Hydrazones Derived from the Hydrazide of 4-Methyl-6-carboxymethylpyrid-2-one

Compound number	Mp, °C (recrystallization solvent)	Formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
V	229–230 (decomp, MeOH)	$C_{11}H_{15}N_3O_2$	59.53 59.37	6.70 6.83	19.12 19.04	59.71	6.83	18.99	75
VI	171–172 EtOH	$C_{12}H_{17}N_3O_2$	61.12 60.99	7.30 7.34	18.24 18.20	61.25	7.28	17.86	76
VII	206–207 EtOH	$C_{16}H_{17}N_3O_2$	67.69 67.48	5.98 6.09	14.93 15.05	67.82	6.04	14.34	75
VIII	216–217 EtOH	$C_{15}H_{15}N_3O_2$	66.51 66.88	5.76 5.67	15.45 15.48	66.89	5.61	15.61	43
IX	206–207 EtOH	$C_{17}H_{19}N_3O_3$	— —	— —	13.25 13.11	—	—	13.41	44
X	220–221 75% EtOH	$C_{17}H_{20}N_4O_2$	65.29 65.54	6.53 6.53	17.84 17.78	65.36	6.45	17.94	57
XI	229–230 75% EtOH	$C_{13}H_{17}N_3O_2S$**	—	—	15.50 15.39	—	—	15.40	75

*Calculated on the 4-methyl-6-ethoxycarbonylpyrid-2-one.

**Found: S 11.29; 11.18% Calculated for S 11.48%

pared in 42% yield by the method of [1, 2], modified by saturating undistilled aminocrotonic ester in dichloroethane with HCl, then refluxing for 30–40 min. 10.2 g of the resultant ester and 50 ml hydrazine hydrate were refluxed together for 20 hr, the mixture cooled, and 1.5 g (23%) 4, 6-dimethylpyrid-2-one, mp 175–177° filtered off [1]. The filtrate was evaporated, the residue treated with EtOH to give 7.3 g (77%) of sufficiently pure hydrazide, mp 257–258° (ex EtOH). Found: C 52.43, 52.49; H 6.04, 6.02, N 23.48; 23.42%. Calculated for $C_8H_{11}N_3O_2$. C 53.02; H 6.12; N 23.19%.

Isopropylidenehydrazide of 4, 6-dimethyl-5-carboxypyrid-2-one (III). 1.3 g (6 mmole) hydrazide I and 15 ml acetone was boiled for 3 hr, the acetone being gradually distilled off, the acetone removed being made up by dry acetone added from a dropping funnel. Near the end a large part of the acetone was distilled off until crystals of hydrazone appeared. After cooling the precipitate was filtered off, and washed with 3 ml cold MeOH, yield 0.55 g (35%) hydrazone III, mp 288–289° (ex MeOH). Found C 59.71, 59.63; H 6.98, 7.13; N 19.04, 19.12%. Calculated for $C_{11}H_{15}N_3O_2$. C 59.71; H 6.83; N 18.99%.

4, 6-Dimethyl-5-carboxypyr-2-one benzlidenehydrazide (IV). 1.81 g (10 mmole) hydrazide I and 1.06 g (10 mmole) benzaldehyde in 50 ml dry EtOH and 50 ml dichloroethane was boiled, the solvent being distilled off and at the same time a mixture of 150 ml dichloroethane and 50 ml EtOH added. Final distilling off of the solvent gave 1.62 g impure hydrazone, and three recrystallizations of this from MeOH gave 0.35 g (13%) pure compound mp 303° (decomp.). Found: C 67.16, 67.29, H 5.72; 5.69, N 15.67; 15.46%. Calculated for $C_{15}H_{15}N_3O_2$. C 66.89; H 5.61; N 15.61%.

4-Methyl-6-carboxymethylpyrid-2-one (α-methylbenzylidene)-hydrazide (V). The starting 4-methyl-6-ethoxycarbonylmethylpyrid-2-one, mp 166–167°, was prepared in 20% yield as described in [1, 2], but with the modification that distilled crystalline aminocrotonic ester in dichloroethane was saturated with HCl with external water cooling (mixture heated up to about 40°), without further heating of the reaction mixture. 1.95 g ester and 0.7 ml hydrazine hydrate in 25 ml dry EtOH was refluxed for 3 hr, cooled, filtered, to give 1.75 g (97%) hydrazide (mp 189–190°). The latter was converted to hydrazone V by reacting with acetophenone and distilling off of the water, with dichloroethane. Yield 2.4 g (75% on the ester). The table gives information regarding this hydrazone and hydrazones VII–XI prepared similarly. Hydrazones V and VI (see table) were, like hydrazone III, prepared with the modification that the reaction was run in the presence of dry EtOH.

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SYNTHESIS OF ESTERS OF N-6-PURINYLAMINO ACIDS

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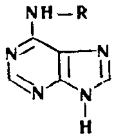
Reaction of esters of amino acids with 6-chloropurine gives a series of hitherto unknown esters of N-6-purinylamino acids, which are potential kinins. The IR spectra of these compounds are determined to characterize them.

Along with auxins and giberellins, kinins (6-N-substituted aminopurines) are known to participate in regulating exchange of plant substances [1, 2]. Of the kin-

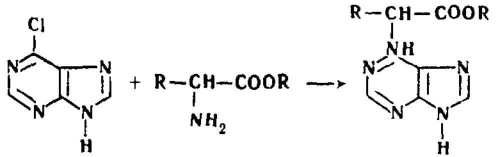


Compound number	R	Mp, °C	Formula	Found, %		Calculated, %		Yield, %
				C	H	C	H	
III	CH_2COOCH_3*	241—242	$C_8H_9N_5O_2$	46.02 45.91	4.66 4.77	46.37	4.38	50
IV	$CH_2COOC_2H_5$	254—255	$C_9H_{11}N_5O_2$	48.77 48.89	4.68 4.73	48.87	5.01	63
V	$CH_2COOC_3H_7$-*n*	225—227	$C_{10}H_{13}N_5O_2$	51.44 51.41	5.66 5.68	51.06	5.53	54
VI	$CH_2COOC_4H_9$-*n*	203—204	$C_{11}H_{15}N_5O_2$	53.03 52.95	6.02 6.13	52.99	6.05	85
VII	$CH_3CHCOOC_2H_5$	199—200	$C_{10}H_{13}N_5O_2$	50.73 50.80	5.57 5.48	51.06	5.53	90
VIII	$CH_2CH_2COOC_2H_5$	184—185	$C_{10}H_{13}N_5O_2$	50.50 50.55	5.51 5.31	51.06	5.53	63
IX	$C_2H_5CHCOOC_2H_5$	190—191	$C_{11}H_{15}N_5O_2$	52.34 52.47	6.11 6.09	52.99	6.05	53
X	$C_2H_5CHCOOC_4H_9$-*n*	177—178	$C_{13}H_{19}N_5O_2$	55.85 55.71	6.90 6.88	56.30	6.86	65
XI	$(CH_3)_2CHCH_2CHCOOC_2H_5$	186—187	$C_{13}H_{19}N_5O_2$	56.24 56.31	6.98 6.97	56.30	6.86	55
XII	$(CH_3)_2CHCH_2CHCOOC_4H_9$-*n*	190—191	$C_{15}H_{23}N_5O_2$	59.34 59.54	7.67 7.49	58.99	7.59	53

*Described in the literature [4], but no elementary analytical data given.

ins, where the substituents are n-alkyl groups, the most active are compounds with 5–6 carbon atoms in the chain [3]. By analogy with these compounds it was of interest to synthesize new kinins, esters of N-6-purinylamino acids containing various numbers of carbon atoms in the side chain, for testing for physiological activity*. Only one representative of compounds of this type is known, the methyl ester of N-6-purinylglycine [4].

The present paper describes the preparation of a number of esters of N-6-purinylamino acids from 6-chloropurine and esters of amino acids:



I II III-XII

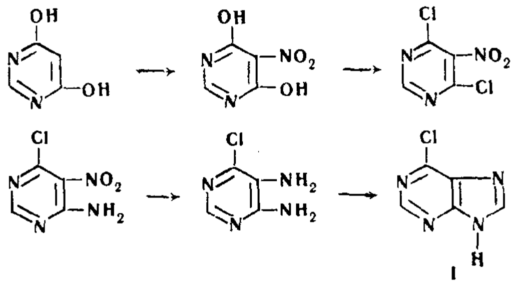
With the exception of the ethyl ester of β-alanine, all reactions were carried out with esters of ⊖-amino acids (II).

When reaction was run with equimolecular quantities of 6-chloropurine, esters of amino acids, and sodium ethoxide, the yields of esters of N-6-purinylamino acids were insignificant. When, instead of the sodium ethoxide, a second equivalent of ester of amino acid is used to take up the hydrogen chloride formed, the yields rise to 50–60%. All the compounds synthesized were colorless, high-melting, and crystalline, insoluble in most organic solvents, slightly soluble in water and ethanol. The table gives the properties of the compounds prepared.

The IR spectra of compounds III–XII differed but little among themselves, and resembled the spectrum of adenine [5, 6]. The frequencies of the absorption bands of the compounds synthesized lie in the ranges characteristic of adenine: 940–920 cm^{-1} (C—H deformation vibrations), 1600–1570 cm^{-1} (C=C group), 1680–1635 cm^{-1} (C=N). Compounds III–XII have a sharp absorption band with frequencies in the range 1750–1725 cm^{-1} for the C=O group in the ester group, lacking in the adenine spectrum.

EXPERIMENTAL

Starting materials. 6-Chloropurine (I) was prepared by the method of [7], by chlorinating hypoxanthine with $POCl_3$, and also as described in [8–11]:



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Esters of amino acids (II) were obtained from the acid as hydrochlorides [12, 13], the ester bases being isolated by treatment with sodium ethoxide in ethanol solution, or aqueous NaOH, followed by extraction with ether, and vacuum-distillation.

Esters of N-6-purinylamino acids (III–XII). a) A suspension of 0.01 mole I in 50 ml EtOH was stirred, and 0.02–0.03 mole II, freshly vacuum-distilled and in 30 ml EtOH, added. The mixture was

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*The biological investigations were carried out by O. N. Kulaeva in the laboratory of Academician A. L. Kursanov, in the Institute of Plant Physiology AS USSR.

stirred for 2 hr at 50–60°, when solution was almost complete. The insignificant quantity of solid I was filtered off, the solvent vacuum-distilled off, the residue treated with 5–10 ml cold water to remove I, the whole filtered, and the solid dried. It was recrystallized from water or EtOH.

b) A solution of Na ethoxide prepared from 0.03 mole Na and 30 ml EtOH was added to a cooled solution of 0.03 mole II hydrochloride in 20–25 ml EtOH. The NaCl was filtered off, and the filtrate added, with stirring, to a suspension of 0.01 mole I in 5–10 ml EtOH, the mixture stirred for 1–2 hr at 50–60°, and further worked up as described in *a* above. The yields obtained by the two methods were identical.

To preclude the possibility of transesterification of esters, in each synthesis the dry alcohol used corresponded to the ester part of the amino acid.

IR spectra were determined with a UR-10 spectrometer, using KBr, NaCl, and LiF prisms, with tablets with KBr.

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ALKYLATION OF 2-AMINOPYRIDINE

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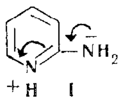
Alkylation of 2-aminopyridine with cyclohexanol or isopropanol in sulfuric acid gives yields of up to 70% of 2-alkylaminopyridines.

As its sodium derivative, 2-aminopyridine is alkylated by alkylating agents, e.g., methyl iodide, to give mixtures of mono and dialkyl substituted derivatives [1]. The literature also describes a method of preparing mixtures of 2-alkylamino and 2-dialkylaminopyridines by passing a mixture of 2-aminopyridine and the appropriate alcohol over a solid catalyst, e.g., Al_2O_3, SiO_2, etc. [2]. Such weak bases as amides of aromatic sulfonic acids [3] and of alkane sulfonic acids [4], and salts of guanidines [5], are readily alkylated by secondary alcohols in 80–85% sulfuric acid. In developing work on alkylation of nitrogen compounds, we undertook the alkylation of 2-aminopyridine. The latter is a monoacid base with pK'_a 6.86 [6], and diacid salts of it have not been described. In formation of salts of 2-aminopyridine, proton addition takes place at the ring nitrogen atom, to give a cation of structure I.



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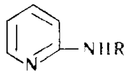

IIa, b

a R = C_6H_{11}
b R = i-C_3H_7

However, cation I has not lost its capacity to react with strong electrophilic reagents, e.g., with nitro cations, and this follows from the nitration of 2-aminopyridine to 2-nitramidopyridine nitrate [7]. Our experiments showed that salts of 2-aminopyridine are alkylated in 80–85% sulfuric acid by cyclohexanol and isopropanol. However, it proved impossible to alkylate 2-aminopyridine with tert-butanol, all the runs giving unchanged 2-aminopyridine with polyisobutene and tert-butanol.

EXPERIMENTAL

2-Cyclohexylaminopyridine (IIa). 9.4 g 2-aminopyridine was dissolved, with cooling (temperature not over 30°), in 100 ml 80% H_2SO_4, and the mixture stirred till the precipitate of sulfate had dissolved completely. Then the solution was heated to 60°, and at that temperature, 10 g cyclohexanol added over a period of 30 min, then the mixture stirred at 60–70° for 6 hr. After cooling to room temperature, it was poured onto 200 g ice, and neutralized with conc. NH_4OH. The solid amide was filtered off, washed with water, and dried. Yield 12 g (70%), mp 105–110°. Transparent crystals, mp 125° (ex n-heptane) [8]. Picrate, minute yellow needles, mp 184–185° (ex EtOH-AcOH) [9].

2-Isopropylaminopyridine (IIb). This was prepared similarly to IIa, from 9.4 g 2-aminopyridine and 9 g iso-PrOH in 100 85% H_2SO_4 for 6 hr at 80°. After neutralization, the base was extracted with ether