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RESEARCHES ON IMIDAZOLES
XXI. 4-Nitro-5-alkyl (aryl, dialkyl)-aminoimidazoles*

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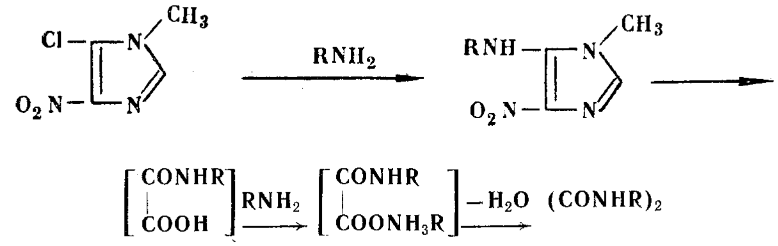
A number of 1-alkyl(1,2-dialkyl)-4-nitro-5-alkyl(aryl, dialkyl) aminoimidazoles are synthesized by reacting 1-alkyl(1,2-dialkyl)-4-nitro-5-chloroimidazoles with aliphatic, aromatic, and heterocyclic amines. Hydrogenation of 1-ethyl-2-methyl-4-nitro-5-(N-morpholino) imidazole in acetic anhydride gives 1-ethyl-2-methyl-4-diacetylamino-5-(n-morpholino) imidazole, characterized as its picrate.

Continuing previous work [1], the action of aliphatic, aromatic, and heterocyclic amines on 1-alkyl(1,2-dialkyl)-4-nitro-5-chloroimidazoles has been investigated with a view to preparing 4-nitro-5-alkyl(aryl, dialky, diaryl) aminoimidazoles, hitherto unknown. Apparently only recently, at the same time as our paper,* German workers prepared 1-methyl-4-nitro-5-alkyl(dialkyl) aminoimidazoles.

It has now been shown that primary and secondary amines readily react with 4-nitro-5-chloroimidazoles to give the corresponding 4-nitro-5-aminoimidazoles (I-XV, Table). Diphenylamine- and 2-methyl-4(5)-nitroimidazole, which do not react with nitrochloroimidazoles even at 120-135°, are excluded; the failure to react is probably due to the low basicity of these amines or to steric hindrance.

According to the equation for the reaction, 1 mole nitrochloroimidazole requires 1 mole amine. However, to carry the reaction to completion, not less than 2 moles (even better 3-5 moles) of amine must be used, as the aminonitroimidazoles formed are very weak bases, and incapable of uniting with the hydrogen chloride evolved.

Replacement of the halogen of nitrochloroimidazoles by an amine group takes place even at 60-70°. In most cases the yields of aminonitroimidazoles were found to be increased at much higher temperatures (100-135°). Only in the cases of butylamine and aniline did carrying out the reaction at 130-145° result in marked decrease in the yields of compounds II and III, and formation of side products, N, N7-dialkyl(diaryl) oximides (XVI and XVII). Apparently formation of oxamides is due to the instability of 4-nitro-5-alkyl(aryl) aminoimidazoles at high temperature, decomposition taking place thus



$$\left[\begin{matrix}\text{CONHR}\\ |\\ \text{COOH}\end{matrix}\right]\xrightarrow{\text{RNH}_2}\left[\begin{matrix}\text{CONHR}\\ |\\ \text{COONH}_3\text{R}\end{matrix}\right]\xrightarrow{-\text{H}_2\text{O}}(\text{CONHR})_2$$

XVI $R=C_4H_9$; XVII $R=C_6H_5$.

Despite the great mobility of the halogen in nitrochloroimidazoles, tertiary amines do not react with them, and it proved impossible to prepare the corresponding quaternary ammonium base salts. Thus when 1-methyl-4-nitro-5-chloroimidazole was heated with triethylamine at 120-130° (4 hr), there was a high recovery of the starting imidazole.

The inertness of triethylamine towards nitrochloroimidazoles made it possible to use that base for capturing the hydrogen chloride, and hence to cut consumption of some primary and secondary amines which were not readily available, or which had high boiling points.

Hydrogenation of 1-ethyl-2-methyl-4-nitro-5-(N-morpholino) imidazole (XIII) in acetic anhydride, with Raney nickel catalyst, gives 1-ethyl-2-methyl-4-diacetylamino-5-(N-morpholino) imidazole (XVIII), characterized as its picrate. This observation indicates the possibility of using aminonitroimidazoles I-XV for synthesis of the corresponding diamino compounds or their acyl derivatives.

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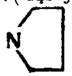
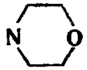
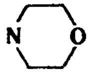
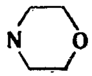
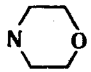
Characteristics of Compounds

Compound No.	R	R′	Mp, °C* (pressure, mm)	Molecular formula	Found,*** %			Calculated, %			Yield, %
					C	H	N	C	H	N	
I	H	$NHCH_2CH_2N(C_2H_5)_2$	90—91.5	$C_{10}H_{19}N_5O_2$	50.19	8.02	28.45	49.76	7.94	29.03	14.7
II	H	NHC_4H_9	110—110.5**	$C_8H_{14}N_4O_2$	48.46	6.96	27.82	48.47	7.12	28.27	83.2
III	H	NHC_6H_5	141—143	$C_{10}H_{10}N_4O_2$	55.38	4.63	25.24	55.04	4.62	25.67	37.4
IV	H	$N(C_2H_5)_2$	88—90	$C_8H_{14}N_4O_2$	48.70	7.07	28.06	48.48	7.12	28.27	73.5
V	CH_3	$N(C_2H_5)_2$	171—172 (1)	$C_{10}H_{18}N_4O_2$	52.69	7.68	—	53.08	8.02	—	84.0
VI	H	$N(C_4H_9)_2$	184 (0.4)	$C_{12}H_{22}N_4O_2$	56.73	8.80	22.08	56.67	8.72	22.03	83.0
VII	CH_3	$N(C_4H_9)_2$	189 (0.4)	$C_{14}H_{26}N_4O_2$	59.40	9.27	19.73	59.55	9.28	19.84	70.1
VIII	C_2H_5	$N(C_4H_9)_2$	149—150 (0.3)	$C_{16}H_{30}N_4O_2$	—	—	17.81	—	—	18.05	73.5
IX	C_3H_7	$N(C_4H_9)_2$	193 (0.5)	$C_{18}H_{34}N_4O_2$	—	—	16.54	—	—	16.55	73.9
X	H		96—97	$C_8H_{12}N_4O_2$	48.97	6.15	28.58	48.97	6.16	28.55	76.5
XI	H		178—179.5	$C_9H_{14}N_4O_2$	51.61	6.94	26.81	51.42	6.71	26.65	99.4
XII	H		216—217.5	$C_8H_{12}H_4O_3$	45.27	5.89	26.45	45.28	5.70	26.40	85.5—90
XIII	CH_3		153—154	$C_{10}H_{16}N_4O_3$	49.73	6.82	23.30	49.99	6.71	23.32	78.4
XIV	C_2H_5		97.5—98.5	$C_{12}H_{20}N_4O_3$	53.70	7.61	21.20	53.72	7.51	20.88	57.0
XV	C_3H_7		70—71.5	$C_{14}H_{24}N_4O_3$	56.58	8.30	18.90	56.74	8.16	18.91	92,5

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* For compounds V–IX, the boiling points under reduced pressure are given. Compound VII solidifies on standing, mp 37-39°. Refractive indices and specific gravities of the liquid compounds: V n_D^{20} 1.5330, d_{20}^{20} 1.1332; VI n_D^{20} 1.5240, d_{20}^{20} 1.0722; VIII n_D^{20} 1.5242; IX n_D^{20} 1.5160; d_{20}^{20} 1.0728.

**The literature [2] gives for compound II: mp 101-106°, yield 61%.

***For analysis the compounds were purified by recrystallizing as follows: I, II, XII, from water; III, from benzene; IV, from carbon tetrachloride; X, from ethyl acetate – petrol ether (3 : 1); XI, XIII, from water, then from ethanol; XIV, from 20% aqueous ethanol; XV, from ether.

Experimental

1-Alkyl-(1, 2-dialkyl)-4-nitro-5-alkyl (aryl, dialkyl) aminoimidazoles (I-XV, table). a. A mixture of 0.025 mole 1-alkyl (1, 2-dialkyl)-4-nitro-5-chloro-imidazole [3], 0.075-0.125 mole amine, and 25-30 ml absolute alcohol was heated for 7-8 hr at 130-132°, in a sealed tube. The solution was heated with decolorizing charcoal, filtered, and the solvent and excess amine distilled off under reduced pressure. With liquid aminonitroimidazoles V, ether was added to the residue, the solution filtered to remove the precipitate of amine hydrochloride, washed with water, dried over sodium sulfate, the solvent distilled off, and the residue distilled under reduced pressure. After distilling off the alcohol, compound I was extracted with methyl chloride. Compound IV crystallized after distilling off the alcohol; it was washed with ether, then with water, and dried. Compound III was prepared at 95-98° (8.5 hr). After distilling off the alcohol it was extracted with chloroform, the solution washed with 2N hydrochloric acid, then with water, and dried. The residue left after distilling off the solvent was washed with ether. Heating of 1-methyl-4 nitro-5-chloroimidazole with butylamine or aniline in alcohol (8-8.5 hr at 130-145°), in the presence of a small amount of copper sulfate, gave, in addition to compounds II and III (yields 5-8%), N, N'-dibutyloxamide (XVI mp 148-149°) and N, N' diphenyloxamide (XVII, mp 245-246°), respectively, isolated in about 50% yields. The mixed melting points with authentic specimens of those compounds [4] were undepressed.

b. A mixture of 5 g(~ 0.03 mole) 1-methyl-4-nitro-5-chloroimidazole, 2.7 g(~ 0.03 mole) morpholine, and 4.7 g(0.005 mole) triethylamine in 20 ml absolute ethanol was heated for 8 hr at 130-132°. After cooling the precipitate of XII was filtered off, washed with water, and dried. Compounds X, XII-XV were prepared similarly. Compound X was isolated after distilling off the alcohol and washing the residue with water.

c. A mixture of 6.45 g(0.04 mole) 1-methyl-4-nitro-5-chloroimidazole, 16 ml piperidine, and 25 ml anhydrous alcohol was refluxed for about 5 hr, cooled, the precipitate filtered off, washed with alcohol, then with water, and dried. Yield of XI 7.45 g, mp 177-178°. A further 0.9 g compound XI, mp 176-177° was obtained by evaporating the alcoholic mother liquor to dryness, then washing the residue with water. Compounds II and XII were prepared similarly. A further quantity of compound II was isolated from the aqueous mother liquors by extracting with chloroform.

Compounds I-IV, X-XV. These were yellow, crystalline compounds, soluble in most organic solvents, in concentrated hydrochloric acid, and in hot water, only very slightly soluble in ether, benzene, carbon tetrachloride and water (in the cold), insoluble in petrol ether. Compounds V-IX were cherry-red viscous liquids, soluble in most organic solvents and concentrated hydrochloric acid, insoluble in cold water and petrol ether. None of the compounds give hydrochlorides and picrates.

1-Ethyl-2-methyl-4-diacetylamino-5-(N-morpholino) imidazole picrate (XVIII). Hydrogen, from a gas holder, was introduced into a solution of 1.33 g XIII in 20 ml acetic anhydride containing 0.7 g Raney nickel catalyst. Hydrogenation took 35 min, and 385 ml hydrogen was absorbed. The solution was filtered, the acetic anhydride distilled off under reduced pressure, absolute alcohol added to the residue, and then distilled off under reduced pressure. The oily residue was dissolved in 10 ml acetone, the solution filtered, and then treated with an acetone solution of 1 g picric acid. The picrate formed was precipitated by ether. Yield 2.17 g(74.8%) mp 170-171° (decomp), yellow crystals mp 184-184.5° (decomp, from alcohol), soluble (on heating) in water, alcohol, ethyl acetate, and glacial acetic acid. Found: C 45.70; H 4.83; N 18.69%. Calculated for $C_{14}H_{22}N_4O_3 \cdot C_6H_2(NO_2)_3OH$: C 45.89; H 4.81; N 18.73%.

REFERENCES

1. P. M. Kochergin, S. G. Verenikina, and K. S. Bushueva, KhGS [Chemistry of Heterocyclic Compounds], 765, 1965.
2. H. Schubert and D. Heydenhauss, J. Pr. Chem., 22, 304, 1963.
3. P. M. Kochergin, KhGS [Chemistry of Heterocyclic Compounds], 761, 1965.
4. P. M. Kochergin and L. S. Bushueva, ZhPKh, 35, 2745, 1962.

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