Methyl Ester of 2-(Carbomethoxy)methylthio-6-morpholinopyrimidine-4-carboxylic Acid (IX). A. Anhydrous sodium carbonate (12.7 g, 120 mmole) was added to a solution of crude VIII (11.1 g, 40 mmole) in absolute methanol (60 ml). Morpholine (3.5 g, 40 mmole) was added dropwise with stirring and the mixture obtained was stirred at room temperature for 4 h and allowed to stand overnight. The solid product was filtered off and recrystallized to give IX.

B. Compound IVc (1 g, 2.9 mmole) was added to a 0.035N solution of sodium methoxide (40 ml) and the mixture stirred for 3 h at room temperature until all of IVc had dissolved. The solution was then concentrated at reduced pressure to one third volume, poured into water (30 ml), and neutralized with dilute hydrochloric acid (1:5). The solid was filtered off and recrystallized to give IX.

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SYNTHESIS OF 2-ARYL- AND 2-HETARYLOXAZOLES FROM THE

OXAZOLINES AND OXAZOLIDINES

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smaller amounts of the nitriles.

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Treatment of 2-phenyl-, 2-(2-furyl)-, and 2-(2-thienyl)oxazolines with nickel peroxide has been found to give, in addition to the dehydrogenation products (2-substituted oxazoles), the fragmentation products (amides of benzoic, furan-2-carboxylic, and thiophen-2-carboxylic acids). This fragmentation appears to give initially the nitriles, which are then converted into the amides by the nickel peroxide. Catalytic dehydrogenation of 2-phenyloxazoline gives low yields of 2-phenyloxazole, the principal product being benzonitrile. Treatment of the Schiff's bases obtained from ethanolamine and aldehydes (benzaldehyde, furfural, and thiophen-2-aldehyde) with nickel peroxide

It has been shown [1] that 1-phenyloxazoline (Ia) on treatment with nickel peroxide is converted to 2-phenyloxazole (IIa). We here describe an analogous syntheses of 2-(2-furyl)-oxazole (IIb) and 2-(2-thienyl)oxazole (IIc). In all cases, although the oxazolines reacted completely, the yields of oxazoles were around 50%. Attempts by us to carry out this dehydrogenation with other oxidants (lead tetraacetate, pyridinium chlorochromate, sulfur, and N,N'-bisbenzenesulfonyl-p-benzoquinoneimine) were successful. Further examination of the aromatization of oxazolines showed that substantial amounts of the amides of the acids (III) [benzoic acid (28%), furan-2-carboxylic (23%), and thiophen-2-carboxylic acid (45%)] remained adsorbed on the nickel peroxide as by-products.

gives trace amounts of the oxazoles, the principal products being the aldehydes, with

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I-III a R=Ph, b R=2-furyl, c R=2-thienyl

We have now found that 2-phenyloxazole is converted into benzamide at a significant rate on treatment with nickel peroxide. Hence, the amides formed under our conditions could arise from the oxazoles rather than the oxazolines, and it was possible that fragmentation of the oxazoles (or oxazolines) would not give rise directly to the amides, but rather to the nitriles, which might then be converted into the amides. Gas-liquid chromatography in the early stages of the reaction of oxazolines with nickel peroxide showed the presence of small amounts of nitriles, which disappeared on longer contact of the reaction mixture with the nickel peroxide. We have now shown, in separate experiments, that under the conditions used to aromatize the oxazolines (boiling with nickel peroxide in benzene) benzonitrile is readily converted to benzamide. In this connectionit is noteworthy that the composition of the nickel peroxide obtained from nickel sulfate and sodium hypochlorite as described in [3] may be represented by the formula NiO_{2.77H2.85} [3], and this oxidant is a source of HO[•] radicals in aprotic solvents. These radicals are able to detach hydrogen from the substrate and add at the free valences to give new C-O bonds [3].

In a search for more selective methods for the preparation of 2-aryloxazoles, we have examined the catalytic dehydrogenation of 2-phenyloxazoline. This method was also found to give benzonitrile, which was not converted to benzamide under these conditions. Experiments carried out at 400°C with an alumina-platinum catalyst gave complex mixtures containing no 2-phenyloxazole (GLC), but small amounts of benzonitrile were found. Clearer results were obtained using a polyfunctional alumina-chromium-platinum catalyst containing rare-earth oxides, used previously for the dehydrogenation of C(4)- and C(5)-hydrocarbons [4] and for their heterocyclization with H₂S [5]. The stability of this catalyst towards sulfur-containing [6] and nitrogenous [7] heterocycles led us to its use for the dehydrogenation of 2-phenyloxazole from 2-phenyloxazoline, but the principal course of the reaction led to the formation of benzonitrile. At 450°C, the catalyzate contained 10% of 2-phenyloxazole, 45% of benzonitrile, and 45% of unreacted 2-phenyloxazoline.

We also examined the aromatization of 2-phenyl-, 2-(2-furyl)-, and 2-(2-thienyl)oxazolidines (IV). It has been suggested (see, e.g., [8]) that such oxazolidines exist in tautomeric equilibrium with the corresponding Schiff's bases (V), the equilibrium favoring the latter [9]. Conversion of the Schiff's bases obtained from aromatic aldehydes and o-aminophenol into 2-arylbenzoxazoles takes place in high yields on treatment with a variety of oxidants, notably lead tetraacetate [10, 11] and nickel peroxide [12] even at ambient temperatures. When we used the Schiff's bases (or oxazolidines), the yields of aryl- and hetaryloxazoles obtained on treatment with nickel peroxide amounted to only a few percent, the principal products being the aldehydes. Furthermore, the phenyl- and furyl-substituted compounds gave small amounts of benzonitrile and 2-cyanofuran. Similar results were obtained when activated manganese dioxide was used. The formation of aldehydes when Schiff's bases are oxidized with lead tetraacetate is well known [13], and the nitriles could be obtained by fragmentation of the oxazoles or the intermediate oxazolines, as described above.



II, IV, V a R = Ph, b R = 2-fury1, c R = 2-thieny1

EXPERIMENTAL

GLC analyses were carried out on an LKhM-80 chromatograph with a flame ionization detector, carrier gas nitrogen, flow rate 20 ml/min, stainless steel columns: 2 mm \times 2 m (5% SE-30 on Chromaton N-AW-DMCS, temperature 165°C) and 2 mm \times 1.5 m (15% Carbowax 20M on Chromaton N-AW-DMCS, temperature 185°C). PMR spectra were obtained on a Tesla BS-467 radiospectrometer (60 MHz) in CCl₄ internal standard TMS.

<u>2-Phenloxazole (IIa)</u>. To a solution of 12 g (82 mmole) of (Ia) in 60 ml of benzene was added 78 g of nickel peroxide [2], and the mixture boiled with stirring for 1 h with periodic removal of samples for GLC. In the sample removed after 30 min, in addition to the

starting material (Ia) and 2-phenyloxazole (IIa), traces of benzonitrile were present, but these were not found in the subsequent sample. To the mixture was added 10 g of nickel peroxide, and the mixture boiled for 1 h (when starting material (Ia) was no longer present according to GLC). The mixture was filtered, and the solid washed with benzene followed by acetone. The combined benzene solution was evaporated and fractionally distilled to give 5.8 g (49%) of the oxazole (IIa), bp 98-100°C (10 mm) [lit. bp [1], 100°C (10 mm)]. The acetone solution, following removal of the acetone, gave 2.8 g (28%) of benzamide (IIIa), mp 126-127°C (lit. mp [14] 130°C).

 $\frac{2-(2-\text{Fury1})\text{oxazole (IIb)}}{2}$ From methyl furan-2-carboxylate and ethanolamine was obtained 94% of the N-(2-hydroxyethyl)amide, bp 176°C (1.6 mm), which on successive treatment with thionyl chloride and KOH solution (as described in [1]) was converted into the oxazoline (Ib), mp 77-79°C (95%) (lit. mp [15], 83°C). To 11.4 g (84 mmole) of (Ib) in 100 ml of benzene was added 66 g of nickel peroxide, and the mixture boiled with stirring for 2 h. The mixture was worked up as described above. From the benzene extract there was obtained 5.0 g (44.5%) of 2-(2-fury1)oxazole (IIb), mp 48-49°C. PMR spectrum: furan ring protons 6.35 (q, 4-H), 6.87 (q, 3-H), 7.45 (br. 5-H); oxazole ring protons 7.7 (s, 4-H), 7.51 ppm (s, 5-H). Found, %: N 10.3. C₇H₅NO₂. Calculated, %: 10.4. From the acetone solution there was isolated 2.2 g (23%) of the amide (IIIb), mp 142-144°C (lit. mp [14], 143°C).

<u>2-(2-Thienyl)oxazole (IIc)</u>. From methyl thiophen-2-carboxylate there was obtained 96% of the N-(2-hydroxyethyl)amide, bp 214°C (1 mm), mp 88-90°C, which was converted as for (Ia) [1] into the oxazoline (Ic) in quantitative yield, mp 58-59°C (lit. mp [16] 60°C). From 4.1 g (27 mmole) of (Ic) by treatment with 23 g of nickel peroxide under the conditions described above there was obtained 1.9 g (46%) of the oxazole (IIc), bp 105°C (10 mm). PMR spectrum: thiophen ring protons 6.98 (q, 4-H), 7.32 (q, 5-H), 7.51 ppm (q, 3-H); oxazole ring protons 7.08 (s, 4-H), 7.55 ppm (s, 5-H). Mp [17] 30°C. From the acetone solution there was obtained 1.54 g (45%) of the amide (IIIc), mp 179-180°C (lit.mp [14], 180°C).

Reaction of 2-Phenyloxazole (IIa) with Nickel Peroxide. To 0.48 g (3.3 mmole) of the oxazole (IIa) in 20 ml of benzene was added 7 g of nickel peroxide, and the mixture boiled with stirring for 1 h. The mixture was filtered and the solid washed with benzene followed by acetone. From the combined benzene washings following removal of the benzene there was obtained 0.24 g (50% recovery) of (IIa), and from the acetone solution 0.1 g (25.5%) of the amide (IIIa).

<u>Reaction of Benzonitrile with Nickel Peroxide.</u> To a solution of 0.5 g (4.5 mmole) of benzonitrile in 25 ml of benzene was added 1 g of nickel peroxide, and the mixture boiled with stirring for 5 min. The mixture was then filtered and the solid washed with benzene followed by acetone. Evaporation of the acetone solution gave 0.3 g of benzamide (IIIa) (51%).

Catalytic Dehydrogenation of 2-Phenyloxazoline (Ia). The experiments were carried out in a flow reactor in a stream of nitrogen over a catalyst of composition 5% Cr_2O_3 , 5% of Polirit, 1% of K₂O, and 81% of γ -Al₂O₃ [18]. At 400°C and a flow rate of 1 h⁻¹, the yield of liquid catalyzate was 80%. When the flow rate was reduced to 0.5 h⁻¹ and the temperature raised to 450°C, the liquid catalyzate (72%) contained (GLC) 4% of 2-phenyloxazole (IIa), 90% of benzonitrile, and 6% of starting material (Ia). When the flow rate was increased to 1 h⁻¹, the liquid catalyzate was found to contain 10% of the oxazole (IIa), 45% of benzonitrile, and 45% of unreacted (Ia).

Reaction of 2-(N-Benzylidenamino)ethanol (Va) with Nickel Peroxide. To a solution of 0.4 g (2.7 mmole) of Va, obtained as described in [9], in 25 ml of benzene was added 3 g of nickel peroxide, and the mixture boiled with stirring for 0.5 h. The mixture was filtered, and the solid washed with benzene followed by acetone. The combined benzene solutions were carefully evaporated. The residue consisted of 0.14 g of a mixture containing (GLC) the oxazole (IIa), benzonitrile, and benzaldehyde in proportions of 16:30:54, corresponding to yields of 8, 14, and 25%. The acetone extract afforded 0.05 g (15.5%) of benzamide. When a solution of 1 g of (Va) in 40 ml of benzene was boiled with 2 g of activated manganese dioxide for 20 min, the ratio of products was 3:13:84.

<u>Reaction of 2-[N-(2-Furfurylideneamino)]ethanol (Vb) with Nickel Peroxide.</u> To a solution of 2.4 g (1.73 mmole) of (Vb), obtained as described in [19], in 50 ml of benzene was added 5 g of nickel peroxide, and the mixture boiled with stirring for 5 min. The solid was filtered off, a further 5 g of nickel peroxide added to the filtrate, the mixture again boiled for 5 min

and filtered, and the combined solids washed with benzene and acetone. The combined benzene solutions were evaporated carefully under reduced pressure to give 0.32 g of solid containing, according to GLC, the oxazole (IIb), furan-2-carbonitrile, and furfural in a ratio of 1:18:81 (yields 0.14, 4, and 16%). The acetone extract gave 0.09 g (5%) of the amide (IIIb).

<u>Reaction of 2-[N-(2-Thienylideneamino)]ethanol (Vc) with Nickel Peroxide.</u> To a solution of 2 g (1.3 mmole) of (Vc), obtained as described in [20], in 50 ml of benzene was added 5 g of nickel peroxide, the mixture stirred at room temperature for 5 h, 4 g of nickel peroxide added, stirring continued for a further 5 h, and the mixture filtered. The solid was washed with benzene, and the combined washings evaporated to give 0.28 g of solid which contained (GLC) the oxazole (IIc) and 2-thiophenaldehyde in a ratio of 14:86, yields 2 and 17% respectively.

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