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INVESTIGATIONS ON IMIDAZOLES

99.* SYNTHESIS AND SOME CONVERSIONS OF ESTERS OF 4- NITRO-5-IMIDAZOLYLMALONIC, -ACETOACETIC, AND -CYANOACETIC ACIDS

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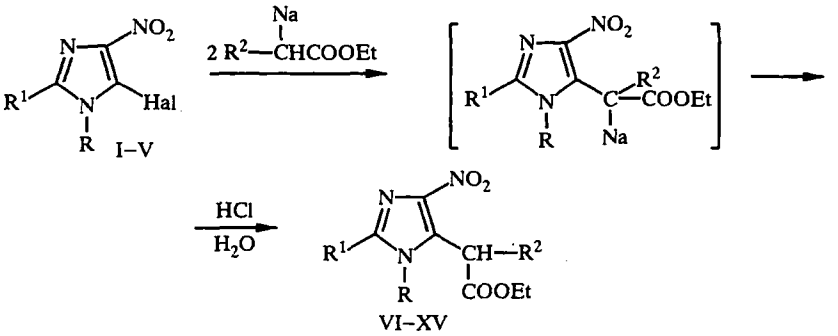
Some esters of 1-alkyl(1,2-dialkyl)-4-nitro-5-imidazolylmalonic, -acetoacetic, and -cyanoacetic acids have been synthesized by the reaction of 5-chloro(bromo)-1-alkyl(1,2-dialkyl)-4-nitroimidazoles with ethyl esters of carboxylic acids indicated. Some conversions of the compounds obtained have been studied, including ketone and acid decomposition, synthesis of derivatives at the COOH and CO groups, and hydrogenation to 4-aminoimidazole derivatives.

The reaction of 5-halo-4-nitroimidazoles with ethyl ester of malonic acid has been studied to some extent [2], but reaction with esters of acetoacetic acid and cyanoacetic acid has not been investigated at all.

We have studied the reaction of 5-chloro(bromo)-1-alkyl(1,2-dialkyl)-4-nitroimidazoles I - V with ethyl esters of malonic, acetoacetic, and cyanoacetic acids. We used a twofold molar excess of the esters to obtain a more complete reaction. Reaction was carried out in anhydrous ethanol in the presence of sodium ethylate, in toluene in the presence of metallic sodium, or in DMF in the presence of sodium hydride. Sodium salts of CH-acids containing the nitroimidazole fragment were obtained. They were converted on solution in water and acidification with hydrochloric acid into ethyl esters of 1-alkyl(1,2-dialkyl)-4-nitro-5-imidazolyl-malonic VI -



I, III - V Hal = Cl; II Hal = Br; I, II, VI, VII, XI - XIV R = Me; III, VIII R = Et; IV, IX R = Pr; V, X, XV R = *i*-Bu; I, VI, XI, XIII R^1 = H; II, VII, XII, XIV R^1 = Me; III, IX R^1 = Et; V, X, XV R^1 = *i*-Pr; VI - X R^2 = COOEt; XI, XII R^2 = COMe; XIII - XV R^2 = CN

*For Part 98 see [1].

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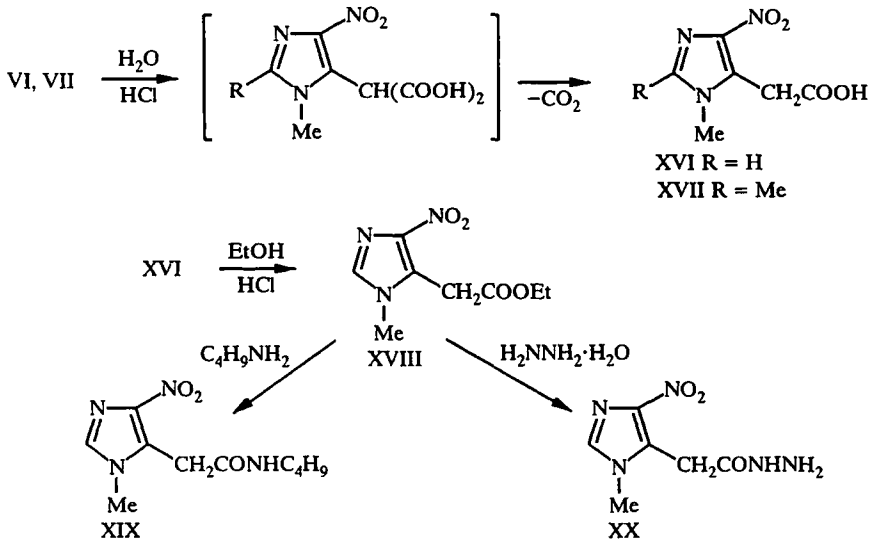
X, -acetoacetic XI and XII, and -cyanoacetic XIII - XV acids. Ester VI, which is described in the literature [2], was obtained by us by a simpler procedure. The oily ester XIII was characterized in the form of its sodium salt XIIIa .

The following peculiarities were noted while studying the reaction of halonitroimidazoles I - V with the CH-acids. When reacting the components in ethanol in the presence of sodium ethylate the reaction may not proceed to completion (as in the case of compound V) or was accompanied by a competing process, viz. substitution of the halogen atom by ethoxyl group. For example, ethyl 1-methyl-4-nitro-5-imidazolylacetoacetate XI (yield 40%) and the previously described 5-ethoxy-1-methyl-4-nitroimidazole [3] (yield 50%) were isolated on reacting 5-chloro-1-methyl-4-nitroimidazole I with ethyl acetoacetate in ethanol in the presence of sodium ethylate. In these cases reaction must be carried out in toluene or in DMF, by adding chloronitroimidazole to a previously prepared suspension of sodium salt of the starting ester. Esters XI, XIV, and XV were obtained in higher yields by this means.

Some conversions of the compounds obtained have been studied in the present work. For example, on heating in hydrochloric acid 1-methyl(1,2-dimethyl)-4-nitro-5-imidazolylmalonic esters VI and VII were subjected to hydrolysis and monodecarboxylation with the formation of 1-methyl(1,2-dimethyl)-4-nitro-5-imidazolylacetic acids XVI and XVII. The ethyl ester XVIII was obtained from the known acid XVI, and the N-butylamide XIX and hydrazide XX were obtained from ester XVIII.



1-Methyl(1,2-dimethyl)-4-nitro-5-imidazolylacetoacetic esters XI and XII were subjected to acid and ketone decompositions. Acid decomposition of ester XI occurs in alcoholic solution of sodium hydroxide and leads to

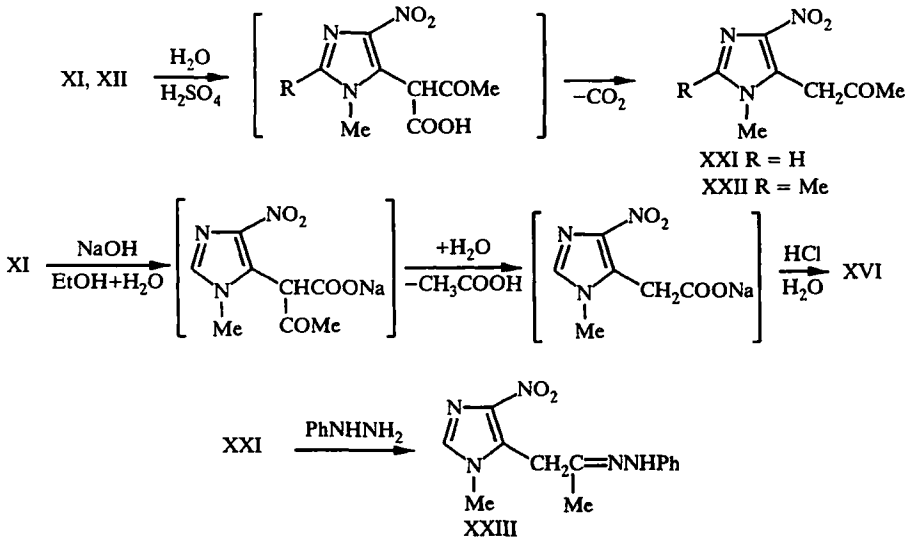


TABLE 1. Characteristics of Compounds VI - XXVIII*

Compound	Empirical formula	Found, % / Calculated, %			mp,°C	Yield, %
		C	H	N		
VI	$C_{11}H_{15}N_3O_6$				66...67*[2]	85
VII	$C_{12}H_{17}N_3O_6$				Oil*[3]	70
VIII	$C_{13}H_{19}N_3O_6$	50,02 / 49,83	6,41 / 6,07	13,60 / 13,41	90...92	57
IX	$C_{15}H_{23}N_3O_6$	53,04 / 52,77	7,10 / 6,74	12,15 / 12,31	57...58	50
X	$C_{17}H_{27}N_3O_6$	55,21 / 55,28	7,22 / 7,71	11,40 / 11,38	124...125	94
XI	$C_{10}H_{13}N_3O_5$	47,20 / 47,05	4,84 / 5,09	16,57 / 16,47	139...140	81
XII	$C_{11}H_{15}N_3O_5$	49,10 / 49,07	5,65 / 5,37	15,55 / 15,60	104	70
XIII	$C_9H_{10}N_4O_4$				Oil*[4]	85
XIIIa	$C_9H_9N_4NaO_4$*[5]	42,09 / 41,53	3,82 / 3,46	21,14 / 21,53	240...242	77
XIV	$C_{10}H_{12}N_4O_4$	47,78 / 47,61	4,89 / 4,76	22,54 / 22,22	122...123	70
XV	$C_{15}H_{22}N_4O_4$	55,25 / 55,88	6,98 / 6,87	16,87 / 17,37	159...160	59
XVI	$C_6H_7N_3O_4$				143...144*[6]	66...85
XVII	$C_7H_9N_3O_4$	42,28 / 42,21	4,64 / 4,52	21,06 / 21,11	168...169	71
XVIII	$C_8H_{11}N_3O_4$	45,09 / 45,07	5,80 / 5,11	20,70 / 19,71	106,5...107,5	95
XIX	$C_{10}H_{16}N_3O_4$	50,07 / 49,99	6,76 / 6,79	23,52 / 23,31	170...170,5	83
XX	$C_6H_9N_5O_3$	36,06 / 36,18	4,64 / 4,52	34,90 / 35,17	178...179	75
XXI	$C_7H_9N_3O_3$	46,20 / 45,90	5,23 / 4,91	23,55 / 22,95	85...87	78
XXII	$C_8H_{11}N_3O_3$	48,90 / 48,70	5,07 / 5,58	21,05 / 21,31	146...148	70
XXIII	$C_{13}H_{15}N_5O_2$	57,50 / 57,14	5,58 / 5,49	25,45 / 25,64	159...160	80
XXIV	$C_{11}H_{17}N_3O_4 \cdot C_6H_3N_3O_7$	42,29 / 42,14	4,39 / 4,13	17,53 / 17,37	175...177	50
XXV	$C_{13}H_{21}N_3O_4 \cdot C_6H_3N_3O_7$	45,06 / 44,53	4,82 / 4,68	16,48 / 16,42	117...118	42
XXVI	$C_8H_{13}N_3O_2 \cdot HCl$	43,42 / 43,73	6,02 / 5,92	18,94 / 19,13	181...182	77
XXVII	$C_{10}H_{18}N_4O \cdot C_6H_3N_3O_7$	43,78 / 43,73	4,78 / 4,82	22,55 / 22,32	155...156	30
XXVIII	$C_7H_{11}N_3O \cdot C_6H_3N_3O_7$	40,48 / 40,83	3,79 / 3,66	21,75 / 21,99	186...188	45

*Substances were purified for analysis by recrystallization as follows: VI, VIII - X from 70% ethanol; XVI - XVIII, XX, XXIII - XXV, XXVII from ethanol; XI, XII, XIIIa, XIV from anhydrous ethanol; XV from isopropanol; XIX from water; XXVI by precipitation with ether from ethanol; XXVIII with ether from aqueous acetone.

*[2]Mp 67°C according to [2].

*[3]Characterized by IR spectrum (see Table 2).

*[4]Characterized as sodium salt XIIIa.

*[5] XIIIa is sodium salt of XIII.

*[6]Mp 144°C according to [2].

TABLE 2. IR Spectral Characteristics and Molecular Ion Peaks (M^+) for Compounds VII - X, XIIIa - XV, XVII - XIX, XXI, and XXII

Compound	M^+	IR spectrum, ν, cm^{-1}		
		NO_2	CO	CN
VII		1350, 1560	1720, 1760	
VIII	313	1350, 1550	1730, 1760	
IX		1350, 1540	1740, 1760	
X	369	1340, 1550	1730, 1760	
XIIIa		1360, 1550	1640	2180
XIV	252	1300, 1500	1760	2260
XV		1310, 1550	1750	2210
XVII		1350, 1510	1720	
XVIII	213	1360, 1560	1720	
XIX		1350, 1550	1680	3300*
XXI	183	1350, 1510	1710	
XXII	197	1350, 1520	1715	

* ν_{NH}

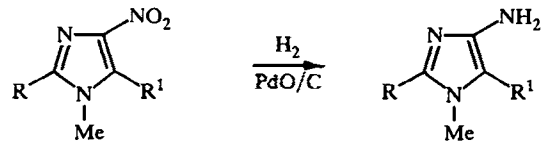
TABLE 3. PMR Spectral Characteristics of Compounds VIII, X, XI, XIV, XIX, and XXI in $CDCl_3$

Compound	Chemical shift, δ, ppm
VIII	1,18...1,36 [10H, m, $(COOC_2H_5)_2$]; 2,45 (3H, s, CH_3); 3,9...4,34 (5H, m, C_2H_5); 5,78 (1H, s, C-H)
X	3,75 (2H, d, J = 7 Hz, CH_2-CH); 4,98 (1H, s, C-H)
XI	1,15 (3H, t, J = 6 Hz, CH_3-CH_2); 1,88 (3H, s, O-CH_3); 3,58 (3H, s, N-CH_3); 4,19 (2H, q, J = 6 Hz, CH_2-CH_3); 7,54 (1H, s, $C_{(2)}$-H); 13,46 (1H, s, C-H)
XIV	1,3 (3H, t, J = 6 Hz, CH_3-CH_2); 2,45 (3H, s, C-CH_3); 3,68 (3H, s, N-CH_3); 4,31 (2H, q, J = 6 Hz, CH_2-CH_3); 6,22 (1H, s, C-H)
XIX*	0,9...1,4 (7H, m, CH_2-CH_2-CH_3); 3,0 (2H, m, CH_2-H); 3,65 (3H, s, N-CH_3); 3,98 (2H, s, CH_2-CO); 7,78 (1H, s, C-H); 8,2 (1H, br s, N-H)
XXI	2,3 (3H, s, CO-CH_3); 3,6 (3H, s, N-CH_3); 4,21 (2H, s, CH_2-CO); 7,38 (1H, s, C-H)

* in DMSO-d_6.

formation of acid XVI identical with the acid obtained by hydrolysis of 4-nitro-5-imidazolylmalonic ester VI.

Ketone decomposition of esters XI and XII occurs on heating in dilute hydrochloric acid. By this reaction the previously unavailable 5-acetonyl-1-methyl-(1,2-dimethyl)-4-nitroimidazoles XXI and XXII were synthesized. The phenylhydrazone XXIII was obtained from ketone XXI.



VI, VII, XVIII, XIX, XXI XXIV–XXVIII

VI, XVIII, XIX, XXI, XXIV, XXVI – XXVIII R = H; VII, XXV R = Me;
VI, VII, XXV R^1 = $CH(COOEt)_2$; XVIII, XXVI R^1 = CH_2COOEt;
XIX, XXVII R^1 = $CH_2CONHC_4H_9$; XXI, XXVIII R^1 = CH_2COMe

The final stage of this work was catalytic hydrogenation of several of the synthesized nitro derivatives of imidazole – compounds VI, VII, XVIII, XIX, and XXI. This reaction occurs readily at room temperature and atmospheric pressure in the presence of catalyst – palladium oxide on carbon. The 4-aminoimidazole derivatives XXIV - XXVIII formed, as reported previously [4, 5], were unstable compounds and resinified markedly during distillation of the solvent. Compounds XXIV, XXV, XXVII, and XXVIII were isolated and characterized as the picrates, and the more stable XXVI as the hydrochloride.

The structures of the compounds obtained were confirmed by data of elemental analysis, IR, and PMR spectra (Tables 1 - 3). Absorption bands for the NO_2 group at 1300-1360 and 1500-1560 cm^{-1} and for the CO group at 1680-1760 cm^{-1} were present in the IR spectra of compounds VII - X, XIIIa, XIV, XV, XVII - XIX, XXI, and XXII. A band for the NH group also appeared in the IR spectrum of N-butylamide XIX at 3300 cm^{-1}, and a band characteristic of the CN group appeared at 2180-2260 cm^{-1} in the spectra of the imidazolylcyanoacetic acid esters XIIIa - XV.

The PMR spectra of 4-nitro-5-imidazolylmalonic esters VIII and X were characterized by the presence of a methyl group proton signal at 5.0 – 5.8 ppm which disappeared on deuterium exchange. The PMR spectra of the other compounds XI, XIV, XIX, and XXI confirmed their structures completely.

EXPERIMENTAL

The PMR spectra of compounds were drawn on a Tesla BS 497 spectrometer with an operating frequency of 100 MHz, internal standard was HMDS. The IR spectra of compounds were taken on a UR 20 instrument in KBr disks. Mass spectra were obtained on a Varian MAT 112 spectrometer with direct insertion of samples into the ion source. Temperature of ionization chamber was 180°C, energy of ionizing electrons 70 eV. The TLC was carried out on Silufol UV 254 plates, visualization was realized with iodine vapors or UV light.

1-Methyl-, 1-ethyl-2-methyl-, 1-propyl-2-ethyl-, and 1-isobutyl-2-isopropyl-5-chloro-4-nitroimidazoles I and III - V were obtained by the procedure [6], and 5-bromo-1,2-dimethyl-4-nitroimidazole II by the procedure [7].

The esters of malonic, acetoacetic, and cyanoacetic acids were used freshly redistilled.

1-Alkyl(1,2-dialkyl)-4-nitro-5-imidazolylmalonic Acid Diethyl Esters VI - X. Diethyl malonate (0.5 mole) was added dropwise to a solution of sodium ethylate (0.05 mole) in anhydrous ethanol (100 ml). The mixture was heated at 60-70°C for 15 min, cooled, and the halonitroimidazole I - V (0.25 mole) was added in small portions during 15 min. The reaction mixture was boiled for 3 h, the solvent distilled off in vacuum, the residue was dissolved in water (50 ml), and extracted with ether (2×25 ml). The aqueous layer was acidified with dilute HCl to pH 5-6, extracted with chloroform, the extract was washed with water, dried over Na_2SO_4, and the solvent distilled off in vacuum. Compounds VI - X were obtained.

Ester VII was a pale yellow oily liquid and was characterized by its IR spectrum. It was used in further reactions as the crude product.

1-Methyl-4-nitro-5-imidazolylacetoacetic Acid Ethyl Ester XI. Ethyl acetoacetate (13 ml, 0.1 mole) was added to finely cut sodium (2.3 g, 0.1 g-atom) in anhydrous toluene (300 ml), and the mixture heated at 100°C (in a bath) for 3 h with vigorous stirring. Chloronitroimidazole I (8.0 g, 0.05 mole) was added to the suspension of sodium acetoacetic ester. The mixture was stirred at 95-97°C for 7 h, cooled, the precipitate of ester XI sodium salt was filtered off, dissolved in water, and neutralized with dilute HCl to pH 6. The solid ester XI which separated was filtered off, washed with water, and dried.

1,2-Dimethyl-4-nitro-5-imidazolylacetoacetic acid Ethyl Ester XII was obtained from bromonitroimidazole II analogously to the synthesis of esters VI - X.

1-Methyl-4-nitro-5-imidazolylcyanoacetic Acid Ethyl Ester XIII and its sodium salt XIIIa. Ethyl cyanoacetate (5.6 g, 0.05 mole) was added dropwise to a solution of sodium ethylate prepared from sodium (1.15 g, 0.05 g-atom) in anhydrous ethanol (200 ml). Chloronitroimidazole I (4.0 g, 0.025 mole) was then added. The mixture was boiled for 3 h, cooled, the solid was filtered off, and dried. Salt XIIIa (8.5 g) contaminated with NaCl was obtained. The solid was dissolved in boiling anhydrous ethanol (200 ml), the hot solution filtered from the solid NaCl, cooled, the precipitate filtered off, and dried. Pure salt XIIIa (5.0 g) was obtained. The salt was

dissolved in water, the solution was acidified to pH 6 with aqueous HCl solution, and ester XIII isolated as pale yellow oily substance.

1,2-Dimethyl-4-nitro-5-imidazolylcyanoacetic Acid Ethyl Ester XIV. Ethyl cyanoacetate (1.13 g, 0.005 mole) was added dropwise to a suspension of sodium hydride (0.24 g, 0.01 mole) in anhydrous DMF (5 ml). Bromonitroimidazole II (1.1 g, 5 mmole) was then added. The mixture was heated at 90-100°C for 3 h, cooled, and solid ester XIV sodium salt filtered off. This was dissolved in water (30 ml) and solution acidified to pH 6 with HCl. The separated solid was filtered off, washed with water, and dried. Ester XIV (0.97 g) was obtained.

1-Isobutyl-2-isopropyl-4-nitro-5-imidazolylcyanoacetic Acid Ethyl Ester XV was obtained from chloronitroimidazole V as described for the synthesis of compound XIV with the difference that the reaction mixture was heated at 30-40°C for 8 h and at 90°C for 30 min. After cooling, water (50 ml) was added, the solid which separated was filtered off, washed with water, and dried. The starting material V was isolated as 25% of that put into the reaction. The filtrate was acidified to pH 6 with HCl, the solid ester XV which separated was filtered off, washed with water, and dried.

1-Methyl(1,2-dimethyl)-4-nitro-5-imidazolylacetic Acids XVI and XVII. A. The acids indicated were obtained from crude esters VI and VII by the procedure [2] with the difference that heating of esters in HCl was conducted at 90-95°C. The yield of acid XVI was 85%, and that of acid XVII 71%.

B. A mixture of ester XI (2.55 g, 0.01 mole) and NaOH (0.4 g, 0.01 mole) in ethanol (50 ml) was boiled for 15 h, and the solvent distilled off in vacuum. The residue was dissolved in water, solution acidified to pH 6 with HCl, the precipitate filtered off, washed with water, and dried. Acid XVI (1.3 g, 66%) was obtained. A mixing test with sample of acid XVI obtained by method A gave no depression of melting point.

1-Methyl-4-nitro-5-imidazolylacetic Acid Ethyl Ester XVIII. A current of dry HCl was passed for 30 min into a suspension of acid XVI (1.85 g, 0.01 mole) in anhydrous ethanol (25 ml) with stirring and cooling. The alcohol was distilled off in vacuum and the residue crystallized on rubbing. The solid was washed with water, filtered off, and dried. The yield of XVIII was 2.1 g, R_f 0.5 (*n*-propanol-acetic acid, 3 : 1).

1-Methyl-4-nitro-5-imidazolylacetic Acid N-Butylamide XIX. A mixture of ester XVIII (2.13 g, 0.01 mole) in n-butylamine (8 ml) was heated at 75-80°C for 1 h, cooled, the solid was filtered off, washed with water, and dried. The yield of amide XIX was 2.0 g.

1-Methyl-4-nitro-5-imidazolylacetic Acid Hydrazide XX. A mixture of ester XVIII (4.2 g, 0.02 mole) and hydrazine hydrate (1.2 g, 0.024 mole) in ethanol (20 ml) was boiled for 30 min. The mixture was cooled, the solid filtered off, washed with water, and dried. The yield of hydrazide (XX) was 3.1 g, R_f 0.32 (*n*-propanol-acetic acid, 3:1).

5-Acetonyl-1-methyl(1,2-dimethyl)-4-nitroimidazoles XXI and XXII. A mixture of ester XI or XII (0.02 mole) in water (100 ml) and concentrated H_2SO_4 (2 ml) was boiled for 5 h, evaporated to small volume, and the oily residue crystallized on rubbing. The solid was filtered off, washed with water, and dried. Ketones XXI and XXII were obtained.

5-Acetonyl-1-methyl-4-nitroimidazole Phenylhydrazone XXIII. Phenylhydrazine (1.0 g, 0.01 mole) and concentrated H_2SO_4 (1 drop) were added to a suspension of ketone XXI (1.83 g, 0.01 mole) in ethanol (20 ml). The mixture was stirred for 1 h, the solid was then filtered off, washed with water, with alcohol, and dried.

4-Amino-1-methyl-5-imidazolylmalonic Acid Diethyl Ester Picrate XXIV. A solution of ester VI (2.85 g, 0.01 mole) in ethanol (50 ml) was hydrogenated in the presence of 5% palladium oxide on carbon (2.0 g), under stirring at 20°C and atmospheric pressure until absorption of hydrogen had ceased. The catalyst was filtered off, washed with ethanol, and the filtrate evaporated to dryness in vacuum. A solution of picric acid (2.3 g, 0.01 mole) in ethanol (20 ml) was added to the uncrystallizable oily residue. The resinified yellow solid isolated was gradually crystallized on cooling to 0°C. The solid was filtered off, washed with ethanol, and dried. Yield was 2.4 g.

Picrate of ester XXV was obtained analogously.

4-Amino-1-methyl-5-imidazolylacetic Acid Ethyl Ester Hydrochloride XXVI. Ester XVIII (2.13 g, 0.01 mole) was hydrogenated under the conditions for synthesis of ester XXIV. After removing the catalyst and distilling off the solvent the oily residue was treated with alcoholic HCl solution (10 ml), and ether (30 ml) was added. The precipitate which separated was filtered off, washed with ether, dried, and compound XXVI (1.69 g) was obtained.

Picrate of 4-Amino-1-methyl-5-imidazolylacetic Acid N-Butylamide was obtained by hydrogenation of amide XIX analogously to the synthesis of compound XXIV.

5-Acetonyl-4-amino-1-methylimidazole Picrate XXVIII was obtained by hydrogenation of ketone XXI under the conditions of synthesis of ester XXIV.

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