THE STRUCTURE OF MONOBROMINATED ETHYL INDOLE-3-CARBOXYLATE AND THE PREPARATION OF 7-BROMOINDOLE[1]

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ABSTRACT

The compound reported by Majima and Kotake as ethyl 6-bromoindole-3-carboxylate, obtained from the monobromination of ethyl indole-3-carboxylate, when saponified, decarboxylated, and the product repeatedly crystallized from alcohol, actually gave a nearly equimolar mixture of 5- and 6-bromoindoles of constant melting point, 74–75°. 7-Bromoindole has been synthesized by two unambiguous routes.

INTRODUCTION

Majima and Kotake have reported the preparation of ethyl 6-bromoindole-3-carboxylate via bromination in acetic acid of ethyl indole-3-carboxylate (1). Their proof of structure rested upon the observation that dibromination, in acetic acid, of ethyl indole-3-carboxylate actually gave ethyl 5,6-dibromoindole-3-carboxylate, a fact established by the isolation of 5,6-dibromoisatin and 4,5-dibromo-2-amino-benzoic acid. Since the *mono*brominated compound gave a monobromoisatin quite different from the authentic 5-bromoisatin previously prepared by Borsche and Jacobs (2) and in view of the established structure of the dibrominated product, it was concluded that monobromination of ethyl indole-3-carboxylate had occurred at position 6. The discrepancy between the melting point of their "6-bromoisatin" (256–258°) and that of Ettinger and Friedlander's 6-bromoisatin (m.p. 263–264°) (3) was attributed to contamination of their monobromoisatin with some 5,6-dibromoisatin.

The monobrominated ethyl indole-3-carboxylate of Majima and Kotake, saponified and decarboxylated in this laboratory, gave a monobromoindole melting at 74–75° which, according to the assignment of the Japanese authors, should be 6-bromoindole. A recently reported unambiguous preparation of 6-bromoindole (4) melting at 94° casts doubt upon Majima and Kotake's structural assignment. This was further intensified by observation in this laboratory of a marked depression of the melting point of a mixture of these two bromoindoles. That the compound melting at 74–75° is neither 4- nor 5-bromoindoles is shown by comparison of their physical constants. Authentic 4-bromoindole (4) is a liquid which we found to boil at 89–92°/0.25 mm and which has a refractive index of 1.6566 at 21°, while 5-bromoindole melts at 88.5–89° (5). Furthermore, the infrared spectra of the 4-, 5-, and 6-bromoindoles failed to correspond with that obtained for the questionable bromoindole.

Since the possibility existed that the as yet unknown 7-bromoindole might actually be the compound synthesized by Majima and Kotake, its preparation was undertaken. The precursor, 7-bromoindole-2-carboxylic acid, was made by two unambiguous routes. The first method entailed the preparation of ethyl pyruvate 2-bromophenylhydrazone, which was then subjected to Fischer ring closure with polyphosphoric acid. The second method involved the conversion of 3-carboxy-2-nitrotoluene (6) to 3-bromo-2-nitrotoluene by the Hunsdiecker reaction (7). A Reissert condensation of 3-bromo-2-nitrotoluene with ethyl oxalate (5), affording optimum yields only after prolonged reaction between the ester and the nitrotoluene at room temperature, gave ethyl 3-bromo-2-nitrophenylpyruvate. This was converted to 7-bromoindole-2-carboxylic acid by the usual reductive ring closure.

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The 7-bromoindole-2-carboxylic acid gave unsatisfactory decarboxylation by the usual procedures (4, 5, 8). However, a modified version of one method (8, 9), in which the acid was refluxed in synthetic quinoline for 48 hours while small amounts of copper chromite (10) were added at frequent intervals, gave a 48% yield of 7-bromoindole. This synthesis now makes available the last of the isomeric benzene ring-monobrominated indoles.

The infrared spectrum and melting point (42–43°) of 7-bromoindole showed conclusively that it was not the "6-bromoindole" derived from the "ethyl 6-bromoindole-3-carboxylate" of Majima and Kotake.

Comparison of the infrared spectra of 5- and 6-bromoindoles suggested that the unknown substance might be a mixture of the two. Accordingly, when samples containing various proportions of the two isomeric bromoindoles were prepared, it was found that a mixture of 45% of 5-bromoindole and 55% of 6-bromoindole gave a spectrum identical in every respect with that of the unknown. The bands at 1308 cm^{-1} for the 5-isomer and at 1329 cm^{-1} for the 6-isomer have nearly equal intensities and can be used as a reasonably good method for estimation of the relative amounts of these two isomers in a mixture. The two isomers can be clearly distinguished by the absorption bands shown in the following table.

Compound	Absorption bands at: (cm^{-1})						
6-Bromoindole	665 (w)	800 (s)	840 (m)	852 (w)	864 (w)	1305 (w)	1329 (s)
5-Bromoindole	664 (s)	788 (s)	Nil	Nil	864 (s)	1308 (s)	1329 (w)

NOTE: w, m, and s are respectively weak, medium, and strong.

Neither the melting point of this mixture (74–75°) nor its composition could be altered by repeated crystallization. Similar constant-melting mixtures of isomeric compounds have been recorded in the literature, a specific example being the isomeric 5- and 7-nitro-1,2,3,4-tetrahydrocarbazoles, a mixture of which crystallizes in equimolecular proportion from a variety of solvents to form a substance of constant composition and melting point (11). However, unlike the case of the tetrahydrocarbazoles, chromatography does not readily separate the 5-bromoindole from the 6-bromoindole. Since a single chromatographic operation using an alumina column did in fact achieve a partial separation, as shown by the change in the infrared spectra of the fractions, it is no doubt possible by repeated and careful chromatography to separate them completely.

We have repeated the bromination of ethyl indole-3-carboxylate as described in the literature and obtained the same results (1). Several crystallizations of the ethyl bromoindole-3-carboxylate from aqueous alcohol failed to alter the melting point of 134–137°. A sample of this substance, passed through a column of activated alumina, gave very little separation. Chromatography of the fractions obtained from this first attempt at separation also gave unsatisfactory results. However, since the melting points of the various fractions did in fact differ somewhat both in value and in range from each other it was assumed that, as for the case of the 5- and 6-bromoindoles, a separation could be achieved by painstaking care. It is to be noted that crystallization of each of these various fractions from diluted alcohol again gave the material of constant melting point of 134–137°.

Hydrolysis of the ester according to the literature (1) gave an acid which upon several crystallizations from 95% alcohol melted at 212°, a fact which had already been recorded (1). No attempt was made to separate this substance into its isomers. Our decarboxylation of this compound in quinoline at 140° afforded a compound whose analysis, following several crystallizations from alcohol, agreed with that of a monobromoindole and is now known to be a nearly equimolar mixture of 5- and 6-bromoindoles (m.p. 74–75°).

This work indicates that not only do 5-bromoindole and 6-bromoindole form a constant-melting mixture, but that their precursors, 5- and 6-bromoindole-3-carboxylic acid and the ethyl ester, do likewise. Whether the precursors are nearly equimolar mixtures is uncertain. However, if that is so, then ease of bromination of ethyl indole-3-carboxylate is approximately equal for the 5 and the 6 positions.

EXPERIMENTAL

All melting points are uncorrected. The 4-bromoindole (4), 5-bromoindole (5), and 6-bromoindole (4) were prepared according to the published procedures.

3-Bromo-2-nitrotoluene

Bromine (24 g, 0.15 mole) was added slowly to a stirred suspension of 41.5 g (0.144 mole) of silver salt of 3-methyl-2-nitrobenzoic acid in anhydrous carbon tetrachloride (350 ml) at 25°. Following the addition, the mixture was heated to reflux for 3 hours, during which time carbon dioxide was evolved. The cooled solution was freed from silver salts and the filtrate washed first with aqueous sodium bisulphite, then with aqueous sodium bicarbonate, and finally with water, and then dried over anhydrous magnesium sulphate. Removal of the sulphate and ether afforded a brown oil which, when steam distilled, yielded 18.0 g of 3-bromo-2-nitrotoluene (58%) melting at 27°, lit. m.p. 27° (12).

Potassium Enolate of Ethyl 3-Bromo-2-nitrophenylpyruvate

Potassium (2.3 g, 0.059 mole) was dissolved in anhydrous ethanol (20 ml). To this solution, diluted with 100 ml of dry ether, was added 8.7 g (0.059 mole) of diethyloxalate and the mixture was then stirred gently for 15 minutes. The addition of an ether solution of 11.0 g (0.05 mole) of 3-bromo-2-nitrotoluene produced a deep orange solution which, left at 25° for 7 days, slowly deposited the potassium salt as an orange precipitate. The solid was collected, washed thoroughly with anhydrous ether, and air-dried, yielding 12.1 g (67%) of product.

Ethyl 3-Bromo-2-nitrophenylpyruvate

When a small portion of the above potassium salt was dissolved in water, cooled to 0°, and acidified carefully with 6 *N* hydrochloric acid, a bright yellow solid precipitated. Crystallization from ethanol gave a melting point of 114–115°, which further crystallization failed to alter. Calc. for $C_{11}H_{10}BrNO_5$: C, 41.84; H, 3.17; N, 4.43. Found: C, 41.83; H, 3.19; N, 4.24.

7-Bromoindole-2-carboxylic Acid

A solution of the potassium enolate of ethyl 3-bromo-2-nitrophenylpyruvate (3.0 g, 0.009 mole) in warm 4 *N* ammonium hydroxide (100 ml) was slowly added, with stirring, to a boiling suspension of ferrous hydroxide prepared by the addition of ammonium hydroxide (6 ml, $d = 0.880$) to a boiling solution of ferrous sulphate heptahydrate (14.0 g, 0.05 mole) in 100 ml of water. The resulting reduction mixture was maintained at 90° for 30 minutes and then filtered from the ferric oxide sludge. The sludge was extracted three times with boiling 2 *N* ammonium hydroxide and the combined filtrate and extracts cooled to 25° and acidified with 6 *N* hydrochloric acid. The solid, collected by suction filtration, when crystallized once from aqueous ethanol gave 1.2 g (60%) of 7-bromoindole-2-carboxylic acid melting at 236–239°. Repeated crystallization gave an analytical sample of melting point 242–244°. Calc. for $C_9H_6BrNO_2$: C, 45.00; H, 2.50; N, 5.83. Found: C, 45.20; H, 2.58; N, 5.99.

7-Bromoindole

A solution of 7-bromoindole-2-carboxylic acid (2.9 g) in synthetic quinoline (20 ml) was refluxed for 48 hours, during which time small amounts of copper chromite (10) catalyst were added at frequent intervals. The cooled reaction mixture was poured into 350 ml of 1 *N* hydrochloric acid and the resulting solution extracted thrice with 150-ml portions of ether. The combined ether extracts, washed twice with 1 *N* hydrochloric acid, once with water, twice with 1 *N* ammonium hydroxide, and then with water, were dried over anhydrous magnesium sulphate. Removal of the ether yielded a yellow oil which was purified by chromatography on an alumina column, using *n*-pentane as eluant, giving 1.13 g (48%) of colorless crystals melting at 42–43°. Calc. for C_8H_6BrN: C, 48.98; H, 3.06; N, 7.14; Br, 40.81. Found: C, 49.08; H, 3.09; N, 7.13; Br, 40.42.

Ethyl Pyruvate 2-Bromophenylhydrazone

A solution containing ethyl pyruvate (15.3 g, 0.13 mole) (13), 2-bromophenylhydrazine (24.1 g, 0.13 mole) (14), and ethanol (50 ml) was refluxed for 1 hour, cooled, and poured into cold water. The precipitated yellow solid, when air-dried and crystallized for ethanol, gave 33.1 g (91%) of product melting at 44–46°. Calc. for $C_{11}H_{13}BrN_2O_2$: C, 46.32; H, 4.56; N, 9.86. Found: C, 46.36; H, 4.63; N, 9.78.

Ethyl 7-Bromoindole-2-carboxylate

A mixture of ethyl pyruvate 2-bromophenylhydrazone (33.1 g) and polyphosphoric acid* (40 g) was slowly heated. When the temperature of the mixture reached 70° a spontaneous exothermic reaction occurred raising the temperature to 150°. The reactants were kept at this temperature for 10 minutes, then cooled and poured into cold water. The ether extracts of this solution when dried with anhydrous magnesium sulphate gave a brown oil which solidified. Crystallization from ethanol yielded 14.3 g (46%) of product, m.p. 85–86°. Calc. for $C_{11}H_{10}BrNO_2$: C, 49.25; H, 3.73; N, 5.22. Found: C, 49.01; H, 3.74; N, 5.17.

When 14.3 g of ethyl 7-bromoindole-2-carboxylate was dissolved in a mixture of ethanol (200 ml) and 2.5 *N* aqueous sodium hydroxide solution (70 ml), refluxed for 2 hours, poured into cold water (1000 ml), and then acidified with 6 *N* hydrochloric acid, a solid deposited which after crystallization from ethanol afforded 7.1 g (55.5%) of product melting at 237–239°. This was found to be identical with the 7-bromoindole-2-carboxylic acid prepared above.

Decarboxylation of the Mixture of 5- and 6-Bromoindole-3-carboxylic Acids

Twelve grams of the monobromoindole-3-carboxylic acid mixture (m.p. 212°) (1) in 25 ml of quinoline was heated to 140° whereupon vigorous evolution of carbon dioxide ensued. The temperature was maintained at 140° for 2.5 hours, after which time no further evolution of carbon dioxide occurred. The reaction mixture was then poured into 300 ml of 1 *N* hydrochloric acid and a dark oil separated. The oil solidified and was collected, washed with 1 *N* hydrochloric acid, and then with water. Crystallization from aqueous alcohol yielded a product melting at 74–75°, which repeated crystallization from aqueous alcohol, skellysolve, or heptane failed to alter. Yield, 4.3 g (46%). Calc. for C_8H_6NBr: C, 49.0; H, 3.1. Found: C, 48.7; H, 2.9.

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REFERENCES

1. R. Majima and M. Kotake. Ber. **63** B, 2237 (1930).
2. W. Borsche and W. Jacobs. Ber. **47**, 360 (1914).
3. L. Ettinger and P. Friedländer. Ber. **45**, 2082 (1912).
4. H. Plieninger, F. Suehiro, K. Suhr, and M. Decker. Ber. **88**, 370 (1955).
5. H. R. Snyder, S. M. Parmerter, and L. Katz. J. Am. Chem. Soc. **70**, 222 (1948).
6. E. Muller. Ber. **42**, 430 (1909).
7. C. V. Wilson. Organic reactions. Vol. 9. John Wiley & Sons, Inc., New York. 1957. p. 332.
8. H. N. Rydon and J. C. Tweddle. J. Chem. Soc. 3499 (1955).
9. D. G. Harvey. J. Chem. Soc. 3760 (1958).
10. Organic Syntheses. Coll. Vol. 2. John Wiley & Sons, Inc., New York. p. 142.
11. B. M. Barclay and N. Campbell. J. Chem. Soc. 530 (1945).
12. L. A. Elson, C. S. Gibson, and J. D. A. Johnson. J. Chem. Soc. 2741 (1929).
13. Organic Syntheses. Vol. 31. John Wiley & Sons, Inc., New York. p. 59.
14. M. Busch and E. Meussdörfer. J. prakt. Chem. **75**, 121 (1907).