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Synthesis and N-Alkylation of 2-Alkyl- and 2-Arylimidazole-4,5-dicarboxylic Acid Esters

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Abstract — Nitration of D-tartaric acid, followed by treatment of the resulting dinitrotartaric acid with ammonia and aldehydes gave 2-phenyl-, 2-(2-pyridyl)-, 2-isopropyl-, and 2-isobutylimidazole-4,5-dicarboxylic acids. Some factors affecting the yield of the final products were revealed, and optimal conditions for their esterification were found. N-Alkylation of 2-substituted imidazole-4,5-dicarboxylates thus obtained involves considerable steric hindrances; therefore, the corresponding N-alkyl derivatives can be obtained in a poor yield only in the presence of such a strong base as 1,8-diazabicyclo[5.4.0]undec-7-ene.
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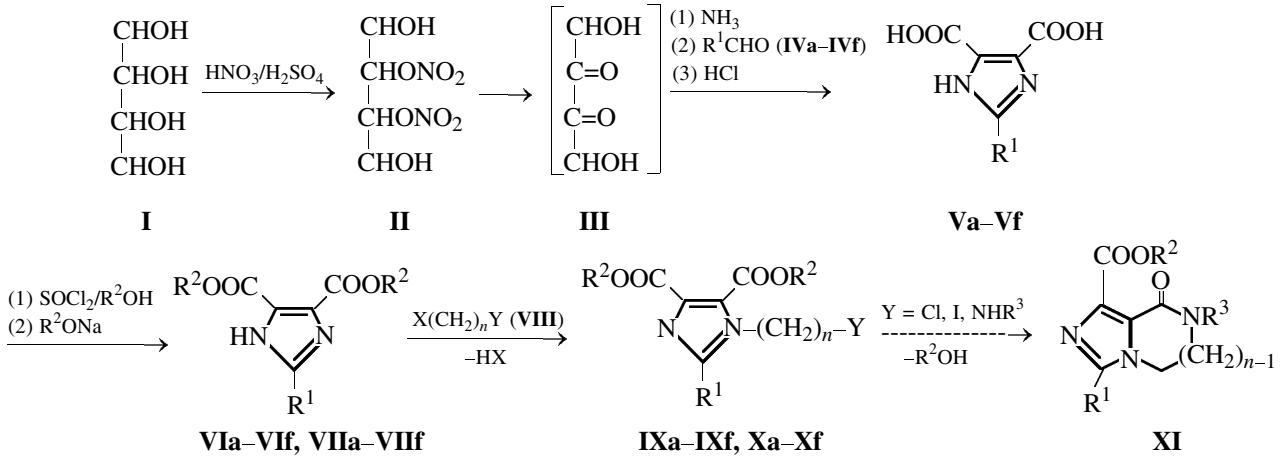
It is known [1–3] that *O,O'*-dinitrotartaric acid **II** (2,3-dinitroxybutanedioic acid) obtained by nitration of D-tartaric acid (**I**) reacts with ammonia and aldehydes **IVa**, **IVe**, and **IVf** to give 2-substituted imidazole-4,5-dicarboxylic acids **Va**, **Ve**, and **Vf**, respectively. Analogous reaction with formaldehyde leads to unsubstituted imidazole-4,5-dicarboxylic acid; it was shown [4, 5] that this reaction involves intermediate formation of α,β-dioxosuccininc acid (**III**). Taking into account the known ability of imidazole-4,5-dicarboxylic acid esters to undergo alkylation at the nitrogen atom [6], it seemed to be interesting to synthesize various derivatives of 2-alkyl- and 2-aryl-imidazole-4,5-dicarboxylates via alkylation with dihaloalkanes **VIII** (X = Br, Y = Cl, n = 2, 3); the subsequent variation of the Y substituent in compounds **IX** and **X** (Y = Cl → **I** → NHR^2) could make it possible to effect cyclization at the ester moiety and obtain new heterocyclic compounds like **XI**. The present communication reports on the results of our attempts to synthesize a wide series of 2-substituted imidazole-4,5-dicarboxylates **VI** and **VII** and effect their N-alkylation to obtain derivatives **IX** and **X**.

The nitration of D-tartaric acid with a mixture of nitric and sulfuric acids at 0°C, followed by treatment



I **II** **III** **Va–Vf**

VIa–VIf, VIIa–VIIf **IXa–IXf, Xa–Xf** **XI**

R^1 = Ph (**a**), $(CH_3)_2CH$ (**b**), $(CH_3)_2CHCH_2$ (**c**), 2-pyridyl (**d**), $MeOCO(CH_2)_6$ (**e**), Me (**f**); **VI, IX**, R^2 = Et; **VII, X**, R^2 = Me.

of the reaction mixture with excess ammonia at –5 to –10°C and an equimolar amount of aldehyde **IVa** or **IVd** or 2 equiv of aldehyde **IVb** or **IIc** at 0°C, led to the formation of 2-aryl- and 2-alkylimidazole-4,5-dicarboxylic acids **Va**–**Vd** in 47, 27, 21, and 17.6% yield (calculated on the initial tartaric acid), respectively. The products are colorless (**Va**–**Vc**) or green (**Vd**) crystalline substances which decompose above 257°C. The synthesis of compounds **Va**–**Vd** is laborious but well reproducible; however, no more than 46 g of the above acids (for imidazole **Va**) can be prepared at once in a 2-l flask.

The structure of compounds was confirmed by the data of elemental analysis and mass and ^{1}H NMR spectra. Acids **Va**–**Vd** showed in the mass spectra the molecular ion peaks whose fragmentation involved successive elimination of two carbon(IV) oxide molecules (for aromatic derivatives **Va** and **Vd**) or elimination of the alkyl substituent followed by simultaneous expulsion of two CO_2 molecules (for 2-alkyl derivatives **Vb** and **Vc**). In the ^{1}H NMR spectra of **Va**–**Vd** we observed signals from protons in the substituent on C^2, a signal from one acid OH proton, and a broadened signal from the NH proton and the second OH group; the latter signal is broadened due to exchange with water present in the solvent.

The different yields of compounds **Va**–**Vd** may be interpreted in terms of various factors. One of these is the stability of aldehydes **IVa**–**IVd** to oxidation to carboxylic acids under the reaction conditions. Among the aldehydes used, pyridine-2-carbaldehyde (**IVd**) is the least stable, and the yield of the corresponding diacid **Vd** is the lowest. Other factors may be the rate of formation of imines in the reaction of dioxosuccinic acid (**III**) with ammonia, their solubility, and possible polymerization during the process. For example, isobutyraldehyde (**IVb**) with ammonia forms insoluble imine trimer; as a result, the yield of **Vb** sharply decreases. Therefore, compound **Vb** was synthesized using excess aldehyde **IVb** which was slowly added to the reaction mixture under vigorous stirring. Preliminary mixing of the aldehyde with an ammonia solution completely inhibited the formation of imidazole **Vb**. The use of excess aldehyde is also desirable in the reactions with accessible aldehydes that give rise to water-soluble imines.

Dicarboxylic acids **Va**–**Vd** were formed initially as the corresponding ammonium salts which were converted into the free acids by treatment with hydrochloric acid. The latter procedure should be performed slowly under vigorous stirring since the reaction mixture is heterogeneous and residual dinitrotartaric acid is very sensitive to HCl.

The reactions of acids **Va**–**Vd** with 2 equiv of thionyl chloride in anhydrous ethanol or methanol gave dicarboxylic ester hydrochlorides **VIa**–**VId** and **VIIa** in 98–99% yield. Free bases **VIa**–**VId** were isolated by treatment with anhydrous potassium carbonate in the corresponding alcohol or with 12% aqueous sodium carbonate on cooling. In both cases, a considerable amount of alcohol was required, and the yields of the free bases did not exceed 80%. The best results (yield 98–99%) were obtained using a concentrated solution of sodium ethoxide or methoxide in ethanol or methanol, respectively. This procedure can be performed just before treatment of esters **VIa**–**VId** and **VIIa** with alkylating agents. The proposed method for the esterification of diacids **Va**–**Vd** is simpler and more effective that the known procedure involving treatment of imidazoledicarboxylic acid with an alcoholic solution of hydrogen chloride [6, 7].

It should be noted that esterification of acids **Va**–**Vc** gives the corresponding esters **VIa**–**VIc** and **VIIa** as monohydrochlorides despite the presence of alkyl substituent in position 2, which enhances the basicity of the imidazole nitrogen atoms. On the other hand, pyridyl-substituted derivative **VId** was isolated as trihydrochloride, though the basicity of the imidazole nitrogen atoms therein is weakened due to conjugation with the pyridine ring.

Taking into account that the maximal yields of imidazoledicarboxylic acid esters (calculated on the initial tartaric acid) were obtained using the substrates derived from most accessible aldehydes, just compounds **VIa**, **VIb**, and **VIIa** were subjected to alkylation. The products were analyzed by NMR spectroscopy and gas chromatography–mass spectrometry (GC–MS), and initial esters **VIa**, **VIb**, and **VIIa** were isolated from the reaction mixtures. The following alkylating systems were used: (a) 1 equiv of EtONa, 1–2 equiv of dihaloalkane **VIIIa** (X = Br, Y = Cl, n = 2), ethanol, 80°C, 24 h; and (b) 1.5 equiv of K_2CO_3, 2 equiv of **VIIIa**, DMF, 110°C, 16 h. In no case alkylation was observed. We also tried to perform theoretically possible addition of **VIa** to oxirane (which was either passed through the reactions mixture or generated in situ from ethylenebromohydrin), vinyl chloride, and vinyl acetate. Typical procedures were as follows: (a) a slight stream of oxirane was bubbled until complete saturation through a 10% solution of compound **VIa** in methanol or THF containing 1–2 drops of water or 3 equiv of oxirane was continuously bubbled through the solution for 2 h at 25°C and for 4 h at 55°C; (b) 2-bromoethanol (**VIIIb**, X = Br, Y = OH, n = 2), 3 equiv, was added dropwise to a 8% solution of 1 equiv of **VIIa** and 3 equiv of sodium methoxide in methanol, and the mixture was

stirred for 2 h at 25°C, for 2 h at 50°C, and for 4 h under reflux; (c) vinyl chloride was bubbled for 2 h at 20°C and for 4 h at 60°C through a 10% solution of **VIIa** in THF containing 1 ml of acetic acid; and (d) a mixture of 1 equiv of **VIIa**, 6 equiv of vinyl acetate (freshly distilled, nonstabilized), and 1 ml of acetic acid in THF was heated for 10 h. After removal of volatile substances under reduced pressure, the residue was analyzed by ^{1}H NMR spectroscopy; in all cases, only unreacted initial imidazole **VIa** or **VIIa** was detected.

The low reactivity of 2-substituted imidazole-4,5-dicarboxylic acid esters toward alkylating agents is likely to result from steric hindrances: Both nitrogen atoms in small imidazole ring are sterically shielded by three substituents in positions 2, 4, and 5. We succeeded in effecting N-alkylation of compounds **VIa** and **VIIa** only in the presence of 1.1 equiv of such a strong base as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) using 7 equiv of dihaloalkane **VIIIa** in acetonitrile (80°C, 27 h) or DMF (110°C, 24 h). According to the ^{1}H NMR data, 35% of **IXa** (n = 2, Y = Cl) and 27% of **Xa** (n = 2, Y = Cl) (MeCN) or 42% of **IXa** and 40% of **Xa** (DMF) were formed from 1 equiv of ester **VIa** or **VIIa**, respectively. The reaction in DMF was accompanied by considerable tarring. By column chromatography on silica gel (hexane–benzene, 4 : 1) we succeeded in isolating compounds **IXa** and **Xa** in 18 and 11% yield, respectively (in the reaction performed in acetonitrile). Presumably, the alkylation process includes deprotonation of imidazoles **VIa** and **VIIa** by the action of DBU, and the resulting anions are more reactive than the neutral molecules. However, the poor yield of the alkylation products (less than 10% on the initial tartaric acid) strongly complicates search for synthetic approaches to heterocycles **XI**, and further studies on the activation of imidazolecarboxylic esters toward electrophiles are necessary.

EXPERIMENTAL

The ^{1}H NMR spectra were measured on a Bruker AM-360 spectrometer at 360.14 MHz using DMSO-d_6 as solvent and reference. The mass spectra (electron impact, 70 eV) were recorded on a MAT-311A spectrometer with direct sample admission into the ion source.

2-Aryl- and 2-alkylimidazole-4,5-dicarboxylic acids Va–Vd *(general procedure).* A 1-l flask was charged with 60 g of powdered *D*-tartaric acid, 130 ml of 70% nitric acid and 130 ml of 98% nitric acid were added in succession, 240 ml of concentrated sulfuric acid was quickly added dropwise under vigorous stirring, maintaining the temperature below 40°C, and the mixture was left to stand for 2 h in an ice bath. The precipitate was filtered on Buchner funnel through glass fiber with protection from atmospheric moisture and thoroughly squeezed over a period no longer than 25 min. The precipitate was immediately transferred into a porcelain beaker containing 850 g of a finely crushed ice, cooled to about –18°C, under continuous stirring with a porcelain spoon. The resulting solution with a temperature of about –10°C was quickly transferred into a 2-l flask, and neutralized with a concentrated ammonia solution (~460 ml) under vigorous stirring and cooling with an acetone–solid CO_2 bath. When the pH value attained 7–8, the cooling bath was removed, 140 ml of an ammonia solution and 0.4 mol of freshly distilled aldehyde **IVa** or **IVd** or 0.8 mol of aldehyde **IVb** or **IVc** were added, and the mixture was stirred for 20 h at –4 to 0°C. The mixture was carefully acidified with concentrated hydrochloric acid (about 90–100 ml) to pH 3 so as to avoid ejection of the reaction mixture with evolved gases (voluminous foam). In the synthesis of compound **Vd**, the mixture was neutralized with hydrochloric acid to pH 7 and was then acidified with acetic acid to pH 5.5. The mixture was filtered, and the mother liquor was immediately utilized as waste. The precipitate was washed with 500 ml of water and 100 ml of cold isopropyl alcohol and dispersed in 400 ml of diethyl ether. The suspension was stirred for 0.5 h, and the precipitate was filtered off and dried at 80–100°C. We thus obtained pure (98–99%) crystalline compounds **Va**–**Vd** in 47, 27, 21, and 17.6% yield, respectively. The maximal yield of **Va** was 46–48 g. The procedure can be scaled up maximally to a 5-l flask (restriction at the neutralization step); however, in this case, the real time of the process considerably increases.

2-Phenylimidazole-4,5-dicarboxylic acid (Va). Decomposition point 265°C. ^{1}H NMR spectrum, δ, ppm: 4.0 br.s (NH, COOH), 7.44 m (3H, H_{arom}), 8.16 d (2H, H_{arom}), 19.78 (1H, COOH). Mass spectrum, *m/z*: 232 $[M]^{+\cdot}$, 188 $[M - CO_2]^+$, 170 $[M - CO_2 - H_2O]^+$, 144 $[M - 2CO_2]^+$. Found, %: C 57.02; H 3.44. $C_{11}H_8N_2O_4$. Calculated, %: C 56.90; H 3.47.

2-Isopropylimidazole-4,5-dicarboxylic acid (Vb). Decomposition point 269°C. ^{1}H NMR spectrum, δ, ppm: 1.31 d (6H, CH_3), 3.26 m (1H, CH), 4.5 br.s (NH, COOH), 19.70 (1H, COOH). Mass spectrum, *m/z*: 198 $[M]^{+\cdot}$, 165 $[M - CH_3 - H_2O]^+$, 156 $[M + H - C_3H_7]^+$, 138 $[M - C_3H_7 - OH]$+, 110 $[M - 2CO_2]^+$. Found, %: C 48.58; H 5.12. $C_8H_{10}N_2O_4$. Calculated, %: C 48.49; H 5.09.

2-Isobutylimidazole-4,5-dicarboxylic acid (Vc). Decomposition point 257°C. ^{1}H NMR spectrum, δ,

ppm: 0.83 d (6H, CH_3), 2.00 m (1H, CH), 2.44 d (2H, CH_2), 7.4 br.s (NH, COOH), 19.68 (1H, COOH). Mass spectrum, *m/z*: 212 $[M]^{+\cdot}$, 179 $[M - CH_3 - H_2O]^+$, 170 $[M + H - C_3H_7]^+$, 165 $[M - 2CH_3 - OH]^+$, 152 $[M - C_3H_7 - OH]^+$, 124 $[M - 2CO_2]^+$. Found, %: C 51.04; H 5.74. $C_9H_{12}N_2O_4$. Calculated, %: C 50.94; H 5.70.

2-(2-Pyridyl)imidazole-4,5-dicarboxylic acid (Vd). Decomposition point 270°C. ^{1}H NMR spectrum, δ, ppm: 3.8 br.s (NH, COOH), 7.43 t (1H, H_{arom}), 7.92 t (1H, H_{arom}), 8.10 d (1H, H_{arom}), 8.63 d (1H, H_{arom}), 19.80 (1H, COOH). Mass spectrum, *m/z*: 233 $[M]^{+\cdot}$, 189 $[M - CO_2]^+$, 171 $[M - CO_2 - H_2O]^+$, 145 $[M - 2CO_2]^+$. Found, %: C 51.63; H 3.06. $C_{10}H_7N_3O_4$. Calculated, %: C 51.51; H 3.03.

Esterification of dicarboxylic acids Va–Vd *(general procedure).* Thionyl chloride, 0.2 mol, was added dropwise to a suspension of 0.05 mol of compound **Va–Vd** in 100 ml of anhydrous ethanol or methanol (the mixture spontaneously warmed up to 45–55°C), and the mixture was heated for 1.5–2.5 h under reflux until it became homogeneous. The mixture was then evaporated under reduced pressure, the residue was treated with 100–150 ml of anhydrous diethyl ether, and the precipitate of **VIa–VId** or **VIIa** hydrochloride was filtered off and dried under reduced pressure. Yield almost quantitative. To isolate free bases **VIa–VId** and **VIIa**, the corresponding hydrochloride was added under vigorous stirring to a concentrated solution of a required amount of sodium ethoxide or methoxide in ethanol or methanol, respectively. The mixture was evaporated, and the residue was washed with water and dried under reduced pressure. The yields of pure compounds **VIa–VId** and **VIIa** were 98–99%. Alternatively, a 12% solution of sodium carbonate was added dropwise to an alcoholic solution of the corresponding hydrochloride to attain pH 4–5, maintaining the temperature below 12°C. The mixture was evaporated by half and cooled to 5°C. The free bases separated as difficultly crystallizable oils; they crystallized only after treatment with cold diethyl ether. The yields did not exceed 80%.

Diethyl 2-phenylimidazole-4,5-dicarboxylate (VIa). mp 200–202°C. ^{1}H NMR spectrum, δ, ppm: 1.31 t (6H, CH_3), 4.29 q (4H, OCH_2), 7.48 m (3H, H_{arom}), 8.08 d (2H, H_{arom}), 13.70 (1H, NH). Mass spectrum: *m/z* 288 $[M]^{+\cdot}$. Found, %: C 62.39; H 5.60. $C_{15}H_{16}N_2O_4$. Calculated, %: C 62.49; H 5.59. Hydrochloride: mp 120–125°C. ^{1}H NMR spectrum, δ, ppm: 1.30 t (6H, CH_3), 4.28 q (4H, OCH_2), 7.34 t (2H, NH_2^+), 7.57 m (3H, H_{arom}), 8.14 d (2H, H_{arom}). Found, %: C 55.28; H 5.36. $C_{15}H_{17}ClN_2O_4$. Calculated, %: C 55.48; H 5.28.

Diethyl 2-isopropylimidazole-4,5-dicarboxylate (VIb). mp 188–190°C. 1H NMR spectrum, δ, ppm: 1.26 d (6H, CH_3), 1.27 t (6H, CH_3), 3.10 m (1H, CH), 4.27 q (4H, OCH_2), 13.10 (1H, NH). Mass spectrum: *m/z* 254 $[M]^{+\cdot}$. Found, %: C 56.74; H 7.16. $C_{12}H_{18}N_2O_4$. Calculated, %: C 56.68; H 7.13. Hydrochloride: mp 98–105°C. ^{1}H NMR spectrum, δ, ppm: 1.25 d (6H, CH_3), 1.28 t (6H, CH_3), 3.17 m (1H, CH), 4.27 q (4H, OCH_2), 7.32 t (2H, NH_2^+). Found, %: C 49.32; H 6.68. $C_{12}H_{19}ClN_2O_4$. Calculated, %: C 49.57; H 6.59.

Diethyl 2-isobutylimidazole-4,5-dicarboxylate (VIc) hydrochloride. mp 95–100°C. ^{1}H NMR spectrum, δ, ppm: 0.87 d (6H, CH_3), 1.29 t (6H, CH_3), 2.08 m (1H, CH), 2.66 d (2H, CH_2), 4.29 q (4H, OCH_2), 7.32 t (2H, NH_2^+). Found, %: C 51.06; H 7.04. $C_{13}H_{21}ClN_2O_4$. Calculated, %: C 51.23; H 6.94.

Diethyl 2-(2-pyridyl)imidazole-4,5-dicarboxylate (VId) trihydrochloride. mp 110–116°C. ^{1}H NMR spectrum, δ, ppm: 1.30 t (6H, CH_3), 4.28 q (4H, OCH_2), 7.36 t (4H, NH_2^+, NH+), 7.54 t (1H, H_{arom}), 8.03 t (1H, H_{arom}), 8.18 d (1H, H_{arom}), 8.70 d (1H, H_{arom}). Found, %: C 41.93; H 4.70. $C_{14}H_{18}Cl_3N_3O_4$. Calculated, %: C 42.18; H 4.55.

Dimethyl 2-phenylimidazole-4,5-dicarboxylate (VIIa). mp 204–207°C. ^{1}H NMR spectrum, δ, ppm: 3.84 s (6H, OCH_3), 7.48 m (3H, H_{arom}), 8.08 d (2H, H_{arom}), 13.75 (1H, NH). Mass spectrum, *m/z*: 260 $[M]^{+\cdot}$. Found, %: C 59.91; H 4.68. $C_{13}H_{12}N_2O_4$. Calculated, %: C 60.00; H 4.65.

Alkylation of 2-substituted imidazole-4,5-dicarboxylic acid esters *(general procedure).* A mixture of 0.05 mol of ester **VIa** or **VIIa**, 0.055 mol of DBU, and 0.35 mol of bromide **VIIIa** in 100 ml of acetonitrile or DMF was stirred for 27 h at the boiling point (in acetonitrile) or for 24 h at 110°C (in DMF). In the latter case, strong tarring occurred. The solvent and excess dihalide **VIIIa** were removed under reduced pressure, and the residue (a viscous oil) was analyzed by ^{1}H NMR spectroscopy. The residue obtained from the reaction mixture in acetonitrile was subjected to chromatography on silica gel in a glass column, 1.5 m × 5 cm, using hexane–benzene (4 : 1) as eluent. The first fraction (R_f 0.22) contained pure compound **IXa** or **Xa**; yield 18 and 11%, respectively.

Diethyl 1-(2-chloroethyl)-2-phenylimidazole-4,5-dicarboxylate (IXa). mp 122–125°C. ^{1}H NMR spectrum, δ, ppm: 1.31 t (6H, CH_3), 3.78 t (2H, CH_2), 4.29 q (4H, OCH_2), 4.58 t (2H, CH2), 7.58 m (3H, H_{arom}), 7.66 d (2H, H_{arom}). Mass spectrum: *m/z* 350 $[M]^{+\cdot}$. Found, %: C 58.07; H 5.57. $C_{17}H_{19}ClN_2O_4$. Calculated, %: C 58.21; H 5.46.

Dimethyl 1-(2-chloroethyl)-2-phenylimidazole-4,5-dicarboxylate (Xa). mp 134–137°C. ^{1}H NMR spectrum, δ, ppm: 3.72 s (6H, OCH_3), 3.78 t (2H, CH_2), 4.58 t (2H, CH_2), 7.59 m (3H, H_{arom}), 7.67 d (2H, H_{arom}). Mass spectrum: *m/z* 322 $[M]^{+\cdot}$. Found, %: C 55.65; H 4.68. $C_{15}H_{15}ClN_2O_4$. Calculated, %: C 55.82; H 4.68.

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