2,4′-, and the 3,4′-bipyridines are similar in value, though the 2,3′ cis value is by far the largest. Thus, it can be inferred that the cis form is preferred for the 2,3′- and the 3,3′-bipyridines, at least as a first approximation.

LITERATURE CITED

(1) Califano, S., Adembri, G., and Sbrana, G., *Spectrochim. Acta* **20**, 385 (1964).
(2) Castellucci, E., Sbrana, G., and Verderame, F.D., *J. Chem. Phys.* **51**, 3762 (1969).
(3) Cheuychit, P., Jones, R.A., and Sasse, W.H.F., *J. Chem. Soc.* 4557 (1964).
(4) Corrsin, L., Fax, B.J., and Lord, R.C., *J. Chem. Phys.* **21**, 1170 (1953).
(5) Cumper, C.W.N., Ginman, R.F.A., and Vogel, A.I., *J. Chem. Soc.* 1188 (1962).
(6) Favini, G., and Gamba, A., *Gazz. Chim. Ital.* **96**, 391 (1966).
(7) Katon, J.E., and Lippincott, E.R., *Spectrochim. Acta* **15**, 627 (1959).
(8) Katritzky, A.R., and Ambler, A.P., "Infrared Spectra" in "Physical Methods in Heterocyclic Chemistry," A.R. Katritzky, Ed., Volume 2, Chapter 10, Academic Press, New York, N. Y., 1963.
(9) Katritzky, A.R., and Hands, A.R., *J. Chem. Soc.* 2202 (1958).
(10) Kovner, M.A., Korostelev, Yu. S., and Berezin, V.I., *Opt. Spektrosk.* **10**, 233 (1961).
(11) Kuffner, F., and Straberger, F., *Monatsh. Chem.* **88**, 793 (1957).
(12) Kulasingam, G.C., McWhinnie, W.R., and Thomas, R.R., *Spectrochim. Acta* **22**, 1365 (1966).
(13) Leont'ev, V.B., Mangutova, Yu. S., Otroshchenko. O.S., and Sadykov, A.S., *Khim. Geterotsikl. Soedin.* **2**, 575 (1966).
(14) Lord, R.C., Marston, A.L., and Miller, J.A., *Spectrochim. Acta* **9**, 113 (1957).
(15) Popov, A.I., Marshall, J.C., Stute, F.B., and Person, W.B., *J. Amer. Chem. Soc.* **83**, 3586 (1961).
(16) Sadtler Standard Spectra, Infrared Spectrogram #13298 (1965) Sadtler Research Labs., Philadelphia, Pa.
(17) *Ibid.*, #5551.
(18) Sbrana, G., Adembri, G., and Califano, S., *Spectrochim. Acta* **22**, 1831 (1966).
(19) Schilt, A.A., and Taylor, R.C., *J. Inorg. Nucl. Chem.* **9**, 211 (1959).
(20) Shindo, H., *Pharm. Bull. (Tokyo)* **5**, 472 (1957).
(21) Simmons, J.D., Innes, K.K., and Begun, G.M., *J. Mol. Spectrosc.* **14**, 190 (1964).
(22) Smith, C.R., *J. Amer. Chem. Soc.* **52**, 397 (1930).
(23) Steele, D., and Lippincott, E.R., *J. Mol. Spectrosc.* **6**, 238 (1961).
(24) Stidham, H.D., and Tucci, J.V., *Spectrochim. Acta* **23A**, 2233 (1967).
(25) Zerbi, G., Crawford, B., and Overend, J., *J. Chem. Phys.* **38**, 127 (1963).

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Methyl Esters of Camphoric and Isocamphoric Acids

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Conclusions of earlier investigators regarding the structure and configuration of a number of the methyl esters of camphoric and isocamphoric acid are corrected. The monomethyl esters of racemic isocamphoric acid are described for the first time. NMR data are presented for all of the methyl esters of racemic camphoric and isocamphoric acid. A GLC procedure for the separation of a mixture of camphorates and isocamphorates and improved method for the partial conversion of dimethyl camphorate to dimethyl isocamphorate are given.

IT is generally believed that when *d*-camphoric acid, (+)-1, is esterified by methanol in the presence of sulfuric acid, the monomethyl ester (m.p. 76° C.), α-methyl hydrogen *d*-camphorate, (+)-2, is obtained along with the dimethyl *d*-camphorate, (+)-3. Saponification of (+)-3 with a limited quantity of base yields the monomethyl ester (m.p. 87° C.), β-methyl hydrogen *d*-camphorate, (+)-4. Similarly, it is generally believed that when *l*-isocamphoric acid, (−)-5, is esterified, the monomethyl ester (m.p. 90° C.), α-methyl hydrogen *l*-isocamphorate, (−)-6, is obtained along with the dimethyl *l*-isocamphorate, (−)-7. Partial saponification of (−)-7 yields the monomethyl ester (oil), β-methyl hydrogen *l*-isocamphorate, (−)-8.

In 1932, Quadrat-I-Khuda (*8*) claimed that the monomethyl esters melting at 76° and 87° C., respectively, were stereoisomers rather than structural isomers. Specifically, he stated that both were β-methyl esters and that the higher melting one should be shown as the epimeric isocamphorate, 8. Qudrat-I-Khuda was aware of the dextro optical rotation of both esters. No reference was made

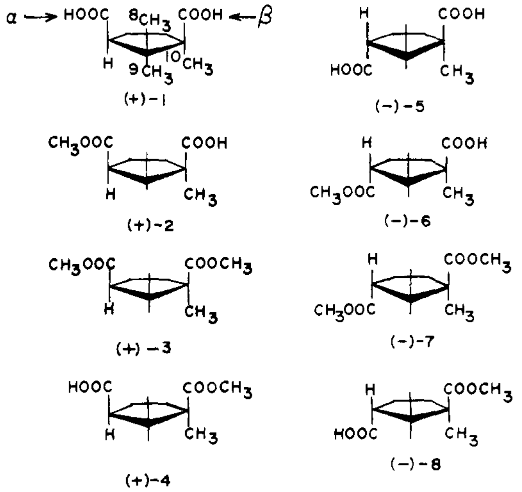

Figure 1. Configurational formulas

to the work of Noyes and Littleton (*6*), who claimed the preparation of (−)-8, an oil. Qudrat-I-Khuda's claim was based on the fact that when either monomethyl ester was treated with thionyl chloride, and the acid chloride so prepared was allowed to react with zinc methyl iodide, one and the same ketonic ester was obtained. He interpreted this to mean that a $=CHCOOH$ group had to be present in each monomethyl ester. This could then become a $=CHCOCl$ group, where epimerization could occur. In 1941, Crouch and Lochte noted, without reference to Qudrat-I-Khuda, that the lower melting but not the higher melting ester undergoes a cis-trans isomerization in the Bouveault and Blanc reduction. It was their belief that the lower melting ester had to contain a $=CHCOOCH_3$ group rather than a $=CHCOOH$ group. In 1949, Simonsen (*9*) suggested that Qudrat-I-Khuda's results (a single acid chloride yielding a single ketonic ester) could be explained if (+)-2 were to undergo a molecular rearrangement under the influence of thionyl chloride to yield the more stable acid chloride of 4, presumably (+)-4. Simonsen did not list an optical rotation value for 4. In 1962, after repeating many of Qudrat-I-Khuda's experiments, this time with the racemic forms of the monomethyl esters, Manzoor-I-Khuda and Qudrat-I-Khuda (*4*) rejected Simonsen's suggestion and restated the claim that 2 and 4 were epimers rather than structural isomers. No reference was made to the work of Crouch and Lochte.

RESULTS AND DISCUSSION

Despite the statement of Hasselstrom and coworkers (*2*) that all camphorates and isocamphorates are probably mixtures of camphorates and isocamphorates, the present authors found no evidence of racemization during the usual acid-catalyzed preparation of (+)-2 and (+)-3 from (+)-1 nor during the similar preparation of (−)-6 and (−)-7 from (−)-5. Each of the diesters, (+)-3 and (−)-7, gave a different peak in a GLC method developed by the authors to separate mixtures of dimethyl camphorate and dimethyl isocamphorate.

The monomethyl camphorate prepared by the partial esterification of *d*-camphoric acid, (+)-1, was the same as that prepared by Qudrat-I-Khuda and melted at 76° C. as claimed by him. The monomethyl ester prepared by the partial saponification of (+)-3 as directed by Qudrat-I-Khuda (limited quantity of base in methanol) also had the claimed melting point of 87° C. While (+)-3 can be made to isomerize rather than saponify under certain conditions, such as with an alkoxide in alcohol (*3*) or better with an alkoxide in a dimethyl sulfoxide–methanol solution, the major reaction occurring in the present case is a saponification of (+)-3 to a monomethyl camphorate. This must be true, because complete saponification of the monoester obtained yields (+)-1 and re-esterification of the monoester with methanol and sulfuric acid yields (+)-3. Because it is a camphorate and because Crouch and Lochte (*1*) reported it to be resistant to base-catalyzed isomerization, it must be (+)-4. By difference then, the lower melting monomethyl *d*-camphorate must be (+)-2.

Although Qudrat-I-Khuda and Manzoor-I-Khuda believed that under hydrolyzing conditions (+)-3 would pass into 7 and then hydrolyze to 8 (with a positive rotation), neither tried to convert (−)-5 to 7 and then hydrolyze to 8. Noyes had done this and had obtained the oil, (−)-8. The present authors repeated this synthesis and also obtained the oil, (−)-8.

Because Qudrat-I-Khuda and Manzoor-I-Khuda had also reported on and questioned the structure of (±)-2, and the configuration of (±)-4, these compounds were also prepared by the present authors. During this study of the racemic monomethyl camphorates and isocamphorates, compounds (±)-6 and (±)-8 were isolated for the first time. For the reasons outlined above there can be no doubt that the monoester (m.p. 87° C.) obtained as a by-product during the esterification of (±)-1 is (±)-2 and the monoester (m.p. 77° C.) obtained by the saponification of (±)-3 is (±)-4. The *dl*-pair which is epimeric with (±)-4 is (±)-8 and the latter melts at 81° C.

EXPERIMENTAL

All temperature measurements are uncorrected. Polarimetric measurements were made on a Kern full-circle polarimeter. The GLC experiments were carried out on a F&M model 500 gas chromatograph using a 2-foot column packed with 10% diethylene glycol succinate (DEGS) on Chromosorb P (60/80 mesh). NMR data were obtained with a Varian A-60A spectrometer with tetramethylsilane (TMS) as internal standard. The starting materials, *d*-camphoric acid, (+)-1 = D-(+)-camphoric acid, melting point 184-86° C., and *dl*-camphoric acid, (±)-1, melting point 206° C., were obtained from the Aldrich Chemical Co. and the Columbia Organic Chemicals Co., respectively. The procedures given for the optically active compounds were also used for the racemic forms. As with all racemic modifications in the solid state, the physical properties are not necessarily the same as those of the optically active forms in the solid state. The physical properties of one enantiomorph and the racemic form of the esters are presented in Table I. The NMR data are given in Table II. In the GLC experiments with the DEGS column, the dimethyl isocamphorates had a shorter retention time than the dimethyl camphorates.

The following compounds were prepared by methods described in the literature: β-methyl hydrogen *d*-camphorate, (+)-4 (*4*); and β-methyl hydrogen *l*-isocamphorate, (−)-8 (*6*).

Dimethyl *d*-Camphorate, (+)-3 and α-Methyl Hydrogen *d*-Camphorate, (+)-2. These compounds were prepared using a simplified method patterned after that used by Noyes and Skinner (*7*) for the preparation of dimethyl *l*-isocamphorate. *d*-Camphoric acid (200 grams) was dissolved in methanol (800 ml.). Concentrated sulfuric acid (160 ml.) was added with cooling. The resulting solution was refluxed for 5 hours. The cooled solution was poured into a crystallizing dish held in a boiling water bath. Air was drawn over the surface to speed the evaporation of the methanol. As soon as the solution began to turn brown, the heating was stopped. The cooled solution was poured into 700 ml. of cold water. Petroleum ether (500 ml.) was added and the mixture was shaken in a separatory funnel. The petroleum ether layer was drawn off and shaken with sodium carbonate solution to extract the monoester. The sodium carbonate solution was acidified at once to obtain the solid α-methyl hydrogen *d*-camphorate, which was recrystallized from Skellysolve B. The petroleum ether containing the diester was filtered through anhydrous sodium sulfate and then placed on a steam bath to remove solvent. Last traces of solvent were removed in a vacuum oven at 100° C. The yield before distillation was 145 grams (64%) of practically pure dimethyl *d*-camphorate. Retention time for the diester was 9.2 minutes on the DEGS column operating at 125° C.

Partial Isomerization of Dimethyl *d*-Camphorate, (+)-3, during Preparation of β-Methyl Hydrogen *d*-Camphorate, (+)-4. Dimethyl *d*-camphorate [17 grams; α_D^{25} 53° (neat, l = 1 dm.)], methanol (50 ml.), and potassium hydroxide (4 grams) were refluxed for 20 minutes according to the procedure of Manzoor-I-Khuda and Qudrat-I-Khuda (*4*). Water (100 ml.) was added, and unsaponified diester was removed by extracting it into ether. The ether was dried with anhydrous sodium sulfate. After removal of the ether, the diester [8.1 grams; α_D^{25} 12° (neat, l = 1 dm.)] was recovered. Two GLC peaks with retention times of 7.2 and 9.2 minutes, respectively, were obtained on the

Table I. Physical Properties

	M. P., ° C		B. P., ° C		$[\alpha]_D$, Degrees (in alcohol)	
Compound	Found	Lit. (ref.)	Found	Lit. (ref.)	Found at 22° C.	Lit. (ref.)
(+)-2	76	77 (*8*)	...	...	52.9 (c 10)	53.9 (*8*)
(±)-2	87	87 (4)	...	...	...	...
(+)-3	...	...	135/12 mm.	144/15 mm (*7*)	47.6 (c 9.1)	47.5 (6)
(±)-3	...	...	137/12 mm.	138/12 mm. (*3*)	...	...
(+)-4	85	86 (*8*)	...	...	44.4 (c 8.1)	45.1 (*8*)
(±)-4	77	77 (*4*)	...	...	...	...
(−)-6	90	90 (*6*)	...	...	−60.3 (c 8.1)	−58.4 (*6*)
(±)-6	90	...	...	...	...	...
(−)-7	...	...	138/14 mm.	142/16 mm. (*7*)	−68.7 (c 8.1)	−66.5 (*7*)
(±)-7	...	...	127/10 mm.	136/12 mm. (*8*)	...	...
(−)-8	(oil)	...	...	...	−47.9 (c 8.1)	−53.1 (*6*)
(±)-8	81	...	...	...	...	...

Table II. NMR Data

		Chemical Shifts of Ring Methyl Protons, δ		
Compound	Solvent	C-8	C-9	C-10
(±)-1	CD_3COCD_3	0.90	1.34	1.25
(±)-2	CCl_4	0.83	1.19	1.19
(±)-3	$CDCl_3$	0.73	1.24	1.20
(±)-4	CCl_4	0.82	1.27	1.20
(±)-5	CD_3COCD_3	1.14	0.92	1.17
(±)-6	$CDCl_3$	1.14	0.87	1.19
(±)-7	$CDCl_3$	1.02	0.85	1.17
(±)-8	$CDCl_3$	1.07	0.92	1.19
(+)-1	CD_3COCD_3[a]	0.88	1.29	1.25
(+)-1	CD_3COCD_3[a]	0.88	...	1.25

[a] Data from Meyer, Lobo, and McCarty (*5*).

DEGS column operating at 125° C. The GLC analysis indicated 33% isocamphorate and 67% camphorate.

Conversion of β-Methyl Hydrogen *d*-Camphorate, (+)-4, to Dimethyl *d*-Camphorate, (+)-3. β-Methyl hydrogen *d*-camphorate (10.7 grams), methanol (40 ml.), and sulfuric acid (8 ml.) were refluxed together for 5 hours. After evaporation of most of the methanol, the solution was poured into 35 ml. of water. The mixture was shaken in a separatory funnel with 25 ml. of petroleum ether. The petroleum ether layer was removed and shaken with 25 ml. of 10% sodium carbonate in water. The petroleum ether was dried with sodium sulfate. After removal of the petroleum ether in a vacuum oven at 90° C., there remained 9.52 grams of dimethyl *d*-camphorate (83%) α_D^{23} + 53° (neat, l = 1 dm.)

Conversion of β-Methyl Hydrogen *d*-Camphorate, (+)-4, to *d*-Camphoric Acid, (+)-1. β-Methyl hydrogen *d*-camphorate (0.50 gram) was refluxed with 10 ml. of 3*N* sodium hydroxide for 18 hours. The solution was acidified with 6*N* hydrochloric acid. The solid which precipitated was recrystallized from hot water. After drying in a vacuum oven at 100° C., there remained 0.31 gram of *d*-camphoric acid (m.p. 189°–90° C.).

***l*-Isocamphoric Acid, (−)-5,** made by the partial isomerization of *d*-camphoric acid using phosphorus pentachloride (*10*), melted at 168°–69° C. [lit. 172.5° C. (*10*)]; $[\alpha]_D^{26}$ − 44.8° (c 8, ethanol) [lit. $[\alpha]_D$ − 46.2° (*10*)].

***dl*-Isocamphoric Acid, (±)-5,** made by the same procedure as the *l*-isocamphoric acid, melted at 190–91° C. [lit, 183–86° C. (*3*)].

Dimethyl *l*-Isocamphorate, (−)-7, and α-Methyl Hydrogen *l*-Isocamphorate, (−)-6, were prepared from *l*-isocamphoric acid and methanol by the procedure used for the preparation of the dimethyl *d*-camphorate. The monomethyl ester, obtained as a solid, was recrystallized from Skellysolve B. The dimethyl *l*-isocamphorate was a colorless oil; α_D^{25} − 70.1° (neat, l = 1 dm.). GLC retention time of the diester was 7.2 minutes on the DEGS column operating at 125° C.

Partial Conversion of Dimethyl *d*-Camphorate, (+)-3, to Dimethyl *l*-Isocamphorate, (−)-7. To 10 ml. (10.6 grams) of dimethyl *d*-camphorate was added 10 ml. of a 2.5% solution of sodium methoxide in methanol. Enough DMSO was added to give a total volume of 100 ml. The solution was allowed to stand at room temperature for 22 hours. At that time the optical rotation of the solution was constant at α_D^{25} 0.66° (l = 1 dm.). The solution was poured into 650 ml. of water. The mixture of diesters was separated from the aqueous DMSO solution by extracting twice into 250-ml. portions of petroleum ether. The petroleum ether solution was filtered through anhydrous sodium sulfate. The solvent was evaporated to obtain 8.8 grams (83%) of isomerized ester; α_D^{25} 4.94° (neat, l = 1 dm.). From the rotations of the pure esters and that of the mixture it was calculated that the mixture contained 39% dimethyl *l*-isocamphorate and 61% dimethyl *d*-camphorate. From the areas under the GLC peaks (each ester gives essentially the same detector response) it was calculated that the mixture contained 38% dimethyl *l*-isocamphorate and 62% dimethyl *d*-camphorate.

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LITERATURE CITED

(1) Crouch, W.W., Lochte, H.L., *J. Amer. Chem. Soc.* **63**, 1331 (1941).

(2) Hasselstrom, T., Balmer, C.E., Coles, H.W., *Ibid.*, **74**, 3944 (1952).

(3) Hirsjarvi, P., *Suom. Kemistilehti* **27B**, 75 (1954); *CA* **49**, 5392h (1955).

(4) Manzoor-I-Khuda, M., Qudrat-I-Khuda, M., *Pakistan J. Sci. Ind. Res.* **5**, 74 (1962); *CA* **58**, 13998e (1963).

(5) Meyer, W.L., Lobo, A.P., McCarty, R.N., *J. Org. Chem.* **32**, 1754 (1967).

(6) Noyes, W.A., Littleton, L.R., *J. Amer. Chem. Soc.* **35**, 75 (1913)

(7) Noyes, W.A., Skinner, G.S., *Ibid.*, **39**, 2692 (1917).

(8) Qudrat-I-Khuda, M., *J. Chem. Soc.* **1930**, 206.

(9) Simonsen, J.L., "The Terpenes," Vol. **II**, p. 376, Cambridge Press, London, 1949.

(10) Walker, J., Wood, J.K., *J. Chem. Soc.* **77**, 383 (1900).

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