CXCVII.—*The Nitro- and Amino-Derivatives of o- and p-Methoxybenzoic Acids and of α - and β -Methoxynaphthoic Acids.*

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IN a former paper (T., 1921, **119**, 1425), a series of nitro- and amino-derivatives of *m*-methoxybenzoic acid was prepared. An attempt has been made to apply similar methods to the preparation of the nitro- and amino-derivatives of *o*- and *p*-methoxybenzoic acids and of α - and β -methoxynaphthoic acids.

Most of the isomeric nitro-compounds of the former two acids have already been described. They have generally been obtained by direct nitration of the hydroxy- and conversion into the methoxy-derivative. It was therefore of some interest to determine the orientation of the nitro-groups in the methoxy-acids. We found that it followed Holleman's rule, mentioned in our last paper. For example, the influence of the carboxyl group in determining the meta-orientation of the nitro-group was shown in the nitration of *o*-methoxybenzoic acid. The nitro-group entered mainly the meta-position to the carboxyl group, as the following figures show :

25 per cent.

27 per cent.

48 per cent.

This is also in accordance with the investigations of Simonsen and Rau (T., 1917, **111**, 224), who showed that the orienting influence of a positive group (methoxyl) becomes very feeble when this group is accompanied by a negative (carboxyl) group in the ortho- or para-position.

The above-mentioned nitro-compounds as well as two of the corresponding amino-compounds have already been prepared by Simonsen and Rau (*loc. cit.*). They oxidised 3-, 4-, and 5-nitro-*o*-tolyl methyl ethers with permanganate and obtained the corresponding nitro-acids. These nitro-compounds were reduced to amino-compounds with ferrous hydroxide, a method which was not found satisfactory, the reduction with stannous chloride yielding better results. The 3-nitro-acid was also obtained by Störmer (*Ber.*, 1911, **45**, 655) by oxidation of the aldehyde, and by Fishman (*J. Amer. Chem. Soc.*, 1920, **42**, 2296) by oxidation of 3-nitro-2-methoxybenzyl alcohol. The 5-nitro-acid was obtained by Simonsen and Rau by diazotising 5-nitro-3-amino-2-methoxybenzoic acid and decomposing the diazo-compound and also by direct nitration (*loc. cit.*). Hale and Robertson (*Amer. Chem. J.*, 1908, **39**, 680), Kraut (*Annalen*, 1869, **150**, 6), and Salkowski (*ibid.*, 1894, **173**, 41), prepared the 4-nitro-compound (m.p. 148–150°), which they mistook for the 5-nitro-compound. The method of formation of the 5-nitro-acid (m. p. 161°) according to Simonsen and Rau offers a sufficient proof of its constitution. The main product obtained by us by nitrating the *o*-methoxy-acid had the m. p. 161° and was identical with the above, and when reduced yielded the same 5-amino-compound described by Simonsen and Rau. According to Holleman's theory, which is in agreement with

our own experience, the entrant nitro-group must yield the 5-nitro derivative.

When *p*-methoxybenzoic acid was nitrated, only one of the two possible nitro-compounds was obtained, the nitro-group entering the meta-position to the carboxyl group. It was found to be identical with the compound of m. p. 189° mentioned by Simonsen and Rau in their paper, but not further investigated by them. The preparation of the methoxybenzoic acids was carried out according to Cohen and Dudley (T., 1910, **97**, 1739), and a satisfactory yield was obtained, but the preparation of α - and β -methoxynaphthoic acids by the same method was found to give a very poor yield and was accordingly modified. The carboxyl group in these two compounds is very easily removed (Nietzki and Guitermann, *Ber.*, 1887, **20**, 1274).

A small amount of α -methyl 1-methoxy-2-naphthoate could be obtained by dissolving α -naphthol-2-carboxylic acid in hot methyl sulphate and introducing the theoretical amount of a concentrated aqueous solution of sodium hydroxide as quickly as possible; but the reaction is too vigorous to be employed on a large scale. When sodium hydroxide was slowly introduced, a continuous evolution of carbon dioxide occurred and the solution then contained α -naphthol and its methyl ether. The yield of methyl 1-methoxy-2-naphthoate could be greatly improved by first preparing the methyl α -naphthol-2-carboxylate by the action of methyl sulphate on α -naphthol-2-carboxylic acid in sodium carbonate solution. The yield of ester was 48 per cent., the unchanged acid being easily recovered. The ester was then methylated by dissolving it in methyl sulphate and introducing a large excess of sodium hydroxide solution. β -Naphthol-1-carboxylic acid was much more easily esterified; for when boiled with methyl alcohol and sulphuric acid, an almost theoretical yield of ester was obtained. This was converted into the methoxy-ester by the method mentioned above and gave a satisfactory yield.

The α - and β -methoxy-naphthoic acids prepared by Cohen and Dudley (*loc. cit.*) were not quite pure. The melting points (120—123°; 126—130° respectively), first observed were the same, but, on conversion into the potassium salts and crystallisation, the acids were obtained in a purer state and showed somewhat higher melting points.

1-Methoxy-2-naphthoic acid gave, when nitrated, only one nitro-derivative, namely, 4-nitro-1-methoxy-2-naphthoic acid. Its constitution was determined as follows: When it was boiled for some minutes with strong hydriodic acid, a compound of m. p. 214° was obtained which was identical with 4-nitro-1-hydroxy-2-naphthoic

acid prepared by König (*Ber.*, 1890, **23**, 807) and by Day (*T.*, 1915, **107**, 1625), who determined its constitution by converting it into 4-nitro- α -naphthol. When nitromethoxynaphthoic acid was boiled for some time with hydriodic acid, the methyl group was removed and the nitro-group reduced, forming 4-amino-1-hydroxy-2-naphthoic acid. The same compound was also prepared by reduction of the above nitro-hydroxy-acid with stannous chloride. The 4-amino-hydroxy-2-naphthoic acid was prepared by Nietzki and Guitermann (*Ber.*, 1887, **20**, 1274), by the action of benzenediazonium chloride on 1-hydroxy-2-naphthoic acid and reduction of the resulting azo-compound, and by Weil and Heerdt (*Ber.*, 1922, **55**, [B], 224), by the action of diazotised sulphanilic acid on 1-hydroxy-2-naphthoic acid and reduction of the azo-compound thus formed. 4-Amino-1-methoxy-2-naphthoic acid obtained by reduction of the nitro-compound with stannous chloride does not form a tin salt (see also Weil and Heerdt, *loc. cit.*), but the hydrochloride, which is less soluble in water than the free amino-compound, separates from the solution.

The nitration of 2-methoxy-3-naphthoic acid yielded a mixture of nitro-derivatives which could not be separated by any of the usual methods. Owing to the high temperature required and the consequent decomposition of the product, the reduction could not be effected in the ordinary way. An attempt to reduce the nitro-compounds with stannous chloride dissolved in glacial acetic acid and saturated with hydrogen chloride gave the desired result. The reduction takes place in the cold. A tin salt was formed which, when treated with hydrogen sulphide, gave the hydrochloride of 6-amino-2-methoxy-3-naphthoic acid. Its constitution was determined as follows: when boiled with hydriodic acid, a compound of m. p. 230–232° was obtained, which on heating for some time with dilute sulphuric acid, yielded the 2:6-dihydroxy-3-naphthoic acid prepared by Schmid (*Ber.*, 1893, **26**, 1118) by the action of caustic potash on 6-sulpho-2-hydroxy-3-naphthoic acid (D.R.-P. 69357, Friedländer, III, 506):

The amino-group in 6-amino-2-methoxy-3-naphthoic acid is not removed when treated in the same way with sulphuric acid, but the acetyl derivative is easily decomposed; and the resulting compound showed no sign of any amino-group being present. Although the replacement of the amino-group by hydroxyl has not been definitely ascertained, the new product has a different melting-point from that of the original methoxy-acid.

EXPERIMENTAL.

Nitration of the Methoxybenzoic Acids.—Fifty grams of *o*-methoxybenzoic acid were dissolved in 500 c.c. of acetic anhydride and cooled in a freezing mixture. A mixture of 25 grams of fuming nitric acid and three times its volume of sulphuric acid was very slowly introduced and well stirred, and the temperature kept at -5° to -8° . The mixture was kept over-night, then poured on to ice, and filtered. The solid was recrystallised from glacial acetic acid and yielded two different nitro-compounds, the 3-nitro-acid of m. p. $194-196^{\circ}$ being less soluble than the 4-nitro-compound of m. p. $147-149^{\circ}$. The mother-liquor, on evaporation, deposited the 5-nitro-compound, which is more soluble in glacial acetic acid than the other isomerides.

p-Methoxybenzoic acid, owing to its insolubility, was nitrated in suspension in acetic anhydride. Only one nitro-compound was obtained; 10 grams of methoxy-acid gave 7.8 grams of 3-nitro-4-methoxybenzoic acid of m. p. $189-190^{\circ}$. It crystallises from glacial acetic acid in pale yellow needles which are insoluble in alcohol (Found: N = 6.99. $C_8H_7O_5N$ requires N = 7.10 per cent.).

4-Amino-2-methoxybenzoic Acid.—This acid was obtained by reduction of the corresponding nitro-compound with stannous chloride. It is soluble in hot water, from which it may be recrystallised. On heating, it slowly changed colour at about 205° and melts completely at $217-218^{\circ}$ (Found: N = 8.24. $C_8H_9O_3N$ requires N = 8.38 per cent.).

3-Carbamido-4-methoxybenzoic Acid.—3-Amino-4-methoxybenzoic acid was dissolved in hydrochloric acid and potassium cyanate added until alkaline. After boiling for some minutes, the product was filtered and washed with water. It is soluble in alcohol, benzene, light petroleum, or ether, but slightly soluble in hot water, from which it crystallises in colourless rosettes which melt at 313° with decomposition (Found: N = 13.58. $C_9H_{10}O_4N_2$ requires N = 13.34 per cent.).

3-Carboethoxy-amino-4-methoxybenzoic Acid.—3-Amino-4-methoxybenzoic acid was dissolved in sodium carbonate solution and chloroformic ester added. After heating for some minutes on the water-bath, the solution was allowed to cool, acidified with hydrochloric acid, and filtered. The product is slightly soluble in water and soluble in alcohol. It was crystallised from dilute alcohol and formed colourless needles, m. p. $227-228^{\circ}$ (Found: N = 5.98. $C_{11}H_{13}O_5N$ requires N = 5.85 per cent.).

1-Methoxy-2-naphthoic Acid.—Thirty grams of 1-naphthol-2-carboxylic acid were dissolved in 200 c.c. of 10 per cent. sodium carbonate solution and 12 grams of methyl sulphate slowly intro-

duced. The mixture was heated on the water-bath and shaken from time to time. After half an hour, the brown precipitate was filtered, washed with cold water, and dried. The yield was 7.5 grams and the m. p. 75–80°. When the same experiment was repeated with more methyl sulphate, the yield was raised to 48 per cent. This reaction did not take place when caustic soda was used instead of sodium carbonate, as the ester is readily hydrolysed by very dilute sodium hydroxide solution.

Ten grams of the ester were dissolved in 18.6 grams of methyl sulphate and heated at about 120° until all was dissolved. Through the top of the reflux condenser 6 grams of sodium hydroxide, dissolved in an equal amount of water, were introduced. A vigorous reaction occurred, which soon ceased. After boiling for two hours, the product was allowed to cool and poured into water which was rendered slightly alkaline. The oil (methyl-ester) which separated was extracted with ether, the ethereal solution dehydrated, and the ether removed. The oil was then hydrolysed with alcoholic potash. The methoxy-acid was obtained in brown crystals which melted at 121–124° (8.4 grams). It could be purified by converting it into the potassium salt, which was twice recrystallised from dilute alcohol. The pure methoxy-acid melts at 126–128° and crystallises from alcohol in colourless needles (Found: C=70.95; H=5.12. Calc., C=71.28; H=4.95 per cent.).

2-Methoxy-1-naphthoic Acid.—The ester was prepared very good in yield according to Cohen and Dudley (*loc. cit.*). It was converted into methoxynaphthoic acid in the same manner as described above.

Twenty grams of β -naphthol-1-carboxylic acid gave 14.4 grams of methoxynaphthoic acid, or 72 per cent. It crystallises from alcohol in colourless prisms, m. p. 126–130°, but after recrystallisation of the potassium salt from dilute alcohol the pure methoxy-acid melts at 133–134° (Found: C=70.95; H=5.18. Calc., C=71.28; H=4.95 per cent.).

4-Nitro-1-methoxy-2-naphthoic Acid.—Methoxynaphthoic acid was nitrated in the manner already described. Ten grams of the acid yielded 8.7 grams of crude nitro-acid, or, after recrystallisation from glacial acetic acid, 6.0 grams of acid, m. p. 195–196° (Found: N=5.52; $C_{12}H_9O_5N$ requires N=5.66 per cent.). It is insoluble in water or benzene, but soluble in alcohol or hot acetic acid, from which it crystallises in pale yellow, silky leaflets.

4-Nitro-1-hydroxy-2-naphthoic acid was prepared by boiling 1 gram of the nitromethoxy-acid for two minutes with strong hydriodic acid. On standing over-night, a crystalline compound (yellow needles) separated which had m. p. 214°.

4-Amino-1-methoxy-2-naphthoic Acid.—Eight grams of the nitro-compound were reduced with stannous chloride, from which the hydrochloride was precipitated free from tin. On dissolving in sodium carbonate solution and precipitating with acetic acid, the free amino-compound was obtained. It melts with decomposition at $190-191^{\circ}$ (4 grams). It is not soluble in cold alcohol, water, glacial acetic acid, or benzene, but is slightly soluble in hot water, from which it crystallises in pale brown needles (Found : $N = 6.25$. $C_{12}H_{11}O_3N$ requires $N = 6.45$ per cent.).

4-Carbamido-1-methoxy-2-naphthoic Acid.—The dry hydrochloride of 4-amino-1-methoxy-2-naphthoic acid was heated with a solution of potassium cyanate in water for some minutes on the water-bath. The precipitate was filtered when cold and washed with water. It is slightly soluble in hot water or benzene, soluble in alcohol or glacial acetic acid, and fairly soluble in ether. It darkens at 170° and melts at $176-177^{\circ}$ with decomposition (Found : $N = 10.58$. $C_{13}H_{12}O_4N_2$ requires $N = 10.77$ per cent.).

4-Carbethoxyamino-1-methoxy-2-naphthoic Acid.—The hydrochloride of 4-amino-1-methoxy-2-naphthoic acid was dissolved in a 10 per cent. aqueous solution of potassium carbonate and shaken with chloroformic ester. After being warmed on the water-bath for a few minutes the precipitate was filtered. It is insoluble in water, fairly soluble in ether, and soluble in hot glacial acetic acid, from which it may be crystallised. It melts at 210° with decomposition (Found : $N = 5.30$. $C_{15}H_{15}O_5N$ requires $N = 5.51$ per cent.).

6-Amino-2-methoxy-3-naphthoic Acid.—The mixture of nitro-2-methoxy-3-naphthoic acids (27 grams) was treated in the cold with a 25 per cent. solution of stannous chloride in glacial acetic acid which was saturated with hydrogen chloride. The reaction began immediately, and was completed by warming on the water-bath for a quarter of an hour; the tin salt separated on cooling. The rest of the tin salt, dissolved in the mother-liquor, was obtained by concentrating and saturating with hydrogen chloride. The precipitate was dissolved in hot water, and hydrogen sulphide passed in until all the tin was precipitated. The filtrate was concentrated by boiling it in a flask fitted with a Bunsen valve to prevent oxidation. The hydrochloride separated in long, brown needles (13 grams). It was converted, by treating it with a concentrated solution of sodium acetate, into the free amino-compound, which crystallises from pyridine in glistening leaflets, m. p. 310° , is soluble in water, alcohol, glacial acetic acid, or hot pyridine, but insoluble in ether or benzene (Found : $N = 6.38$. $C_{12}H_{11}O_3N$ requires $N = 6.45$ per cent.).

The amino-compound is easily diazotised and then gives red azo-colours with α - and β -naphthols and resorcinol. The *sulphate* crystallises from alcohol in long, yellow needles which melt at 196° . It is less soluble in water than the free amino-compound.

The *acetyl* derivative was obtained by boiling the amino-compound with acetic anhydride and sodium acetate for two hours. When the resulting solution was concentrated, the acetyl derivative separated. It is soluble in alcohol or glacial acetic acid, slightly soluble in ether or benzene, but insoluble in water. It crystallises from dilute alcohol in slightly brown, short prisms which melt sharply at 193° . When heated on the water-bath for one hour with a 4 per cent. solution of sulphuric acid, a colourless precipitate was obtained on cooling, which, after being recrystallised from dilute alcohol, melted at 240 – 241° . It is soluble in hot alcohol, but insoluble in water. It cannot be diazotised and does not form any salts with mineral acids. It is probably 6-hydroxy-2-methoxy-3-naphthoic acid.

6-Amino-2-hydroxy-3-naphthoic Acid. — 6-Amino-2-methoxy-3-naphthoic acid was heated on the water-bath for half an hour with a 20 per cent. solution of hydriodic acid. On cooling, yellow needles separated which were filtered and converted into the free amino-compound by the addition of sodium acetate. The hydroxy-acid is soluble in alcohol, ether, or ethyl acetate, but slightly soluble in hot water, benzene, or chloroform, and insoluble in light petroleum. Recrystallised from dilute alcohol, it forms long, pale yellow needles or rosettes which partly decompose above 210° , finally melting at 230 – 232° . It gives a red colour with very dilute ferric chloride and a green colour with sulphuric acid. It is easily diazotised, and then gives a red azo-colour with α - and β -naphthols and resorcinol (Found: $N=7.07$. $C_{11}H_9O_3N$ requires $N=6.89$ per cent.).

When boiled for seven hours with a 4 per cent. solution of sulphuric acid and then evaporated to a small volume, a yellow precipitate was obtained which, after being recrystallised from dilute alcohol, melted at 227 – 228° and showed all the properties of 2 : 6-hydroxy-3-naphthoic acid.

6-Carbamido-2-methoxy-3-naphthoic Acid. — The hydrochloride of 6-amino-2-methoxy-3-naphthoic acid was heated with a concentrated solution of potassium cyanate on the water-bath for some minutes. When cold, the liquid was acidified with hydrochloric acid, and the precipitate filtered and washed with water. It is soluble in alcohol, slightly soluble in hot water, but insoluble in ether, benzene, chloroform, or light petroleum. When recrystallised from dilute alcohol, it melts at 215 – 216° (Found: $N=10.59$. $C_{13}H_{12}O_4N_2$ requires $N=10.76$ per cent.).

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6-Carbamido-2-hydroxy-3-naphthoic Acid.—This compound was prepared in the same manner as described above and recrystallised from water. It is soluble in alcohol, pyridine, or hot water, but insoluble in ether or benzene. It began to darken at 200° and melted at $340\text{--}341^{\circ}$ (Found: 11.35. $\text{C}_{12}\text{H}_{10}\text{O}_4\text{N}_2$ requires N = 11.38 per cent.).

Attempts to prepare the carbethoxyamino-derivative by the action of chloroformic ester on the amino-group gave a sticky mass which could not be crystallised.

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