RELATIONSHIP BETWEEN THE STRUCTURE AND PROPERTIES OF AMINO ALCOHOLS AND THEIR DERIVATIVES

IX.* N-ALKYLATION OF IMIDAZOLE AND SYNTHESIS OF ALCOHOLS CONTAINING AN N-IMIDAZOLYL GROUP

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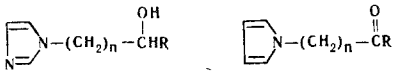
Methods have been developed for the alkylation of imidazole by unsaturated compounds and ω-bromoacetophenone in the presence of weakly alkaline agents. Several new alcohols and ketones containing N-imidazolyl groups were obtained.

The presence of an imidazole ring and a hydroxyl group is characteristic for the active center of many hydrolytic enzymes—cholinesterases, chymotrypsin, etc. [2]. This evoked interest in the creation of similar model monomeric [2, 3] and polymeric structures. This study is devoted to the preparation of aliphatic-aromatic alcohols of the I and II type which contain N-imidazolyl groups. Of the compounds of this type, only 2-(N-imidazolyl)ethanol [5] and some polysubstituted derivatives [6,7] have been previously described.†

The starting compounds for the synthesis of alcohols I and II were the corresponding ketones (III and IV), which were obtained by alkylation of imidazole with phenyl vinyl ketone and ω-bromoacetophenone, respectively.



I, II III–V

I, III n=2, R=C_6H_5; II, IV n=1, R=C_6H_5, V n=2, R=OCH_3

We have studied the reaction of imidazole with phenyl vinyl ketone, phenyl isopropenyl ketone, and methyl acrylate under the conditions described in [9] for the reaction of benzimidazole with acrylic acid derivatives in dioxane in the presence of tetrabutylammonium hydroxide hydrate (in the case of III) or triethylamine (in the case of V). The expected compounds could be obtained in both cases, but the yield was 13-30% because of the simultaneous polymerization of the starting unsaturated compounds. An attempt to obtain β-(N-imidazolyl)isobutyrophenone via a similar method was unsuccessful, since the product of the addition of imidazole to phenyl isopropenyl ketone decomposed completely on distillation.

The structure of III was confirmed by the IR spectrum, which contained a band from the valence vibrations of the C=O group at 1675 cm^{-1} and bands at 1200-1600 cm^{-1} which, on the one hand, are characteristic for N-substituted imidazoles [10, 11] and, on the other, for aliphatic-aromatic amino ketones [11]. A maximum at 243 nm, which is characteristic for the C_6H_5CO chromophore in amino ketones [12], is observed in the UV spectrum of III. The structure of V was confirmed by the IR and PMR spectra (see Experimental).

*See [1] for communication VIII.

†In patent [8] there is a reference to the preparation of 2-(N-imidazolyl)-1-phenylethanol (II), but no constants whatsoever are presented.

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To obtain N-imidazolylacetophenone (IV), we used the reaction of imidazole with ω-bromoacetophenone in the presence of excess triethylamine. The structure of IV was confirmed by the IR and UV spectra, which are similar to the spectra of III. The use of the stronger alkaline agents generally used in the alkylation of substituted imidazoles [13], viz., sodium amide or sodium ethoxide, despite the data in [8], did not result in the formation of IV but induced pronounced resinification of the mixture. In these cases, only a substance characterized by absorption at 260 nm in the UV spectrum and at 1627 cm^{-1} in the IR spectrum (and by the absence of absorption at 1700 cm^{-1}) could be isolated from the reaction mixture by chromatography with a column filled with Al_2O_3. This product apparently arises as the result of cleavage of the imidazole ring under the influence of alkaline agents to the initiall formed quaternary ammonium salt [14]. Its structure could not be accurately established.

We obtained alcohols I and II by reduction of ketones III and IV with sodium borohydride. Both alcohols are white, crystalline substances with IR spectra containing bands at 3200-3300 cm^{-1}, which are characteristic for the valence vibrations of the OH group, and the fundamental bands of the imidazole and benzene rings; their spectra did not have any absorption at 1700 cm^{-1}, which is characteristic for the starting ketones.

EXPERIMENTAL*

The IR spectra of mineral oil suspensions were obtained with a Perkin–Elmer 257 spectrophotometer (I-IV) or with a UR-10 spectrophotometer in the case of V (in a thin layer). The UV spectra in alcohol were obtained with an SF-4A spectrophotometer. The PMR spectrum of a CCl_4 solution was obtained with an RS-60 spectrometer. Thin-layer chromatography was carried out on activity II Al_2O_3 with ethyl acetate–methanol (15 : 1) as the mobile phase; the spots were developed with iodine.

3-(N-Imidazolyl)-1-phenylpropanol (I). A suspension of 0.35 g (0.0092 mole) of sodium borohydride in 1 ml of water was added at 0° to a solution of 0.9 g (0.00465 mole) of III in 15 ml of methanol, and the mixture was allowed to stand at 20° for 12 h and refluxed for 10 h. It was then vacuum evaporated, and the residue was washed with water and recrystallized from acetone to give 1.8 g (55%) of I with mp 103-104°. Found %: C 71.8; H 7.2; N 13.9. $C_{12}H_{14}N_2O$. Calculated %: C 71.3; H 6.9; N 13.9. IR spectrum (cm^{-1}): 3150-3250 s,b (ν_{OH}), 1600 m, 1512 s, 1486 s, 1450 s, 1355 s, 1280 s, 1230 s, 740 s, and 723 s.†

2-(N-Imidazolyl)-1-phenylethanol (II). This was similarly obtained in 67% yield and had mp 146-148° (from acetone). Found %: C 69.8; H 6.5; N 15.0. $C_{11}H_{12}N_2O$. Calculated %: C 70.2; H 6.4; N 14.9. IR spectrum (cm^{-1}): 3100-3200 s,b (ν_{OH}), 1590 m, 1510 s, 1450 s, 1344 m, 1280 m, 1230 s, 752 s, and 720 s.

β-(N-Imidazolyl)propiophenone (III). A total of 4 g (0.03 mole) of phenyl ketone and 0.3 g of tetrabutylammonium hydroxide were added to a solution of 2 g (0.03 mole) of imidazole in 10 ml of dioxane, the mixture was stirred for 1 h, vacuum evaporated, and water was added to the residue to give 0.8 g (13%) of III with mp 96-98° (from acetone). Found %: C 71.6; H 6.1; N 14.2. $C_{12}H_{12}N_2O$. Calculated %: C 72.0; H 6.0; N 14.0. IR spectrum (cm^{-1}): 1675 vs (ν_{CO}), 1588 m, 1575 m, 1445 s, 1372 s, 1227 s, 1206 s, and 749 s. UV spectrum: λ_{max} 243 nm, ε 8750.

α-(N-Imidazolyl)acetophenone (IV). Triethylamine [8.8 g (0.087 mole)] was added to a solution of 5 g (0.074 mole) of imidazole in 150 ml of benzene, and 14.7 g (0.074 mole) of ω-bromoacetophenone in 20 ml of benzene was then added with stirring. The reaction mixture was refluxed for 1 h, the hot solution was filtered, the precipitate was washed with hot acetone, and 6.8 g (50%) of IV with mp 97-99° (from acetone) was precipitated from the filtrate with ether.‡ Found %: C 70.0; H 5.5; N 15.0. $C_{11}H_{10}N_2O$. Calculated %: C 70.9; H 5.4; N 15.0. IR spectrum (cm^{-1}): 1690 (ν_{CO}), 1592 s, 1575 s, 1500 s, 1446 s, 1353 s, 1339 s, 1220 vs, 758 s, 740 s. UV spectrum: λ_{max} 245 nm, ε 10,700.

Methyl 3-(N-Imidazolyl)propionate (V). Methyl acrylate [8.6 g (0.1 mole)] was added to a solution of 6.8 g (0.1 mole) of imidazole in 16 ml of triethylamine, and the mixture was allowed to stand for 6 days at room temperature and heated for 2 h on a boiling-water bath. The triethylamine was removed, and the residue was vacuum distilled to give 4.6 g (30%) of V with bp 89-90° (0.15 mm) and n_D^{22} 1.4925 [15]. Found %:

* With the participation of N. V. Soboleva.

† Only the most characteristic bands are indicated in all of the IR spectra.

‡ In [8] the product obtained by the reaction of bromoacetophenone with imidazole in the presence of sodium ethoxide had mp 117-118°.

C 54.7; H 6.8; N 18.4. $C_7H_{10}N_2O_2$. Calculated %: C 54.5; H 6.5; N 18.2. IR spectrum (cm^{-1}): 1737 vs (ν_{CO}), 1532 s, 1445 s, 1368 s, 1296 s, 1266 s, 1234 vs, 1216 vs, 1181 s, 755 vs. PMR spectrum (δ, ppm, hexamethyldisiloxane standard): 2.78 (CH_2-CO, triplet, J 6.7 Hz); 3.60 (OCH_3); 4.28 ($N-CH_2$, triplet, J 6.7 Hz); 7.03, 7.17 (4-H, 5-H); 7.68 (2-H).

Reaction of ω-Bromoacetophenone with Imidazole in the Presence of Sodium Ethoxide. Imidazole [3.4 g (0.05 mole)], followed by 4 g (0.02 mole) of ω-bromoacetophenone in 20 ml of alcohol, was added to a solution of sodium ethoxide (from 1.3 g of sodium in 60 ml of alcohol) and the mixture was refluxed for 2 h. The precipitate was filtered, the filtrate was evaporated to dryness in vacuo, and the residue was chromatographed with a 600 × 30 mm column filled with Al_2O_3 using benzene, followed by benzene–ether (1 : 1), as the eluant. The product isolated (0.8 g) had mp 163-164° (from acetone). Found %: N 7.4. IR spectrum (cm^{-1}): 1638 vs, 1595 s, 1542 s, 1480 s, 1442 s, 1350 s, 1306 s, 727 s. UV spectrum: λ_{max} 260 nm, ε 6320. The hydrochloride had mp 221-223° (from alcohol). Found %: N 6.0; Cl 10.0.

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