SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF A SERIES OF MONO- AND BICYCLIC PYRAZOLE DERIVATIVES

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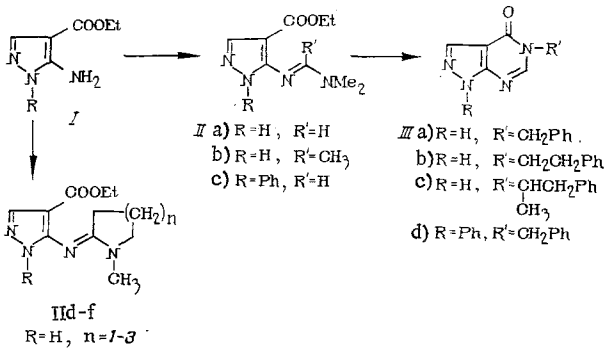
The interaction of 3-amino-4-carboethoxypyrazole (I) with amide acetals and lactams was used earlier [1] to prepare a series of N-(4-carboethoxypyrazol-3-yl) amidines (II) which were used as starting materials for the preparation of derivatives of pyrazolo [3, 4-d] pyrimidines (III) [2].

Since a number of pyrazole derivatives possess high anti-inflammatory activity [3], we continued the synthesis and study of related types of compounds in order to search among them for biologically active compounds.



The intent of the present work was to study the anti-inflammatory activity of the known compounds IIa, b, d-f, IIIa-c [1, 2], and to compare their activity with that of the corresponding N-phenyl analogs (IIc and IIId). In addition, the preparation of the corresponding isoxazole derivatives (IVa, b) also was undertaken.

All of the indicated N-heterylamidines (II) were characterized by PMR spectroscopy. It should be noted that in the PMR spectrum (in DMSO-d_6) of the derivatized formamidine (IIa), the "amidine-type" of dimethylamino group produces signals of equal intensity and size at 2.96 and 3.04 ppm, while the dimethylamino group of the acetamidine analog (IIb) forms a narrow signal as a 6-proton singlet at 2.99 ppm. A similar difference was observed earlier for amidines of another series [2] and is explained by steric inhibition of conjugation in the amidine fragment of compound IIb as a result of the 6-methyl group. These data are in good agreement with earlier conclusions about the comparative degree of conjugation in both compounds (IIa, b) based on measurement of ionization constants [1].

Treatment of 5-amino-4-carboethoxyisoxazole (V) with the diethyl acetal (VI) or with N-methylvalerolactam diethyl acetal (VII) did not give the expected N-(4-carboethoxyisoxazol-5-yl)amidines (IVa, b). The IR spectra of the compounds obtained (VIIIa, b) showed a sharp $-CN$ group absorption, and the PMR spectra (in CF_3COOH) did not show the presence of the aromatic proton in position 3 of the isoxazole ring. The spectral data, as well as the results of elemental analyses, indicated the possibility of an enamidine structure (VIIIa, b) for the compounds obtained.

A similar type of isoxazole ring opening, for example by the action of sodium ethoxide, is well known [4]. It also is known that amide acetals in solution are in equilibrium with ambident cations and alkoxy anions [5]. The latter possibly may be the cause of the isoxazole ring opening under the conditions of the reaction of V with the amide- and lactam acetals (VI, VII).

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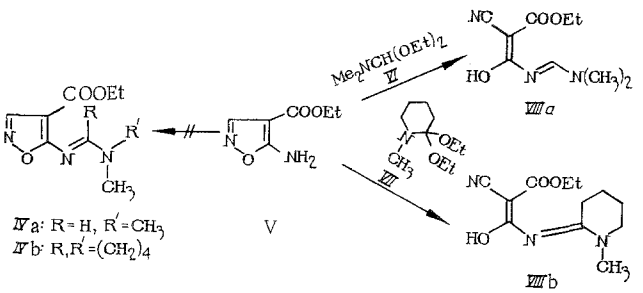
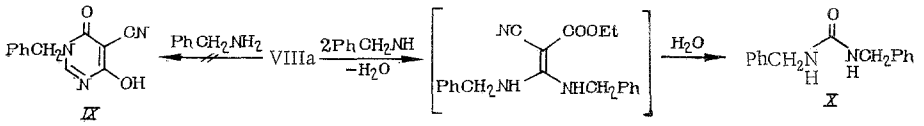
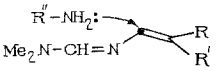


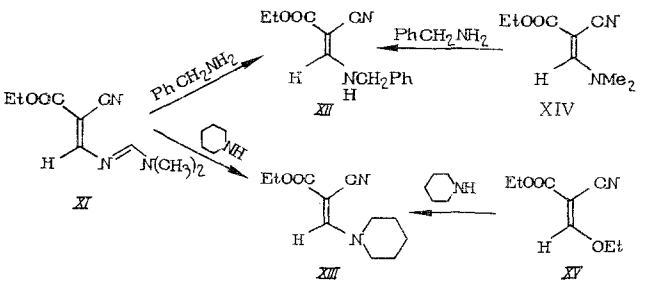
In subsequent stages of the work, an attempt was made to synthesize derivatives of 4,6-dioxopyrimidine (IX) from the enamidine (VIIIa) by analogy with the cyclization of amidine II into derivatives of pyrazolo-pyrimidine (III). Thus, compound VIIIa was treated with benzylamine. However, instead of the expected pyrimidine (IX), a compound was obtained which, according to elemental analysis and mass spectrometry, was the dibenzyl urea X. This reaction apparently proceeds according to the following scheme:



The suggested scheme indicates one important circumstance: the enamidine transamination reaction does not take place on the "amidine" meso-carbon atom (as in N-heterylamidines), but on the "enamidine" α-position:



For verification of this proposition, the enamidine XI was treated with benzylamine and piperidine as we described earlier [6]. The resulting products were the enamines XII and XIII, which were identified by vapor phase chromatography (VPC) with samples obtained by alternate synthesis. Compound XII was prepared from α-carboethoxy-β-dimethylaminoacrylonitrile (XIV) and benzylamine, and the enamine XIII was prepared from α-carboethoxy-β-ethoxyacrylonitrile (XV) and piperidine.



Consequently, a system containing a double bond adjacent to amidine and carboethoxy groups is useful for pyrimidine synthesis only in the case when the double bond is included in an aromatic ring.

For "enamidines," on the other hand, the reaction takes place by means of "displacement" of the form-amidine group, and formation of the corresponding enamine.

EXPERIMENTAL PHARMACOLOGY SECTION

The anti-inflammatory activity of the compounds was studied on nonhybrid male rats weighing 130-150 g by means of edema of the paw produced by subplantar introduction of 0.1 ml of 1% aqueous solution of carrageenin [7]. The magnitude of the swelling reaction was evaluated by the change of volume of the paw. The presence of analgetic activity was determined by the increase of the pain sensitivity threshold of rats on immersion of the tail in water at 49°C [8]. The compounds were injected with a probe in a dose of 100 mg/kg as suspensions in 1% starch paste into the stomach 1 h before introduction of the carrageenin, and the pain sensitivity threshold was determined. The activity of the compounds was indicated by comparison with the action of amido-

TABLE 1. Anti-inflammatory and Analgetic Activity of Pyrazole Derivatives (100 mg/kg dose)

Compound	Reduction in carrageenin edema, % less than initial	Increase in pain sensitivity threshold, % of original
IIa	29	23
IIb	13†	0
IIc	10†	0
IId	25	10†
IIe	13	10†
IIf	38	47
IIIa	36	15
IIIb	0*	0*
IIIc	0	0
IIId	0	0
VIIIa	7†	0
VIIIb	20	0
Aminopyrine	57	14
Methampyrone	52	49
Phenylbutazone	52	59

*No effect.

†Difference from control was insignificant at P = 0.05.

pyrin (aminopyrine), analgin (methampyrone), and butadione (phenylbutazone) at doses of 100, 100, and 50 mg/kg, respectively.

The acute toxicity on 16-17 g male mice by intragastric introduction also was determined.

As shown in the experiments, among the new pyrazole derivatives is a series of compounds possessing anti-inflammatory activity (cf. Table 1). Basically, these carboethoxypyrazole derivatives (compounds IIa-f) contain a formamidino, iminopiperidino, iminopyrrolidino, acetamidino, and particularly an iminohexahydroazepinyl residue, as substituents in position 3 of the pyrazole ring. Preparations of these compounds decreased the carrageenin edema of rat paws by 10-38%, and showed weak analgetic effects. The activity of these compounds only approaches that of phenylbutazone and other contemporary anti-inflammatory preparations. The derivatives of pyrazolopyrimidine and enamidines have little activity, with the exception of compounds IIIa and VIIIb, which show weak anti-inflammatory effects.

All of the studied compounds were of low toxicity on introduction into the stomach; LD_{50} was 1100-1600 mg/kg.

EXPERIMENTAL CHEMISTRY SECTION

N,N-Dimethyl-N'-(4-carboethoxy-1-phenylpyrazol-5-yl)formamidine Hydrochloride (IIc). A mixture of 5 g (0.032 mole) of 3-amino-4-carboethoxy-2-phenylpyrazole and 5.22 g (0.0355 mole) of dimethylformamide acetal in 25 ml of dry benzene was boiled for 6 h, evaporated to dryness, and the residue was dissolved in acetone and acidified to pH 2 with concentrated hydrochloric acid to give 3.8 g (39%) of IIc hydrochloride, mp 173-175°C (from isopropanol). Found, %: C 55.83; H 5.92; N 17.7; Cl 10.65. $C_{15}H_{19}N_4O_2Cl$. Calculated, %: C 55.81; H 5.90; N 17.36; Cl 11.01.

5-Benzyl-4-oxo-1-phenylpyrazolo [3, 4-d] pyrimidine (IIId). A mixture of 2 g (0.007 mole) of IIc and 2.5 g (0.0234 mole) of benzylamine was heated in the presence of TosOH at 150-180°C for 4 h and kept overnight. Filtration of the resulting precipitate then gave 0.5 g (23.6%), mp 165-167°C (from DMF). Found, %: C 71.52; H 4.47; N 18.63; $C_{18}H_{14}N_4O$. Calculated, %: C 71.52; H 4.64; N 18.54.

N,H-Dimethyl-N'-α-hydroxy-β-carboethoxy-β-cyanovinylformamidine (VIIIa). A mixture of 5 g (0.032 mole) of 2-amino-3-carboethoxyisoxazole and 8.8 g (0.06 mole) of dimethylformamide acetal in 25 ml of dry toluene was boiled for 3 h, cooled, and the resulting precipitate was filtered off to give 4.08 g (60.5%), mp 188-190°C (from DMF). Found, %: C 51.04; H 6.18; N 20.05. $C_9H_{13}N_3O$. Calculated, %: C 51.18; H 6.16; N 19.9.

2-[(α-Hydroxy-β-carboethoxy-β-cyanoethylene)imino]-1-methylpiperidine (VIIIb). A mixture of 3.75 g (0.023 mole) of 2-amino-3-carboethoxyisoxazole and 4.95 g (0.0265 mole) of N-methylvalerolactam acetal in 20 ml of dry benzene was boiled for 3 h. The resulting precipitate was filtered off and washed with benzene to give

4.55 g (79.5%), mp 195-198°C (from alcohol). Found, %: C 57.33; H 6.63; N 16.90. $C_{12}H_{17}N_3O_3$. Calculated, %: C 57.37; H 6.77; N 16.73.

Reaction of VIIIa with Benzylamine. A mixture of 1 g (0.00475 mole) of VIIIa and 1.02 g (0.0095 mole) of benzylamine was boiled at 180°C in the presence of TosOH for 3 h, cooled, and treated with ether to give 0.25 g (23%), mp 159-161°C (from acetone). Found, %: C 75.32; H 6.79; N 11.62. $C_{15}H_{16}N_2O$. Calculated, %: C 75; H 6.67; N 11.67. PMR spectrum (CF_3COOH), δ ppm: 4.47 (CH_2Ph), 7.3 (Ph). Mass Spectrum: M^+·240.

N-(β-Carboethoxy-β-cyanovinyl)benzylamine (XII). A. A mixture of 3.36 g (0.02 mole) of enamine XI and 4.6 g (0.04 mole) of benzylamine in 45 ml of absolute alcohol was boiled in the presence of TosOH for 10 h, and then evaporated to dryness. The residue was treated with petroleum ether to give 4.6 g (~100%) of XII, mp 102-103°C (from isopropanol). Found, %: C 67.67; H 6.24; N 12.0. $C_{13}H_{14}N_2O_2$. Calculated, %: C 67.70; H 6.13; N 12.17.

B. A mixture of 1 g of XI and 1.07 g of benzylamine was heated for 4 h at 150°C. By VPC, the major product of the reaction was XII.

N-(β-Carboethoxy-β-cyanovinyl)piperidine (XIII). A. A mixture of 10 g (0.063 mole) of α-carboethoxy-β-ethoxyacrylonitrile and 6 g (0.07 mole) of piperidine was boiled for 3 h and distilled under vacuum (bp 180-182°C/1 mm Hg), followed by treatment with pentane to give 10.15 g (78%) of XIII, mp 38-40°C (from pentane). Found, %: C 63.57; H 7.65; N 13.54. $C_{11}H_{16}N_2O_2$. Calculated, %: C 63.46; H 7.69; N 13.46.

B. A mixture of 1 g XI and 0.45 g of piperidine was boiled for 4 h. The major product, according to VPC analysis, was XIII. The mixture was distilled under vacuum to give 0.7 g of XIII, bp 168-176°C/1-2 mm Hg, mp 38-39°C (from pentane).

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