# Synthesis and Determination of Maximum Rotatory Power of (+)-(*S*)-5-*s*-Butyl-2(1*H*)-pyridinone



G. Chelucci*, M. Marchetti, F. Soccolini and C. Botteghi

Istituto di Chimica Applicata, Università di Sassari,
Via Vienna, 2, 07100 Sassari, Italy

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Optically active (*S*)-5-*s*-butyl-2(1*H*)-pyridinone (**6**) is obtained by reaction of 2-*s*-butylacrolein (**1**) and *N*-(carbamylmethyl)pyridinium chloride. The relationship between optical activity and minimum optical purity is determined.

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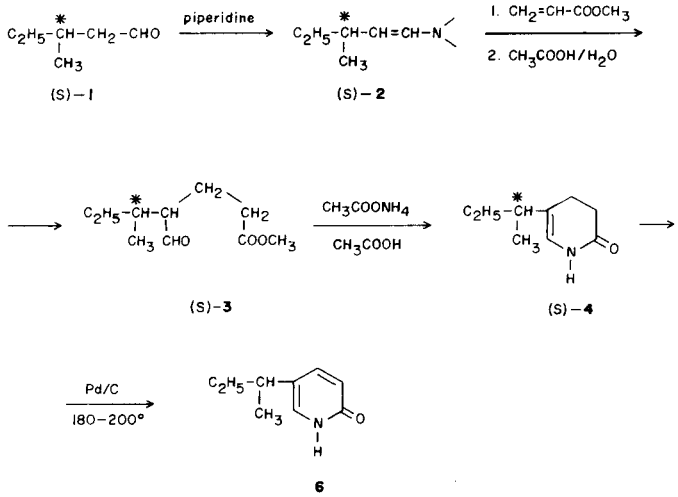
In connection with other synthetic projects, we needed optically active 2(1*H*)-pyridinones, in which the asymmetric center of an alkyl substituent was adjacent to the heterocyclic ring. Indeed, 2(1*H*)-pyridinones are known to be the starting material of choice for 2-chloro- or 2-bromopyridines [1], from which a number of variously substituted pyridines are accessible [2].

To our knowledge, no optically active title compounds are described in the literature so far; on the other hand, few general methods exist in the literature to prepare 2(1*H*)-pyridinones with alkyl substituents [3].

This paper is concerned with the synthesis of (+)-(*S*)-5-*s*-butyl-2(1*H*)-pyridinone (**6**) and with the determination of the relationship between optical activity and minimum optical purity.

Cyclization of 4-formylbutanoic acid derivatives with ammonium acetate [4] and dehydrogenation of the 3,4-dihydro-2(1*H*)-pyridinone formed seemed to us the most convenient and expeditious method to obtain **6** (Scheme 1).

Scheme 1




(S)-1 (S)-2 (S)-3 (S)-4 6

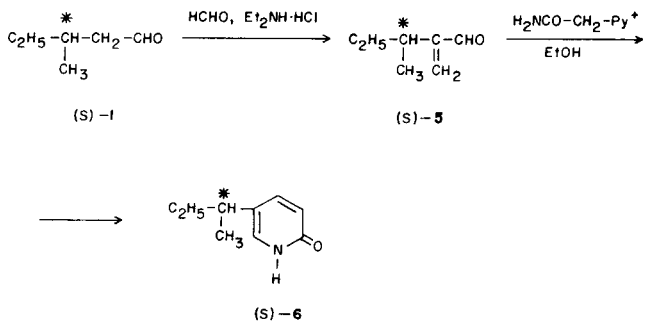
The alkylation reaction of the piperidino-enamine of (−)-(*S*)-3-methylpentanal (**2**) with methyl acrylate in acetonitrile [5] provided us with a very simple method to obtain the necessary aldehydo-ester **3** (Scheme 1). Compound **4** $[\alpha]_D^{25}$ +46.33, was prepared with very high yield (≥90%).

However, the dehydrogenation of **4** to the final product **6** put us in difficulty which we were unable to overcome in a convenient way. In fact, heating **4** in the presence of palladium metal on charcoal [6] at 180-200° without solvent was very effective for the chemical (≈80%) but not the optical yield: actually, compound **6** recovered after the dehydrogenation reaction resulted nearly racemic. Indeed, olefinic substrates with a chiral center adjacent to the double bond undergo moderate racemization when hydrogenated on palladium catalysts even at room temperature [7]; thus, we believe that this fact may be responsible in our case of the loss of the optical activity.

Several experiments requiring milder reaction conditions have been attempted to preserve the optical activity of **4** during its conversion into **6**; they include: i) the use of nitrobenzene as a hydrogen-acceptor in boiling toluene [8]; ii) the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidizing agent at room temperature [9]; iii) the use of 96% sulfuric acid at room temperature [10]. All these methods proving to be unsuccessful, we were forced to devise a different synthetic approach to **6**.

It was known that cynnamaldehydes underwent cycloaddition with *N*-(carbamylmethyl)pyridinium chloride giving about 40-75% of 4-aryl-2(1*H*)-pyridinones [11,12]. We tried to achieve the same result using optically active 2-*s*-butylacrolein as the $\alpha,\beta$-unsaturated aldehydic partner, although 2-substituted acroleins are not reported to be employed in such cycloadditions.

Scheme 2



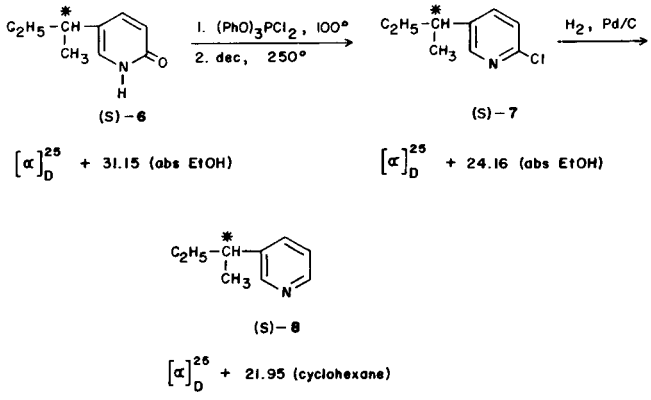

(S)-1 (S)-5 (S)-6

Thus, heating of a mixture of *(S)*-**5** (95% min o.p.) and *N*-(carbamylmethyl)pyridinium chloride followed by thermal decomposition at about 200° of the primary reaction adduct produced **6**, $[\alpha]_D^{25}$ +31.15 (ethanol), in 40% yield (Scheme 2).

To evaluate the loss of optical activity occurring during the rather severe cycloaddition step (**5** → **6**), we chemically correlated **6** with the known (+)-*(S)*-3-*s*-butylpyridine (**8**) [13] (Scheme 3). Compound **6** was converted in (+)-*(S)*-2-chloro-3-*s*-butylpyridine (**7**), $[\alpha]_D^{25}$ +24.16 (ethanol), by reaction with triphenoxyphosphorus dichloride [1] in 70% yield; then the halogen atom was easily removed through hydrogenolysis catalyzed by palladium metal on charcoal [14]. Compound **8**, obtained chemically pure in 85% yield, showed $[\alpha]_D^{25}$ +21.95 (cyclohexane); this value is consistent within the experimental errors with the maximum rotatory power of **8** recently reported [15].

It is noteworthy that, in spite of the proximity of the asymmetric center, no racemization occurs either during the cyclization reaction (**5** → **6**) (Scheme 2), or during the drastic halogenation of **6** to **7** (Scheme 3).

Scheme 3




## EXPERIMENTAL

Boiling points are uncorrected. The gc controls were effected on a Perkin-Elmer 3920-B gas chromatograph, using 1 m × 2 mm column packed with 5% SE-30 on Chromosorb W and operating at programmed temperature between 70 and 200°. The ir spectra were recorded on a Perkin-Elmer 157 spectrometer. The nmr spectra were obtained with a Varian T 60 spectrometer in deuteriochloroform solutions using tetramethylsilane as an internal standard ($\delta$ = 0). Mass spectra were measured with a Hitachi Perkin-Elmer RMU-6L mass spectrometer operating at 70 eV. The optical rotations were taken on a Perkin-Elmer 241 polarimeter in 1 dm tubes. Elemental analyses were performed by Perkin-Elmer Elemental Analyzer model 240-B.

Materials.

*(S)*-1-Piperidino-3-methyl-1-pentene was prepared in 90% yield from (−)-*(S)*-3-methylpentanal and piperidine by a conventional method [16]. (+)-*(S)*-2-*s*-Butylacrolein, $[\alpha]_D^{25}$ +29.12 (neat, o.p. 95%), was prepared according to the procedure described by R. Menicagli *et al.* [17]. *N*-(carbamylmethyl)pyridinium chloride was prepared according to A. H. Cook, *et al.* [18].

Methyl 4-Formyl-5-methylheptanoate (**3**).

To an ice-cooled solution of *(S)*-1-(*N*-piperidino)-3-methyl-1-pentene (58.4 g, 0.35 mole) in acetonitrile (260 ml), methyl acrylate (37.4 g, 0.43 mole) dissolved in acetonitrile (88 ml) was added during half an hour. The mixture was stirred at room temperature for 5 hours and then heated to reflux. After 36 hours, acetic acid (21 ml) and water (140 ml) were added and refluxing was prolonged for an additional 8 hours. After cooling, the reaction mixture was extracted with ether, washed with saturated sodium chloride and dried over anhydrous sodium sulfate. Removal of the solvent and distillation *in vacuo* gave **3** as a diastereomeric mixture 95% pure by gc, yield, 48 g (73%), bp 75° (5 mm Hg); nmr: $\delta$ 9.65-9.52 (m, CHO, 1H), 3.63 (s, $OCH_3$, 3H).

*Anal.* Calcd. for $C_{10}H_{18}O_3$: C, 64.5; H, 9.7. Found: C, 64.3; H, 9.9.

5-*s*-Butyl-3,4-dihydro-2(1*H*)-pyridinone (**4**).

Methyl 4-formyl-5-methylheptanoate (45.3 g, 0.24 mole) in benzene (85 ml) was added to a solution of ammonium acetate (22.6 g, 0.29 mole) in acetic acid (20 ml). After 3 hours refluxing, the solvent was removed at reduced pressure, the residue was neutralized with 10% aqueous sodium hydrogen carbonate and extracted with ether. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated. Distillation *in vacuo* of the oily residue gave pure **4** (gc), yield, 33.5 g (90%), bp 94-95° (0.1 mm Hg); $[\alpha]_D^{25}$ +46.33 (c 5.2 absolute ethanol); ir (neat): 1665 $cm^{-1}$ (C=O); nmr: $\delta$ 9.5-9.2 (broad, NH, 1H), 5.87 (d, H-6, 1H); ms: 153 ($M^+$, 19), 124 (M-29, 100).

*Anal.* Calcd. for $C_9H_{15}NO$: C, 70.5; H, 9.9; N, 9.1. Found: C, 70.4; H, 10.1; N, 8.8.

5-*s*-Butyl-2(1*H*)-pyridinone (**6**).

a) 5-*s*-Butyl-3,4-dihydro-2(1*H*)-pyridinone (10.8 g, 0.07 mole) was stirred at 180° for 3 hours in the presence of 10% palladium on charcoal (2.14 g). The mixture was suspended in methanol and filtered. After removal of the solvent and distillation *in vacuo*, 8.4 g (79%) of pure **6** (gc) were obtained, bp 115° (0.05 mm Hg); $[\alpha]_D^{25}$ −0.25 (c 5.2, absolute ethanol); ir (neat): 1660 $cm^{-1}$ (C=O), 1625 $cm^{-1}$ (C=C); nmr: $\delta$ 9.9 (broad, NH, 1H), 7.4-7.1 (m, H-4 and H-6, 2H), 6.6 (d, H-3, 1H); ms: 151 ($M^+$, 19), 122 (M-29, 100).

*Anal.* Calcd. for $C_9H_{13}NO$: C, 71.5; H, 8.7; N, 9.3. Found: C, 71.3; H, 8.8; N, 9.1.

b) To a solution of *N*-(carbamylmethyl)pyridinium chloride (8.2 g, 47 mmoles) in methanol (130 ml) a 40% solution of dimethylamine (5 ml) and 2-*s*-butylacrolein (5 g, 45 mmoles) were added. After 10 hours refluxing, the solvent was distilled off and the dark residue was decomposed by heating at 200° for 10 minutes. Extraction with boiling benzene, removal of the solvent and bulb-to-bulb distillation afforded pure **6** (gc); yield, 2.8 g (41%); $[\alpha]_D^{25}$ + 31.15 (c 2.62, absolute ethanol). Spectral data (ir, nmr, ms) and elemental analysis were consistent with the expected structure.

2-Chloro-5-*s*-butylpyridine (**7**).

5-*s*-Butyl-2(1*H*)-pyridinone ($[\alpha]_D^{25}$ +31.15) (3.5 g, 23 mmoles) was added to a mixture of phosphorus pentachloride (4.82 g, 23 mmoles) and phenol (6.5 g, 69 mmoles) previously heated at 100° for 5 hours. The reaction was heated at 100° for an additional 5 hours; after this time, the resulting adduct was decomposed by heating at 250° for 15 minutes [1]. Extraction with ether (2 × 15 ml) was followed by several washings with 5% aqueous sodium hydroxide, in order to remove the excess of phenol. The combined ether extracts were dried over anhydrous sodium sulfate, the solvent evaporated and the residue distilled *in vauco* to give 2.77 g (71%) of **7**, 96% pure by gc, bp 85° (0.3 mm Hg); $[\alpha]_D^{25}$ +24.16 (c 2.4, absolute ethanol); nmr: $\delta$ 8,06 (d, H-6, 1H, $J_{6,4}$ = 2.5 Hz), 7.35 (dd, H-4, 1H), 7.10 (d, H-3, 1H, $J_{3,4}$ = 6 Hz); ms: 169 ($M^+$, 34), 140 (M-29, 100).

*Anal.* Calcd. for $C_9H_{12}ClN$: C, 63.7; H, 7.1; N, 8.3. Found: C, 63.9; H, 7.2; N, 8.0.

3-*s*-Butylpyridine (**8**).

2-Chloro-5-*s*-butylpyridine (1.02 g, 6 mmoles) dissolved in absolute methanol (60 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium on charcoal (0.50 g) [14]. After one hour the hydrogen absorption had stopped, the suspension was filtered and the filtrate was acidified with 5% hydrochloric acid; the methanol was evaporated and the residue made strongly alkaline with 10% aqueous sodium hydroxide. Extraction with ether (2 × 10 ml), drying over anhydrous sodium sulfate and removal of the solvent gave crude **8**, which was purified by distillation at reduced pressure, yield, 0.69 g (85%), bp 74° (15 mm Hg); $[\alpha]_D^{25}$ +21.95 (c 6.02, cyclohexane). Compound **8** resulted identical with an authentic sample [13,15].

## REFERENCES AND NOTES

[1] D. G. Coe, H. N. Rydon and B. L. Tonge, *J. Chem. Soc.*, 323 (1957).

[2] M. M. Boudakian, "Pyridine and its Derivatives", Supplement, Part 2, R. A. Abramovitch, ed, John Wiley, New York, NY, 1975, p 420.

[3] L. E. Overman, S. Tsuboi, J. P. Roos and G. F. Taylor, *J. Am. Chem. Soc.*, **102**, 747 (1980) and references therein.

[4] D. K. Bamerjee, P. Sengupta and S. K. Das Gupta, *J. Org. Chem.*, **19**, 1516 (1954).

[5] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrel, *J. Am. Chem. Soc.*, **85**, 207 (1963).

[6] F. Brody and P. H. Ruby, "Pyridine and its Derivatives", Part 1, E. Klingsberg, ed, Interscience Publishers, Inc., New York, NY, 1960, p 231.

[7] D. J. Cram, *J. Am. Chem. Soc.*, **74**, 5518 (1952).

[8] G. Brieger and T. J. Nestrick, *Chem. Rev.*, **74**, 567 (1974).

[9] D. Walker and J. D. Hiebert, *Chem. Rev.*, **67**, 153 (1967).

[10] A. I. Meyers and G. Garcia-Munoz, *J. Org. Chem.*, **29**, 1435 (1964).

[11] J. Thesing and A. Müller, *Chem. Ber.*, **90**, 711 (1957).

[12] M. A. Akhtar, W. G. Brouwer, J. A. D. Jeffreys, C. W. Gemenden, W. I. Taylor, R. N. Seelye and D. W. Stanton, *J. Chem. Soc. C*, 859 (1967).

[13] D. Tatone, T. C. Dich, R. Nacco and C. Botteghi, *J. Org. Chem.*, **40**, 2987 (1975).

[14] J. P. Wibaut and E. C. Kooyman, *Rec. Trav. Chim.*, **63**, 231 (1944).

[15] G. Asara, C. Botteghi, S. Gladiali and F. Soccolini, *Synth. Commun.*, **13**, 1129 (1983).

[16] C. Botteghi, G. Caccia and S. Gladiali, *Synth. Commun.*, **9**, 69 (1979).

[17] R. Menicagli and M. L. Wis, *J. Chem Res. (S)*, 262 (1978).

[18] A. H. Cook, J. Downer and B. Hornung, *J. Chem. Soc.*, 502 (1941).