50 g. in 400 ml. of $CH_3OH$) with ozone (1.65 mmoles/min.) at dry ice-acetone temperature until a slight excess was present (10) was followed by purging with nitrogen and addition of 50 ml. of dimethylsulfide (12). The solution was stirred 1 hour at -60 to -70°, 1 hour at 0°, and at room temperature overnight. (The reaction was incomplete after 1 hour at room temperature.) Excess dimethylsulfide and methanol were evaporated at reduced pressure. The residue was taken up in ether and washed twice with 50 ml. of saturated sodium chloride solution. The residue obtained by evaporation was indicated to be *ca.* 60% aldehyde by nmr (integration of the -CHO peak). This material (50 g.) was treated with 150 ml. of anhydrous hydrazine in 300 ml. of ethylene glycol. The solution was stirred and heated at 100-108° for 1 hour, cooled to room temperature, treated slowly with 60 g. potassium hydroxide pellets, distilled until the pot temperature reached 200° (*ca.* 200 ml. of distillate was collected), refluxed at 200-210° for 2 hours, cooled, and poured into 1 l. of water (15). Hydrochloric acid was added to acidify the solution, which was then extracted with three 500 ml. portions of ether. The ether was washed twice with 100 ml. portions of saturated sodium chloride and dried (Drierite). Evaporation left 27 g. of crude (*R*)-(+)-3-methylhexanoic acid, which was esterified with ethanol containing sulfuric acid (4). Distillation of the crude product gave a 54% overall yield (from citronellic acid) of ethyl (*R*)-(+)-3-methylhexanoate, b.p. 79° (21 mm), $n_D^{18}$ 1.4125, $[\alpha]_D^{22}$ +0.18° (neat), $d^{22}$ 0.865 [lit. (4) b.p. 174-175°, $n_D^{18}$ 1.4148, $[\alpha]_D$ +0.47° (neat)]; nmr (deuteriochloroform) 249 Hz (q, 2.0, $CH_2O$), 130 (m, 3.2, -$CH$-$CH_2$-$\overset{O}{\overset{\|}{C}}$-), 40-90 (m, 12.8, aliphatic CH). Glc on 10% EGSS-X (Applied Science Laboratories) indicated 5% of impurity.

(*R*)-(+)-3-Methylhexanoic Acid (**4a**).

Ester **4b** (3 ml., 2.58 g.) was refluxed 1 hour under nitrogen with 100 ml. of 10% potassium hydroxide in ethanol (95%). The solution was poured into 500 ml. of water and extracted with ether (two 100 ml. portions). Acidification (1:1 hydrochloric acid) and re-extraction with ether yielded 2.37 g. of crude acid which was distilled, b.p. 115-119° (20 mm), $[\alpha]_D^{22}$ +2.55° (neat), $n_D^{18}$ 1.4255, $d^{22}$ 0.918 [lit. (4) b.p. 92-93° (8 mm), $[\alpha]_D$ + 2.49°, $n_D^{27}$ 1.4209]; nmr (deuteriochloroform) 697 Hz (s, 1.0, COO*H*), 130 (m, 3.0, $\gtrless$*CH*-$CH_2$-CO), 78 (m, 4.0, $CH_2$-$CH_2$), 53 (m, 5.9, $CH_3$).

(*R*)-(+)-Diethyl 2-Pentylmalonate (**8**).

The method of Floyd and Miller (13) was modified (16). In oven dried apparatus 26.8 g. (0.555 mole) of 50% mineral oil suspension of sodium hydride was washed twice with 100 ml. portions of ether and dried under a stream of nitrogen. Dry ether (130 ml.), diethyl oxalate (185 ml., dried by distilling off 15 ml. from 200 ml.), ester **4b** (43.9 g., 0.278 mole), and 2-3 drops of ethanol were added. (Ethanol accelerated the reaction, presumably by formation of sodium ethoxide.) The mixture was stirred and refluxed for 30 hours. Gas chromatography of an acidified aliquot on EGSS-X at 135° showed the reaction to be complete. Acidification (64 ml. of acetic acid) and addition of water caused separation of an organic phase which was extracted with ether (three 200 ml. portions). The combined organic layers were washed with water, sodium bicarbonate solution, and saturated sodium chloride solution and dried over Drierite. Ethyl oxalate and any **4b** were removed by vacuum distillation (b.p. 40-45° at 1 mm) after evaporation of ether. The residue was decarbonylated *in a hood* at 160-170° and 120-160 mm. Progress of the decarbonylation was followed by gas chromatography (above conditions). Vacuum distillation yielded 40.9 g. (64%) of essentially pure (by glc) **8**, which was redistilled for physical measurements, b.p. 115° (6 mm), 104° (2 mm), $n_D^{20}$ 1.4277, $d^{22}$ 0.972, $[\alpha]_D^{22}$ + 0.62° (1 dm, neat); lit. (17) b.p. 103-104° (4 mm), $n_D^{20}$ 1.4273 for racemate; nmr 254 Hz (q, 3.9., $CH_2O$), 194 (d, 1.0, $\gtrless$*CH*-CO), 135 (m, 1.2, $\gtrless$*CH*), 40-90 (m, 15.9, aliphatic C*H*).

(*R*)-(+)-Diethyl Ethyl-2-pentylmalonate (**5**).

By the procedure of Beres, *et al.*, (18), for preparing diethyl ethyl-*t*-butylmalonate (sodium hydride and bromoethane in *N,N*-dimethylformamide), malonic ester **8** (15.0 g., 0.065 mole) was converted by reaction with ethyl iodide (30.0 g., 0.200 mole) to **5** (12 g., 71%), b.p. 128° at 7 mm, 103° at 0.6 mm. A center cut was redistilled through a spinning band column. It then had $n_D^{20}$ 1.4364; $[\alpha]_D^{22}$ + 14.95°, $d^{20}$ 0.9705 [lit. (2) b.p. 123-124° at 10 mm, $n_D^{25}$ 1.4336, $d_4^{25}$ 0.9607, $[\alpha]_D^{25}$ + 11.62°]; nmr (deuteriochloroform) 253 Hz (q, 3.9, $CH_3CH_2O$-), 118 (q + m, 3.4, $CH_3CH_2$ + $\gtrless$*CH*), 40-90 (m, 18.2, aliphatic CH).

(*R*)-(+)-Diethyl allyl-2-pentylmalonate (**11**).

By the above procedure, malonic ester **8** (5.3 g., 0.0205 mole) and redistilled 3-chloropropene (5.7 g., 0.075 mole) yielded 3.42 g. (46%) of **11**, b.p. 84° at 0.05 mm, $n_D^{20}$ 1.4449, $d^{22}$ 0.976, $[\alpha]_D^{22.5}$ + 16.44° [lit. (19) b.p. 137-140° (15 mm) for racemate]; nmr (deuteriochloroform) 290-380 Hz (m, 3.1, $CH$=$CH_2$), 252 (q, 3.9, $CH_2O$) 161 (d, 2.1, $CH_2$-CH=), 125 (m, 1.5, $\gtrless$*CH*), 40-90 (m, 15.4, aliphatic CH).

(*R*)-(+)-5-Ethyl-5-(2′-pentyl)barbituric acid (**6**).

Dry dimethylsulfoxide (500 ml., distilled from calcium hydride and stored over molecular sieve), malonic ester **5** (11.5 g., 0.044 mole), and urea (13.4 g., 0.223 mole) were stirred and treated with a 50% dispersion of sodium hydride in mineral oil (4.4 g., 0.092 mole). After 2 hours at room temperature, glc on an aliquot showed no ester (**5**) remaining. The mixture was poured into 2.5 l. of chilled water, extracted with three 500 ml. portions of ether, acidified (1:1 hydrochloric acid), and re-extracted (three 500 ml. portions of ether). The latter extracts were combined, washed with water and saturated sodium chloride solution, dried (Drierite), and evaporated to leave 7.3 g. (73%) of crude **11**. Recrystallization from ethyl acetate (50 ml.)/hexane (150 ml.) yielded a total of 5.52 g. (55%) of (*R*)-(+)-pentobarbital (**6**), shown to be pure by

tlc (5-10% acetone/chloroform on silica gel $HF_{254}$). Sublimation [100-110° (0.001 mm)] gave the analytical sample: nmr (deuteriochloroform) 567 Hz (s, 1.9, N*H*), 129 (q + m, 3.2, $CH_3CH_2$ + >C-*H*), 100-140 (m, 12.9, aliphatic CH); ir (methylene chloride) 3375, 3220, 3100, 3060 (N-H), 2969, 2940 sh, 2880 (C-H), 1760, 1730, 1710 $cm^{-1}$ (C=O); uv max (phosphate buffer, *p*H 9) 238 mμ (ε, 9025); mass spectrum (70 ev, 90°) m/e 226 ($M^+$), 197, 156 (base), 141 (identical with that of genuine *RS*-pentobarbital). The sample for rotation was sublimed three times (to constant rotation).

*Anal.* Calcd. for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.51; H, 8.02; N, 12.39.

(*R*)-(+)-5-Allyl-5-(2′-pentyl)barbituric Acid (**12**).

By a procedure similar to the above, malonic ester **11** (0.50 g., 1.85 mmole), urea (0.555 g., 9.2 mmoles) and 50% sodium hydride (0.177 g., 3.7 mmoles) in dimethylsulfoxide gave **12** (0.158 g., 35%) after preparative tlc (10% acetone/chloroform) and two crystallizations from ethyl acetate/hexane. Sublimation [90-95° (0.001 mm)] gave the analytical sample; nmr (deuteriochloroform), 562 Hz (s, 1.7, N*H*), 298-370 (m, 3.5, C*H*=$CH_2$), 169 (d, 1.8, $CH_2$-CH=), 135 (m, 1.2, >C*H*), 40-110 (m, 9.8, aliphatic CH); mass spectrum (70 ev, 80°) m/e 238 ($M^+$), 195, 169 (base), 168, 124, 97. The sample for rotation was sublimed twice.

*Anal.* Calcd. for $C_{12}H_{18}N_2O_3$: C, 60.48; H, 7.61; N, 11.76. Found: C, 60.42; H, 7.49; N, 11.75.

(*R*)-(+)-5-Ethyl-5-(2′-pentyl)-2-thiobarbituric Acid (**9**).

Preparation from ester **8** and thiourea (20) followed by recrystallization (ethyl acetate/hexane) and sublimation [130-140° (0.001 mm)] gave **9**; nmr (DMSO-$d_6$) 755 Hz (s, 1.5, N*H*), 117 (q + m, 3.3, $CH_3CH_2$ + >C*H*), 30-100 (m, 13.2, aliphatic CH); mass spectrum (70 ev, 100°) m/e 242 ($M^+$), 172 (base), 157, 97.

*Anal.* Calcd. for $C_{11}H_{18}N_2O_2S$: C, 54.40; H, 7.42; N, 11.54; S, 13.20. Found: C, 54.34; H, 7.44; N, 11.43; S, 13.46.

(*R*)-(+)-5-Allyl-5-(2′-pentyl)-2-thiobarbituric Acid (**10**).

Preparation from ester **11** and thiourea (20) followed by recrystallization (ethyl acetate/hexane) and sublimation [100-110° (0.001 mm)] yielded **10**, nmr (deuteriochloroform) 580 Hz, (s, 1.9, N*H*), 298-370 (m, 3.1, C*H*=$CH_2$), 171 (d, 2.1, $CH_2$-CH=), 135 (m, 1.1, >CH), 40-100 (m, 9.8, aliphatic CH); mass spectrum (70 ev, 70°) m/e 254 ($M^+$), 185, 184 (base), 183, 169.

*Anal.* Calcd. for $C_{12}H_{18}N_2O_2S$: C, 56.66; H, 7.13; N, 11.02; S, 12.61. Found: C, 56.75; H, 7.06; N, 10.96; S, 12.62.

(*R*)-(+)-5-(2′-pentyl)barbituric Acid (**7**).

Condensation of ester **8** and urea with sodium ethoxide in ethanol and purification by sublimation [150-160° (0.001 mm)] yielded **7**: nmr (DMSO-$d_6$) 673 Hz (s, 1.8, N*H*), 199 (d, 1.2, CH-C(=O)-), 135 (m, 0.8, >C*H*), 82 (m, 3.9, $CH_2CH_2$), 40-70 (m, 6.4, $CH_3$); mass spectrum (70 ev, 120°) m/e 198 ($M^+$), 155, 128 (base), 85, 70, 69, 55.

*Anal.* Calcd. for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.32; H, 7.09; N, 14.28.

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REFERENCES

(1a) This work was carried out under Contract No. PH 43-65-1057 with the National Institute of General Medical Sciences, National Institutes of Health. (b) Presented at the 156th National Meeting of the ACS, Abstracts, MEDI 14, 1968.

(2) E. C. Kleiderer and H. A. Shonle, *J. Am. Chem. Soc.*, **56**, 1772 (1934).

(3) J. Knabe and K. Philipson, *Arch. Pharm.*, **299**, 333 (1966).

(4) J. Cason and R. A. Coad, *J. Am. Chem. Soc.*, **72**, 4695 (1950).

(5) I. A. Holliday and N. Polgar, *J. Chem. Soc.*, 2934 (1957).

(6) S. Stälberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, **25A**, No. 10 (1948).

(7a) A. Fredga, *ibid.*, **14B**, No. 27 (1941); **15B**, No. 23 (1942). (b) For chemical evidence see D. S. Noyce and D. B. Denny, *J. Am. Chem. Soc.*, **76**, 768 (1954); D. S. Noyce and J. H. Canfield, *ibid.*, **76**, 3630 (1954). (c) For a discussion of these correlations see J. A. Mills and W. Klyne in "Progress in Stereochemistry," Vol. I, W. Klyne, Ed., Academic Press, Inc., New York, N. Y., 1954, Chapter 5.

(8) E. J. Eisenbraun and S. M. McElvain, *J. Am. Chem. Soc.*, 77, 3383 (1955); See also references 6 and 7.

(9) For discussion and references see P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, 1965, p. 77.

(10) C. G. Overberger and H. Kaye, *J. Am. Chem. Soc.*, **89**, 5640 (1967).

(11) J. Plesek, *Chem. Listy*, **50**, 1854 (1956); *Chem. Abstr.*, **51**, 4314 (1957).

(12) J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Letters*, 4273 (1966).

(13) D. E. Floyd and S. E. Miller, *J. Am. Chem. Soc.*, **69**, 2354 (1947).

(14a) F. I. Carroll and R. Meck, *J. Org. Chem.*, in press. (b) Optical rotatory dispersion curves were determined by Dr. K. H. Dudley of the Center for Pharmacology and Toxicology, University of North Carolina at Chapel Hill.

(15) *Cf.* the Wolff-Kishner procedure of S. Sarel and Y. Yanuka, *J. Org. Chem.*, **24**, 2018 (1959).

(16) *Cf.* N. Green and F. B. LaForge, *J. Am. Chem. Soc.*, **70**, 2287 (1948).

(17) H. A. Shonle, A. K. Keltch, and E. E. Swanson, *ibid.*, **52**, 2440 (1930).

(18) J. A. Beres, D. E. Pearson, and M. T. Bush, *J. Med. Chem.*, **10**, 1078 (1967).

(19) K. Abe, T. Ishisaka, and Y. Tsukamoto, *J. Pharm. Soc. Japan*, **75**, 891 (1955).

(20) D. L. Tabern and E. H. Volwiler, *J. Am. Chem. Soc.*, **57**, 1961 (1935).

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