

SYNTHESES OF STIPITATIC ACID AND HINOKITIOL

Yasumitsu Tamura,\* Tatsuya Saito, Hiroshi Kiyokawa, Ling-Ching Chen  
and Hiroyuki Ishibashi  
Faculty of Pharmaceutical Sciences, Osaka University  
133-1, Yamada-kami, Suita, Osaka, Japan

(Received in Japan 3 August 1977; received in UK for publication 3 October 1977)

The tropolone synthesis through 1,3-dipolar cycloaddition of 1-methyl-3-oxidopyridinium (1), reported recently by Katritzky and his co-workers,<sup>1</sup> seems to be of preparative significance. However, because of the difficulty of obtaining 1-methyl-3-oxidopyridinium derivatives, application of the method is practically quite limited. It is worthwhile to prepare the suitable 1-methyl-3-oxidopyridiniums, and investigate an applicability of the Katritzky's method to some pharmacologically interesting tropolones. The present paper deals with the total syntheses of stipitatic acid (2)<sup>2</sup> and hinokitiol (3)<sup>3</sup> through 1,3-dipolar cycloadditions of 5-methoxy(4)- and 5-isopropyl(5)-1-methyl-3-oxidopyridiniums, respectively.

Condensation of ethyl sarcosinate and chloroacetone followed by base-catalyzed cyclization of the resulted ethyl N-acetylsarcosinate gave a 30% yield of 1-methylpiperidine-3,5-dione [6, mp 195-199°(dec)],<sup>4</sup> which was subsequently converted to 5-methoxy-1-methyl-1,6-dihydro-3(2H)-pyridone (7, mp 71-72°) by treatment with methanol and sulfuric acid in yield of 73%. When the enol ether 7 was treated with m-chloroperbenzoic acid (MCPBA) in methylene chloride, 5-methoxy-1-methyl-3-oxidopyridinium (4) was obtained quantitatively as hygroscopic crystals (mp 55-57°). The structure of the betaine 4 was proved by the following spectral evidences. The ir spectrum showed no absorption in carbonyl region, and the nmr spectrum displayed O-methyl, N-methyl, and three aromatic protons, whose chemical shifts resembled those reported for the betaine 1<sup>5</sup> (see Table 1). 1,3-Dipolar cycloaddition of 4 with ethyl propiolate in

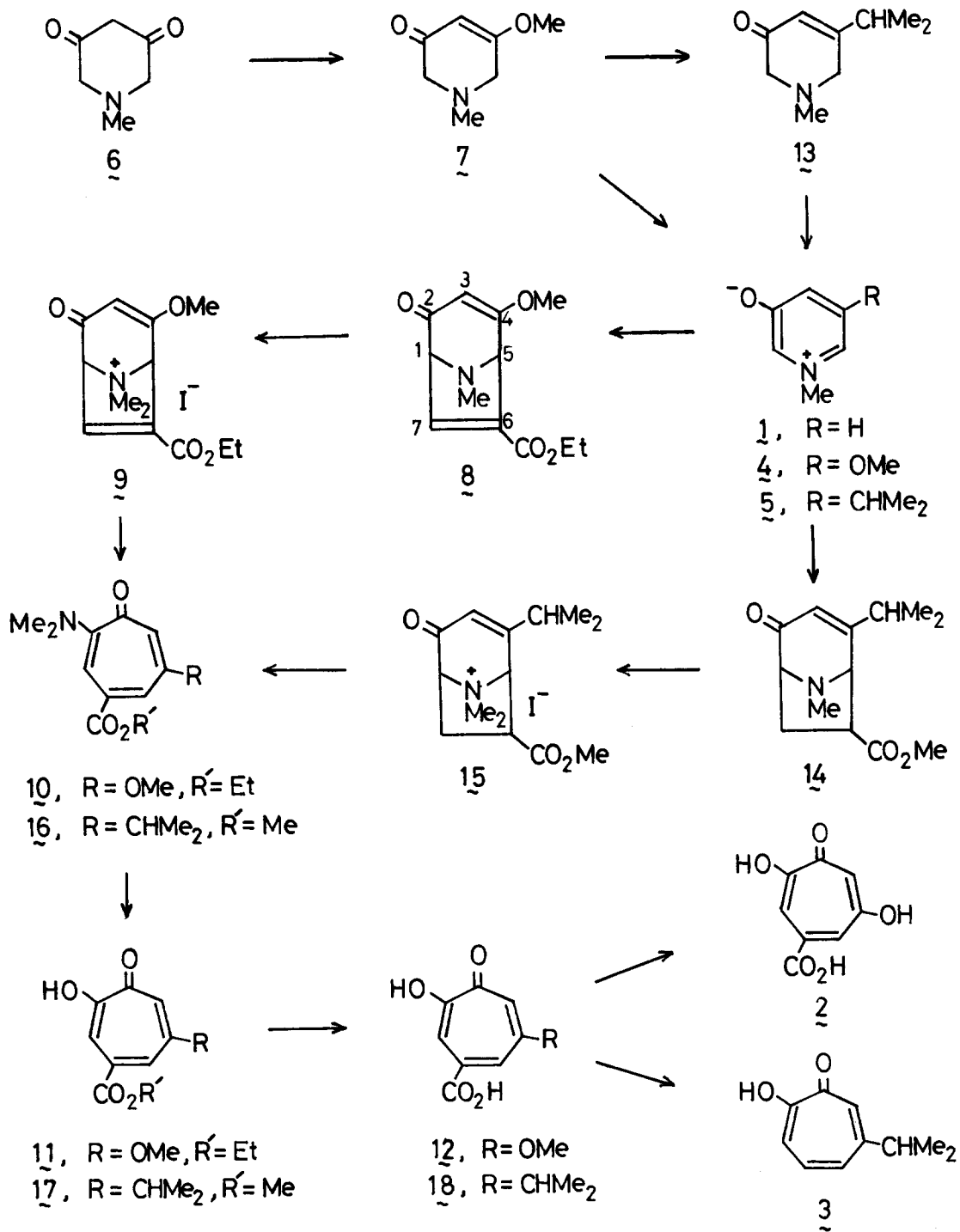


Table 1: Nmr spectra for 1-methyl-3-oxidopyridiniums (DMSO-d<sub>6</sub>, δ)

compd.	H-2	H-4	H-5	H-6	N-Me
<u>1</u> <sup>5</sup>	7.30	6.90	7.21	7.35	3.73
<u>4</u>	7.10	6.50	—	7.15	3.74
<u>5</u>	7.27	6.88	—	7.33	3.98

refluxing tetrahydrofuran gave the oily adduct 8 in yield of 87%. The structure of 8 was confirmed by the following spectral data: ir (CHCl<sub>3</sub>, ν<sub>max</sub>) 1715, 1660, and 1600 cm<sup>-1</sup>; nmr (CDCl<sub>3</sub>) δ 1.32 (t, -CH<sub>2</sub>CH<sub>3</sub>, J=7.0 Hz), 2.46 (s, NCH<sub>3</sub>), 3.71 (s, OCH<sub>3</sub>), 3.94 (bd, H-1), 4.25 (q, -OCH<sub>2</sub>-, J=7.0 Hz), 4.73 (bs, H-5), 5.30 (s, H-3), and 7.14 (d, H-7, J=3.0 Hz). Quarternization of 8 with methyl iodide in ethyl acetate afforded the methiodide 9 [mp 140-141°(dec)] in yield of 42%. Ring cleavage of 9 was effected by stirring in sodium bicarbonate solution at room temperature to give ethyl 2-dimethylamino-6-methoxytropone-4-carboxylate(10) in yield of 79%: mp 80-81°; ir (KCl, ν<sub>max</sub>) 1720, 1610, 1590, and 1500 cm<sup>-1</sup>; nmr (CDCl<sub>3</sub>) δ 1.38 (t, -CH<sub>2</sub>CH<sub>3</sub>, J=7.0 Hz), 3.09 [s, N(CH<sub>3</sub>)<sub>2</sub>], 3.80 (s, OCH<sub>3</sub>), 4.36 (q, -OCH<sub>2</sub>-, J=7.0 Hz), 6.50 (d, H-7, J=3.0 Hz), 6.97 (bs, H-3), and 7.25 (m, H-5); uv (EtOH, λ<sub>max</sub>) 264 (log ε 4.16), 294 (3.97), and 356 (3.65) nm. Dimethylaminotropone 10 was quantitatively transformed to the tropolone carboxylic ester 11 (mp 153-155°; lit.<sup>2</sup> 154-155°) by treating with 10% hydrochloric acid at 50-60°. Hydrolysis of 11 with 1N potassium hydroxide at 60° afforded the corresponding tropolone carboxylic acid 12 (mp 257-260°; lit.<sup>2</sup> 262-264°) in yield of 98%. Demethylation of 12 by heating with 48% hydrobromic acid at 110° gave stipitatic acid [2, mp 280°(dec)] quantitatively.

Hinokitiol (3) was synthesized by a similar sequence of reactions. Grignard reaction of the enol ether 7 with isopropyl magnesium bromide and successive aromatization of the resulted enone 13 (its picrate, mp 143-145°) with MCPBA in methylene chloride afforded the oily 5-isopropyl-1-methyl-3-oxidopyridinium(5) in an almost quantitative yield. The nmr spectrum supported the structure 5 (see Table 1). Refluxing a tetrahydrofuran solution of 5 and methyl acrylate caused 1,3-dipolar cycloaddition to give the oily adduct 14 in yield of 74%. The nmr spectrum of 14 established the exo-configuration of the

methoxycarbonyl group due to the lack of coupling between H-5<sup>6</sup> and H-6. The adduct 14 was quarternized with methyl iodide to afford the salt 15 (mp 165-167°) in yield of 76%. Treatment of 15 with sodium bicarbonate solution caused Hofmann elimination and simultaneous dehydrogenation,<sup>1a</sup> giving methyl 2-dimethyl-amino-6-isopropyltropone-4-carboxylate (16) in yield of 77%: bp 170-180° (bath temperature, 0.3mm); ir (CHCl<sub>3</sub>,  $\nu_{\max}$ ) 1725, 1610, and 1590 cm<sup>-1</sup>; nmr (CDCl<sub>3</sub>)  $\delta$  1.25 [d, -CH(CH<sub>3</sub>)<sub>2</sub>, J=7.0 Hz], 2.80 [m, -CH(CH<sub>3</sub>)<sub>2</sub>, J=7.0 Hz], 3.11 [s, N(CH<sub>3</sub>)<sub>2</sub>], 3.91 (s, OCH<sub>3</sub>), 6.90 (bs, H-7), 7.12 (bs, H-3), and 7.38 (bs, H-5). The tropolone carboxylic ester 17 (mp 82-83°) was obtained by treatment of 16 with 10% hydrochloric acid in yield of 98%. Hydrolysis of 17 with 1N potassium hydroxide gave the tropolone carboxylic acid 18 (mp 180-182°) in a 92% yield. Decarboxylation of the acid 18 with copper chromite in quinoline at 230° afforded hinokitiol (3, mp 49-50°) in yield of 45%. Synthetic stipitatic acid (2) and hinokitiol (3) were identical with authentic specimens (2, mp 282°; 3, 49.5-52°) in all respects.

#### References and Footnotes

1. a) A.R. Katritzky and Y. Takeuchi, J. Am. Chem. Soc., 92, 4134 (1970); b) N. Dennis, A.R. Katritzky, and Y. Takeuchi, Angew. Chem. Int. Ed. Engl., 15, 1 (1976).
2. For the synthesis of stipitatic acid, see J.R. Bartels-Keith, A.W. Johnson, and W.I. Taylor, J. Chem. Soc., 2352 (1951).
3. For other syntheses of hinokitiol, see T. Nozoe, S. Seto, K. Kikuchi, T. Mukai, S. Matsumoto and M. Murase, Proc. Japan Acad., 26, 43 (1950); T. Nozoe, S. Seto, K. Kikuchi and H. Takeda, ibid., 27, 146 (1951); T. Nozoe, S. Seto and T. Sato, ibid., 30, 473 (1954); W. von E. Doering and L.H. Knox, J. Am. Chem. Soc., 75, 297 (1953); J.W. Cook, R.A. Raphael and A.I. Scott, J. Chem. Soc., 695 (1951); K. Tanaka and A. Yoshikoshi, Tetrahedron, 27, 4889 (1971).
4. Satisfactory elemental analyses were obtained for all crystalline compounds.
5. A.R. Katritzky and Y. Takeuchi, J. Chem. Soc. (c), 473 (1971).
6. The signal for H-5 appeared as a singlet at  $\delta$  3.98.