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SYNTHESIS OF TRIFLUOROMETHYL DERIVATIVES OF PYRAZOLIDINE- AND 2-PYRAZOLINE-1-CARBOXAMIDES AND PYRAZOLIDINE- AND 1-PYRAZOLINE-CARBOTHIOAMIDES

A. V. Sanin, V. G. Nenaidenko, V. S. Kuz'min, and E. S. Balenkova

The reactions of enones containing trifluoromethyl groups with semicarbazide in basic media proceed unequivocally to give pyrazolidine-1-carboxamides. The direction of the reactions of these enones with thiosemicarbazide depends on their structure; the reaction products are pyrazolidine- and 2-pyrazoline-1-carbothioamides. An enone containing a CF_3 group and an ethoxy group capable of replacement reacts with semicarbazide to give 2-pyrazoline-1-carboxamide and with thiosemicarbazide to give the double addition product, 5-(1-thiosemicarbazido)-2-pyrazoline-1-carbothiamide.

Fluoroheterocyclic compounds have been extensively studied [1, 2] in light of their high biological activity [3]. Trifluoromethyl derivatives of enones are convenient and promising starting compounds for the synthesis of heterocycles with a CF_3 group. Methods of synthesis for such enones have been intensively developed in the past decade [4, 5].

The reaction of enones with hydrazines is the classical method for the synthesis of pyrazoles and pyrazolines, but this method has not been studied sufficiently relative to enones with a trifluoromethyl group. Only the synthesis of trifluoromethylpyrazolines from fluoroacetylated vinyl ethers (β-alkoxyvinyltrifluoromethylketones) has been described [6, 7]. We have already studied the reactions of hydrazine, phenylhydrazine, and methylhydrazine with trifluoromethyl-containing enones lacking an alkoxy substituent, and obtained pyrazolines and pyrazolidines with a CF_3 group [8]. A feature of these reactions is formation of stable pyrazolidines containing a *gem*-aminoalcohol fragment stabilized by the electron-withdrawing effect of the CF_3 group. Dehydration of these pyrazolidines upon heating or maintaining at room temperature leads to the corresponding pyrazolines.

Semicarbazide and its derivatives are multifunctional nucleophiles. The reaction of these compounds with enones holds both theoretical and practical interest since the reaction products often display biological activity [9, 10]. Contradictory data have been reported on the structure of the products of the reactions of unsaturated ketones with semicarbazide derivatives. Structures with a five- [11, 12], six- [13], and seven-membered ring [14] have been proposed. The greatest evidence is found for the formation of five-membered heterocycles, namely, pyrazoline-1-carboxamides and pyrazoline-1-carbothiamides based on x-ray diffraction structural analysis [15].

The reactions of trifluoromethyl-containing enones with semicarbazide derivatives have not yet been examined.

In continuation of a study of the synthesis of trifluoromethylheterocycles, we investigated the reaction of various enones containing a CF_3 group (I-VII) with semicarbazide and thiosemicarbazide under various conditions. We have already shown that enones lacking a trifluoromethyl group react to give heterocyclic derivatives in acid media (upon heating with semicarbazide hydrochloride or thiosemicarbazide hydrochloride in ethanol at reflux) [11, 15] or close-to-neutral media (in the presence of a slight excess of sodium acetate) [12]. A study of the reaction of enone I with semicarbazide and thiosemicarbazide in acid media showed that semicarbazone VIII and thiosemicarbazone IX are formed under these conditions in almost quantitative yields. These products are stable in both acid and basic media (various bases such as amines, NaOH, and sodium ethylate were used) and have no tendency to cyclize.

M. V. Lomonosov Moscow State University, 119899 Moscow, Russia. N. S. Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, 117907 Moscow, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 634-644, May, 1998. Original article submitted October 3, 1997.

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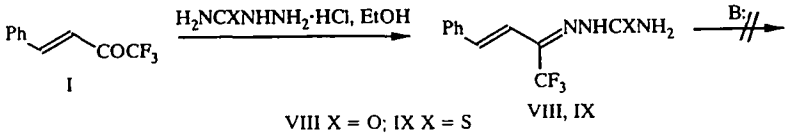
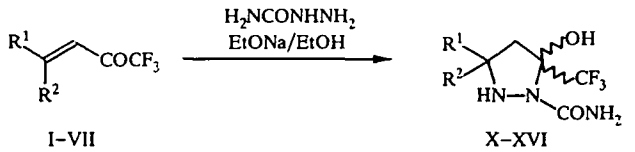


The reaction in close-to-neutral media (in the presence of sodium acetate) leads to the formation of a mixture of products. Thus, we studied the reaction of enones I-VII with semicarbazide and thiosemicarbazide in basic media in the presence of an equimolar amount of sodium ethylate. The reaction with semicarbazide proceeds regiospecifically to give 5-trifluoromethylpyrazolidine-1-carboxamides X-XVI in 46-78% yield (Table 1).



I–VII X–XVI

I, V, X, XIV R^1 = Ph; II, XI R^1 = 2-thienyl III, XII R^1 = 1-methyl-1H-2-pyrrolyl
IV, XIII R^1 = 1H-3-indolyl ; I–IV, X–XIII R^2 = H, V, XIV R^2 = Me;
VI, XV R^1, R^2 = $-CH_2CH_2CH_2-$; VII, XVI R^1, R^2 =

The structures of X-XVI were demonstrated by PMR, ^{13}C NMR, and IR spectroscopy. The finding of signals for two protons at $C_{(4)}$ at 2.2-2.8 ppm in the PMR spectra and a characteristic quartet for $C_{(5)}$ at 92.6-94.2 ppm in the ^{13}C NMR spectra with $^2J_{C\text{-}F}$ = 31-34 Hz indicates lack of C=C or C=N bonds in these compounds. Additional evidence for their structure is found in the doublets or singlets for $N_{(2)}H$ at 4.4-5.2 ppm, broad singlets for the NH_2 protons at 5.5-5.8 and 6.3-6.6 ppm, and OH group singlets at 7.0-7.3 ppm in the PMR spectra taken for solutions in CD_3CN.

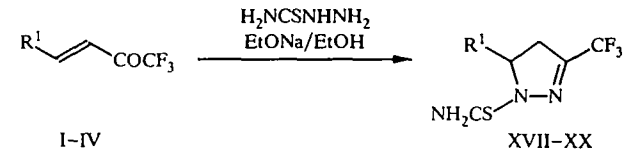
Theoretically, the reactions of enones I-V containing one or two different substituents at $C_{(4)}$ with semicarbazide may lead to two isomers of the corresponding pyrazolidine-1-carboxamides X-XIV. However, the NMR spectral data indicate that enones I-IV with one substituent (R^2 = H) react stereoselectively with predominant formation of only one of the isomers of X-XIII. The amount of the minor isomer did not exceed 5%. The structure of the major isomer of pyrazolidine-1-carboxamide X was established by x-ray diffraction structural analysis. The bulky Ph and CF_3 substituents occupy pseudoequatorial positions (Fig. 1), i.e., product X is the thermodynamically favored isomer. Similar stereochemistry for the formation of trifluoromethylheterocycles were found in cases studied in our previous work [16-18]. The bond lengths and angles for X are given in Tables 3 and 4.

The reaction of enone V gives a 3:1 mixture of isomers of pyrazolidine-1-carboxamide XIV, presumably because enone V has two substituents at $C_{(4)}$ (R^1 = Ph, R^2 = Me) and, thus, the energy difference between the two isomers is less than in the case of X-XIII. Since the phenyl group is a bulkier substituent than the methyl group, the isomer with pseudoequatorial position of the Ph groups and CF_3 group is likely predominant.

The reaction of enones I-VII with thiosemicarbazide leads to various products, depending on the structure of the starting enone. The reactions of enones I-IV containing a single substituent at $C_{(4)}$ give 3-trifluoromethyl-2-pyrazoline-1-carbothioamides XVII-XX, while the reactions of enones V-VII, which have two substituents, give 5-trifluoromethylpyrazolidine-1-carbothioamides XXI-XXIII.

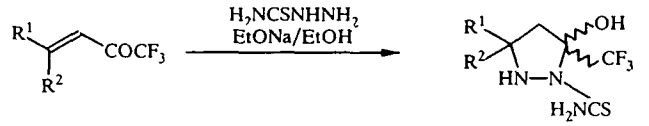
The structure of XVII-XXIII was established by PMR, ^{13}C NMR, and IR spectroscopy. The PMR and ^{13}C NMR spectra of pyrazolidine-1-carbothioamides XXI-XXIII are analogous to the spectra of pyrazolidine-1-carboxamides XIV-XVI (the difference lies in the presence of a ^{13}C NMR signal for the CS fragment at 177.8-182.0 ppm instead of the carbonyl group signal at 159.7-162.5 ppm). The PMR spectra of 2-pyrazoline-1-carbothioamides XVII-XX show signals for the two protons at $C_{(4)}$ at 2.8-3.7 ppm, indicating the lack of a C=C double bond and signals for the two NH_2 group protons at 6.4-7.3 ppm. The characteristic signal for $C_{(3)}$ in the ^{13}C NMR spectra of these compounds at 145.3-147.0 ppm is a quartet with $^2J_{C\text{-}F}$ = 38-39 ppm, indicating a C=N double bond in these compounds.

The NMR spectra of the product of enone V with thiosemicarbazide, pyrazolidine-1-carbothioamide XXI indicate a 4:3 isomer mixture, as in the case of the product of the reaction of this enone with semicarbazide to give XIV.



I–IV XVII–XX

I, XVII R^1 = Ph; II, XVIII R^1 = 2-thienyl ; III, XIX R^1 = 1-methyl-1H-2-pyrrolyl
IV, XX R^1 = 1-H-3-indolyl



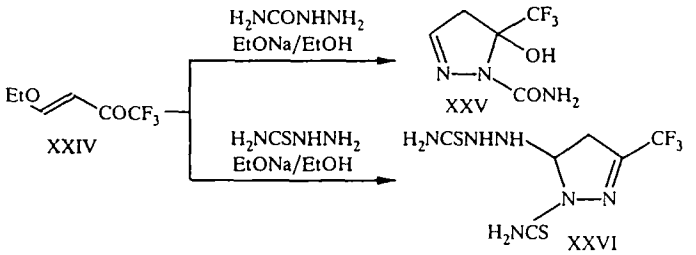
V–VII XXI–XXIII

V, XXI R^1 = Ph, R^2 = Me; VI, XXII R^1, R^2 = $-CH_2CH_2CH_2-$;
VII, XXIII R^1, R^2 =

The differences in the reactions of enones I-IV with semicarbazide and thiosemicarbazide may be attributed to several factors. The acidity of the amide proton of thiosemicarbazide and semicarbazide $H_2NNHCXNH_2$, the proton of the OH group of pyrazolidine-1-carboxamides X-XVI and pyrazolidine-1-carbothioamides XXI-XXIII, and protons of the thioamide NH_2 group in 2-pyrazoline-1-carbothioamides XVII-XX is about the same (calculations indicate that their pK_a is in the range 10.5-12.0). Thus, both the starting compounds (semicarbazide or thiosemicarbazide) and reaction products in the reaction medium in the presence of sodium ethylate in ethanol exist as anions, and the reaction proceeds under equilibrium conditions. Steric factors may play a significant role. The $CSNH_2$ group is bulkier than the $CONH_2$ group and, thus, steric hindrance in its products in the reaction with thiosemicarbazide probably has a greater effect on the course of the reaction. The CF_3 group in its bulk is intermediate between the isopropyl and *tert*-butyl groups [19]. Thus, in the case of enones I-IV, which have a single substituent, the reaction may proceed such that the $CSNH_2$ group is oriented toward the substituent at $C_{(4)}$ and not the CF_3 group.

Pyrazolidine-1-carboxamides X-XVI and pyrazolidine-1-carbothioamides XXI-XXIII are stable compounds and cannot be dehydrated to give the corresponding pyrazolines upon heating in toluene at reflux in the presence of *p*-toluenesulfonic acid for 48 h in contrast to pyrazolidines obtained from trifluoromethyl-containing enones and hydrazines [8]. This discrepancy is related to the presence of a substituent at $N_{(1)}$ such that formation of a C=N double bond is impossible and elimination of a proton from the carbon atom is, in all likelihood, severely hindered.

The reaction of enone XXIV, which has an ethoxy group at $C_{(4)}$ capable of replacement, with semicarbazide and thiosemicarbazide in a basic medium leads to 5-trifluoromethylpyrazoles [6, 7]. We have found that the reactions of enone XXIV with semicarbazide and thiosemicarbazide proceed to give 2-pyrazoline-1-carboxamide XXV in 73% yield and 5-(1-thiosemicarbazido)-2-pyrazoline-1-carbothioamide XXVI in 22% yield, respectively.



XXIV XXV XXVI

Thus, the direction of the reactions of enone XXIV with semicarbazide and thiosemicarbazide is in accord with the direction observed for the reaction with monosubstituted enones I-IV. The addition of two thiosemicarbazide molecules to a single enone molecule occurs in the latter case with replacement of the ethoxy group. The reaction of thiosemicarbazide with 1,3-diketones also leads to double addition products, namely, 5-(1-thiosemicarbazido)-2-pyrazoline-1-carbothioamides [20, 21].

The PMR spectra of XXV and XXVI have signals for the two protons at $C_{(4)}$ at 2.9-3.5 ppm. Furthermore, the PMR spectrum of 2-pyrazoline-1-carbothioamide XXVI displays signals for the protons of the thiosemicarbazide residue: a doublet

TABLE 1. Elemental Analysis Data, Melting Points, and Yields for VIII-XXIII

Compound	Chemical Formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
VIII	$C_{11}H_{10}F_3N_3O$	51.40 51,37	4.05 3,92	* —	188...190 dec.	91
IX	$C_{11}H_{10}F_3N_3S$	48.25 48,35	3.70 3,69	—	165...166 dec.	93
X	$C_{11}H_{12}F_3N_3O_2$	48.15 48,00	4.44 4,39	—	131...132 dec.	46
XI	$C_9H_{10}F_3N_3O_2S$	38.39 38,43	3.59 3,58	—	142...143 dec.	51
XII	$C_{10}H_{13}F\ 3N_4O_2$	43.06 43,17	4.55 4,71	—	165...167 dec.	57
XIII	$C_{13}H_{13}F_3N_4O_2$	49.94 49,68	4.27 4,17	—	146...147 dec.	62
XIV	$C_{12}H_{14}F_3N_3O_2$	49.65 49,83	4.79 4,88	14.67 14,53	121...122 dec.	59
XV	$C_8H_{12}F_3N_3O_2$	40.23 40,17	4.98 5,06	17.65 17,57	140...141 dec.	65
XVI	$C_{14}H_{20}F_3N_3O_2$	52.92 52,66	6.28 6,31	13.13 13,16	222...223 dec.	78
XVII	$C_{11}H_{10}F_3N_3S$	48.29 48,35	3.83 3,69	15.22 15,38	141...142 dec.	25
XVIII	$C_9H_8F_3N_3S_2$	38.54 38,70	2.91 2,89	—	154...155 dec.	31
XIX	$C_{10}H_{11}F_3N_4S$	43.15 43,47	3.94 4,01	—	145...147 dec.	41
XX	$C_{13}H_{11}F_3N_4S$	49.70 50,00	3.64 3,55	—	160...161 dec.	54
XXI	$C_{12}H_{14}F_3N_3OS$	47.27 47,21	4.60 4,62	13.90 13,76	134...135 dec.	61
XXII	$C_8H_{12}F_3N_3OS$	37.41 37,64	4.74 4,74	16.39 16,46	129...131 dec.	63
XXIII	$C_{14}H_{20}F_3N_3OS$	50.18 50,14	5.99 6,01	12.67 12,53	200...202 dec.	77
XXV	$C_5H_6F_3N_3O_2$	30.30 30,47	2.98 3,07	—	150...151	73
XXVI	$C_6H_9F_3N_6S_2$	25.26 25,17	3.09 3,17	—	233...234 dec.	22

*Elemental analysis for nitrogen not performed.

for $N_{(1)}H$ at 5.92 ppm coupled to $C_{(5)}H$ (^3J = 3.0 Hz), singlet for $N_{(2)}H$ at 8.79 ppm, and four broadened singlets for the protons of the two NH_2 groups. The ^{13}C NMR spectrum of XXV has a characteristic quartet for $C_{(5)}$ at 89.31 ppm with $^2J_{C-F}$ = 38.8 Hz and a signal for $C_{(3)}$ at 144.42 ppm, indicating a C=N double bond at this carbon atom. The ^{13}C NMR spectrum of XXVI has a quartet for $C_{(5)}$ at 144.33 ppm with $^2J_{C-F}$ = 38.0 Hz and signals for the carbon atoms of the two CS groups at 177.55 and 183.13 ppm.

Thus, semicarbazone VIII and thiosemicarbazone XIX were obtained in acid media. The formation of heterocyclic compounds occurs in basic media. The reactions with semicarbazide proceed unequivocally to give pyrazolidine-1-carboxamides X-XVI. The direction of the reactions with thiosemicarbazide depends on the structure of the starting ketone; the reaction products are pyrazolidine- and 2-pyrazoline-1-carbothioamides XVII-XXIII.

We also studied the reactions of enone XXIV containing an ethoxy group capable of being replaced. The direction of these reactions is in accord with the behavior found for enones I-IV containing a single substituent at $C_{(4)}$. The product of double addition XXVI was obtained in the reaction of XXIV with thiosemicarbazide.

The structures and compositions of these products were demonstrated using IR, PMR, and ^{13}C NMR spectroscopy and confirmed by elemental analysis.

TABLE 2. IR, PMR, and ^{13}C NMR Spectra of VIII-XXIII

Compound	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm	^{13}C NMR spectrum, δ, ppm
1	2	3	4
VIII	1720 (C=O), 3250, 3480 (NH, NH_2)	7,16 (1H, d. q, $C_{(3)}H$, ^3J = 16,7, $^4J_{C-F}$ = 1,7 Hz); 7,32...7,40 (3H, m, 3H Ph); 7,47 (1H, d. q, $C_{(4)}H$, ^3J = 16,7, $^5J_{C-F}$ = 1,4 Hz); 7,73...7,77 (2H, m, 2H Ph)	112,21 ($C_{(3)}$); 121,85 (q, CF_3, $^1J_{C-F}$ = 273 Hz); 128,52 (2C Ph); 129,39 (2C Ph); 130,31 (C Ph); 133,22 (q, $C_{(2)}$, $^2J_{C-F}$ = 32,5 Hz); 136,21 (C quat. Ph); 138,38 ($C_{(4)}$); 157,54 (CO)
IX	3300, 3450 (NH, NH_2)	7,31 (1H, d. q, $C_{(3)}H$, ^3J = 16,6, $^4J_{C-F}$ = 1,7 Hz); 7,40...7,47 (3H, m, 3H Ph); 7,57 (1H, d. q, $C_{(4)}H$, ^3J = 16,6, $^5J_{C-F}$ = 1,3 Hz); 7,73...7,78 (2H, m, 2H Ph), 7,91 (1H, br. s., NH_2); 7,98 (1H, br. s., NH_2); 10,52 (1H, br. s., NH)	112,10 ($C_{(3)}$); 121,78 (q, CF_3, $^1J_{C-F}$ = 275 Hz); 128,60 (2C Ph); 129,41 (2C Ph); 130,58 (C Ph); 133,95 (q, $C_{(2)}$, $^2J_{C-F}$ = 33,7 Hz); 136,02 (C quat. Ph); 139,61 ($C_{(4)}$); 181,54 (CS)
X	1690 (C=O), 2800...3400 (OH), 3340, 3490 (NH, NH_2)	2,57 (1H, t, $C_{(4)}H$-a, ^2J = ^3J = 13,3 Hz); 2,77 (1H, d. d, $C_{(4)}H$-e, ^2J = 13,3, ^3J = 5,5 Hz); 4,41 (1H, d, $N_{(2)}H$, ^3J = 13,0Hz); 4,51 (1H, t.d,. $C_{(3)}H$, ^3J = 13,1, ^3J = 5,5 Hz); 5,78 (1H, br. s , NH_2); 6,33 (1H, br. s , NH_2); 7,04 (1H, s, OH), 7,32...7,43 (5H, m, Ph)	45,46 ($C_{(4)}$); 61,61 ($C_{(3)}$); 93,62 (q, $C_{(5)}$, $^2J_{C-F}$ = 32,8 Hz); 124,51 (q, CF_3, $^1J_{C-F}$ = 288 Hz); 127,26 (2C Ph); 129,10 (C Ph); 129,32 (2C Ph); 135,82 (C quat. Ph); 160,53 (CO)
XI	1680 (C=O), 2800...3400 (OH), 3350, 3480 (NH, NH_2)	2,52 (1H, t, $C_{(4)}H$-a, ^2J = ^3J = 12,3 Hz); 2,72 (1H, d. d, $C_{(4)}H$-e, ^2J = 13,0, ^3J = 5,4 Hz); 4,58 (1H, t. d, $C_{(3)}H$, ^3J = 12,1, ^3J = 5,4 Hz); 4,83 (1H, d, $N_{(2)}H$, ^3J = 12,8 Hz); 5,77 (1H, br. s, NH_2); 6,38 (1H, br. s, NH_2); 6,98 (1H, d. d, $C_{(4)}$ thiophene ^3J = 5,1, ^3J = 3,5 Hz); 7,08 (1H, d.t, $C_{(3)}$ thiophene ^3J = 3,5, ^4J = 1,1 Hz); 7,16 (1H, s, OH); (1H, d. d, $C_{(5)}$ thiophene ^3J = 5,1, ^4J = 1,1 Hz)	46,76 ($C_{(4)}$); 57,76 ($C_{(3)}$), 94,14 (q, $C_{(5)}$, $^2J_{C-F}$ = 32,8 Hz); 125,25 (q, CF_3, $^1J_{C-F}$ = 281 Hz,); 127,03; 127,29; 128,17 (3C thiophene); 138,88 (C quat. thiophene); 161,37 (CO)
XII	1680 (C=O), 2800...3400 (OH), 3340, 3480 (NH, NH_2)	2,60 (1H, d. d, $C_{(4)}H$-e, ^2J = 13,4, ^3J = 4,8 Hz); 2,67 (1H, d. d, $C_{(4)}H$-a, ^2J = 13,4, ^3J = 10,0 Hz); 3,68 (3H, s, CH_3); 4,44 (1H, d. d, $C_{(3)}H$, ^3J = 10,0, ^3J = 4,8 Hz); 4,46 (1H, s, $N_{(2)}H$); 5,68 (1H, br. s NH_2); 6,00 (1H, d. d, $C_{(4)}$ pyrrole , ^3J = 3,7, ^3J = 2,8 Hz); 6,15 (1H, d. d, $C_{(3)}$ pyrrole , ^3J = 3,7, ^4J = 1,8 Hz); 6,42 (1H, br. s, NH_2); (1H, d. d, $C_{(5)}$ pyrrole , ^3J = 2,8, ^4J = 1,8 Hz); 7,25 (1H, s, OH)	34,95 (CH_3); 45,07 ($C_{(4)}$); 55,32 ($C_{(3)}$), 93,80 (q, $C_{(5)}$, $^2J_{C-F}$ = 32,6 Hz); 108,28; 108,64; 125,64 (3C pyrrole); 126,09 (q, CF_3, $^1J_{C-F}$ = 284 Hz); 138,09 (C quat. pyrrole); 162,11 (CO)
XIII	1680 (C=O), 2800...3400 (OH), 3400, 3420, 3460 (NH, NH_2)	2,73 (2H, d, $C_{(4)}H_2$, ^3J = 7,0 Hz); 4,71 (1H, t, $C_{(3)}H$, ^3J = 7,0 Hz); 5,58 (1H, br. s NH_2); 6,61 (1H, br. s, NH_2); 7,10 (1H, t, $C_{(5)}H$ or $C_{(6)}H$ indole , ^3J = 7,6 Hz); 7,18 (1H, t, $C_{(6)}H$ or $C_{(5)}H$ indole , ^3J = 7,6 Hz); 7,27 (1H, s, $C_{(2)}H$ indole); 7,43 (1H, d, $C_{(4)}H$ or $C_{(7)}H$ indole , ^3J = 8,0 Hz); 7,74 (1H, d, $C_{(7)}H$ or $C_{(4)}H$ indole , ^3J = 8,0 Hz); 9,37 (1H, br. s, OH); 10,23 (1H, br. s, NH indole)	45,10 ($C_{(4)}$); 55,60 ($C_{(3)}$); 93,50 (q, $C_{(5)}$, $^2J_{C-F}$ = 31,8 Hz); 112,56 (C indole); 126,20 (q, CF_3, J_{C-F} = 285 Hz); 120,19; 120,41 (2C indole); 121,45 (C quat. indole); 123,10; 123,98 (2C indole); 129,28, 136,85 (2C quat. indole); 162,41 (CO)

TABLE 2 (continued)

1	2	3	4
XIV*	1685 (C=O), 2800...3400 (OH), 3265, 3340, 3480 (NH, NH_2)	Major isomer signals : 1,51 (3H, s, CH_3); 2,66 (1H, d, $C_{(4)}H$, ^2J = 13,4 Hz); 2,74 (1H, d, $C_{(4)}H$, ^2J = 13,4 Hz); 5,14 (1H, s, $N_{(2)}H$); 5,62 (1H, br. s, NH_2); 6,59 (1H, br. s, NH_2); 7,32...7,44 (5H, m, Ph) Minor isomer signals 1,44 (3H, s, CH_3); 2,54 (1H, d, $C_{(4)}H$, ^2J = 14,1 Hz); 3,15 (1H, d, $C_{(4)}H$, ^2J = 14,1 Hz); 5,17 (1H, s, $N_{(2)}H$); 5,62 (1H, br. s, NH_2); 6,59 (1H, br. s, NH_2); 7,32...7,44 (3H, m, 3H Ph); 7,64...7,68 (2H, m, 2H Ph)	Major isomer signals : 26,72 (CH_3); 48,49 ($C_{(4)}$); 65,31 ($C_{(3)}$); 93,10 (q, $C_{(5)}$, $^2J_{C-F}$ = 33,5 Hz); 124,31 (q, CF_3, $^1J_{C-F}$ = 286 Hz); 125,30 (2C Ph); 127,59 (C Ph); 128,71 (2C Ph); 143,78 (C quat. Ph); 161,10 (CO) Minor isomer signals : 27,61 (CH_3); 49,10 ($C_{(4)}$); 65,69 ($C_{(3)}$); 93,10 (q, $C_{(5)}$, $^2J_{C-F}$ = 33,4 Hz); 124,35 (q, CF_3, $^1J_{C-F}$ = 285 Hz); 126,21 (2C Ph); 127,02 (C Ph); 128,11 (2C Ph); 143,90 (C quat. Ph); 159,79 (CO)
XV	1660 (C=O), 2800...3300 (OH), 3280, 3330, 3480 (NH, NH_2	1,80...2,22 (6H, m, $3CH_2$ cyclobut.); 2,24 (1H, d, $C_{(4)}H$, ^2J = 13,3 Hz); 2,49 (1H, d, $C_{(4)}H$, ^2J = 13,3 Hz); 4,90 (1H, s, $N_{(2)}H$); 5,55 (1H, br. s, NH_2); 6,42 (1H, br. s, NH_2); 7,09 (1H, s, OH)	14,80; 27,19; 32,71 ($3CH_2$ cyclobut.); 48,32 ($C_{(4)}$); 63,91 ($C_{(3)}$); 92,65 (q, $C_{(5)}$, $^2J_{C-F}$ = 33,3 Hz); 124,25 (q, CF_3, $^1J_{C-F}$ = 287 Hz); 161,01 (CO)
XVI	1670 (C=O), 2800...3400 (OH), 3320, 3480 (NH, NH_2)	1,55...2,38 (15H, m, 14H adamant.); $C_{(4)}H$); 2,73 (1H, d, $C_{(4)}H$, ^2J = 13,8 Hz); 4,57 (1H, s, $N_{(2)}H$); 5,80 (1H, br. s, NH_2); 6,35 (1H, br. s, NH_2); 7,29 (1H, s, OH)	27,01; 27,11; 31,29; 33,17; 33,24 (2C); 34,30; 36,61; 37,28; (9C adamant.); 46,70 ($C_{(4)}$); 66,91 ($C_{(3)}$); 92,71 (q, $C_{(5)}$, $^2J_{C-F}$ = 31,7 Hz); 124,20 (q, CF_3, $^1J_{C-F}$ = 284 Hz); 161,13 (CO)
XVII	3275, 3445 (NH_2)	2,85 (1H, d. d, q, $C_{(4)}H$-e, ^2J = 18,8 Hz, ^3J = 4,3, $^4J_{C-F}$ = 1,3 Hz); 3,56 (1H, d. d. q, $C_{(4)}H$-a, ^2J = 18,8 Hz, ^3J = 12,1 Hz, $^4J_{C-F}$ = 1,8 Hz); 5,92 (1H, d. d, $C_{(5)}H$, ^3J = 12,1, ^3J = 4,3 Hz); 6,48 (1H, br. s, NH_2); 6,98 (1H, br. s, NH_2); 7,01...7,06 (2H, m, 2H Ph); 7,14...7,26 (3H, m, 3H Ph)	40,85 ($C_{(4)}$); 64,37 ($C_{(5)}$); 119,64 (q, CF_3, $^1J_{C-F}$ = 271 Hz); 125,21 (2C Ph); 128,04 (C Ph); 129,05 (2C Ph); 140,70 (C quat. Ph); 146,04 (q, $C_{(3)}$, $^2J_{C-F}$ = 38,8 Hz); 178,54 (CS)
XVIII	3280, 3450 (NH_2)	3,02 (1H, d. d, $C_{(4)}H$-e, ^2J = 18,8, ^3J = 2,4 Hz); 3,51 (1H, d. d, $C_{(4)}H$-a, ^2J = 18,8, ^3J = 11,4 Hz); 6,26 (1H, d. d, $C_{(5)}H$, ^3J = 11,4, ^3J = 2,4 Hz); 6,62 (2H, br. s, NH_2); 6,83 (1H, d, $C_{(4)}H$, thiophene ^3J = 4,2 Hz); 6,91 (1H, s, $C_{(3)}H$ or $C_{(5)}H$ thiophene); 7,11 (1H, d, $C_{(5)}H$ or $C_{(3)}H$ thiophene, ^3J = 4,2 Hz)	40,57 ($C_{(4)}$); 59,84 ($C_{(5)}$); 119,41 (q, CF_3, $^1J_{C-F}$ = 270 Hz); 125,05; 125,24; 126,76 (3C thiophene); 142,52 (C quat. thiophene); 145,35 (q, $C_{(3)}$, $^2J_{C-F}$ = 38,6 Hz); 177,98 (CS)
XIX	3300, 3360, 3420 (NH_2)	2,98 (1H, d. d. q, $C_{(4)}H$-e, ^2J = 18,6, ^3J = 4,3, $^4J_{C-F}$ = 1,3 Hz); 3,68 (1H, d. d. q, $C_{(4)}H$-a, ^2J = 18,6, ^3J = 11,8, $^4J_{C-F}$ = 1,8 Hz); 3,69 (3H, s, CH_3); 5,82 (1H, d. d, $C_{(5)}H$ or $C_{(3)}H$ pyrrole, ^3J = 3,7, ^4J = 1,8 Hz); 5,96 (1H, d. d, $C_{(4)}H$ pyrrole, ^3J = 3,7, ^3J = 2,6 Hz); 5,98 (1H, d. d, $C_{(5)}H$, ^3J = 11,8, ^3J = 4,3 Hz); 6,55 (1H, d, d, $C_{(3)}H$ or $C_{(5)}H$ pyrrole, ^3J = 2,6, ^4J = 1,8 Hz); 6,90 (1H, br. s, NH_2); 7,23 (1H, br. s, NH_2)	34,39 (CH_3); 40,97 ($C_{(4)}$); 58,68 ($C_{(5)}$); 108,51; 108,16 (2C pyrrole); 121,56 (q, CF_3, $^1J_{C-F}$ = 272 Hz); 122,92 (C pyrrole); 133,96 (C quat. pyrrole); 146,40 (q, $C_{(3)}$, $^2J_{C-F}$ = 38,9 Hz); 179,95 (CS)

TABLE 2 (continued)

1	2	3	4
XX	3250, 3300, 3430 (NH, NH_2)	3,04 (1H, d. d, $C_{(4)}H$-e, ^2J = 18,8, ^3J = 3,8 Hz); 3,69 (1H, d. d, $C_{(4)}H$-a, ^2J = 18,8, ^3J = 12,0 Hz); 6,31 (1H, d. d, $C_{(5)}H$, ^3J = 12,0, ^3J = 3,8 Hz); 6,99 (1H, t, $C_{(5)}H$ or $C_{(6)}H$ indole, ^3J = 7,6 Hz); 7,09 (1H, t, $C_{(6)}H$ or $C_{(5)}H$ indole, ^3J = 7,6 Hz); 7,15 (1H, s, $C_{(2)}H$ indole,); 7,28 (1H, d, $C_{(4)}H$ or $C_{(7)}H$ indole, ^3J = 8,0 Hz); 7,35 (1H, d, $C_{(7)}H$ or $C_{(4)}H$ indole,, ^3J = 8,0 Hz)	40.25 ($C_{(4)}$); 60,23 ($C_{(5)}$); 112,83 (C indole.); 115,73 (C quat. indole.); 118,97; 120,29 (2C indole.); 122,11 (q, CF_3, $^1J_{C-F}$ = 269 Hz); 122,66; 125,04 (2C indole); 125,41; 138,44 (2C quat. indole.); 146,97 (q, $C_{(3)}$, $^2J_{C-F}$ = 38,3 Hz); 180,08 (CS)
XXI †	2800...3500 (OH), 3280, 3440, 3500 (NH, NH_2)	Major isomer signals 1,47 (3H, s, CH_3); 2,80 (1H, d, $C_{(4)}H$, ^2J = 13,4 Hz); 2,85 (1H, d, $C_{(4)}H$, ^2J = 13,4 Hz); 5,29 (1H, s, $N_{(2)}H$); 7,13 (1H, br. s,, NH_2); 7.32...7,47 (5H, m. Ph); 7,57 (1H, br. s,. NH_2); 8,61 (1H, s, OH) Minor isomer signals 1,48 (3H, s, CH_3); 2,72 (1H, d, $C_{(4)}H$, ^2J = 14,2 Hz); 3,24 (1H, d $C_{(4)}H$, ^2J = 14,2 Hz); 5,35 (1H, s, $N_{(2)}H$); 7,12 (1H, br. s, NH_2); 7,32...7,47 (3H, m, 3H Ph); 7,58...7,62 (2H, m, 2H Ph); 7,81 (1H, br. s, NH_2); 8,02 (1H, s, OH)	Major isomer signals 27,56 (CH_3); 50,49 ($C_{(4)}$); 64,80 ($C_{(3)}$); 95,35 (q, $C_{(5)}$, $^2J_{C-F}$ = 32,5 Hz); 125,05 (q, CF_3, $^1J_{C-F}$ = 287 Hz); 126,19 (2C Ph); 128,71 (C Ph); 129,68 (2C Ph); 143,82 (C quat. Ph); 181.96 (CS) Minor isomer signals 28,21 (CH_3); 51,30 ($C_{(4)}$); 65,16 ($C_{(3)}$); 95,32 (q, $C_{(5)}$, $^2J_{C-F}$ = 31,8 Hz); 124,53 (q, CF_3, $^1J_{C-F}$ = 287 Hz); 126,68 (2C Ph); 128,09 (C Ph); 129,18 (2C Ph); 144,38 (C quat. Ph); 180,10 (CS)
XXII	2800...3400 (OH), 3340, 3440 (NH, NH_2)	1,75...2,24 (6H, m, $3CH_2$ cyclobut.); 2,41 (1H, d, $C_{(4)}H$, ^2J = 13,5 Hz); 2,59 (1H, d, $C_{(4)}H$, ^2J = 13,5 Hz); 5,01 (1H, s, $N_{(2)}H$); 6,92 (1H, br. s, NH_2); 7,61 (1H, br.s, NH_2); 8,28 (1H, s, OH)	14,71; 27,20; 32,69 ($3CH_2$ cyclobut.); 49,32 ($C_{(4)}$); 62,60 ($C_{(3)}$); 94,05 (q, $C_{(5)}$, $^2J_{C-F}$ = 32,3 Hz); 124,12 (q, CF_3, $^1J_{C-F}$ = 288 Hz); 180,81 (CS).
XXIII	2800...3400 (OH), 3330, 3450 (NH, NH_2)	1,55...1,91 (12H, m, 12H adamant.); 1,97...2,05 (1H, m, H adamant.); 2,15 (1H, d, $C_{(4)}H$, ^2J = 14,0 Hz); 2,20...2,27 (1H, m, H adamant.); 2,78 (1H, d, $C_{(4)}H$, ^2J = 14,0 Hz); 4,60 (1H, s, $N_{(2)}H$); 6,69 (1H, br. s,, NH_2); 7,50 (1H, br. s,, NH_2); 8,29 (1H, s, OH)	26,47; 26,52; 31,10; 32,89 (2C); 33,11; 33,90; 36.09; 36,79 (9C adamant.); 47,52 ($C_{(4)}$); 65,13 ($C_{(3)}$); 93,65 (q, $C_{(5)}$, $^2J_{C-F}$ = 31,5 Hz); 123,65 (q, CF_3, $^1J_{C-F}$ = 288 Hz); 179,61 (CS).
XXV	1690 (C=O), 2900...3500 (OH), 3290, 3490 (NH_2)	3,16 (1H, d. q, $C_{(4)}H$, ^2J = 19,8, $^4J_{C-F}$ = 1,5 Hz); 3,40 (1H, d, $C_{(4)}H$, ^2J = 19,8 Hz), 5,94 (2H, br.s,, NH_2), 6,30 (1H, s, $C_{(3)}H$), 7,00 (1H, s, OH)	45,30 ($C_{(4)}$); 89,31 (q, $C_{(5)}$, $^2J_{C-F}$ = 38,8 Hz); 123,61 (q, CF_3, $^1J_{C-F}$ = 285 Hz); 144,42 ($C_{(3)}$); 156,39 (CO)
XXVI	3260, 3370, 3440 (NH, NH_2)	2,90 (1H, d, $C_{(4)}H$-e, ^2J = 19,4 Hz); 3,45 (1H, d. d. $C_{(4)}H$-a, ^2J = 19,4, ^3J = 10,2 Hz); 5,71 (1H, d. d, $C_{(5)}H$. ^3J = 10,2 Hz, ^3J = 3,0 Hz); 5,92 (1H, d, $N_{(1)}H$ thiosemicarbazide), ^3J = 3,0 Hz); 7,51 (1H, br. s, NH_2); 7,76 (1H, br.s, NH_2); 7.84 (1H, br.s, NH_2); 8,42 (1H, br.s, NH_2); 8,79 (1H, s, $N_{(2)}H$ thiosemicarbazide),	34,03 ($C_{(4)}$); 75,67 ($C_{(5)}$); 119,82 (q, CF_3, $^1J_{C-F}$ = 271 Hz); 144,33 (q, $C_{(3)}$, $^2J_{C-F}$ = 38,0 Hz); 177,55 (CS); 183,13 (CS)

*3:1 Isomer mixture.

† 4:3 Isomer mixture.

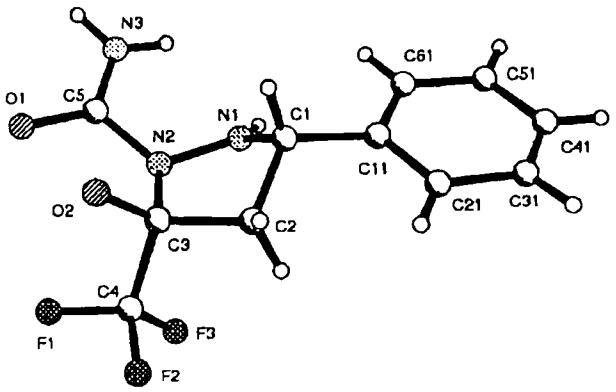


Fig. 1. Structure of X.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were taken on a Varian VXR-400 spectrometer at 400 MHz and a Bruker AMX 400 spectrometer at 100 MHz in $CDCl_3$, CD_3CN, CD_3OD, and DMSO-d_6 with TMS as the internal standard. The IR spectra were taken on a UR-20 spectrometer for Vaseline mulls. The thin-layer chromatographic analysis was carried out on Silufol UV-254 plates and developed by an acidic $KMnO_4$ solution and iodine vapor. The x-ray diffraction structural analysis of X was carried out on an Enraf—Nonius CAD-4 diffractometer using λMoK_α radiation and graphite monochromator. The structure was solved by the direct method using the SHELX program. The pK_a calculation was carried out using the ACD/pK_a 1.0 program from Advanced Chemistry Development (1994-1997).

Trifluoromethyl-containing enones I and VI were obtained according to our previous procedure [22], V and VII were obtained according to our previous procedure [23], IV was obtained according to Gorbunova [24], and XXIV was obtained according to Hojo et al. [25].

The major crystallographic data for monoclinic crystals of X: a = 5.565(9), b = 27.040(6), c = 9.431(9) Å, α = 90.00°, β = 94.53(9)°, V = 1417(2) Å^3, Z = 4, space group $P2_1/c$. Calculations were carried out for 2367 reflections with $F > 3\sigma$. R_w = 8.1%.

(E)-4-(2-Thienyl)-1,1,1-trifluoro-3-buten-2-one (II) was obtained by the condensation of 2-thienylcarbaldehyde and 1,1,1-trifluoroacetone according to Mead et al. [26]. The product was purified by chromatography on a silica gel column using 1:1 hexane—benzene as the eluent and crystallized from hexane at −20°C. The yield of yellow crystalline II was 29%, mp 37-38°C. IR spectrum: 1550 (C=C), 1680 cm^{-1} (C=O). PMR spectrum: 6.70 (1H, d, $C_{(3)}H$, ^3J = 15.6 Hz), 7.07 (1H, d.d, $C_{(4)}H$ thiophene, ^3J = 3.7, 5.0 Hz), 7.40 (1H, d, $C_{(3)}H$ or $C_{(5)}H$ thiophene, ^3J = 3.7 Hz), 7.50 (1H, d, $C_{(5)}H$ or $C_{(3)}H$ thiophene, ^3J = 5.0 Hz), 7.99 ppm (1H, d, $C_{(4)}H$, ^3J = 15.6 Hz). ^{13}C NMR spectrum: 114.92 ($C_{(3)}$), 116.33 (q, CF_3, $^1J_{C-F}$ = 290 Hz), 128.89, 132.01, 134.76 (3 thiophene C or 2 thiophene C and $C_{(4)}$), 138.92 (quat. thiophene C), 142.14 (thiophene C or $C_{(4)}$), 179.63 ppm (q, CO, $^2J_{C-F}$ = 35.0 Hz). Found: C, 46.59; H, 2.36; S, 15.52%. Calculated for $C_8H_5F_3OS$: C, 46.60; H, 2.44; S, 15.55%.

(E)-4-(1H-2-Pyrrolyl)-1,1,1-trifluoro-3-buten-2-one (III) was obtained from 1-methylpyrrole and enone XXIV according to the method described for enone IV [24]. The reaction mixture was maintained for 48 h at room temperature and passed through a short silica gel column. The reaction mixture was additionally eluted with CH_2Cl_2. The combined solutions were evaporated and the residue was distilled in vacuum to give III as an orange liquid in 53% yield, bp 85-87°C (1 mm Hg), mp 17-18°C. IR spectrum: 1580 (C=C), 1690 cm^{-1} (C=O). PMR spectrum: 3.66 (3H, s, CH_3), 6.17-6.20 (1H, m, $C_{(4)}H$ pyrrole), 6.61 (1H, d, $C_{(3)}H$, ^3J = 15.2 Hz), 6.84-6.88 (2H, m, $C_{(3)}H$ and $C_{(5)}$ pyrrole), 7.80 ppm (1H, d, $C_{(4)}H$, ^3J = 15.2 Hz). ^{13}C NMR spectrum: 34.22 (CH_3), 109.71, 111.03, 116.39 (2 pyrrole C, $C_{(3)}$), 116.79 (q, CF_3, $^1J_{C-F}$ = 289 Hz), 129.58 (quat. pyrrole C), 130.96 (pyrrole C), 136.42 ($C_{(4)}$), 179.26 ppm (q, CO,$^2J_{C-F}$ = 33.6 Hz). Found: C, 53.07; H, 4.09%. Calculated for $C_9H_8F_3NO$: C, 53.21; H, 3.97%.

Semicarbazone VIII and Thiosemicarbazone IX (general method). A mixture of 0.50 g (10 mmoles) enone I and 15 mmoles semicarbazide hydrochloride or thiosemicarbazide hydrochloride in 25 ml ethanol was heated at reflux for 6 h. The

TABLE 3. Bond Lengths in 1-Pyrazolidinecarboxamide X

Bond	d, Å	Bond	d, Å
$C_{(5)}$—$O_{(1)}$	1,25(1)	$C_{(5)}$—$N_{(2)}$	1,38(1)
$C_{(5)}$—$N_{(3)}$	1,34(1)	$F_{(1)}$—$C_{(4)}$	1,33(1)
$N_{(2)}$—$N_{(1)}$	1,432(9)	$N_{(2)}$—$C_{(3)}$	1,49(1)
$O_{(2)}$—$C_{(3)}$	1,387(9)	$C_{(1)}$—$C_{(2)}$	1,53(1)
$C_{(1)}$—$N_{(1)}$	1,48(1)	$C_{(1)}$—$C_{(11)}$	1,52(1)
$C_{(2)}$—$C_{(3)}$	1,53(1)	$F_{(3)}$—$C_{(4)}$	1,33(1)
$C_{(3)}$—$C_{(4)}$	1,52(1)	$F_{(2)}$—$C_{(4)}$	1,35(1)
$C_{(31)}$—$C_{(41)}$	1,36(2)	$C_{(31)}$—$C_{(21)}$	1,43(2)
$C_{(41)}$—$C_{(51)}$	1,38(2)	$C_{(11)}$—$C_{(61)}$	1,41(1)
$C_{(11)}$—$C_{(21)}$	1,40(1)	$C_{(61)}$—$C_{(51)}$	1,41(2)

TABLE 4. Bond Angles in 1-Pyrazolidinecarboxamide X

Bond angle	ω, deg.	Bond angle	ω, deg
$O_{(1)}$—$C_{(5)}$—$N_{(2)}$	118,2(8)	$O_{(1)}$—$C_{(5)}$—$N_{(3)}$	124,4(8)
$N_{(2)}$—$C_{(5)}$—$N_{(3)}$	117,3(8)	$C_{(5)}$—$N_{(2)}$—$N_{(1)}$	117,8(6)
$C_{(5)}$—$N_{(2)}$—$C_{(3)}$	121,8(7)	$N_{(1)}$—$N_{(2)}$—$C_{(3)}$	110,5(6)
$C_{(2)}$—$C_{(1)}$—$N_{(1)}$	103,4(6)	$C_{(2)}$—$C_{(1)}$—$C_{(11)}$	115,0(7)
$N_{(1)}$—$C_{(1)}$—$C_{(11)}$	110,8(7)	$C_{(1)}$—$C_{(2)}$—$C_{(3)}$	102,1(7)
$N_{(2)}$—$N_{(1)}$—$C_{(1)}$	102,9(6)	$N_{(2)}$—$C_{(3)}$—$O_{(2)}$	113,2(7)
$N_{(2)}$—$C_{(3)}$—$C_{(2)}$	104,0(6)	$N_{(2)}$—$C_{(3)}$—$C_{(4)}$	108,1(7)
$O_{(2)}$—$C_{(3)}$—$C_{(2)}$	112,5(7)	$O_{(2)}$—$C_{(3)}$—$C_{(4)}$	108,4(7)
$C_{(2)}$—$C_{(3)}$—$C_{(4)}$	110,5(7)	$F_{(1)}$—$C_{(4)}$—$F_{(3)}$	107,2(8)
$F_{(1)}$—$C_{(4)}$—$C_{(3)}$	113,0(8)	$F_{(1)}$—$C_{(4)}$—$F_{(2)}$	105,5(8)
$F_{(3)}$—$C_{(4)}$—$C_{(3)}$	113,4(8)	$F_{(3)}$—$C_{(4)}$—$F_{(2)}$	106,8(8)
$C_{(3)}$—$C_{(4)}$—$F_{(2)}$	110,5(8)	$C_{(41)}$—$C_{(31)}$—$C_{(21)}$	121,0(1)
$C_{(31)}$—$C_{(41)}$—$C_{(51)}$	120,0(1)	$C_{(1)}$—$C_{(11)}$—$C_{(61)}$	118,4(8)
$C_{(1)}$—$C_{(11)}$—$C_{(21)}$	120,3(8)	$C_{(61)}$—$C_{(11)}$—$C_{(21)}$	121,3(9)
$C_{(11)}$—$C_{(61)}$—$C_{(51)}$	119,0(1)	$C_{(41)}$—$C_{(51)}$—$C_{(61)}$	121,0(1)
$C_{(31)}$—$C_{(21)}$—$C_{(11)}$	117,6(9)		

solution was evaporated to 10-15 ml and 15 ml water was added. The solution was cooled to 0°C. The crystalline product was filtered off, washed with water, and dried in vacuum.

Pyrazolidine-1-carboxamides(X-XVI),Pyrazolidine-1-carbothioamides(XXI-XXIII),2-Pyrazoline-1-carboxamide (XXV) and 2-Pyrazoline-1-carbothioamides (XVII-XX, XXVI) (general method). A mixture of 15 mmoles semicarbazide hydrochloride or thiosemicarbazide hydrochloride and 20 mmoles sodium ethylate in 25 ml ethanol was heated at reflux for 15 min and cooled to room temperature. Then, 10 mmoles enone I-VII or XXIV was added. The mixture was maintained at room temperature for 10 h and poured into 30 ml saturated aq. NH_4Cl. The products of the reactions of enones V-VII and XXIV, namely, XIII-XVI, XX-XXIII, and XXVI, were crystallized from mixture obtained over 1-5 h, filtered off, washed with 10-15 ml water, and dried in vacuum. The products of enones I-III, namely, X-XII and XVII-XIX, were extracted with four 20-ml portions of CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate and evaporated. The reaction products were crystallized from diethyl ether by adding small portions of hexane. The reaction mixture in the case of enone XXIV with semicarbazide was evaporated to 5-10 ml and 15 ml saturated aq. NH_4Cl was added. The mixture was maintained at 0°C for 1 h and the precipitate of 2-pyrazoline-1-carboxamide XXV was filtered off, washed with 10 ml ice water, and dried in vacuum.

The elemental analysis data, melting points, and yields of VIII-XXIII are given in Table 1. The IR, PMR, and ^{13}C NMR spectra of VIII-XXIII are given in Table 2.

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