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RESEARCH ON BENZOIMIDAZOLE DERIVATIVES

XVIII. The Reaction of 2-Amino-1-Alkylbenzoimidazoles with Some Halogen Substituted Esters[*]

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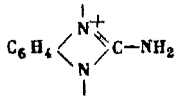
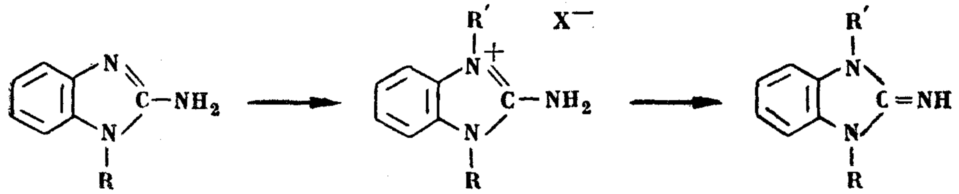
When 2-amino-1-alkylbenzoimidazoles react with alkyl chloroacetates and β-chloroethyl benzoates, alkylation is at the N hetero-atom. The resultant salts on treatment with alkalies give 1,3-substituted 2-iminobenzoimidazolines (2-imino-2,3-dihydrobenzimidazoles).

Continuing a study of alkylation of 2-amino-1-alkylbenzoimidazoles (I) [2, 3], 1-methyl substituted Ia was heated with methyl and heptyl chloroacetates. It was shown that alkylation takes place at the nitrogen hetero-atom (see also [4]), giving the salts IIa, b. When treated with excess caustic alkali, these compounds underwent hydrolysis at the carboalkoxy group, being converted into the sodium salt of 2-imino-1-methylbenzoimidazolyl-3-acetic acid (IIIa). The free acid IIIb, which apparently exists as the betaine, is obtained by the action of sodium methoxide (1 equivalent) on the hydrochloride of its ester (IIa, b), even in the cold. Due to the effect of the neighboring imidazole ring, hydrolysis of the carboalkoxy group takes place so readily, that all attempts to isolate the base corresponding to salts IIa, b were unsuccessful.

The conclusion that the acid IIIb is a derivative of the imino- form of 2-aminobenzoimidazole, was based on comparison of electronic spectra of methanol solutions of the free acid, its sodium salt, and its hydrochloride (see figure). The absorption curves for those compounds are analogous to that for 2-imino-1,3-diethylbenzoimidazoline (IV) [3], and its hydrochloride (IVa)[**], and differ from the spectra of 2-amino-1-alkylbenzoimidazoles (Ia, b) (cf. [5]). The structure assumed for IIIa, b is supported by the observation that on boiling a solution of the salt IIIa with 10% sodium hydroxide solution, there is abundant evolution of ammonia. The spectra of the hydrochlorides of esters IIa, b are almost identical with the spectra of the acids IIIb.

V 
$C_6H_4 < N^+ \, N > C{-}NH_2$

V



I II III

I: a) R = Me; b) R = Et

II: a) R = Me; R' = CH_2CO_2Me; b) R = Me; R' = $CH_2CO_2(CH_2)_6Me$; c) R = Me; R' = CH_2CO_2H; d) R = Et; R' = CH_2CH_2OCOPh; e) R = Et; R' = CH_2CH_2OH.

III: a) R = Me; R' = CH_2CO_2Na; b) R = Me; R' = CH_2CO_2H; c) R = Et; R' = CH_2CH_2OCOPh; d) R = Et; R' = CH_2CH_2OH.

The action of β-chloroethyl benzoate on 2-amino-1-ethylbenzoimidazole (Ib) gives the benzoimidazole salt IId, giving on treatment with cold dilute alkali the base IIIc; unlike IIa, b, hydrolysis of the ester group in this compound takes place rapidly only on heating. The saponification product, 2-imino-1-methyl-3-β-hydroxyethylbenzoimidazoline (IIId) is also obtained as the hydrochloride, starting from Ib and ethylene chlorohydrin. The structure of IIIc, d, as that of derivatives of 2-iminobenzoimidazoline (2-imino-2,3-dihydrobenzoimidazole), is based on a study of their electronic spectra (see table).

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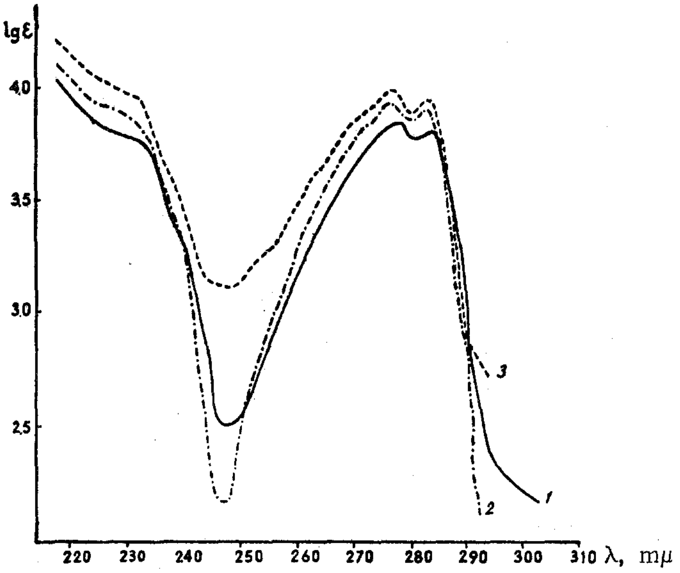
[*] For Part XVII, see [1].

[**] Apparently in water and alcohol solution, III and IV have a chromophoric group V, formed by addition of a proton to the imino- group, and displacement of electrons towards the exocyclic N atom.



UV absorption spectra in methanol. Concentration, 10^{-5} M. 1) 2-Imino-1-methylbenzoimidazolyl-3-acetic acid; 2) 2-imino-1-methylbenzoimidazolyl-3-hydrochloride; 3) 2-imino-1-methylbenzoimidazolyl-3-sodium salt.

Experimental

2-Imino-1-methyl-3-carbomethoxybenzoimidazoline hydrochloride (2-amino-1-methyl-3-carbomethoxymethylbenzoimidazolium chloride) (IIa). A mixture of 1.47 g 2-amino-1-methylbenzoimidazole [6] and 4.5 ml methyl chloroacetate was maintained at 100° for 5 min. The products were cooled, and the solidified melt triturated with ether, to

UV absorption spectra of derivatives of 2-iminobenzoimidazoline and 2-aminobenzoimidazole in methanol.

Compound no.	Compound	λ_{min} (lg ε)	λ_{max} (lg ε)
IIIb	3-Imino-1-methylbenzoimidazoline-3-acetic acid	248 (2.51)	234*; 278; 284 (3.73) (3.85) (3.83)
IIIa	" (Na salt)	248 (3.12)	232*, 276; 283 (3.96) (4.01) (3.96)
IIc	" (hydrochloride)	248 (2.16)	232*; 277; 283 (3.85) (3.94) (3.92)
IIa	" [ethyl ester (hydrochloride)]	246 (2.67)	234*; 276; 282 (3.81) (3.99) (3.99)
IIb	" [heptyl ester (hydrochloride)]	246 (2.71)	232*; 276; 282 (3.90) (3.93) (3.91)
IIIc	2-Imino-1-ethyl-3-β-benzoylhydroxyethylbenzoimidazoline	252 (3.11)	232*; 277; 283 (4.18) (3.87) (3.86)
IId	" (hydrochloride)	252 (3.15)	232*; 277; 283 (4.28) (3.96) (3.94)
IIId	2-Imino-1-ethyl-3-β-hydroxyethylbenzoimidazoline	248 (2.81)	232*; 277; 283 (3.90) (3.93) (3.91)
IIe	" (hydrochloride)	248 (2.65)	232*; 277; 283 (3.88) (3.92) (3.90)
IV	2-Imino-1, 3-diethylbenzoimidazoline . .	247 (3.04)	233*; 277; 283 (3.91) (3.97) (3.94)
IVa	" (hydrochloride)	247 (2.63)	232*; 277; 283 (3.80) (3.86) (3.83)
Ia	2-Amino-1-methylbenzoimidazole. . . .	234; 260 (3.57) (3.07)	248**; — 283 (3.74) (3.89)
Ib	2-Amino-1-ethylbenzoimidazole	234; 260 (3.65) (3.19)	248 — 283 (3.78) (3.91)

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*Inflection

**Band center

give 2.35 g product, recrystallized from methanol-ether, colorless needles mp 247°. Found: C 51.58, 51.41; H 5.61, 5.55%. Calculated for $C_{11}H_{14}ClN_3O_2$: C 51.67; H 5.52%.

2-Imino-1-methyl-3-carbo-n-heptoxymethylbenzoimidazoline hydrochloride (IIb). This salt was prepared by heating a mixture of 1.47 g 2-amino-1-methylbenzoimidazole, 5 ml heptyl chloroacetate [7], and 0.5 ml methanol at 120-125°. Yield 3.1 g; recrystallized from methanol-ether, prisms, mp 236°. Found: Cl 10.57, 10.48%. Calculated for $C_{17}H_{26}ClN_3O_2$: Cl 10.62%.

2-Imino-1-methylbenzoimidazoline-3-acetic acid (IIIb). 6.6 ml 1 N methanolic sodium methoxide (1 equivalent) was added to a saturated solution of 1.7 g 2-imino-3-carboxymethyl-1-methylbenzoimidazoline hydrochloride. The methanol was vacuum-distilled off from the solution which was neutral to litmus, and the residue recrystallized from 90% methanol-ether, to give needles or long flat prisms, mp 283°, with 0.5 molecules of water. The compound is readily soluble in water, almost insoluble in non-polar solvents. Yield 1.2 g. Found: N 19.86, 19.73%. Calculated for $C_{10}H_{11}N_3O_2 \cdot 0.5H_2O$: N 19.62%.

On prolonged heating (120°, 20 days), 2-imino-1-methylbenzoimidazoline-3-acetic acid lost 1.5 molecules of water. Apparently the dehydration product was a lactam; it eagerly absorbed water, giving the original acid.

2-Imino-1-methylbenzoimidazoline-3-acetic acid hydrochloride precipitated in quantitative yield when an equal volume of concentrated hydrochloric acid was added to an aqueous solution of the acid. Mp 275° (from alcohol-ether). Found: Cl 14.54, 14.65%. Calculated for $C_{10}H_{11}N_3O_2 \cdot HCl$: Cl 14.68%.

Sodium salt (IIIa).

a) An excess of 50% sodium hydroxide solution was added to an aqueous solution of 1.5 g IIb, when a precipitate of IIIa, and heptyl alcohol separated. Acetone was then added, and the acetone layer, rendered turbid by the sodium salt, separated off. It was filtered and the sodium salt recrystallized from methanol-ether. Colorless leaflets, not melting up to 340°. An aqueous solution of the salt was alkaline to litmus. Found: Na 10.21, 10.08%. Calculated for $C_{10}H_{10}N_3O_2Na$: Na 10.18%. On crystallizing from aqueous methanol, it gave a hydrate with 2 molecules of water. Found: H_2O 13.77, 13.54%. Calculated for $C_{10}H_{10}N_3O_2 \cdot 2H_2O$: H_2O 13.69%.

b) 0.5 g IIa was dissolved in 5 ml 10% sodium hydroxide solution. It was more difficult to free the precipitated salt from alkali than when using method (a).

2-Imino-1-ethyl-3-β-benzoylhydroxyethylbenzoimidazoline hydrochloride (IId). A mixture of 1.61 g Ib and 5 ml β-chloroethylbenzoate was heated for 1 hr in an oil bath at 140°. The precipitate was filtered off and washed with ether. Yield 1.2 g, needles mp 264° (from methanol-ether). Found: N 12.22, 12.15%. Calculated for $C_{18}H_{19}N_3 \cdot HCl$: N 12.15%.

2-Imino-1-ethyl-β benzoylhydroxyethylbenzoimidazoline (IIIc). A mixture of 0.35 g IId and 0.85 ml 1 N sodium hydroxide solution was triturated in a mortar, the precipitate filtered off, washed with water, and recrystallized from cold methanol ether. Mp 266° (decomp). Found: N 13.32, 13.37%. Calculated for $C_{18}H_{19}N_3O_2$: N 13.58%.

2-Imino-1-ethyl-3-β-hydroxyethylbenzoimidazoline (IIId). This compound was prepared similarly to IIIb, by the action of sodium methoxide on IId, but with heating on a water bath. The base was also formed by treating IIe with concentrated alkali; it was extracted with hot benzene. Mp 131° (from benzene-heptane). Found: C 64.57, 64.42; H 7.54, 7.40%. Calculated for $C_{11}H_{15}N_3O$: C 64.34; H 7.36%.

IIe hydrochloride. A solution of 0.8 g Ib in 1.5 ml ethylene chlorohydrin was heated for 30 min at 135°, and the salt of IIe separated from the solution with ether. Yield 75%, mp 230° (from methanol-ether). Found: C 54.73, 54.73; H 6.88, 6.84%. Calculated for $C_{11}H_{15}N_3O \cdot HCl$: C 54.67; H 6.67%.

REFERENCES

1. A. M. Simonov and A. F. Pozharskii, KhGS, 203, 1965.
2. N. D. Vitkevich and A. M. Simonov, ZhOKh, 30, 2868, 1960.
3. A. M. Simonov and Yu. M. Yutilov, ZhOKh, 32, 2670, 1962.
4. West German Patent 1069634, 1959; C. A., 55, 21147, 1961.
5. Yu. M. Yutilov, Transactions of the 4th Scientific Conference of Fellows of Rostov University, 110, 1962.
6. A. M. Simonov and N. D. Vitkevich, ZhOKh, 30, 590, 1960.
7. V. P. Denisenko and A. I. Lopushanskii, ZhOKh, 32, 734, 1962.

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