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Preparation of 2-Imidazole- and 2-Thiazolecarbaldehydes

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Aldehydes derived from thiazole and imidazole have been prepared by different methods and the yields are compared. The methods of choice were found to be either addition of dimethylformamide to the suitable lithium derivative or oxidation of the corresponding carbinol by selenium dioxide, except in the case of imidazole-2-carbaldehyde where reductive debenzylation of *N*-benzylimidazole-2-carbaldehyde diethylacetal was the only fruitful method.

In connection with a current polarographic investigation [1] a series of aldehydes derived from imidazole and thiazole with the carbaldehyde group in the 2-position was needed. The following methods for the preparation of 2-thiazolecarbaldehydes [2–10] have been reported: a) Chromic acid oxidation of the corresponding carbinols [2,7,10] (yields not stated); b) ozonolysis of a 2-styrylthiazole [3] followed by catalytic reduction (yield 47 % of crude product); c) reaction of 2-thiazolyldiazonium salts with formaldoxime [4] (yield 10—15 %); d) reaction between 2-thiazolyllithium and *N*-methylformanilide [5] (yield 30 %); e) McFadyen-Stevens synthesis [5] (low yield of impure 4-methyl-2-thiazolecarbaldehyde); f) periodate oxidation of a carbohydrate derivative [8] (yield not reported); g) hydrolysis of some quaternary pyridinium salt nitrones [9] (fair yield).

Attempts to oxidize 2-methylimidazole by selenium dioxide [11] have been reported, but only a molecular compound was isolated and no oxidation occurred. However, oxidation of the carbinols of *N*-methyl- and *N*-benzylimidazole in chloroform at room temperature with manganese dioxide have recently [12] been found to give the aldehydes in yields up to 60 %.*

As the syntheses reported in the literature [2–11] gave unsatisfactory yields a development of better methods seemed warranted. Four methods have been investigated: A) Addition of *N*,*N*-dimethylformamide to lithium derivatives; B) selenium dioxide oxidation of carbinols; C) selenium dioxide oxidation of methyl derivatives; D) nitric acid oxidation of carbinols. A summary of the results obtained is given in Table 1.

* *Note added in proof.* After the submitting of this paper the preparation of 2-imidazolecarbaldehyde has been reported. (Schubert, H. and Rudorf, H.-D. *Angew. Chem.* **78** (1966) 715).

Table 1. Yields (%) of 2-thiazole- and 2-imidazolecarbaldehydes. Size of batch: 0.1—0.2 mole.

Aldehyde	Method A	Method B	Method C	Method D
2-Thiazolecarbaldehyde	61	61	4	9
4-Methyl-2-thiazolecarbaldehyde	61	51	17	Trace
5-Methyl-2-thiazolecarbaldehyde	54	—	—	—
N-Benzyl-2-imidazolecarbaldehyde	68	98	Trace	Trace
N-Methyl-2-imidazolecarbaldehyde	65	43	Trace	Trace
2-Imidazolecarbaldehyde	—	Trace	—	Trace

METHOD A. ADDITION OF DIMETHYLFORMAMIDE TO LITHIUM DERIVATIVES

$$R-Li \xrightarrow[2)\ H_2O]{1)\ DMF} RCHO \qquad (1)$$

By substituting dimethylformamide (DMF) for *N*-methylformanilide [5] and using a longer reaction time (20 h instead of 1/2 h) the yield was doubled and the fractionation of the reaction mixture was simplified for 2-thiazolecarbaldehyde; *N*-methylformanilide and *N*-methylaniline have boiling points rather close to that of the aldehydic product, whereas DMF boils considerably lower. This procedure was then adopted for the compounds shown in Table 1.

The organometallic compounds were prepared by direct metalation of the parent heterocycles [17,18] with butyllithium in diethyl ether at low temperatures except in the case of 2-thiazolyllithium where halogen-metal interconversion was found preferable. The method cannot be used for the preparation of *N*-unsubstituted imidazoles as they metalate at the nitrogen atom.

From mechanistic considerations [5] the addition of the organometallic compound to DMF would be preferable and good yields (70 %) have been obtained [13] of 3-thiophenecarbaldehyde by "reverse addition". As the organometallic compounds in the present series are rather unstable at temperatures above —40° it was found more convenient to use a rapid, direct addition of excess of DMF to the lithium derivative. The same procedure has been applied in the isothiazole series [14] with good results.

METHOD B. SELENIUM DIOXIDE OXIDATION OF PRIMARY ALCOHOLS

$$RCH_2OH \xrightarrow[100°,\ dioxane]{SeO_2} R-CHO \qquad (2)$$

Oxidation of a primary alcohol by selenium dioxide (2) in refluxing dioxane has not been widely used in heterocyclic chemistry, but the method has been found to give fair to very good yields (Table 1) in the thiazole and imidazole series.

The reaction requires a rather long reaction time (3 to 10 days), and oxidation of the aldehydes formed might occur. Some of the acids thus formed are sensitive to heat and decarboxylate easily to the parent heterocyclic base.

N-Benzyl-2-imidazolemethanol was found to form the aldehyde in a practically quantitative yield. This aldehyde seems more resistant towards oxidation with selenium dioxide than the other aldehydes of this series.

N-Methyl-2-imidazolemethanol yielded a mixture of *N*-methylimidazole and the aldehyde; the reaction mixture was analysed by NMR-spectroscopy. Isolation of the aldehyde was only possible after acetalisation.

2-Imidazolemethanol reacted very slowly with selenium dioxide in a mixture of dioxane and ethanol, but much faster in butanol. Only traces of the aldehyde were detected with 2,4-dinitrophenylhydrazine and no product was isolated. Manganese dioxide has been found [12] to oxidize 2-imidazolemethanol directly to the carboxylic acid.

METHOD C. SELENIUM DIOXIDE OXIDATION OF ACTIVATED METHYL GROUPS

$$R-CH_3 \xrightarrow[100°,\ dioxane]{SeO_2} R-CHO \qquad (3)$$

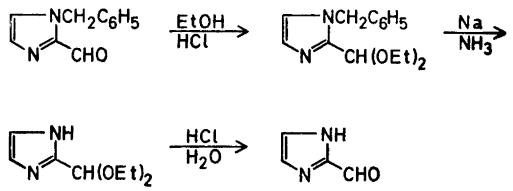
Oxidation of a reactive methyl group to an aldehyde group by selenium dioxide is a standard reaction in heterocyclic chemistry and works quite well in the cases of the condensed analogues 2-methylbenzothiazole [15] and 2-methylbenzimidazole.[11] The results in Table 1 show that this reaction is poorly suited for the synthesis of 2-thiazolecarbaldehydes and unsuitable for the preparation of 2-imidazolecarbaldehydes.

METHOD D. NITRIC ACID OXIDATION OF PRIMARY ALCOHOLS

$$R-CH_2OH \xrightarrow{HNO_3} R-CHO + R-COOH \qquad (4)$$

The reaction (4) has been found useful in the synthesis of 4-imidazolecarbaldehyde,[16] but the results in Table 1 obtained by following the procedure of Pyman [16] show that the method is unsuitable for the preparation of 2-thiazolecarbaldehydes and 2-imidazolecarbaldehydes.

2-Imidazole aldehyde



(5)

Neither of the methods A, B, C, or D was found suitable for the preparation of 2-imidazolecarbaldehyde. This compound was obtained from *N*-benzyl-2-imidazole aldehyde in fair yield by the reactions shown in eqn. (5). The debenzylation by means of sodium in liquid ammonia is a general reaction of *N*-benzylimidazoles.[19]

The 2-thiazolecarbaldehydes are slightly yellowish oils with a characteristic, aromatic odour; *N*-benzyl-2-imidazolecarbaldehyde is a colour- and odourless oil, while the *N*-methyl- and *N*-unsubstituted 2-imidazolecarbaldehydes are solids. Some derivatives (acetals, phenylhydrazones, 2,4-dinitrophenylhydrazones, oximes, aniles) have been prepared for further characterisation of the aldehydes.

The NMR-spectra of the aldehydes show that there is a long-range coupling [20] between the proton in the aldehyde group and protons in the aromatic ring. Similar effects are found in some other aromatic aldehydes, *e.g.* in the furan [33] and thiophene series.

The choice between the methods A and B may depend on the availability of the starting material, and as the parent bases mostly are precursors of the 2-carbinols, the direct addition of DMF to the metalated heterocyclic base would in most cases be preferable; only the very high yield of aldehyde from the selenium dioxide oxidation of *N*-benzyl-2-hydroxymethylimidazole (and the easy synthesis of this compound) may favour the method B in this case. *N*-Substituted imidazoles can be hydroxymethylated in the 2-position in high yield with aqueous formaldehyde under pressure,[19,24] while thiazole gives only a low yield of carbinol by this procedure.[25] By a modification of an earlier method [22] the 2-hydroxymethylthiazoles can be obtained in high yield from the lithium derivatives and gaseous formaldehyde; the recent process [23] using paraformaldehyde at room temperature does not seem to be applicable at the low temperatures necessary here. The methyl compounds used in the selenium dioxide oxidations (C) were also available from the lithium derivatives by reaction with methyl sulphate, analogously to the procedure of Gilman.[21]

EXPERIMENTAL

Materials not specified below were commercially available and used without further purification. Microanalyses were made by Strauss and Weiler, Oxford, Ilse Beetz, Kronach, Alfred Bernhardt, Mülheim, and our Analytical Department. IR-spectra were recorded on a Perkin-Elmer Infracord Spectrophotometer and NMR-spectra on a Varian Model A-60 Spectrometer. All melting and boiling points are uncorrected.

Starting materials

N-*Benzylimidazole* was prepared according to Jones [19] or more conveniently by an elegant one-step alkylation [26] of imidazole in liquid ammonia. By substitution of benzyl chloride for benzyl bromide and extraction with hot tetrahydrofuran followed by cooling to −80° in dry ice the inconvenient distillation was avoided and yields of 80−90 % of pure, white crystals, m.p. 70−72° (71−72°) [19] were easily obtained on a 1/2-mole scale.

N-*Methylimidazole*, b.p.$_9$ 75−77° (b.p.$_{18}$ 97°),[26] n_D^{25} 1.4965 was prepared by the same method [26] in yields of about 60 % (72 %).[26]

2-Bromothiazole, b.p.$_{12}$ 61−62° (b.p.$_{20}$ 70.5°),[28] n_D^{25} 1.5900 was prepared according to Ganapathi and Venkataraman [27] in yields of 60−75 % (90 %).[28]

4-Methylthiazole, b.p.$_{40}$ 54° (b.p.$_{780}$ 132.9°),[28] n_D^{25} 1.5215, was prepared in benzene in 70 % yield from chloroacetone (0.8 mole), formamide (0.9 mole), and phosphorus pentasulfide (0.25 mole) by following the procedure described for 2,4-dimethylthiazole;[29] working without solvent [27] is uncontrollable on a larger scale.

5-Methylthiazole, b.p.$_{40}$ 62−63°, (b.p.$_{100}$ 82.8°),[28] n_D^{25} 1.5260, was prepared analogously from α-bromopropanol [30] (a fraction b.p.$_{85}$ 50−60°, n_D^{20} 1.4930 was used without further purification) (0.3 mole), formamide (0.4 mole) and phosphorus pentasulfide (0.08 mole) in 8−10 % yield. Better yields are obtained in dioxane medium.[28,31]

2,4-Dimethylthiazole. 0.21 mole of butyllithium [32] in 200 ml of ether was cooled (under nitrogen) below −75°; 19.8 g (0.2 mole) of 4-methylthiazole in 50 ml of ether were added during 1/2 h keeping the temperature below −70°. The resulting clear, light-yellow solution was stirred cold for further 1 1/2 h, and 30 ml (0.33 mole) of redistilled methyl sulphate in 25 ml of ether were quickly added with only little evolution of heat; the mixture was stirred cold overnight (bath-temperature −10° the next morning) and cautiously hydrolysed by addition of 125 ml of 4 N hydrochloric acid with external cooling. The layers were separated and the ether layer was washed twice with 25 ml of 4 N hydrochloric acid. The combined acid extracts were made strongly alkaline with sodium hydroxide, extracted 4 times with ether which was then dried over potassium hydroxide. After removal of the solvent the oily residue was fractionated *in vacuo* giving 17.1 g (75 %) of 2,4-dimethylthiazole, b.p.$_9$ 32−34°, (143−145°),[29] n_D^{25} 1.5055.

2-Methylthiazole was prepared [8] analogously from 2-bromothiazole in 60 % yield, b.p. 125−128° (126.5°),[28] n_D^{25} 1.5140. Strict control of the temperature in the halogen-metal exchange step is necessary, otherwise the organometallic solution becomes dark-brown.

N-*Benzyl-2-methylimidazole*. *N*-Benzylimidazole (15.8 g, 0.1 mole) in 250 ml of ether was cooled to −50°C under nitrogen with stirring; the base precipitated and was metalated with 0.108 mole of butyllithium in ether at −45°C during 1/2 h giving a practically clear, slightly reddish-brown solution which was stirred for further 1 h at −50°C. (The temperature should not vary much from −50°C as the lithium reagent precipitates below −55°C and will not redissolve by warming up to −35°C). Methyl sulphate (15 ml, 0.165 mole) in 20 ml of ether was added in one portion and the reaction mixture worked up as described above, except that chloroform was used for the extractions; the chloroform was dried over potassium carbonate. Yield 13.9 g (81 %) of a viscous colourless oil, b.p.$_{0.15}$ 100−103°, n_D^{25} 1.5660. Redistillation: b.p.$_{0.1}$ 100°, n_D^{25} 1.5660. (Found: C 76.41; H 6.94; N 16.01. Calc. for $C_{11}H_{12}N_2$: C 76.71; H 7.02; N 16.27).

1,2-Dimethylimidazole was prepared analogously, except that in this case continuous extraction with chloroform (60 h) was used. Yield 11.2 g (68 %) of a colourless oil, b.p.$_9$ 81−83°, n_D^{25} 1.4950. Redistillation: b.p.$_{8.5}$ 80−81°, n_D^{25} 1.4945. (Found: C 62.22; H 8.21; N 29.51. Calc. for $C_5H_8N_2$: C 62.47; H 8.39; N 29.14).

2-Hydroxymethylthiazole. A solution of 0.3 mole of 2-thiazolyllithium was prepared as described above; 20 g of dry paraformaldehyde was depolymerized in a fractionating flask by heating it in an oil bath at 200−220° and the gaseous formaldehyde swept with a slow stream of nitrogen [22] through the wide-bore (12 mm) side-arm ending 1 cm above the surface of the reaction mixture (efficient cooling is essential). The mixture was stirred in the bath overnight and then cautiously hydrolyzed with 200 ml of 4 N hydrochloric acid. The layers were separated and, after filtration from some unreacted paraformaldehyde, the ether layer washed twice with 25 ml of 4 N hydrochloric acid. The combined acid layers were made strongly alkaline and continuously extracted for

65 h with a 4:1:1 mixture of ether, alcohol, and chloroform; the organic layer was dried over sodium sulphate. After removal of the solvent *in vacuo* the residue, 33.1 g (96 %), solidified on standing. Recrystallisation from abs. ethanol gave 27.7 g (80 %) of a pure product, m.p. 65—66° (66°).[22] *Hydrochloride*, m.p. 126—127° (abs. ethanol) (126.5—127°).[25]

4-Methyl-2-hydroxymethylthiazole was prepared by the same procedure, except that the resulting oily residue (92 %) from the continuous extraction (45 h) did not crystallize and was distilled giving 81 % of a slightly yellowish oil, b.p.$_9$ 121—124°, n_D^{25} 1.5495. Redistillation: b.p.$_9$ 124°, n_D^{25} 1.5502. (Found: C 46.78; H 5.42; N 10.40; S 25.04. Calc. for C_5H_7ONS: C 46.51; H 5.47; N 10.85; S 25.79). *Hydrochloride*, m.p. 146—147° (abs. ethanol). (Equiv. wt. of chloride: Found: 166.2. Calc.: 166.6).

N-*Benzyl-2-hydroxymethylimidazole* was prepared according to Jones [19] and isolated in 80—90 % yield as the hydrochloride which was dissolved in aqueous potassium carbonate and the solution extracted 3 times with a 1:1 mixture of ether and methanol; after drying over potassium carbonate the solvent was removed *in vacuo* leaving in a practically quantitative yield a light-brown solid residue, m.p. 94—95° (toluene). (Found: C 70.29; H 6.32. Calc. for $C_{11}H_{12}ON_2$: C 70.18; H 6.32).

N-*Methyl-2-hydroxymethylimidazole* was prepared analogously using a great excess of formaldehyde and a temperature of 120° for 20 h; these modifications raised the crude yield from that obtained by Grindley and Pyman [24] (50 %) to 90 % or more. The product was preferably purified by removal of unreacted N-methylimidazole by steam-distillation and removal of the solvent *in vacuo* at temperatures below 50°. The semi-solid residue was recrystallized twice from chloroform, m.p. 112° (116°).[24]

2-Hydroxymethylimidazole. *N*-Benzyl-2-hydroxymethylimidazole (34.5 g 0.184 mole) was suspended in 50 ml of ether and 150 ml of liquid ammonia were added; sodium in small pieces was added with strring and cooling to −35° until a dark-blue (or greenish) colour persisted; stirring was continued for 15 min, solid ammonium chloride was added until the colour disappeared, and the mixture was left overnight for evaporation of the ammonia. To the solid residue was cautiously added some water and 75 ml of 4 N hydrochloric acid, and the solvent was removed *in vacuo* on a water bath below 50° until crystals appeared. The residue was made basic with solid potassium carbonate and continuously extracted for 90 h with a 4:1:1 mixture of ether, alcohol and chloroform. Removal of the organic solvent left 13.8 g (76 %) of a light-brown solid, m.p. 114—115° (abs. ethanol). Continued extraction for further 115 h gave 3.1 g thus raising the yield of crude product to 94 % (47 % [19] as the picrate). (Found: C 48.98; H 6.11; N 28.81. Calc. for $C_4H_6ON_2$: C 48.97; H 6.17; N 28.56).

Aldehydes from lithium derivatives

2-Thiazolecarbaldehyde. To a solution of 0.2 mole of 2-thiazolyllithium kept below −70° (prepared as described above) were quickly added 25 ml (0.3 mole) of redistilled dimethylformamide in 20 ml of ether; efficient cooling was necessary. The reaction mixture was stirred overnight while the temperature of the cooling bath slowly rose to 0°; after addition of a little crushed ice 125 ml of 4 N hydrochloric acid were cautiously added and the layers separated. The ether layer was washed twice with 25 ml of 4 N hydrochloric acid, the combined acid extracts were made slightly alkaline with potassium carbonate and extracted 4 times with ether which was then dried over sodium sulphate. After removal of the solvent the residue was fractionated *in vacuo*; obtained were 13.8 g (61 %) of a light-yellow oil, b.p.$_{11}$ 62—64°, n_D^{25} 1.5700. Redistillation: b.p.$_{10.5}$ 63°, n_D^{25} 1.5720 (b.p.$_3$ 37°).[4,5] (Found: C 42.08; H 2.84; N 12.41; S 28.16. Calc. for C_4H_3ONS: C 42.49; H 2.67; N 12.39; S 28.30). Principal bands in the IR-spectrum (cm^{-1}): 3140(m), 2980(m), 1700(s), 1480(s), 1395(s), 1335(m), 1320(m), 1230(s), 1145(m), 1060(m), 780(s). The *diethylacetal* was prepared by refluxing 0.08 mole of the aldehyde overnight in a mixture of 80 ml of ethanol and 10 ml of conc. hydrochloric acid and isolated in 57 % yield by fractionation *in vacuo*, b.p. 102—104°, n_D^{25} 1.4855. Redistillation: b.p.$_9$ 103—104°, n_D^{25} 1.4855. (Found: C 51.24; H 6.97; N 7.93. Calc. for $C_9H_{13}O_2NS$: C 51.33; H 7.00; N 7.48). The *anile* was prepared in practically quantitative yield by keeping equimolar amounts of the aldehyde and aniline for 15 min at 100°; the mixture solidified on cooling, m.p. 76—77° (ethanol). (Found: C 64.17; H 4.42. Calc. for $C_{10}H_8N_2S$: C 63.82; H 4.29). *Phenylhydrazone*, m.p. 117—118° (50 % aqueous ethanol) (120°).[4] (Found: C 59.17;

H 4.56. Calc. for $C_{10}H_9N_3S$: C 59.10; H 4.46). *2,4-Dinitrophenylhydrazone*, m.p. 241–243° (ethanol). (Found: C 42.41; H 2.49. Calc. for $C_{10}H_7O_4N_5S$: C 40.96; H 2.41). *Oxime*, m.p. 117° (water). (Found: C 37.51; H 3.20. Calc. for $C_4H_1ON_2S$: C 37.51; H 3.15).

The other aldehydes in Table 1 were prepared similarly from ethereal solutions of the lithium reagents; the imidazolecarbaldehydes were extracted with chloroform.

4-Methyl-2-thiazolecarbaldehyde, light-yellow oil, b.p.$_{10}$ 73–75° (61 %), n_D^{25} 1.5590. Redistillation: b.p.$_{11}$ 75.5–76°, n_D^{25} 1.5580. (Found: C 47.25; H 3.82; N 10.75; S 25.48. Calc. for C_5H_5ONS: C 47.25; H 3.97; N 11.02; S 25.18). Principal bands in the IR-spectrum (cm^{-1}): 3140(w), 2975(m), 1695(s), 1500(m), 1460(s), 1290(m), 1230(s), 1140(w), 962(m), 868(m), 742(m). *Diethylacetal*, light-yellow oil, b.p.$_{10}$ 113–115° (56 %), n_D^{25} 1.4870. Redistillation: b.p.$_9$ 112–113°, n_D^{25} 1.4868. (Found: C 53.39; H 7.40; N 7.44. Calc. for $C_9H_{15}O_2NS$: C 53.72; H 7.51; N 6.96). *Anile*, yellow oil, solidified on standing in the refrigerator, m.p. 45° (ligroin). (Found: C 64.93; H 4.84. Calc. for $C_{11}H_{10}N_2S$: C 65.33; H 4.98). *Phenylhydrazone*, m.p. 179–180° (ethanol). (Found: C 61.34; H 5.12. Calc. for $C_{11}H_{11}N_3S$: C 60.82; H 5.10). *2,4-Dinitrophenylhydrazone*, m.p. 254–256° (ethanol). (Found: C 43.13; H 2.93. Calc. for $C_{11}H_9O_4N_5S$: C 43.00; H 2.95).

5-Methyl-2-thiazolecarbaldehyde, yellowish oil, b.p.$_{10}$ 80–81° (54 %) (b.p.$_3$ 49–50),[4] n_D^{25} 1.5645. Redistillation: b.p.$_{10}$ 80–80.5°, n_D^{25} 1.5655. (Found: C 47.35; H 4.09; N 11.30; S 24.95. Calc. for C_5H_5ONS: C 47.25; H 3.97; N 11.02; S 25.18). Principal bands in the IR-spectrum (cm^{-1}): 2965(m), 1680(s), 1495(m), 1410(s), 1325(m), 1285(m), 1230(s), 1140(m), 860(m), 772(s). *Anile*, m.p. 97° (ethanol). (Found: C 64.71; H 4.73. Calc. for $C_{11}H_{10}N_2S$: C 65.33; H 4.98). *Phenylhydrazone*, m.p. 164° (ethanol) (133°).[4] (Found: C 60.82; H 5.06. Calc. for $C_{11}H_{11}N_3S$: C 60.82; H 5.10). *2,4-Dinitrophenylhydrazone*, m.p. 277° (ethanol). (Found: C 42.92; H 2.88. Calc. for $C_{11}H_9O_4N_5S$: C 43.00; H 2.95).

N-*Benzyl-2-imidazolecarbaldehyde*, colourless oil, b.p.$_{0.1}$ 109–111° (68 %), n_D^{25} 1.5930. Redistillation: b.p.$_{0.1}$ 110°, n_D^{25} 1.5935. (Found: C 70.49; H 5.08; N 14.92. Calc. for $C_{11}H_{10}ON_2$: C 70.95; H 5.41; N 15.05. Principal bands in the IR-spectrum (cm^{-1}): 2960(m), 1675(s), 1485(m), 1460(m), 1440(m), 1395(s), 1325(s), 1150(m), 915(m), 768(s), 715(m). *Diethylacetal*, colourless oil, b.p.$_{0.2}$ 120–130° (78 %), n_D^{25} 1.5275. Redistillation: b.p.$_{0.05}$ 109–110°, n_D^{25} 1.5240. (Found: C 69.14; H 7.74; N 10.55. Calc. for $C_{15}H_{20}O_2N_2$: C 69.20; H 7.74; N 10.76). *Anile*, m.p. 63° (ligroin). (Found: C 77.93; H 5.79. Calc. for $C_{17}H_{15}N_3$: C 78.13; H 5.79). *Phenylhydrazone*, m.p. 168° (ethanol) (164°).[12] (Found: C 74.39; H 5.99. Calc. for $C_{17}H_{16}N_4$: C 73.89; H 5.84). *2,4-Dinitrophenylhydrazone hydrochloride*, m.p. 202–204°. (ethanol-hydrochloric acid). (Found: C 49.74; H 4.04. Calc. for $C_{17}H_{15}O_4N_6Cl$: C 50.82; H 3.74. Equiv. wt. of chloride: Found: 396, 413. Calc.: 402.8). *Oxime*, m.p. 166° (ethanol-water) (170°).[12] (Found: C 65.25; H 5.49. Calc. for $C_{11}H_{11}ON_3$; C 65.67; H 5.51).

N-*Methyl-2-imidazolecarbaldehyde*, colourless oil which crystallized on standing, b.p.$_{12}$ 89–95° (65 %), n_D^{25} 1.5370, m.p. 34–37° (closed tube). Recrystallisation: m.p. 38–39° (tetrahydrofuran) (32–34°).[12] (Found: C 54.63; H 5.52; N 25.27. Calc. for C_5H_6ON: C 54.54; H 5.49; N 25.44). Due to sublimation this substance should be kept in a well-stoppered bottle. Principal bands in the IR-spectrum (CCl_4, cm^{-1}): 2970(m), 1680(s), 1475(m), 1400(s), 1370(m), 1320(m), 1280(m), 1150(m), 913(m). *Diethylacetal*, colourless oil, b.p.$_9$ 109–112° (45 %), n_D^{25} 1.4680. Redistillation: b.p.$_{10}$ 115°, n_D^{25} 1.4705. (Found: C 58.67; H 8.60. Calc. for $C_9H_{16}O_2N_2$: C 58.67; H 8.75). *Phenylhydrazone*, m.p. 119–120° (ethanol). (Found: C 66.16; H 5.90. Calc. for $C_{11}H_{12}N_4$: C 65.98; H 6.04). *2,4-Dinitrophenylhydrazone hydrochloride*, m.p. 287–288° (ethanol-hydrochloric acid). (Equiv. wt. of chloride: Found: 335. Calc.: 326.7).

Aldehydes by selenium dioxide oxidation of methanols

2-Thiazolecarbaldehyde. A mixture of 5.55 g (0.05 mole) of finely powdered selenium dioxide, 5 ml of water, and 75 ml of dioxane was heated with stirring until dissolution, and 11.5 g (0.1 mole) of 2-hydroxymethylthiazole in 25 ml of dioxane were added and refluxed for 45 h with stirring. The selenium (3.7 g, 94 %) was filtered off after cooling to room temperature, 10 ml of conc. hydrochloric acid were added and the solvent evaporated *in vacuo* on a water bath kept below 50°. To the dark oily residue was added excess of potassium carbonate and ether; the ethereal solution was dried over sodium

sulphate; after filtration and removal of the solvent the residue was fractionated *in vacuo*, yielding 6.9 g (61 %) of the aldehyde, b.p.$_9$ 57—65°, n_D^{25} 1.5705.

4-Methyl-2-thiazolecarbaldehyde was prepared analogously (120 h of oxidation, quantitative isolation of selenium) in 51 % yield, b.p.$_9$ 72—82°, n_D^{25} 1.5560.

N-*Benzyl-2-imidazolecarbaldehyde* was prepared analogously (70 h of oxidation, quantitative isolation of selenium) in 98 % yield, b.p.$_{0.1}$ 108—110°, n_D^{25} 1.5930. Due to the higher boiling points of the imidazolecarbaldehydes addition of hydrochloric acid before evaporation of the solvent is not necessary.

N-*Methyl-2-imidazolecarbaldehyde* was obtained contaminated with some N-methylimidazole after 11 days of oxidation (addition of about 30 % of ethanol was necessary to get a homogeneous system, 82 % of selenium was isolated); a fraction (65 %), b.p.$_{0.2}$ 44—47°, n_D^{25} 1.5290, was collected, and analysis by NMR-spectroscopy showed the presence of 33 % of *N*-methylimidazole. The composition of the mixture was not changed much by redistillation, but after acetalisation (as described above) it was possible to isolate a rather pure fraction of the diethylacetal in a modest overall yield.

2-Imidazolecarbaldehyde. Traces of this compound could be detected with 2,4-dinitrophenylhydrazine after 9 days of oxidation in 50 % ethanol-dioxane; 20 % of selenium was isolated. The aldehyde could not be isolated. On oxidation in butanol for further 50 h practically all the selenium dioxide was reduced to selenium, but the now reddish-brown solution contained only traces of aldehyde; no products were isolated.

Selenium dioxide oxidation of active methyl compounds. The oxidation was performed as described above for the oxidation of the carbinols; somewhat longer reaction times were necessary. *2-Thiazolecarbaldehyde* and *4-methyl-2-thiazolecarbaldehyde* were isolated as impure fractions (contaminated with unreacted methylthiazoles) in 4 % and 17 % yield, respectively. The 2-methylimidazoles were hardly attacked by selenium dioxide in dioxane after 9 days; traces of aldehyde could be detected with 2,4-dinitrophenylhydrazine, but only little selenium was isolated. The use of butanol as solvent gave only a little increase of the reaction rate and it was not possible to isolate 2-imidazolecarbaldehydes from the resulting reaction mixtures.

Oxidation of methanols by nitric acid was performed according to Pyman [16] with a three-fold excess of conc. nitric acid, except that the free bases and not the hydrochlorides were used, and the acid solutions were not evaporated. Using the procedure described above only impure 2-thiazolecarbaldehyde could be isolated in 9 % yield; none of the other aldehydes could be isolated.

2-Imidazolecarbaldehyde diethylacetal. 11.1 g (0.043 mole) of *N*-benzyl-2-imidazolecarbaldehyde diethylacetal in 30—40 ml of ether were cooled in a bath of −40° and 150 ml of liquid ammonia were cautiously added. With stirring and cooling, very small pieces of sodium were added until a dark brownish-blue colour persisted; on further stirring for 1/2 h the solution became reddish-brown; excess of solid ammonium chloride was added and the ammonia evaporated overnight. The residue was extracted with hot methylene chloride, the solution filtered and the solvent evaporated *in vacuo*. Yield 7.6 g (practically quantitative) of a brownish solid, which by recrystallisation from methylene chloride gave 5.3 g (73 %) of light-brown needles, m.p. 112—113°; after recrystallisation or sublimation *in vacuo* m.p. 116°. (Found: C 56.62; H 8.17; N 16.71. Calc. for $C_8H_{14}O_2N_2$: C 56.45; H 8.29; N 16.46).

2-Imidazolecarbaldehyde. 1.0 g (0.0059 mole) of the above mentioned acetal was kept overnight at 80° in a closed flask with 2 ml of 4 N hydrochloric acid; after cooling excess potassium carbonate, 100 ml of chloroform, and some anhydrous magnesium sulphate were added. Evaporation of the solvent *in vacuo* left 450 mg (80 %) of light yellow *2-imidazolecarbaldehyde* (decomp. about 195°, closed tube) (ethanol-tetrahydrofuran). (Found: C 49.91; H 4.12; N 29.04. Calc. for $C_4H_4ON_2$: C 49.99; H 4.20; N 29.16). Principal bands in the IR-spectrum (KBr-disc, cm^{-1}): 3150(m), 3010(m), 2900—2500(s), 1855(w), 1680(s), 1455(m), 1410(s), 1330(s), 1260(m), 1230(s), 1205(m), 975(m), 930(m), 890(m), 870(m). *Phenylhydrazone*, m.p. 155—156° (ethanol). (Found: C 65.20; H 5.48. Calc. for $C_{10}H_{10}N_4$: C 64.50; H 5.41). *2,4-Dinitrophenylhydrazone hydrochloride*, m.p. 310—312° (ethanol-hydrochloric acid). (Found: C 39.54; H 3.09. Calc. for $C_{10}H_9O_4N_6Cl$: C 39.78; H 2.98. Equiv. wt. of chloride: Found 328. Calc.: 302.7).

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