TRANSFORMATIONS OF IMIDAZO[4,5-*f*]QUINOLINE

I. Action of Methylating Agents on Imidazo[4,5-*f*]Quinoline and its 3-Substituted Derivatives

A. M. Simonov, B. I. Khristich, and V. G. Poludnenko

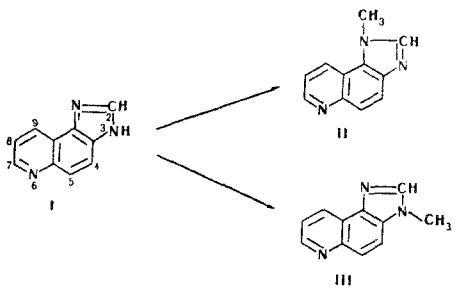
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 5, pp. 927–930, 1967

UDC 547.831.1'785.5

Treatment of imidazo[4, 5-*f*]quinoline and some of its 3-substitution products with methyl halides and methyl benzenesulfonate gives as the main reaction products N-methylimidazoquinolinium salts, which can also be synthesized from 5, 6-dimainoquinolines. Methylation at the N atom of the imidazole ring is only a side reaction. Treatment with trimethylphenylammonium hydroxide introduces a methyl radical into the NH group of imidazoquinoline, giving a mixture of 1-and 3-substitution products.

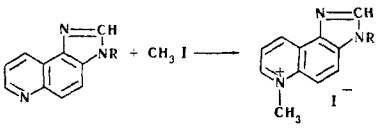
In connection with the investigation of reactions of imidazoquinoline (**I**) [1] and its derivatives [2], the synthesis of alkyl-substituted derivatives of **I** was undertaken, for which purpose the latter and some 3-substituted derivatives (IVb–d) were treated with methylating agents. Naturally, reaction would then be expected to occur at the N atom of the quinoline or imidazole ring, and at both nitrogen atoms simultaneously.

Alkylation with trimethylphenylammonium hydroxide [3, 4] gave a mixture of 1- and 3-methylimidazoquinolines (**II** and **III**), which could be separated by chromatographing on alumina. The structures of these reaction products were readily established because a 3-methyl substitution product had previously been obtained from 6-bromo-5-nitroquinoline [5].



When an ethanol solution of **I** was heated with one equivalent of methyl iodide, the main reaction product came out as a yellow crystalline product. Analysis showed it to be a monomethyl derivative, and treating it with alkali did not convert it to **II** and **III**, so that it was the quinolinium salt **Va**, a structure also proved by the preparation of **Va** from an N-methyl-5, 6-diaminoquinolinium salt (see below). Methylation of **I** gives, moreover, a small amount (about 9%) of imidazole ring methylation products (**II** and **III**), which could be isolated from the mother liquor.

Treatment of 3-substituted derivatives of imidazoquinoline (**IVb–d**) with methyl iodide under the above conditions gave a main reaction product, which precipitated out, that was an imidazoquinolinium salt (**V**)



IV V

a R=H, b R=CH_3, c R=C_6H_5, d R=$C_6H_5CH_2$

as well. Carrying out the reaction in benzene with a 10-fold excess of MeI also raised the yield of quinolinium salts considerably, to 91–95%.

The structure of compounds **V** is shown by the following reactions. 5, 6-Diaminoquinoline [6, 7] and its position 6 NH group substitution products (**VIa–d**) were heated with methyl benzenesulfonate in boiling benzene, giving products which, like the methyl iodide methylation products of 6-amino- and 6-diethylaminoquinoline [9], must be quinolinium salts (**VII**). Actually, if the alkylation occurred at one of the amino groups, treatment of aqueous solutions of the salts with alkali would lead to separation of a precipitate of a base, which is not observed experimentally. The analytical data show that dimethylation with involvement of one of the amino groups does not take place. The results obtained when cyclizing these salts confirm these conclusions.

Table 1

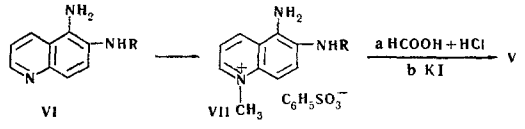
N-Methyl-3-R-imidazo[4, 5-*f*]quinolinium Iodides

Compound	R	Mp, °C	Formula	Found, %			Calculated, %			Yield, %	
				C	H	N	C	H	N	In EtOH	In benzene
Va	H	234–235	$C_{11}H_{10}IN_3$	42.30	3.33	13.69	42.47	3.24	13.51	73	—
Vb	CH_3	282	$C_{12}H_{12}IN_3$	—	—	12.89	—	—	12.92	65	91
Vc	C_6H_5	269–270	$C_{17}H_{14}IN_3$	52.98	3.82	—	52.72	3.65	—	70	95
Vd	$C_6H_5CH_2$	264–265	$C_{18}H_{16}IN_3$	53.84	4.21	10.73	53.88	4.02	10.47	68	95

Table 2

N-6-Substituted 1-Methyl-5, 6-diaminoquinolinium Benzenesulfonates

Compound	Substituent R at the 6-NH_2 group	Mp, °C	Formula	Found, %			Calculated, %			Yield %
				C	H	N	C	H	N	
VIIa	H	209—210	$C_{16}H_{17}N_3O_3S$	—	—	12.63	—	—	12.68	80
VIIb	CH_3	262—263.5	$C_{17}H_{19}N_3O_3S$	58.79	5.32	12.11	59.11	5.54	12.17	76
VIIc	C_6H_5	260—262	$C_{22}H_{21}N_3O_3S$	—	—	10.28	—	—	10.31	72
VIId	$C_6H_5CH_2$	259	$C_{23}H_{23}N_3O_3S$	65.36	5.56	10.12	65.53	5.50	9.97	78



a R=H, b R=CH_3,
c R=C_6H_5 d R=$C_6H_5CH_2$

Imidazole ring closure in salts **VII** takes place readily when they are heated with 80% formic acid containing hydrochloric acid. By reaction with hydriodic acid or a salt of the latter the compounds formed are converted to iodide, identical with the products of reaction of methyl iodide with imidazoquinolines **IV**. Hence it can be taken that the structure assumed for salts **V** is proven.

Quaternization at the N atom of the quinoline ring also takes place on melting together equimolecular amounts of 3-phenyl- and 3-benzylimidazo[4, 5-*f*]quinoline with methyl benzenesulfonate, since treatment with hydriodic acid converts the products to the iodides **V**.

EXPERIMENTAL

1- and 3-methylimidazo[4, 5-*f*]quinoline. 1.69 g (10 mM) imidazo[4, 5-*f*]quinoline was introduced into an ethanol solution of trimethylphenylammonium hydroxide prepared from 2.94 g trimethylphenylammonium benzenesulfonate [3]. Then the EtOH was distilled off in an oil bath, and the residue kept at 122° for 1 1/2 hr, then acidified with AcOH, and the dimethylaniline steam distilled off. The residue was made alkaline and extracted with $CHCl_3$. The extract gave 1.42 g (78%) mixed isomers.

TLC of the mixture on alumina gave 2 spots, visualized in UV light. The compound with R_f 0.19 was 3-methylimidazoquinoline [2], that with R_f 0.07 was 1-methylimidazoquinoline. To separate the isomers 0.2 g substance was dissolved in 15 ml $CHCl_3$ and column chromatographed on alumina with $CHCl_3$ eluant, UV light being used to check the separation. Yield of compound mp 190° was 0.114 g, identical with 3-methylimidazoquinoline, prepared synthetically [2]; yield of compound mp 187° 0.26 g, which was 1-methylimidazoquinoline (colorless needles). The hitherto undescribed 1-methylimidazoquinoline was analyzed. Found: C 71.91, 71.84; H 4.80; 4.69%, calculated for $C_{11}H_9N_3$: C 72.11; H 4.95%.

5-Nitro-6-phenylaminoquinoline. 0.90 g (3 mM) 6-bromo-5-nitroquinoline was dissolved in 5 ml aniline, and the solution heated at 130° for 4 hr in the absence of oxygen of the air. Then the aniline was steam distilled off. Orange needles mp 102° (ex EtOH), soluble in benzene, ether, and dilute acids, yield 0.52 g (56%). Found: C 68.00; 68.20; H 4.21; 4.26%, calculated for $C_{15}H_{11}N_3O_2$: C 67.92; H 4.18%.

5-Amino-6-phenylaminoquinoline. 5 g (0.02 mole) 5-nitro-6-phenylaminoquinoline was reduced with 10 g Fe in 45 ml conc. HCl plus 75 ml water, by heating on a steam bath. The solution was filtered hot, and on cooling 5-amino-6-phenylaminoquinoline hydrochloride came out (3.5 g). It was dissolved in water, and the free base liberated by treatment with alkali. Yield 2.2 g (50%), minute yellow prisms, mp 190° (ex benzene). Found: N 18.08; 18.15%, calculated for $C_{15}H_{13}N_3$: N 17.86%.

3-Phenylimidazo[4, 5-*f*]quinoline. 4 g 5-amino-6-phenylaminoquinoline hydrochloride and 13 ml formic acid were gently refluxed together for 6 hr. The formic acid was then vacuum distilled off, the residue dissolved in water, and boiled with active charcoal, the solution filtered and made alkaline. Yield 2.4 g, colorless plates, (ex benzene), soluble in EtOH, mp 164.5°. Found: C 78.17; 78.08; H 4.55; 4.61%, calculated for $C_{16}H_{11}N_3$: C 78.35; H 4.52%.

Action of methylating agents on imidazoquinolines.

a) N-methylimidazoquinolinium iodides and their 3-substitution products were prepared by heating a solution of the appropriate imidazoquinoline (3 mM compound, 5-7 ml EtOH) with MeI (3-12 mM) at 60°-65° for 4 hr. The solid was filtered off and recrystallized from EtOH. The salts were high-melting yellow compounds (Table 1).

The filtrate obtained after removing **Va** (Table 1) was evaporated, dissolved in a small amount of water, the solution made strongly alkaline and extracted repeatedly with ether. The $CHCl_3$ was evaporated to give 0.05 g material. Chromatography showed the presence of 1- and 3-methylimidazolquinolines. 3-Methylimidazoquinoline (mp 190°) was isolated by column chromatography.

b) Heating the 3-substituted derivatives (3 mM) in benzene with a large excess (0.03-0.04 mole) MeI at 60°-65° for 3-4 hr, gave considerably higher yields of methiodides (see Table 1).

c) A ground mixture of equivalent quantities of 3-phenylimidazoquinoline and methyl benzenesulfonate was carefully heated at 50°-55°. The mixture first melted, then solidified. Crystallization from EtOH gave colorless substance mp 269°-270°, yield 90%. Treatment of an EtOH solution of this salt with hydriodic acid gave a compound identical with **Vc** Found: N 10.14%, calculated for $C_{23}H_{19}N_3O_3S$: N 10.07%.

6-Methyl-3-benzylimidazoquinolinium benzenesulfonate was prepared similarly. Yield 88%, minute colorless needles, mp 261°-262° (ex EtOH). Found: N 9.73%, calculated for $C_{24}H_{21}N_3O_3S$: N 9.74%.

6-Methylimidazo[4, 5-*f*]quinolinium chloride. 0.84 g (5 mM) imidazoquinoline was dissolved in 14 ml of an EtOH solution of MeCl (10 mM), and the mixture heated in an autoclave at 70° for 4 hr. The solution was vacuum evaporated, the residue crystallized from EtOH-acetone. Minute colorless prisms, mp 256°. Treatment with hydriodic acid in ethanol solution gave an iodide mp 234°-235°. Found: N 19.36; 19.28%, calculated for $C_{11}H_{10}ClN_3$: N 19.13%.

1-Methyl-5, 6-diaminoquinolinium benzenesulfonate and its N-6 substituted derivatives. Benzene solutions of diaminoquinolines **VI** (10 mM) and methyl benzenesulfonate (15 mM) were refluxed in the absence of oxygen of the air for 4-5 hr. The precipitates were filtered off and washed with benzene, to give minute violet flaky crystals (ex EtOH) (Table 2).

A solution of 5 mM methyl benzene sulfonate **VII** in 20 ml 80% formic acid was refluxed for 4 hr with 1 ml conc. HCl, the products vacuum evaporated, the residue dissolved in EtOH, and 0.5 ml conc. hydriodic acid added, whereupon yellow crystals of the iodides **V** came down.

REFERENCES

1. R. Huisgen, Ann., **559**, 101, 1948.

2. B. I. Khristich and A. M. Simonov, KhGS, 611, 1966.
3. V. M. Rodionov, Bull. soc. chim. [Chemistry of Heterocyclic Compounds], France, **45**, 109, 1929.
4. A. M. Simonov, ZhOKh, **22**, 2006, 1952.
5. W. La Coste, Ber., **15**, 1918, 1882.
6. A. Kaufmann and O. Zeller, Ber., **50**, 1629, 1917.
7. W. C. J. Ross, J. Chem. Soc., **223**, 1948.
8. A. Claus and L. Schnell, J. pr. Chem., **53**, 119, 1896.
9. W. O. Sykes, J. Chem. Soc., 4430, 1965.

18 January 1966 Rostov-on-Don State University