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SOME REACTIONS OF SYSTEMS CONTAINING THE IMIDAZOLE RING

V. Properties of Naphth [1, 2-d] imidazole and Imidazo [4, 5-f] quinoline Derivatives

B. I. Khristich and A. M. Simonov

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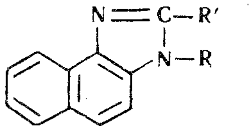
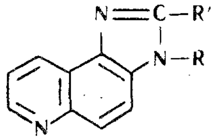
Behavior towards sodamide is compared for 3-benzyl- and 3-methyl substituted naphth [1, 2-d] imidazole and imidazo [4, 5-f] quinoline derivatives. The following are synthesized: 2-amino derivatives of 3-benzylnaphtho- [1, 2-d] imidazole (by direct amination), and of 3-benzylimidazo [4, 5-f] quinoline (ammonolysis of a 2-chloro substituted compound).

It was previously shown that the possibility of direct amination of imidazole systems at a CH group in the imidazole ring depends on the nature of the ring annelated to it [1, 2]. For further research on this reaction, we have synthesized some hitherto undescribed derivatives of napth [1, 2-d] imidazole and imidazo [4, 5-f] quinoline, and compared their behaviors towards sodamide.

3-Benzylnaphth [1, 2-d] imidazole (Ia), prepared by benzylating naphth [1, 2-d] imidazole, readily reacts with sodamide in dimethylaniline at 110° C, to give a 75% yield of the 2-amino derivative Ic. On the other hand, it was not possible, under the same conditions, to effect direct amination of 3-benzylimidazo [4, 5-f] quinoline (IIa) (synthesized from 5-nitro-6-bromoquinoline). Reaction of sodamide with 3-methylimidazo [4, 5-f] quinoline (IIb)* does not lead to formation of a 2-amino derivative, though the analogously constituted naphthimidazole compound (Ic) readily undergoes this reaction [2].



Ia $R=CH_2C_6H_5$; $R'=H$;
b $R=CH_3$; $R'=H$;
c $R=CH_2C_6H_5$; $R'=NH_2$;



IIa $R=CH_2C_6H_5$; $R'=H$;
b $R=CH_3$; $R'=H$;
c $R=CH_2C_6H_5$; $R'=NH_2$;
d $R=CH_2C_6H_5$; $R'=Cl$.

Thus, unlike the naphthalene ring, the quinoline ring deactivates towards sodamide position 2 in the imidazole ring fused to it. 2-Amino-3-benzylimidazo [4, 5-f] quinoline (IIc) can be synthesized only by treating 2-chloro-3-benzimidazo [4, 5-f] quinoline (IId) with ammonia in the presence of a copper salt. IId is obtained by the action of phosphorus oxychloride on 3-benzylimidazolono [4, 5-f]-quinoline.

When a 3-substituted imidazo [4, 5-f] quinoline is treated with sodamide, the quinoline ring is not substituted as well. Evidently this is due to the action of the imidazole ring on it, since our results showed that under the same conditions, quinoline readily gives α-aminoquinoline (yield 85%).

Experimental

3-Benzylnaphtho [1, 2-d] imidazole (Ia). 3.5 g naphth [1, 2-d] imidazole [4] was benzylated in alkali solution with 7.5 g leucotrope by a modification of the method described in [3], the difference being that the precipitate obtained by decanting off the solutions was filtered off, and decomposed by vacuum-heating. The residue was washed with ether, and the 1-substituted compound obtained by repeated recrystallization from EtOH. The imidazole Ia separated from solutions as minute prisms, mp 170° C, soluble in benzene and acetone. Yield 1 g. The substance was identical with the compound prepared by reacting 1-amino-2-benzylaminonaphthalene [5] with formic acid. Found: C 83.75, 83.73; H 5.52, 5.47%. Calculated for $C_{18}H_{14}N_2$: C 83.69; H 5.46%.

2-Amino-3-benzylnaphth [1, 2-d] imidazole (Ic). 0.9 g Ia and 0.7 g $NaNH_2$ in 6 ml dimethylaniline were heated at 110° for 1 hr 30 min, with mechanical stirring, H_2 being evolved. 0.5 ml water was added with cooling, then the precipitate of amine (0.75 g) filtered off. Colorless minute needles (ex pyridine), mp 256° C. Found: C 79.07, 79.20; H 5.62, 5.62%. Calculated for $C_{18}H_{15}N_3$: C 79.09; H 5.53%.

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*In xylene solution neither IIa, IIb, nor, surprisingly, Ia, are aminated.

2-(p-Nitrobenzylideneamino)-3-benzylnaphth [1, 2-d] imidazole. Prepared by heating together a solution of the amine and p-nitrobenzaldehyde (3 mole) in pyridine on a water-bath. Red prisms (ex pyridine), mp 271° C. Found: C 74.09, 74.11; H 4.64, 4.60%. Calculated for $C_{25}H_{18}N_4O_2$: C 73.88; H 4.46%.

5-Nitro-6-methylaminoquinoline. A solution of 2.5 g 5-nitro-6-bromoquinoline [6] in 15 ml EtOH was heated for 4 hr at 100° C in an autoclave with 5 ml of a saturated solution of $MeNH_2$ in EtOH. Yield almost quantitative. Orange needles (ex EtOH), mp 190° C, soluble in benzene and acetone. Found: C 59.39, 59.09; H 4.37, 4.42%. Calculated for $C_{10}H_9N_3O_2$: C 59.11; H 4.46%.

5-Amino-6-methylaminoquinoline. A solution of 1.5 g 5-nitro-6-methylaminoquinoline in 10 ml EtOH plus 20 ml concentrated HCl was heated, and 6.7 g $SnCl_2 \cdot 2H_2O$ in 5 ml concentrated HCl plus 10 ml EtOH added. On cooling, pale orange crystals of a complex salt separated, and these were filtered off, dissolved in water, and decomposed with H_2S. Yield 0.9 g, pale yellow small crystals (ex aqueous EtOH), mp 179–180° C, soluble in benzene. Found: N 24.11, 24.12%. Calculated for $C_{10}H_{11}N_3$: N 24.26%.

3-Methylimidazo [4, 5-f] quinoline (IIb). 1.8 g 6-methylamino-5-aminoquinoline, 20 ml HCOOH, and 2 ml concentrated HCl were refluxed together for 4 hr. Yield 1.8 g, needles (ex benzene), mp 189–190° C, soluble in EtOH, $CHCl_3$, and acetone. Found: C 72.36, 72.31; H 5.06, 5.02%. Calculated for $C_{11}H_9N_3$: C 72.11; H 4.95%.

No H_2 was evolved when the compound was heated with $NaNH_2$, in dimethylaniline at 120° C, or xylene at 130° C. All that could be isolated from the reaction products was a small amount of the starting material, and resinous material.

5-Nitro-6-benzylaminoquinoline. A solution of 15.2 g 6-bromo-5-nitroquinoline and 14.8 ml benzylamine in 40 ml toluene was mechanically stirred and gently refluxed for 5 hr 30 min. The precipitate was washed first with EtOH, then with hot water. Yield 12.5 g. Orange needles mp 179° C (ex benzene), soluble in acetone, slightly soluble in EtOH. Found: N 15.29, 14.98%. Calculated for $C_{16}H_{13}N_3O_2$: N 15.05%.

5-Amino-6-benzylaminoquinoline hydrochloride. 3.5 g 5-nitro-6-benzylaminoquinoline was carefully ground (in a mortar) with 20 ml concentrated HCl and 50 ml H_2O, then vigorously stirred and heated on a water bath, and 8.7 g Fe powder added. When the starting material had dissolved, the solution was quickly filtered. Golden-yellow needles of diamine dihydrochloride separated out of solution; they decomposed about 160°C. Yield 3.3–3.4 g. Found: Cl 22.40%. Calculated for $C_{16}H_{15}N_3 \cdot 2HCl$: Cl 22.01%.

3-Benzylimidazo [4, 5-f] quinoline. Prepared by heating 1.6 g 5-amino-6-benzylaminoquinoline dihydrochloride with 4 ml HCOOH, at 125–135° C (10 hr). Yield 1.21 g (94%), minute colorless needles (ex aqueous EtOH), mp 158° C. Readily soluble in acetone and hot benzene. Found: C 78.59, 78.89; H 5.10, 5.06%. Calculated for $C_{17}H_{13}N_3$: C 78.74; H 5.05%.

When the compound was heated with sodamide in boiling xylene, no change was observed, and the starting material was recovered. Heating in dimethylaniline was unaccompanied by H_2 evolution, and resulted in formation of a substance which rapidly resinified in air.

2-Hydroxy-3-benzylimidazo [4, 5-f] quinoline. 3.3 g 5-amino-6-benzylaminoquinoline dihydrochloride was fused with 3.6 g urea and held at 140° C. Yield 2.2 g. Minute colorless needles (ex EtOH), mp 280° C, insoluble in benzene, moderately soluble in hot dilute alkalies and acids. Found: C 74.39, 74.33; H 4.89, 4.85%. Calculated for $C_{17}H_{13}N_3O$: C 74.17: H 4.76%.

2-Chloro-3-benzylimidazo [4, 5-f] quinoline (IId). A suspension of 0.7 g imidazolone in 5 g $POCl_3$ was refluxed until solution had taken place (about 12 hr). Yield 0.68 g, fine colorless needles (ex EtOH), mp 170–171° C, moderately soluble in acetone, dioxane, and benzene. Found: C 69.40, 69.31; H 4.20, 4.37%. Calculated for $C_{17}H_{12}ClN_3$: C 69.51; H 4.12%.

2-Amino-3-benzylimidazo [4, 5-f] quinoline. 0.5 g IId, 15 ml EtOH, 0.3 g $CuSO_4$, 0.1 g CuCl, 4 ml concentrated NH_4OH, and 4 ml water (added to dissolve the Cu salts) were autoclaved together for about 30 hr. Water was then added, the precipitate filtered off, and dissolved with heating in 20 ml 10% HCl. On cooling, the hydrochloride of the starting material separated (0.24 g). NH_4OH precipitated from the filtrate the 2-amino derivative IIc, which was dissolved in 10% HCl, and reprecipitated. Yield 0.23 g, colorless fine crystalline product (ex pyridine), mp 273° C, insoluble in benzene, slightly soluble in hot EtOH. Found: C 74.47, 74.44; H 5.17, 5.16; N 20.43, 20.54%. Calculated for $C_{17}H_{14}N_4$: C 74.43; H 5.14; N 20.42%.

2-(p-Nitrobenzylideneamino)-3-benzylimidazo [4, 5-f] quinoline. Prepared by heating the amine with p-nitrobenzaldehyde (3 mole) in pyridine for 1 hr. Pale orange prisms (ex pyridine), mp 262–263° C. Found: C 70.70, 70.96; H 4.48, 4.32%. Calculated for $C_{24}H_{17}N_5O_2$: C 70.75; H 4.21%.

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Rostov-on-Don State University