45. *Preparation of Water-soluble Derivatives of 2-Methylnaphthalene.*

By D. O. Holland and F. A. Robinson.

The preparation of several new water-soluble derivatives of 2-methylnaphthalene is described; some of them possess considerable vitamin-K activity.

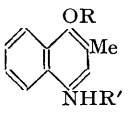
During a search for new water-soluble analogues of vitamin K attention has been directed to the preparation of derivatives of 4-amino-2-methyl-1-naphthol (Emmett, Kamm, and Sharp, *J. Biol. Chem.*, 1940, **133**, 285), 1 : 4-diamino-2-methylnaphthalene (Baker and Carlson, *J. Amer. Chem. Soc.*, 1942, **64**, 2658; Veldstra and Wiardi, *Rec. Trav. chim.*, 1942, **61**, 547), and 2-methyl-1 : 4-naphthaquinone 4-monoxime (Dam, Glavind, and Karrer, *Helv. Chim. Acta*, 1940, **23**, 224), all of which possess considerable vitamin-K activity.

Although the hydrochlorides of the two bases are water-soluble, they are not very stable; attempts were therefore made to prepare stable, water-soluble derivatives with similar biological activity. *4-Amino-2-methyl-1-naphthoxyacetic acid* (I; R = $CH_2 \cdot CO_2H$, R′ = H) was prepared by the series of reactions that Jacobs and Heidelberger (*J. Amer. Chem. Soc.*, 1917, **39**, 2188) used for the preparation of 4-aminonaphthoxyacetic acid (cf. Howard, *Ber.*, 1897, **30**, 545) from 4-acetamido-2-methyl-1-naphthol and chloroacetic acid.

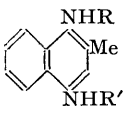
Reaction of the naphthoxy-acid with ethyl chloroacetate in the presence of sodium hydroxide (Jacobs and Heidelberger, *loc. cit.*) yielded *N-4-carboxymethoxy-3-methyl-1-naphthylglycine ethyl ester* (I; R = $CH_2 \cdot CO_2H$, R′ = $CH_2 \cdot CO_2Et$); the free acid was unstable in air.

All attempts to prepare the corresponding 4-hydroxy-acid (I; R = H, R′ = $CH_2 \cdot CO_2H$)

from 4-amino-2-methyl-1-naphthol either by reaction with chloroacetic acid or *via* the cyanide (I; R = H, R′ = CH_2·CN) by reaction with formaldehyde, sodium metabisulphite, and potassium cyanide, were unsuccessful. Since the analogous compound, *p*-hydroxyphenylglycine, can readily be prepared from *p*-aminophenol by both these routes (Meldola, *J.*, 1917, **111**, 552; Galatis, *Helv. Chim. Acta*, 1921, **4**, 574) it would appear that the marked instability of 4-amino-2-methylnaphthol extends to this derivative.



(I.)



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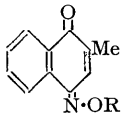

(III.)

Indeed, the preparation of the corresponding N-4-*amino*-3-*methyl*-1-*naphthylglycine* (II; R = H, R′ = CH_2·CO_2H) from 1 : 4-diamino-2-methylnaphthalene, which is more stable than the aminonaphthol, proved to be more successful, although the product was rather unstable. It was synthesised by the method used by Jacobs and Heidelberger (*J. Amer. Chem. Soc.*, 1917, **39**, 1457) for the preparation of *p*-aminophenylglycine. These workers found that, although the reaction of *p*-aminoacetanilide with chloroacetic acid or its ethyl ester in the presence of bases led mainly to *p*-acetamidophenyldiglycine, the reaction of ethyl chloroacetate with excess of *p*-aminoacetanilide gave the required *p*-acetamidophenylglycine ethyl ester together with *p*-aminoacetanilide hydrochloride. By applying this reaction to the preparation of (II), it has been possible to convert 4-acetamido-3-methyl-1-naphthylamine almost completely into N-4-*acetamido*-3-*methyl*-1-*naphthylglycine ethyl ester* (II; R = Ac, R′ = CH_2·CO_2Et), *N*-4-amino-3-methyl-1-naphthylglycine being obtained on acid hydrolysis. 4-Acetamido-3-methyl-1-naphthylamine was prepared by nitrating 1-acetamido-2-methylnaphthalene (Vesely and Kapp, *Rec. Trav. chim.*, 1925, **44**, 360) and reducing the product catalytically with Raney nickel. The preparation of this compound from 2-methyl-1 : 4-naphthaquinol (Baker and Carlson, *loc. cit.*) was less satisfactory.

Since 2-methyl-1 : 4-naphthaquinol bistrimethylaminoacetate chloride has been shown to possess considerable vitamin-K activity (*idem, ibid.*), the analogous 4-*trimethylaminoacetamido*-2-*methyl*-1-*naphthol chloride* (I; R = H, R′ = CO·CH_2·NMe_3Cl) was prepared. It was synthesised in good yield from 4-*chloroacetamido*-2-*methyl*-1-*naphthol*, obtained by the action of excess of chloroacetyl chloride on the hydrochloride of 4-amino-2-methyl-1-naphthol in the presence of sodium acetate (cf. Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1917, **39**, 1442; Rolf, *ibid.*, 1919, **41**, 460), and trimethylamine at room temperature. The corresponding *triethyl chloride* (I; R = H, R′ = CO·CH_2·NEt_3Cl) could be obtained only in very small yield on heating the reactants, but 4-*pyridylacetamido*-2-*methyl*-1-*naphthol chloride* (I; R = H, R′ = CO·CH_2·C_5H_4N,HCl) was formed in good yield under these conditions. These derivatives were readily soluble in water.

Attempts were next made to prepare water-soluble derivatives of 2-methyl-1 : 4-naphthaquinone 4-oxime (III; R = H) similar to those described above. 2-*Methyl*-1 : 4-*naphthaquinone* 4-*carboxymethyl oxime* (III; R = CH_2·CO_2H) was readily prepared by the action of carboxymethoxyamine semihydrochloride (Borek and Clarke, *J. Amer. Chem. Soc.*, 1936, **58**, 2020; Anchel and Schoenheimer, *J. Biol. Chem.* 1936, **114**, 539) on the quinone at pH 3·0, direct action of chloroacetic acid or ester on the quinone oxime in the presence of sodium hydroxide and other bases being unsuccessful.

2-*Methyl*-1 : 4-*naphthaquinone* 4-β-*diethylaminoethyl oxime hydrochloride* (III; R = C_2H_4·NEt_2,HCl) was also readily synthesised from the quinone and β-*diethylaminoethoxyamine* at pH 3·5; it is readily soluble in water. The reagent was prepared by the reaction of acetoxime with β-diethylaminoethyl chloride, followed by acid hydrolysis of the *acetone* β-*diethylaminoethyl oxime* first formed (cf. B.P. 301,956). From the mode of preparation of the last compound and the fact that an electrometric titration with hydrochloric acid revealed the presence of only one basic centre, it would appear to be the required *O*-ether (cf. Thompson and Baer, *J. Amer. Chem. Soc.*, 1940, **62**, 2094; Brady, Dunn, and Goldstein, *J.*, 1926, 2386).

The structure of the two substituted oximes described above was assumed by analogy with the reaction of hydroxylamine with 2-methylnaphthaquinone which is known to give the 4-oxime.

Finally, the *potassium* salt of 2-methyl-1 : 4-naphthaquinone 4-oxime-*O*-sulphonic acid (III; R = SO_3K) was obtained in moderate yield by the action of hydroxylamine-*O*-sulphonic acid (Sommer, Schulz, and Nassau, *Z. anorg. Chem.*, 1925, **147**, 142) on the quinone. The

compound was readily soluble in water and on warming with acid it was quickly converted into the 4-oxime.

A summary of the biological results obtained with some of the compounds described above is given below. The rough sorting test used was carried out on chicks given a vitamin-K-deficient diet for three weeks, a 0·2% concentration of sulphamethazine being added to the drinking water during the last week.

Compound.	Activity.
2-Methyl-1 : 4-naphthaquinone	1·0 (standard)
4-Amino-2-methyl-1-naphthol hydrochloride	0·2
4-Acetamido-2-methyl-1-naphthol	<0·2
4-Acetamido-2-methyl-1-naphthoxyacetic acid	<0·2
4-Amino-2-methyl-1-naphthoxyacetic acid	<0·2
N-4-Carboxymethoxy-3-methyl-1-naphthylglycine ethyl ester	<0·2
N-4-Acetamido-3-methyl-1-naphthylglycine ethyl ester	0·2
N-4-Amino-3-methyl-1-naphthylglycine	0·2
4-Trimethylaminoacetamido-2-methyl-1-naphthol chloride	0·2
2-Methyl-1 : 4-naphthaquinone 4-oxime	0·2
2-Methyl-1 : 4-naphthaquinone 4-carboxymethyl oxime	0·2
Potassium 2-methyl-1 : 4-naphthaquinone-4-oxime-*O*-sulphonate	0·2

Experimental.

All m. p.s are uncorrected.

4-Amino-2-methyl-1-naphthoxyacetic Acid.—4-Amino-2-methyl-1-naphthol hydrochloride was prepared in 55% yield from 2-methyl-1 : 4-naphthaquinone essentially by the method of Sah and Brüll (*Ber.*, 1941, **74**, 552).

To an intimate mixture of finely powdered 4-amino-2-methyl-1-naphthol hydrochloride (10 g.) and fused sodium acetate (5 g.) were added acetic anhydride (5 c.c.) and acetic acid (20 c.c.). The mixture became warm with partial solution of the solid material, and then changed to a solid magma. This was heated on the steam-bath for 1 hr., kept at room temperature for 2 days, and diluted well with water to yield 4-acetamido-2-methyl-1-naphthol as a pink powder (10 g.; 98%); it recrystallised from alcohol (charcoal) as colourless microscopic needles, m. p. 211—212° (Found: C, 72·5; H, 6·1; N, 6·3. Calc. for $C_{13}H_{13}O_2N$: C, 72·5; H, 6·05; N, 6·5%.).

A solution of 4-acetamido-2-methyl-1-naphthol (18·4 g.) and chloroacetic acid (8·1 g.) in water (200 c.c.) containing sodium hydroxide (6·85 g.) was evaporated to *ca.* 75 c.c., further chloroacetic acid (4·0 g.) and sodium hydroxide (3·45 g.) in water (100 c.c.) added, and the mixture reconcentrated to *ca.* 100 c.c. The resulting brown solution was neutralised with dilute hydrochloric acid (Congo-red), and the precipitated solid after being washed with water was recrystallised from alcohol (charcoal) to yield *4-acetamido-2-methyl-1-naphthoxyacetic acid* as a cream-coloured solid, m. p. 208—210° (from 100°) (18 g.; 77%). On recrystallisation from alcohol it formed tiny needles, m. p. 211—211·5° (Found, after drying at 150°: C, 65·5; H, 5·6; N, 5·2. $C_{15}H_{15}O_4N$ requires C, 66·0; H, 5·5; N, 5·1%).

The acetamidonaphthoxyacetic acid (11 g.) was heated under reflux with 15% hydrochloric acid (100 c.c.) for 3 hrs. The clear orange-red solution on cooling deposited a pale pink solid which was washed, dissolved in hot water, and treated with excess of aqueous sodium acetate containing a little sodium hydrosulphite (dithionite), *4-amino-2-methyl-1-naphthoxyacetic acid* separating as a white solid, m. p. 191° (decomp.) (8·6 g.; 86%). It was recrystallised from aqueous alcohol containing sodium dithionite as tiny needles of the same m. p. (Found: C, 67·2; H, 6·0; N, 6·2. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·7; N, 6·1%).

N-4-Carboxymethoxy-3-methyl-1-naphthylglycine Ethyl Ester.—A solution of 4-amino-2-methyl-1-naphthoxyacetic acid (10 g.) and ethyl chloroacetate (5·3 g.) in a mixture of N-sodium hydroxide (45 c.c.) and alcohol (50 c.c.) was heated under reflux for 8 hrs. in an atmosphere of nitrogen. An oil separated on cooling which solidified on scratching. This was recrystallised from aqueous alcohol (charcoal), m. p. 137—138° (decomp.) (7·2 g.; 52%) (Found: C, 64·4; H, 6·0; N, 4·4. $C_{17}H_{19}O_5N$ requires C, 64·4; H, 6·0; N, 4·4%).

N-4-Amino-3-methyl-1-naphthylglycine.—A solution of 4-acetamido-3-methyl-1-naphthylamine (6·8 g.) and ethyl chloroacetate (2·1 g.) in 50% aqueous alcohol (25 c.c.) was heated under reflux for 5 hrs., the resulting solution cooled in the ice-chest, and the deposited *N-4-acetamido-3-methyl-1-naphthylglycine ethyl ester* (3·9 g.) filtered off, washed with water, and dried, m. p. 188—192°. The filtrate was rendered alkaline with sodium hydrogen carbonate, the solid obtained dissolved in 50% alcohol (20 c.c.), and the solution heated under reflux with fresh ethyl chloroacetate (1·5 c.c.) to yield a further 2·5 g. of the glycine ester. Repetition of the process gave a further quantity of the crude ester (1·0 g.). The combined solids recrystallised from methyl alcohol as colourless needles, m. p. 192—194° (Found: C, 67·6; H, 6·5; N, 9·3. $C_{17}H_{20}O_3N_2$ requires C, 68·0; H, 6·7; N, 9·3%).

The acetamidonaphthylglycine ester (2·2 g.) was heated under reflux for 1 hr. in 15% hydrochloric acid (20 c.c.) in an atmosphere of nitrogen. The resulting solution was concentrated in a vacuum practically to dryness, and the residue dissolved in hot water (*ca.* 150 c.c.). The red solution after the addition of a little sodium dithionite was treated with charcoal to yield an orange solution which was rendered alkaline with sodium acetate. The resulting *N-4-amino-3-methyl-1-naphthylglycine* (0·53 g.) recrystallised from aqueous acetic acid as a light brown powder, m. p. 203—204° (decomp.) (Found: N, 12·2, $C_{13}H_{14}O_2N_2$ requires N, 12·2%).

4-Chloroacetamido-2-methyl-1-naphthol.—To a solution of 4-amino-2-methyl-1-naphthol hydrochloride (25 g.) in a mixture of acetic acid (180 c.c.) and a saturated solution of sodium acetate (180 c.c.), chloroacetyl chloride (25 c.c.) was added dropwise with stirring while the temperature of the mixture

was kept at *ca.* 10°. After the addition, stirring was continued for 1 hr., and then the pink solid was removed and washed well with water (23·5 g.; 79%). The *compound* was recrystallised from aqueous acetic acid containing a little sodium dithionite, forming colourless needles, m. p. 220—221° (decomp.) (Found : C, 62·5; H, 4·8; N, 5·4; Cl. 14·2. $C_{13}H_{12}O_2NCl$ requires C, 62·5; H, 4·8; N, 5·6; Cl, 14·2%).

4-*Trimethylaminoacetamido*-2-*methyl*-1-*naphthol Chloride*.—A suspension of the chloroacetamido-compound (7 g.) in an acetone solution of trimethylamine (100 c.c. of 5%) was shaken for 4 hrs. at room temperature, to yield the quaternary *chloride* as an almost white powder, m. p. 230° (decomp.) (6·65 g.; 77%). It was recrystallised from acetone–methyl alcohol, forming microscopic irregularly shaped crystals, m. p. 232° (decomp.) (Found : C, 62·2; H, 6·8; N, 9·4; Cl, 11·2. $C_{16}H_{21}O_2N_2Cl$ requires C, 62·3; H, 6·8; N, 9·1; Cl, 11·5%).

4-N-*Pyridylacetamido*-2-*methyl*-1-*naphthol Chloride*.—A solution of the chloroacetamido-compound (2 g.) in a mixture of dry pyridine (3 c.c.) and methyl ethyl ketone (20 c.c.) was heated under reflux for 5 hrs., the quaternary *chloride* slowly separating as an orange gum. After removal of the ketone mother-liquor, the gum was heated with a little dry methyl alcohol to yield a pale pink solid, m. p. 260° (decomp.) (2·05 g.; 77·5%). On recrystallisation from acetic acid–ethyl acetate, the compound was obtained as a cream-coloured powder of unchanged m. p. (Found : C, 65·8; H, 5·3; N, 8·0; Cl, 10·8. $C_{18}H_{17}O_2N_2Cl$ requires C, 65·7; H, 5·2; N, 8·5; Cl, 10·8%).

4-*Triethylaminoacetamido*-2-*methyl*-1-*naphthol Chloride*.—A suspension of the chloroacetamido-compound (2 g.) in a mixture of triethylamine (3 c.c.) and acetone (25 c.c.) was heated under reflux for 5 hrs., the solid gradually dissolving. After removal of most of the acetone from the resulting solution, the residue was diluted with water and the solid filtered off. The aqueous filtrate was concentrated in a vacuum to leave an orange oil, which on treatment with hot acetone yielded the quaternary *chloride* as a pale pink powder (0·1 g.). It was recrystallised from methyl alcohol–acetone (charcoal), forming a white powder, m. p. 235° (decomp.) (Found : N, 7·9; Cl, 10·0. $C_{19}H_{27}O_2N_2Cl$ requires N, 8·0; Cl, 10·1%).

2-*Methyl*-1 : 4-*naphthaquinone* 4-*Carboxymethyl Oxime*.—Acetoxime (49 g.) was allowed to react with chloroacetic acid (71 g.) in a solution of sodium hydroxide according to the method of Borek and Clarke (*loc. cit.*), and the resulting crude acetone carboxymethyl oxime (45 g.) hydrolysed by heating under reflux with 3N-hydrochloric acid (450 c.c.) for 1 hr. The hydrolysate was concentrated in a vacuum to *ca.* 60 c.c., treated with 40% sodium hydroxide solution to pH 3·0, and diluted to 120 c.c. Alcohol (120 c.c.) and 2-methyl-1 : 4-naphthaquinone (20 g.) were then added, the mixture heated under reflux for 1 hr., and the resulting brown solution cooled and diluted well with water, crude 2-*methyl*-1 : 4-*naphthaquinone* 4-*carboxymethyl oxime* separating as a buff-coloured solid. This was dissolved in a warm solution of sodium hydrogen carbonate, the unreacted quinone (1·7 g.) removed, and the filtrate acidified. The precipitated oxime (15 g.; 58%) was recrystallised from alcohol (charcoal), forming pale yellow platelets, m. p. 162° (decomp.) (Found : C, 63·5; H, 4·7; N, 5·7. $C_{13}H_{11}O_4N$ requires C, 63·7; H, 4·5; N, 5·7%).

Acetone β-Diethylaminoethyl Oxime.—To a solution of sodium (9·2 g.) in dry alcohol (300 c.c.) were added acetoxime (14·6 g.) and β-diethylaminoethyl chloride hydrochloride (34·4 g.), and the mixture heated under reflux for 2 hrs. After cooling, the sodium chloride was removed, the orange filtrate acidified with a small excess of hydrochloric acid, and the solution concentrated in a vacuum at low temperature. The resulting syrup was made alkaline with 20% sodium hydroxide solution and the ammoniacal liquid extracted into ether. After removal of solvent, the residue was distilled in a vacuum to give two fractions : (i) b. p. 50—56°/12 mm. (6·1 g.), (ii) b. p. 70—79°/12 mm. (17·4 g.). The main fraction, on redistillation, yielded *acetone β-diethylaminoethyloxime*, b. p. 77—78°/12 mm. (Found : C, 63·3; H, 11·7; N, 16·7. $C_9H_{20}ON_2$ requires C, 62·8; H, 11·6; N, 16·3%). Fraction (i) (Found : C, 62·5; H, 12·4; N, 11·3%) was discarded.

β-Diethylaminoethoxyamine.—Acetone β-diethylaminoethyl oxime (5 g.) was heated under reflux in 3N-hydrochloric acid (50 c.c.) for 1 hr., the solution concentrated in a vacuum, and the resulting yellow syrup made alkaline with sodium hydroxide to yield, after extraction with ether, crude *β-diethylaminoethoxyamine* (4·0 g.). This was distilled under low pressure, b. p. 67—69°/13 mm. (Found : C, 54·8; H, 12·0; N, 20·5. $C_6H_{16}ON_2$ requires C, 54·6; H, 12·1; N, 21·2%). The *hydrochloride*, m. p. 117—119° (slight decomp.), was prepared from a portion of the concentrated syrup, dried in a vacuum at 100° over phosphoric oxide, and the resulting gum crystallised by solution in a small volume of alcohol and precipitation with ether and benzene (Found : C, 35·5; H, 8·8; N, 13·6; Cl, 35·0. $C_6H_{16}ON_2,2HCl$ requires C, 35·5; H, 8·8; N, 13·8; Cl, 35·0%).

2-*Methyl*-1 : 4-*naphthaquinone* 4-*β Diethylaminoethyl Oxime Hydrochloride*.—To a solution of β-diethylaminoethoxyamine (5 g.) in 50% alcohol (60 c.c.) adjusted to pH 3·5 with dilute hydrochloric acid, 2-methylnaphthaquinone (5 g.) was added, and the mixture heated under reflux for 1 hr. The resulting orange-red solution was treated with a little hydrochloric acid and extracted with ethyl acetate which removed a little unreacted quinone (0·5 g.). The aqueous layer was then made strongly alkaline and the yellow oil that separated was extracted into ether. After drying and removal of solvent, the residue (6·25 g.) was heated in a vacuum at 100° to remove unreacted diethylaminoethoxyamine, and the residue diluted with dry ethyl acetate and saturated with hydrogen chloride to yield the required *hydrochloride* as a pale yellow powder; it recrystallised from alcohol–ethyl acetate in the same form, m. p. 179° (decomp) (Found : C, 62·8; H, 7·4; N, 8·9; Cl, 11·0. $C_{17}H_{23}O_2N_2Cl$ requires C, 63·3; H, 7·1; N, 8·7; Cl, 11·0%).

Potassium 2-*Methyl*-1 : 4-*naphthaquinone* 4-*Oxime*-O-*sulphonate*.—Hydroxylamine-*O*-sulphonic acid (1·14 g.) was dissolved in ice-water (2 c.c.), and the solution diluted carefully with dioxan (10 c.c.), the temperature being kept at 0°. To this mixture were added first a solution of 2-methyl-1 : 4-naphthaquinone (1·72 g.) in dioxan (6 c.c.) and then a 50% aqueous-alcoholic solution of potassium hydroxide (2 c.c. of 14%). The final mixture was left in the ice-chest for 24 hrs. with occasional shaking, and the precipitated solid filtered off, washed with alcohol and ether (1·25 g.), and then extracted with hot alcohol. The required *potassium* salt separated from the alcoholic extract after concentration as very

pale yellow needles, m. p. 158° (decomp.) (0·65 g.; 20%) (Found: C, 40·9; H, 3·4; N, 4·3; S, 9·7. $C_{11}H_8O_5NSK,H_2O$ requires C, 40·9; H, 3·1; N, 4·3; S, 9·9%).

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