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New Approach to the Synthesis of *trans*-Aconitic Acid Imides

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Abstract—N-arylimides of *trans*-aconitic acid were prepared by boiling the acid in a glacial acetic acid with N-arylamines. N-Arylamides of the *trans*-aconitic acid were obtained as intermediates in the course of the synthesis of the corresponding imides. The condensation of the *trans*-aconitic acid amides with hydrazine afforded arylamides of 1-amino-2,6-dioxo-1,2,3,6-tetrahydropyridine-4-carboxylic acid and proved the *cis* configuration of the initial amides.

Imides of maleic acid are widely used to prepare polymers in engineering, medicine, and pharmacology [1]. However the characteristics of derivatives obtained depend primarily on the copolymer structure than on the maleic anhydride proper. This circumstance is due to the presence of only two reactive groups: the anhydride structure and the double bond. Unlike the maleic acid the aconitic acid (**I**) contains in its molecule additionally a free carboxy group capable to be involved into versatile reactions. The corresponding polymers, aconitic acid derivatives, may have more branched and complex structure and wider application opportunities.

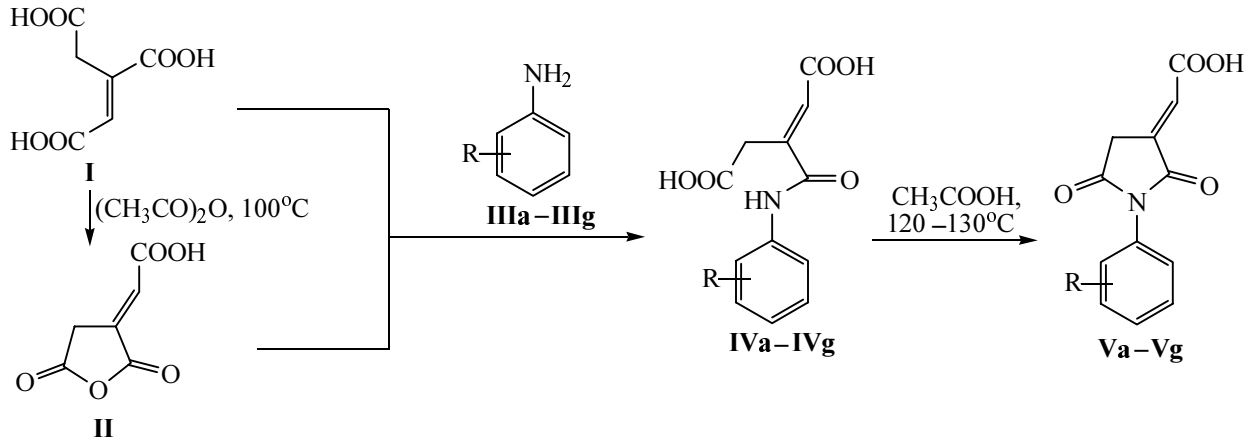
We formerly reported on preparation of *trans*-aconitic acid imides [2]. The urgent problem is the development of a cheap prepartion procedure for the derivatives of *trans*-aconitic acid (**I**) avoiding the intermediate stage of the synthesis of unstable anhydride **II.**

To this end we synthesized a number of the *trans*-aconitic acid derivatives by different methods (also through anhydride **II** for comparison of reaction products) and under versatile conditions (see scheme).

We failed to obtain imides **V** in the presence of acetic anhydride in the reaction medium. The products prepared did not contain double bonds (did not cause bromine decoloration) and could not be isolated in a crystalline state. Presumably a reaction occurred between the acetic anhydride and the double bond of the aconitic acid. The use of acetic acid instead of sodium acetate also does not afford imides although both schemes mentioned are applied to the preparation of maleimides [3, 4].

The best results were obtained by boiling the *trans*-aconitic acid with arylamines in a glacial acetic acid. Obviously here forms an anhydride that immediately enters into the reaction with amine. Similar compounds with

Scheme 1.



R = H (**a**), *p*-COOH (**b**), *m*-COOH (**c**), *p*-COOEt (**d**), *p*-SO_2NH_2 (**e**), *p*-Br (**f**), *p*-Me (**g**).

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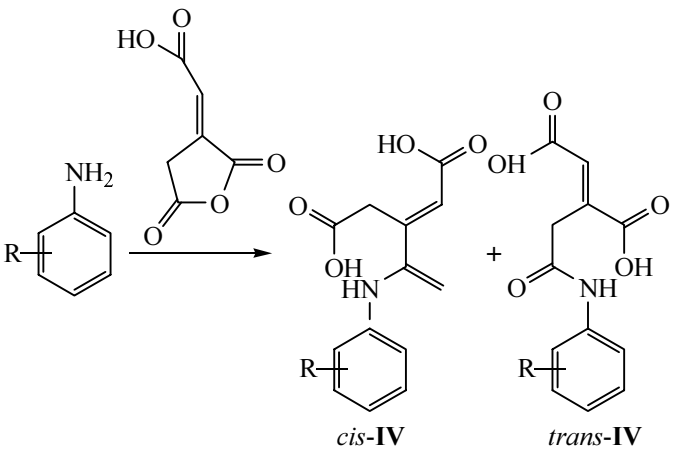
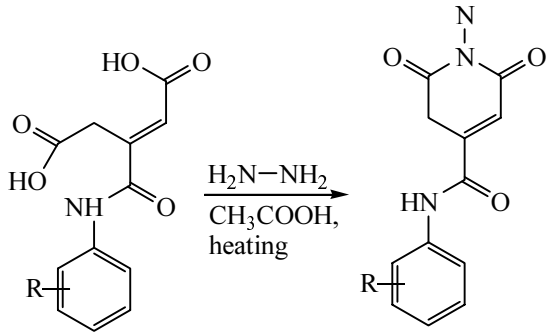
Scheme 2.



cis-**IV** *trans*-**IV**

Scheme 3.



cis-**IVa–IVg** **VIa–VIg**

the same characteristics were obtained by reaction of aconitic anhydride with amines, but the reaction ended faster (within 20 min). The attempts to obtain aconitic acid imides without heating from compounds **II** and **III** both in the glacial acetic acid and in acetic anhydride were unsuccessful.

For maleimides and aconitic acid imides a reaction with a sodium hydroxide solution is a characteristic test: A substance forms of bright red (orange) color that decolorized in time. This reaction is used for imides identification on chromatograms and in reaction mixtures [4]. Amides **IV** failed to pass this test.

The attempts at recrystallization of imides **V** from ethanol and 2-propanol resulted in destruction of imides and in formation of esters. The attempt at recrystallization in a mixed solvent (ethanol–water, 2-propanol–water) led to imides polymerization. In solvents immiscible with water imides **V** are well soluble at any temperature.

The optimum procedure for imides **V** purification proved to be their freezing off from a mixture of acetic acid with water, 1:1. Imides precipitated as round crystals of various color after the solvent crystals melted.

The typical analytical feature of imides in the IR spectra is a bifurcated unsymmetrical absorption band at 1700–1720 cm^{-1}, characteristic of the C=O bond in the structure of the imide ring, whereas the carbonyl groups of amides appear as a single absorption band in the region 1700–1710 cm^{-1}. An analogous bifurcated band is also observed in the spectra of maleimides. But here both bands are symmetrical.

Amides **IV** were isolated in pure crystalline state only in reaction of compounds **II** and **III** occurring in the cold, whereas in reaction carried out in the cold between acid **I** and amine **III** amides did not form. This fact evidences that the aconitic anhydride formed however in the glacial acetic acid but only at heating.

trans-Aconitic acid amides may exist as two isomers (Scheme 2).

As seen from the structural formula , the *trans*-isomer of amide **IV** cannot build up a pyridine heterocycle in reaction with hydrazine; this reaction is characteristic of *cis*-aconitic acid [the reaction between the *cis*-aconitic anhydride and hydrazine gives rise to 4-(3,6-dioxypyridazyl)acetic acid] [5]. In reaction between the *trans*-aconitic acid amides and hydrazine formed arylamides of 1-amino-2,6-dioxo-1,2,3,6-tetrahydropyridine-4-carboxylic acid **VIa–g**. These bright yellow compounds are well soluble in water (in contrast to hydrazides, amides, and imides of the aconitic acid). Inasmuch as the reaction furnished the products in high yields (60–85%) we concluded that from anhydride **II** formed predominantly the *cis*-isomer **IV** of the aconitic acid arylamide (Scheme 3).

EXPERIMENTAL

IR spectra of imides and amides synthesized were recorded on a spectrophotometer Specord M-80 from KBr pellets. ^1H NMR spectra were registered on spectrometer Bruker WP-200SY at operating frequency 200 MHz β $CDCl_3$.

***trans*-Aconitic anhydride.** To 1.7 g (0.01 mol) of *trans*-aconitic acid was added 1.9 ml (0.02 mol) of acetic anhydride. The reaction mixture was kept at the room temperature for 15 min. The acetic acid formed and unreacted acetic anhydride were distilled off in a vacuum in the cold. The aconitic anhydride precipitated. Yield 0.69 g (44%). The anhydride was recrystallized from the glacial acetic acid and was stored in a desiccator over

H_2SO_4 due to its high hydophilism and low stability. mp 46–47°C.

Arylamides IVa–IVg of *trans*-aconitric acid. To a solution of 3.12 g (0.02 mol) of *trans*-aconitic anhydride (**II**) in 10 ml of glacial acetic acid was added at stirring 0.02 mol of N-arylamine **IIIa–IIIg**, and the mixture was stirred at room temperature till the amine completely dissolved. Then the reaction mixture was left standing for 2 h. The separated precipitate was filtered off and recrystallized from the glacial acetic acid.

Compound IVa, mp 186–187°C, yield 79%. ^{1}H NMR spectrum, δ, ppm: 2.90 s (2H, C$\underline{H}_2$), 6.91 s (1H, C$\underline{H}$), 7.0–7.77 m (H_{arom}), 8.0 s (1H, N$\underline{H}$), 12.0 d (2H, COO$\underline{H}$). Found, %: C 58.1; H 4.6; N 5.5. $C_{17}H_{11}NO_5$. Calculated, %: C 57.8; H 4.4; N 5.6.

Compound IVb, mp 292–293°C, yield 79%. ^{1}H NMR spectrum, δ, ppm: 2.90 s (2H, C$\underline{H}_2$), 6.91 s (1H, C$\underline{H}$), 7.85–8.1 m (H_{arom}), 8.0 s (1H, N$\underline{H}$), 12.0 d (2H, COO$\underline{H}$). Found, %: C 53.0; H 3.9; N 4.8. $C_{13}H_{11}NO_7$. Calculated, %: C 53.2; H 3.8; N 4.8.

Compound IVc, mp 301–302°C, yield 86%. ^{1}H NMR spectrum, δ, ppm: 2.91 s (2H, C$\underline{H}_2$), 6.91 s (1H, C$\underline{H}$), 7.45–8.5 m (H_{arom}), 8.0 s (1H, N$\underline{H}$), 12.0 d (2H, COO$\underline{H}$). Found, %: C 53.3; H 3.6; N 4.9. $C_{13}H_{11}NO_7$. Calculated, %: C 53.2; H 3.8; N 4.8.

Compound IVd, mp 170–171°C, yield 82%. ^{1}H NMR spectrum, δ, ppm: 1.3 t (3H, C$\underline{H}_3$), 2.9 s (2H, C$\underline{H}_2$), 4.29 s (2H, C$\underline{H}_2$), 6.1 s (1H, CH), 7.5–7.95 m (H_{arom}), 8.0 s (1H, N$\underline{H}$), 11.0 d (2H, COOH). Found, %: C 56.1; H 4.9; N 4.3. $C_{15}H_{15}NO_7$. Calculated, %: C 56.1; H 4.7; N 4.4.

Compound IVe, mp 182–183°C, yield 85%. ^{1}H NMR spectrum, δ, ppm: 2.0 d (2H, N$\underline{H}_2$), 2.90 s (2H, C$\underline{H}_2$), 6.90 s (1H, C$\underline{H}$), 7.90–7.95 m (H_{arom}), 8.0 s (1H, N$\underline{H}$), 11.0 d (2H, COO$\underline{H}$). Found, %: C 43.7; H 3.6; N 8.5. $C_{12}H_{12}N_2O_7S$. Calculated, %: C 43.9; H 3.7; N 8.5.

Compound IVf, mp 252–253°C, yield 75%. ^{1}H NMR spectrum, δ, ppm: 2.90 s (2H, C$\underline{H}_2$), 6.91 s (1H, C$\underline{H}$), 7.40–7.53 m (H_{arom}), 8.0 s (1H, N$\underline{H}$), 12.0 d (2H, COO$\underline{H}$). Found, %: C 44.1; H 3.0; N 4.2. $C_{12}H_{10}BrNO_5$. Calculated, %: C 43.9; H 3.1; N 4.3.

Compound IVg, mp 210–212°C, yield 92%. ^{1}H NMR spectrum, δ, ppm: 2.30 t (3H, C$\underline{H}_3$), 6.91 s (1H, C$\underline{H}$), 7.0–7.5 m (H_{arom}), 8.0 s (1H, N$\underline{H}$), 12.0 d (2H, COO$\underline{H}$). Found, %: C 59.1; H 4.8; N 5.4. $C_{13}H_{13}NO_5$. Calculated, %: C 59.3; H 5.0; N 5.3.

***trans*-Aconitic acid arylimides Va–g.** *a.* To a solution of 3.12 g (0.02 mol) of *trans*-aconitic anhydride (**II**) in 10 ml of glacial acetic acid was added at stirring 0.02 mol of N-arylamine **IIIa–g**, and the mixture was heated for 20 min. Then the hot mixture was poured into a porcelain dish that was placed into an ice bath. In the course of freezing the reaction mixture was carefully stirred by a glass rod in order to obtain finely crystalline dispersion (frozen acetic acid and imide). An equal volume of water was added to the mixture, and the content of the dish was stirred till the acetic acid melted. The round crystals of imide remaining in the precipitate were filtered off. The recrystallization was performed in the same fashion by freezing imides out of the glacial acetic acid.

b. To a solution of 1.7 g (0.01 mol) of To a solution of *trans*-aconitic acid (**I**) in 10 ml of glacial acetic acid was added 0.01 mol of N-arylamine **III**, and the mixture was heated for 60 min. Then the hot mixture was poured into a porcelain dish, and the freezing out of the product was carried out as described in the procedure *a.* The recrystallization was performed in the same fashion by freezing imides out of the glacial acetic acid. IR and ^{1}H NMR spectra of imide prepared by methods *a* and *b* showed the identity of the samples.

Compound Va, mp 152–153°C, yield 48%. ^{1}H NMR spectrum, δ, ppm: 2.95 s (2H, C$\underline{H}_2$), 6.9 s (1H, C$\underline{H}$), 7.0–7.77 m (H_{arom}), 12.0 s (1H, COO$\underline{H}$). Found, %: C 63.2; H 3.6; N 6.0. $C_{12}H_9NO_4$. Calculated, %: C 62.3; H 3.9; N 6.1.

Compound Vb, mp 264–265°C, yield 70%. ^{1}H NMR spectrum, δ, ppm: 2.9 s (2H, C$\underline{H}_2$), 6.9 s (1H, C$\underline{H}$), 7.85–8.0 m (H_{arom}),12.0 s (1H, COO$\underline{H}$). Found, %: C 56.2; H 3.2; N 5.3. $C_{13}H_9NO_6$. Calculated, %: C 56.7; H 3.3; N 5.1.

Compound Vc, mp 260–262°C, yield 62%. ^{1}H NMR spectrum, δ, ppm: 2.9 s (2H, C$\underline{H}_2$), 6.9 s (1H, C$\underline{H}$), 7.45–8.51 m (H_{arom}),12.0 s (1H, COO$\underline{H}$). Found, %: C 57.1; H 3.6; N 5.4. $C_{13}H_9NO_6$. Calculated, %: C 56.7; H 3.3; N 5.1.

Compound Vd mp 149–150°C, yield 70%. ^{1}H NMR spectrum, δ, ppm: 1.3 t (3H, C$\underline{H}_3$), 2.9 s (2H, C$\underline{H}_2$), 6.85 s (1H, C$\underline{H}$), 7.75–7.95 m (H_{arom}), 11.0 s (1H, COO$\underline{H}$). Found, %: C 58.1; H 4.4; N 4.8. $C_{15}H_{13}NO_6$. Calculated, %: C 59.4; H 4.3; N 4.6.

Compound Ve, mp 146–147°C, yield 75%. ^{1}H NMR spectrum, δ, ppm: 2.90 s (2H, C$\underline{H}_2$), 6.90 s (1H, C$\underline{H}$), 7.75–7.95 m (H_{arom}), 11.0 s (1H, COO$\underline{H}$). Found, %: C 46.0; H 3.2; N 8.8. $C_{12}H_{10}N_2O_6S$. Calculated, %: C 46.4; H 3.2; N 9.0.

Compound Vf, mp 211–212°C, yield 70%. ^{1}H NMR spectrum, δ, ppm: 2.90 s (2H, C$\underline{H}_2$), 6.85 s (1H, C$\underline{H}$),

7.85–8.00 m (H_{arom}), 12.0 s (1H, COO<u>H</u>). Found, %: C 46.6; H 2.2; N 4.2. $C_{12}H_8BrNO_4$. Calculated, %: C 46.5; H 2.6; N 4.5.

Compound Vg, mp 195–196°C, yield 60%. ^{1}H NMR spectrum, δ, ppm: 2.35 t (3H, C<u>H</u>$_3$), 2.85 s (2H, C<u>H</u>$_2$), 6.90 s (1H, C<u>H</u>), 7.0–7.52 m (H_{arom}), 12.0 s(1H, COO<u>H</u>). Found, %: C 63.5; H 4.0; N 5.7. $C_{13}H_{11}NO_4$. Calculated, %: C 63.7; H 4.5; N 5.7.

c. In 10 ml of glacial acetic acid was dissolved 0.01 mol of *trans*-aconitic acid N-arylamide **IVa–IVg**, and the solution was heated for 30 min. Then the hot mixture was poured into a porcelain dish, and the freezing out of the product and subsequent recrystallization was carried out as described in the procedure *a.* According to IR and ^{1}H NMR spectra the imides thus obtained were identical to compounds prepared by procedures *a* and *b*.

1-Amino-2,6-dioxo-1,2,3,6-tetrahydropyridine-4-carboxylic acid arylamides VIa–VIg. To 0.02 mol of an appropriate arylamide **IVa–IVg** in a porcelain dish was added 0.1 ml (0.02 mol) of hydrazine hydrate, and the mixture was vigorously stirred with a gless rod till the mixture turned thick. The formed needle-like crystals of bright yellow to intensely orange color were ground in a mortar and recrystallized from 2-propanol.

Compound VIa, mp 116–118°C, yield 45%. ^{1}H NMR spectrum, δ, ppm: 2.0 s (2H, N<u>H</u>$_2$), 2.85 s (2H, C<u>H</u>$_2$), 7.3 s (1H, C<u>H</u>), 7.0–7.64 m (H_{arom}), 8.2 s (1H, N<u>H</u>). Found, %: C 58.5; H 4.4; N 16.9. $C_{12}H_{11}N_3O_3$. Calculated, %: C 58.8; H 4.5; N 17.1.

Compound VIb, mp 210–211°C, yield 73%. ^{1}H NMR spectrum, δ, ppm: 2.0 s (2H, N<u>H</u>$_2$), 2.85 c (2H, C<u>H</u>$_2$), 7.3 s (1H, C<u>H</u>), 7.45–8.51 m (H_{arom}), 12.0 s (1H, COO<u>H</u>). Found, %: C 54.1; H 3.9; N 14.7. $C_{13}H_{11}N_3O_5$. Calculated, %: C 54.0; H 3.8; N 14.5.

Compound VIc, mp 215–216°C, yield 52%. ^{1}H NMR spectrum, δ, ppm: 2.0 s (2H, N<u>H</u>$_2$), 2.85 s (2H, C<u>H</u>$_2$), 7.3 s (1H, C<u>H</u>), 7.45–8.51 m (H_{arom}), 12.0 s (1H, COO<u>H</u>). Found, %: C 54.2; H 3.9; N 14.7. $C_{13}H_{11}N_3O_5$. Calculated, %: C 54.0; H 3.8; N 14.5.

Compound VId, mp 122–123°C, yield 48%. ^{1}H NMR spectrum, δ, ppm: 1.3 t (3H, C<u>H</u>$_3$), 2.0 s (2H, N<u>H</u>$_2$), 2.85 s (2H,C<u>H</u>$_2$), 4.3 (2H, C<u>H</u>$_2$), 7.3 s (1H, C<u>H</u>), 7.8–8.1 m (H_{arom}), 8.2 s (1H, N<u>H</u>). Found, %: C 56.6; H 4.7; N 13.4. $C_{15}H_{15}N_3O_5$. Calculated, %: C 56.8; H 4.8; N 13.2.

Compound VIe, mp 105–106° C, yield 70%. ^{1}H NMR spectrum, δ, ppm: 2.0 s (4H, N<u>H</u>$_2$), 2.85 s (2H,C<u>H</u>$_2$), 7.3 s (1H, C<u>H</u>), 7.7–8.0 m (H_{arom}), 8,2 s (1H, N<u>H</u>), 12.0 s (1H, COO<u>H</u>). Found, %: C 44.2; H 3.9; N 17.5. $C_{12}H_{12}N_4O_5$ S. Calculated, %: C 44.4; H 3.7; N 17.3.

Compound VIf, mp 196–198°C, yield 64%. ^{1}H NMR spectrum, δ, ppm: 2.0 s (2H, N<u>H</u>$_2$), 2.85 s (2H, C<u>H</u>$_2$), 7.3 s (1H, C<u>H</u>), 7.4–7.6 m (H_{arom}), 8.2 s (1H, N<u>H</u>). Found, %: C 44.6; H 3.2; N 12.9. $C_{12}H_{10}BrN_3O_3$. Calculated, %: C 44.5; H 3.1; N 13.0.

Compound VIg, mp 154–155°C, yield 55%. ^{1}H NMR spectrum, δ, ppm: 2.0 s (2H, N<u>H</u>$_2$), 2.35 s (3H, Met), 2.8 s (2H, C<u>H</u>$_2$), 7.3 s (1H, C<u>H</u>), 7.0–7.52 m (H_{arom}), 8.2 s (1H, NH). Found, %: C 60.5; H 5.2; N 16.4. $C_{13}H_{13}N_3O_3$. Calculated, %: C 60.2; H 5.0; N 16.2.

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