# SYNTHESIS OF 4-METHYL-5-ALKYL-2-IMIDAZOLINONES

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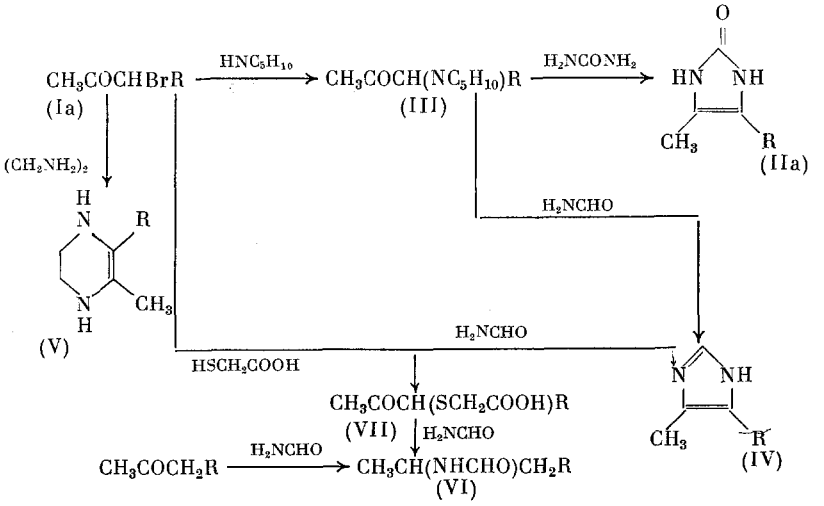
In our previous work [1], we showed that the action of urea on 3-bromo-2-alkanones (Ia) and (Ib) in ethyleneglycol in the presence of potassium carbonate gives 4-methyl-5-alkyl-2-imidazolinones (IIa) and (IIb). A further study of this reaction revealed that 50-60% yields of (IIa) and (IIb) may be achieved only by strict maintenance of the temperature regime and the use of no more than 1 g of starting (Ia) and (Ib).

In order to develop a more convenient method for the conversion of 3-halo-2-alkanones to 4-methyl-5-alkyl-2-imidazolinones, we examined the effect of various substituents, additives and HBr acceptors on the course of the cyclocondensation of urea with (Ia). These studies showed that stable 50-60% yields of (IIa) are achieved by carrying out the reaction of urea with (Ia) using charges of greater than 10 g in N,N-diethylacetamide in the presence of piperidine, $MgCO_3$ and $ZnCl_2$ at about 200°C. The reaction proceeds by nucleophilic substitution of the bromine atom by a piperidine residue and subsequent reaction of the intermediate piperidino derivative (III) with urea [1]. $MgCO_3$ acts as the HBr acceptor and inhibitor of tar formation. $Na_2CO_3$, $K_2CO_3$, and $CaCO_3$ act to inhibit tar formation to a lesser extent. The use of formamide instead of N,N-diethylacetamide leads to a sharp decrease in the yield of (IIa) and formation of 4-pentylimidazole (IV) as a side product. Imidazole (IV) was identified by comparison with samples obtained by the action of formamide on bromoketone (Ia) and piperidino ketone (III) according to Citterio and Minisci [2]. Unsatisfactory results were also obtained by the replacement of piperidine with other amines such as morpholine, diethylamine, methylamine, dimethylamine, and ethylenediamine. Bromoketone (Ia) in the presence or absence of urea undergoes cyclocondensation with ethylenediamine to form 2-methyl-4-pentyl-5,6-dihydropyrazine (V).

2-Formamidooctane (VI) was obtained upon the replacement of piperidine by thioglycolic acid and carrying out the reaction of (Ia) with urea in formamide. The conversion of (Ia) to (VI) presumably proceeds through the nucleophilic substitution of bromine by the thioglycolic acid residue with subsequent desulfuration and reductive amidation of the intermediate sulfidoketone (VII) by the Leuckart reaction. Support for this scheme was found in the formation of N-substituted formamide (VI) upon heating formamide with an authentic sample of sulfide (VII) obtained from (Ia) and thioglycolic acid. Amide (VI) was identified by comparison with a sample prepared by the reaction of 2-octanone with formamide according to the Leuckart procedure.




R = $(CH_2)_4CH_3$

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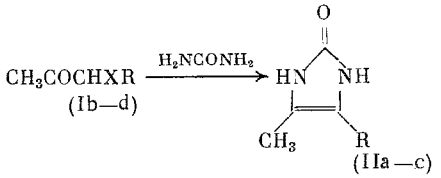
A system containing piperidine, N,N-diethylacetamide, $MgCO_3$, and $ZnCl_2$ also proved suitable for the cyclocondensation of urea with other 3-halo-2-alkanones. For example, the reaction of 3-bromo-2-heptanone (Ib), 3-chloro-2-butanone (Ic) or 3-chloro-2-octanone (Id) with urea in the presence of a mixture of piperidine, N,N-diethylacetamide, $ZnCl_2$ and $MgCO_3$ gave the corresponding 4-methyl-5-alkylimidazolinones (IIa)-(IIc) in yields up to 60%.




R = $(CH_2)_3CH_3$ (Ib), (IIb); $(CH_2)_4CH_3$ (Id), (IIa); $CH_3$ (Ic), (IIc); X = Br (Ib), Cl (Ic, d).

2-Imidazolinones (IIa)-(IIc) were identified according to their PMR spectra and by comparison with authentic samples.

## EXPERIMENTAL

The PMR spectra were taken on Varian 60-IL and Tesla BS-497 spectrometers with HMDS as the internal standard. The mass spectra were taken on a Varian MATCH-6 spectrometer. Thin-layer chromatography was taken on UV-254 Silufol plates with development by iodine vapor, and, in the case of the 2-imidazolinones, also by $FeCl_3$.

4-Methyl-5-pentyl-2-imidazolinone (IIa). A sample of 10 ml piperidine was added gradually to 10.4 g 3-bromo-2-octanone and 20 ml N,N-diethylacetamide and maintained for 1 h at about 20°C and then 20 g urea, 1 g $ZnCl_2$ and 10 g ground $MgCO_3$ was added. The mixture was stirred for 2 h at 195-205°C, cooled to about 20°C, treated with 100 ml 10% acetic acid, and maintained for 24 h at 0°C. The residue was filtered off and washed with water and ether to give 5.2 g (62%) (IIa), mp 242-244°C (from 4:1 ethyl acetate–ethanol), $R_f$ 0.85 (1:1 ethyl acetate–ethanol as eluent). PMR spectrum in $CF_3CO_2H$ (δ, ppm): 0.90 t ($CH_3$), 1.32 m [$(CH_2)_3$], 1.90 s ($CH_3$), 2.30 t ($CH_2$).

A sample of 8 ml $SO_2Cl_2$ was added gradually with stirring to a mixture of 16 g 2-octanone and 14 ml $CH_2Cl_2$ and maintained for 1 h at about 20°C. The mixture was distilled in vacuum to give 13 g 3-chloro-2-octanone (Id), bp 89-92°C (20 mm). PMR spectrum in $CCl_4$ (δ, ppm): 0.83 t ($CH_3$), 1.25 m [$(CH_2)_4$], 2.18 s ($CH_3$), 4.10 t (CH). Chloroketone (Id) was used in the next step without further purification.

A sample of 12.5 ml piperidine was added to 11.5 g chloroketone (Id) and 10 ml N,N-diethylacetamide and maintained for 24 h at about 20°C. Then, 20 g urea, 1 g $ZnCl_2$ and 7.5 g ground $MgCO_3$ was added and the mixture was stirred for 1.5 h at 200-210°C. The above treatment gave 3.5 g (29%) (IIa), mp 242-244°C (from 4:1 ethyl acetate–ethanol).

4-Methyl-5-butyl-2-imidazolinone (IIb). By analogy to the procedure for (IIa), the action of a mixture of 14 ml piperidine, 28 ml N,N-diethylacetamide, 1.2 g $ZnCl_2$, 28 g urea and 14 g $MgCO_3$ on 13.6 g 3-bromo-2-heptanone gave 5.8 g (53%) (IIb), mp 263-265°C, $R_f$ 0.75 (1:1 ethyl acetate–ethanol as eluent). PMR spectrum in $CF_3CO_2H$ (δ, ppm): 0.83 t ($CH_3$), 1.30 m ($CH_2CH_2$), 1.92 s ($CH_3$), 2.30 t ($CH_2$).

4,5-Dimethyl-2-imidazolinone (IIc). By analogy to the procedure for (IIa), the action of a mixture of 20 ml piperidine, 10 ml N,N-diethylacetamide, 25 g urea, 1 g $ZnCl_2$ and 15 g $MgCO_3$ on 13 g 3-chlorobutanone [3] over 1 h at 195-205°C gave 7.5 g (55%) (IIc). The compound decomposes over 230°C [3]. $R_f$ 0.50 (1:1 ethyl acetate–ethanol as eluent). PMR spectrum in $CF_3CO_2H$ (δ, ppm): 1.93 s ($2CH_3$).

4-Methyl-5-pentylimidazole (IV). A mixture of 4 g 3-bromo-2-octanone and 15 ml formamide was heated for 2 h at 200-205°C, cooled to about 20°C, diluted with water, treated with excess $K_2CO_3$ and extracted with ether. The extract was dried over $K_2CO_3$ and evaporated. Distillation of the residue in vacuum gave 1.5 g (52%) (IV) bp 138-141°C (2 mm), mp 40-42°C, $R_f$ 0.64 (Alufol, ethanol). PMR spectrum in $CCl_4$ (δ, ppm): 0.78 t ($CH_3$), 1.30 m [$(CH_2)_3$], 2.10 s ($CH_3$), 7.33 s (CH). Found, %: C 71.26, H 10.49, N 18.72, $M^+$ 152. $C_9H_{16}N_2$. Calculated, %: C 71.48, H 10.00, N 18.52, mol. mass 152.

Analogously, the action of 15 ml formamide on 4 g 3-piperidino-2-octanone [4] and subsequent chromatography of the reaction product on a column packed with grade-II alumina and 1:1 ethyl acetate–acetone as eluent gave 0.30 g (10%) (IV), mp 40-42°C, $R_f$ 0.63 (Alufol, ethanol).

2-Methyl-3-pentyl-5,6-dihydropyrazine (V). A sample of 8 ml ethylenediamine was added gradually with stirring to a solution of 4 g 3-bromo-2-octanone (Ia) in 20 ml ethanol, maintained for 1 h at about 20°C and then for 2 h at 90-100°C. The mixture was diluted with water, treated with excess $K_2CO_3$ and extracted with ether. The extract was dried over $K_2CO_3$ and evaporated. The residue was distilled in vacuum to give 1.5 g (47%) (V), bp 60-63°C (3 mm), $n_D^{20}$ 1.4610, $R_f$ 0.62 (Alufol, ethanol). PMR spectrum in $CCl_4$ (δ, ppm): 0.85 t ($CH_3$), 1.23 m [$(CH_2)_3$], 2.02 s ($CH_3$), 2.30 t ($CH_2$), 3.20 br. s ($2CH_2$). Found, %: C 71.48, H 11.73, N 16.82, $M^+$ 168. $C_{10}H_{20}N_2$. Calculated, %: C 71.37, H 11.98, N 16.65; mol. mass 168.

3-(Carboxymethylthio)-2-octanone (VII). A sample of 1 ml thioglycolic acid and 2 ml triethylamine was added gradually with stirring to a solution of 2.5 g 3-bromo-2-octanone in 20 ml ethanol, maintained for 48 h at about 20°C, diluted with water, treated with excess $Na_2CO_3$ and extracted with ether. The alkaline solution was acidified with concentrated hydrochloric acid and extracted with ether. The extract was dried over $MgSO_4$ and evaporated. The residue was distilled in vacuum to give 1.52 g (58%) (VII), bp 118-121°C (4 mm), $n_D^{20}$ 1.4877. PMR spectrum in $CCl_4$ (δ, ppm): 0.83 t ($CH_3$), 1.25 m [$(CH_2)_4$], 2.18 s ($CH_3$), 3.13 s ($SCH_2CO_2H$), 3.27 t (CH). Found, %: C 54.79, H 8.28, S 14.81. $C_{10}H_{18}O_3S$. Calculated, %: C 55.02, H 8.31, S 14.69.

2-Formamidooctane (VI). A mixture of 4.3 g sulfidoketone (VII) and 20 ml formamide was heated for 4 h at 200-205°C, diluted with water, treated with excess $K_2CO_3$ and extracted with ether. The extract was dried over $K_2CO_3$ and evaporated. The residue was distilled in vacuum to give 1.42 g (46%) (VI), mp 110-112°C (2 mm), $n_D^{20}$ 1.4496, $R_f$ 0.60 (Alufol, ethanol). PMR spectrum in $CCl_4$ (δ, ppm): 0.81 t ($CH_3$), 21.5 m [$CH_3$, $(CH_2)_5$], 3.87 m (CH). Found, %: C 68.37, H 12.21, N 8.56, $M^+$ 157. $C_9H_{19}NO$. Calculated, %: C 68.74, H 12.18, N 8.91; mol. mass 157.

A mixture of 4 g 2-octanone and 15 ml formamide was heated for 4 h at 200-205°C and the treatment described above gave 2.82 g (63%) (VI), bp 110-112°C (2 mm), $n_D^{20}$ 1.4478.

## CONCLUSIONS

4-Methyl-5-alkyl-2-imidazolinones were synthesized by heating 3-halo-2-alkanones with a mixture of piperidine, N,N-diethylacetamide, urea, zinc chloride and magnesium carbonate.

## LITERATURE CITED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