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C–C RECYCLIZATIONS OF SOME 2,7-DISUBSTITUTED 6-ETHOXYCARBONYLPYRAZOLO[1,5-*a*]PYRIMIDINES

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Condensation of ethyl ethoxymethyleneacetoacetate and ethyl ethoxymethylenecyanoacetate in ethanol with 3-substituted 3-aminopyrazoles and 5-amino-1,2,4-triazole gave the 2-substituted 6-ethoxy-carbonyl-7-methyl- and 7-amino-6-ethoxycarbonylpyrazolo[1,5-a]pyrimidines as well as 7-amino-6-ethoxycarbonyl-1,2,4-triazolo[1,5-a]pyrimidine. In the presence of alkali these rearranged to 2-substituted 6-acetyl-7-hydroxy- and 6-carbamoyl-7-hydroxypyrazolo[1,5-a]pyrimidines respectively and also to 6-carbamoyl-7-hydroxy-1,2,4-triazolo[1,5-a]pyrimidine. According to ^{1}H (including NOESY) NMR spectroscopic data there were formed, along with the cyclization products, noncyclic condensation adducts (as cyano derivatives) from ethyl ethoxymethylenecyanoacetate with 5-aminopyrazoles. In the presence of alcoholic alkaline solution these were also transformed in high yield to 6-carbamoyl-7-hydroxypyrazolopyrimidines. When refluxed for a longer time in 12% aqueous alcoholic alkaline solution the 6-ethoxycarbonyl-2,7-dimethylpyrazolo[1,5-a]pyrimidine and 6-acetyl-7-hydroxy-2-methylpyrazolo[1,5-a]pyrimidine recyclize to give 6-carboxy-2,7-dimethyl- and 2,7-dimethylpyrazolo[1,5-a]pyrimidines.

Keywords: pyrazolo[1,5-*a*]pyrimidine, 1,2,4-triazolo[1,5-*a*]pyrimidine, rearrangement, recyclization.

The report concerns a study of the recyclization of condensed pyrimidines containing a bridging nitrogen atom which, on the basis of the atom substitution proceeding in the heterocycle, is a C–C recyclization, i.e. it is accompanied by substitution of the carbon atom of the heterocycle by another (exo ring) carbon atom. A similar rearrangement has previously been reported in a series of noncondensed 2-substituted 5-ethoxy-carbonyl-4-methyl(4-amino)pyrimidines. Upon heating in sodium ethylate or alkaline solution they are converted to the corresponding 2-substututed 5-acetyl(carbamoyl)-4-hydroxypyrimidines [1-4] as well as in a series of condensed pyrimidine systems, *viz*. pyrazolo[1,5-*a*]pyrimidines and 1,2,4-triazolo[1,5-*a*]pyrimidines [5].

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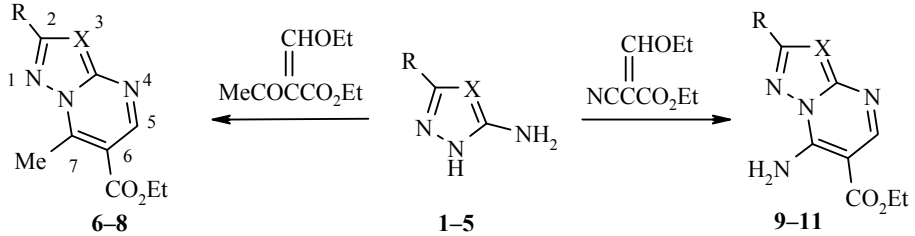
We have previously shown [5] that certain 6-ethoxycarbonyl-7-methylpyrazolo[1,5-*a*]pyrimidines and 6-ethoxycarbonyl-7-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine are converted by treatment with alkali to the corresponding 6-acetyl-7-hydroxyazolo[1,5-*a*]pyrimidines.

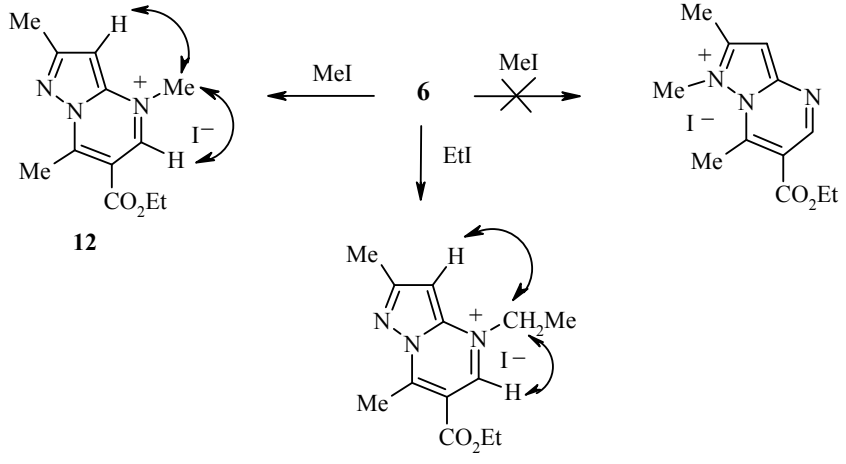
In extending these studies we have examined the possibility of carrying out similar rearrangements amongst a series of condensed bicyclic pyrimidines containing a methyl or amino group in the pyrimidine ring, specifically in the case of 2-substituted 6-ethoxycarbonyl-7-methylpyrazolo[1,5-*a*]- and 7-amino-6-ethoxycarbonylpyrazolo[1,5-*a*]pyrimidines and also 7-amino-6-ethoxycarbonyl-1,2,4-triazolo[1,5-*a*]pyrimidine. Models of the studied compounds **6-8** containing a methyl group in position 7 of the pyrazolo[1,5-*a*]pyrimidine have been synthesized by condensation of the ethyl ethoxymethyleneacetoacetate with the 3-substituted 5-aminopyrazoles **1, 3,** and **4** in ethanol. The 7-aminoazolo[1,5-*a*]pyrimidines **9-11** were prepared by reaction of ethyl ethoxymethylenecyanoacetate with aminoazoles containing an amidine or guanidine fragment, specifically, with 5-amino-3-methyl- and 5-amino-3-phenylpyrazoles **1** and **2** and also 5-amino-1,2,4-triazole (**5**).



6–8 **1–5** **9–11**

1–4, **6–10** X = CH, **1**, **6**, **9** R = Me, **2**, **10** R = Ph, **3**, **7** R = *o*-ClC_6H_4, **4**, **8** R = *o*-BrC_6H_4;
5, **11** R = H, X = N

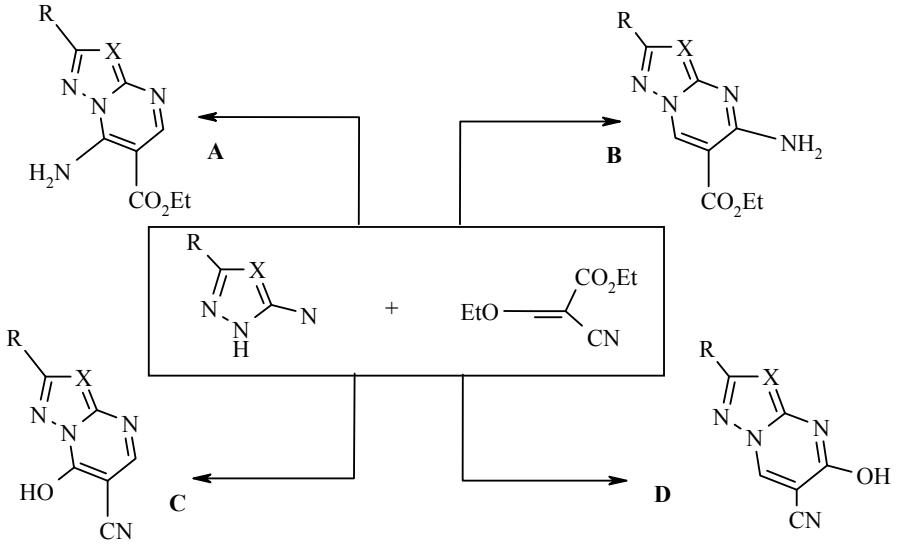
The structure of compounds **6-8** including the presence of ethoxycarbonyl and methyl groups in the pyrimidine ring (i.e. condensation proceeds on account of the acetyl and ethoxymethylene fragments of the reagent) was confirmed through their ^{1}H NMR spectra. The position of the methyl group in the pyrimidine ring of compounds **6-8** (position 5 or 7) was determined using the NOESY ^{1}H NMR method for the iodomethylates of these systems. In particular, in the spectrum of compound **12** (the iodomethylate of compound **6**) a clear interaction was noted between the protons of the N-methyl group and the pyrazole ring CH and this pointed to alkylation at the N(4) atom. In the spectrum of this compound there was observed an obvious cross peak between the signal for this same N-methyl group and the pyrimidine ring proton which is unambiguous evidence for their closely related position in the molecule. It is significant that any kind of interaction of the two



12 **13**

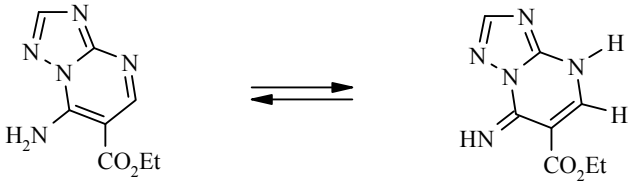
methyl groups in the molecule is absent and this is additional evidence that the methyl group in compound **6**, as also in compounds **7** and **8**, is at position 7 of the pyrazolo[1,5-*a*]pyrimidine, i.e. distant from the N(4) atom. A similar interaction was also noted by us in the ^{1}H NMR spectrum of compound **13** (the iodoethylate of the pyrazolo[1,5-*a*]pyrimidine **6**).

In the realization of the condensation of the 5-aminoazoles **1, 2,** and **5** with ethyl ethoxymethylene-cyanoacetate we have proposed (or at least not ruled out) that the reaction could occur by different routes both from the viewpoint of the groups taking part in the cyclization and by the direction of cyclization. In our opinion there may be 8 or more substances as cyclization products bearing in mind the presence of three reactive centers in the molecule of the ethoxymethylene derivative and also the ambident nature of the α-aminoazoles (with, correspondingly, possible cyclization to form a pyrimidine or pyridine ring with aminopyrazoles or isomeric 1,2,4-triazolopyrimidines with 1,2,4-triazoles). Hence, in these reactions of forming the azolo[1,5-*a*]pyrimidines (taking into account the undoubtedly greater activity of the ethoxymethylene group when compared to the nitrile and ester groups) the cyclization can lead to one of the azolopyrimidines **A-D** given below.



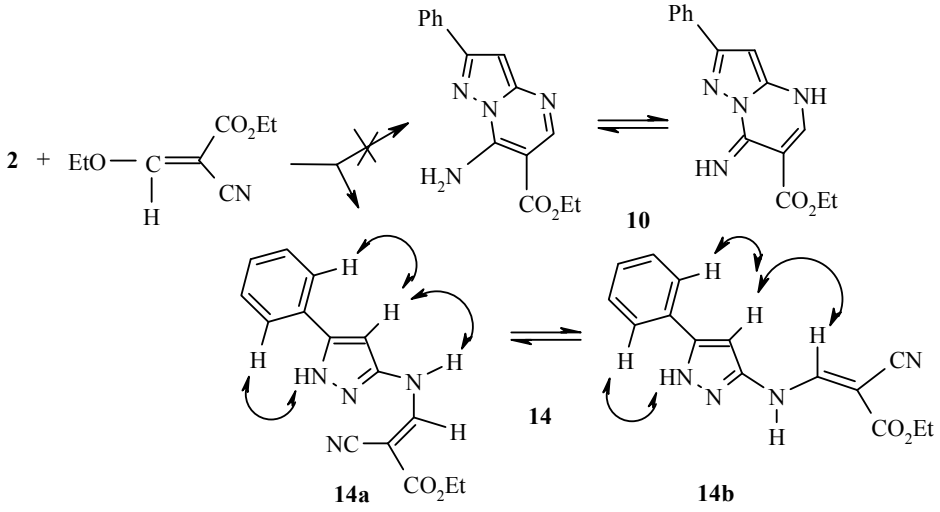
It was turned out that the spectrum of the triazolo[1,5-*a*]pyrimidine **11** showed signals for the ester group protons, a triazole ring proton singlet, and also two proton doublets with a broadened signal for a further proton (proposed to be NH groups). On the basis of this data we consider that compound **11** exists in the tautomeric form **11a**, which explains the splitting of the signals of the H-5 proton and the neighboring NH group.

A more complex picture is noted in the ^{1}H NMR spectra of compounds **9** and **10**. The ^{1}H NMR spectrum of the condensation product of 5-amino-3-phenylpyrazole (**2**) with ethyl ethoxymethylenecyanoacetate shows, in place of spectrum of the expected compound **10**, two sets of signals pointing to the presence in



11 **11a**

solution of two compounds (possibly two conformer forms of the same compound). In addition to signals for ethyl and phenyl group protons there are observed two doublet signals which we assign to the proton of the exocyclic double bond and the NH (^3J = 13.5 Hz). The spectrum of the material isolated also shows the presence of two pairs of doublets for the pyrazole ring protons H-4 and NH (^4J = 2.1 Hz). Evidently the compound produced is the noncyclic cyano derivative **14** without closure of the pyrimidine ring. The proposal was confirmed by the presence in the IR spectrum of nitrile stretching vibrations at 2220 cm^{-1} and also by the presence in the mass spectrum of a fragment corresponding to cleavage of this group. The presence in the spectrum of two sets of signals, the changes in intensities of which alter with the nature of the solvent used, is explained by the potential existence of hindered rotation around the exocyclic C(3)–N partial double bond in compound **14** and hence giving the forms **14a** and **14b**.

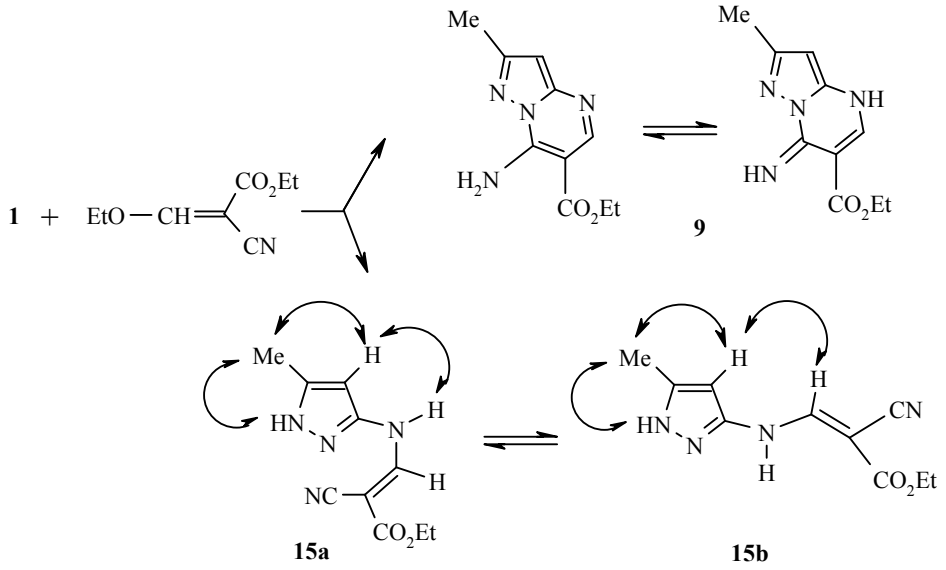


As is evident from the NOESY 2D spectrum for this compound, the phenyl group is found at position 5 of the pyrazole ring and is confirmed by the presence of a strong NOE for the phenyl ring *ortho* protons both with the NH proton and also with H-4. An NOE is observed in conformer **14a** between the H-4 and exocyclic NH proton and in conformer **14b** between the H-4 and the N–CH.

Study of the ^{1}H NMR spectra of the compound separated as a result of treating the 5-amino-3-methylpyrazole (**1**) with ethyl ethoxymethylenecyanoacetate showed three sets of signals corresponding to the pyrazolopyrimidine **9** (about 20%) with two conformational forms of the noncyclic cyano derivative **15** (about 40% of each). The NOESY spectrum of compounds **15a** and **15b** repeats the relationship found in the spectrum of compound **14**, in fact showing the presence of an NOE between the methyl group protons at position 5 of the pyrazole ring and the NH and H-4 protons. An NOE is also seen between the pyrazole H-4 ring proton and a proton of the exocyclic multiple bond.

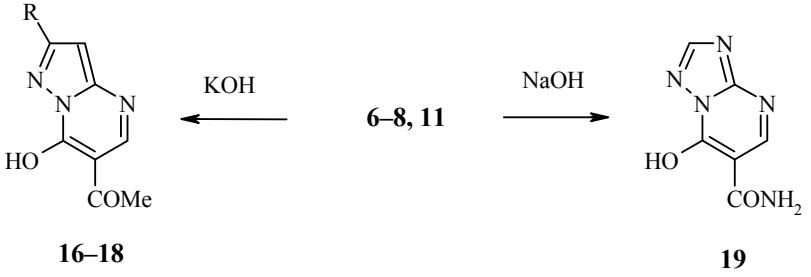
The existence of a nitrile group in this sample (i.e. the presence of the noncyclic compound) is noted in the IR spectrum. The mass spectrometric study carried out to clarify the structure of the condensation product might be uninformative since the molecular weights of compounds **9** and **15** are identical. However, in the mass spectrum, a fragment which corresponded to cleavage of a CN group was observed and this points the presence of the open form **15**.

The synthesis of all of the azolopyrimidines listed occurs in quite high yield (60-86%) with short refluxing of the aminoazoles **1-5** in alcohol with the corresponding ethoxymethylene derivatives. The triazolo derivative **11** is the exception and is formed (in 79% yield) only by refluxing the reagents in alcohol for 5 h. As noted above, however, reaction with the cyanoacetate derivative is markedly more difficult.



Rearrangement of the pyrazolo[1,5-*a*]pyrimidines **6-8** to give the corresponding 6-acetyl-7-hydroxy-pyrazolo[1,5-*a*]pyrimidines **16-18** generally proceeds rapidly at room temperature in the presence of an alcoholic alkaline solution over several minutes, even at room temperature. A salt of the 7-hydroxy derivative is initially formed and acidification gives the 7-hydroxy derivatives **16-18**.

The rearrangement product of the triazolopyrimidine **11** (the 6-carbamoyl-7-hydroxy-1,2,4-triazolo-[1,5-*a*]pyrimidine (**19**)) is prepared in 51% yield only by refluxing compound **11** for 5 h in alcoholic alkaline solution. In the short term (within minutes) in refluxing alkaline solution of the triazolo[1,5-*a*]pyrimidine **11** the reaction does not go to completion and gives a mixture of the starting and final reaction products.



16 R = Me, **17** R = *o*-ClC_6H_4, **18** R = *o*-BrC_6H_4

It should be noted that reaction of compound **16** in an alcoholic solution of sodium ethylate gave the water soluble sodium salt of the 6-acetyl-7-hydroxy-2-methylpyrazolo[1,5-*a*]pyrimidine (**20**).

The ^1H NMR spectra of all of the recyclization products showed the absence of signals for the ester protons which characterize the starting materials and the appearance of a broadened signal for a hydroxyl group proton.

We were unable to synthesize the pyrazolopyrimidines **9** and **10** in a pure state (without the formation of the corresponding non cyclic forms). Hence in the reaction with alcoholic base solution we have introduced the samples separated, in fact the phenyl derivative **14** and the 2-methyl derivative of the pyrazolopyrimidine **9** as a mixture with the corresponding cyano derivative **15**.

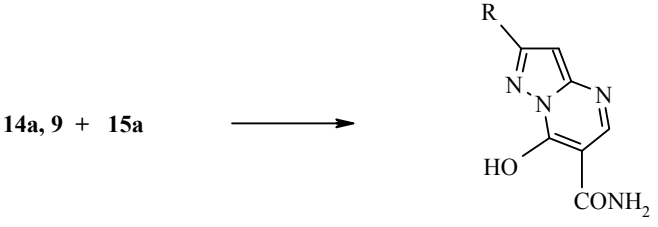
Short heating in base of the phenyl derivative **14** and the mixture of the pyrazolo[1,5-*a*]pyrimidine **9** with the noncyclic cyano derivatives **15** gave high yields of the corresponding 6-carbamoyl-7-hydroxy-

TABLE 1. Characteristics of the Synthesized Compounds **6-24**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f*	Yield, %
		C	H	N			
6	$C_{11}H_{13}N_3O_2$	60.03 / 60.26	5.71 / 5.98	19.40 / 19.17	111-112	0.69	86
7	$C_{16}H_{14}ClN_3O_2$	60.59 / 60.86	4.60 / 4.47	13.49 / 13.31	124-125	0.80	63
8	$C_{16}H_{14}BrN_3O_2$	53.51 / 53.35	3. 70 / 3. 92	11.41 / 11.67	109-110	0.9	60
9, **15a**, and **15b**	$C_{10}H_{12}N_4O_2$	54.29 / 54.54	5.31 / 5.46	25.71 / 25.44	191-192	0.56	77
11	$C_8H_9N_5O_2$	46.04 / 46.38	4.18 / 4.37	34.04 / 33.81	235-236	0.61	69
12	$C_{11}H_{13}N_3O_2 \times MeI$	40.13 / 39.90	4.26 / 4.47	11.41 / 11.63	167-168	—	95
13	$C_{11}H_{13}N_3O_2 \times EtI$	41.39 / 41.61	5.05 / 4.84	10.98 / 11.20	154-155	—	75
14a and **14b**	$C_{15}H_{14}N_4O_2$	64.09 / 63.82	5.17 / 5.00	19.56 / 19.85	206-207	0.38	75
16	$C_9H_9N_3O_2$	56.78 / 56.54	4.50 / 4.74	22.21 / 21.98	>300	0.63	93
17	$C_{14}H_{10}ClN_3O_2$	58.19 / 58.45	3.59 / 3.50	14.87 / 14.61	221–222	0.60	57
18	$C_{14}H_{10}BrN_3O_2$	50.41 / 50.62	3.27 / 3.03	12.89 / 12.65	233–234	0.60	76
19	$C_6H_5N_5O_2$	39.97 / 40.23	2.98 / 2.81	38.85 / 39.10	>300	0.36	51
20	$C_9H_8N_3NaO_2$				—	—	90
21	$C_8H_8N_4O_2$	50.15 / 50.00	4.03 / 4.17	29.39 / 29.16	>300	0.45	86
22	$C_{13}H_{10}N_4O_2$	61.68 / 61.41	4.11 / 3.96	22.30 / 22.04	>300	0.54	94
23	$C_9H_9N_3O_2$	56.29 / 56.54	4.51 / 4.74	22.19 / 21.98	>330 (subl.)	0.65	48 (A) 25 (B)
24	$C_8H_9N_3$	65.54 / 65.29	6.01 / 6.16	28.38 / 28.55	220 (subl.)	0.68	37 (A) 58 (B)

* Systems: benzene-acetone, 3: 1 (compounds **6, 9, 14a,b, 15a,b, 24**) and 1:1 (compounds **7, 8, 11, 16-19, 21-23**).

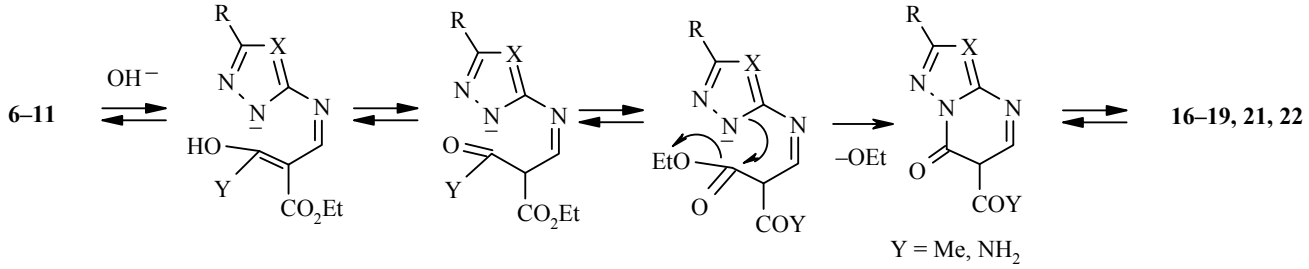
2-substituted pyrazolo[1,5-*a*]pyrimidines **21** and **22**. Evidently the action of base occurs initially to give cyclization of compounds **14** and **15** to the corresponding 7-aminopyrazolo[1,5-*a*]pyrimidines **9** and **10** which readily cyclize in the reaction conditions to compounds **21** and **22**.



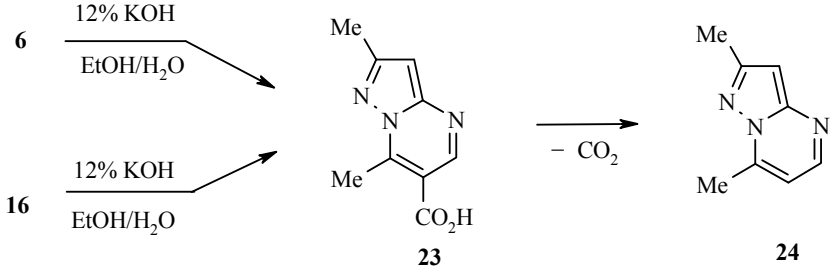
21, 22

21 R = Me, **22** R = Ph

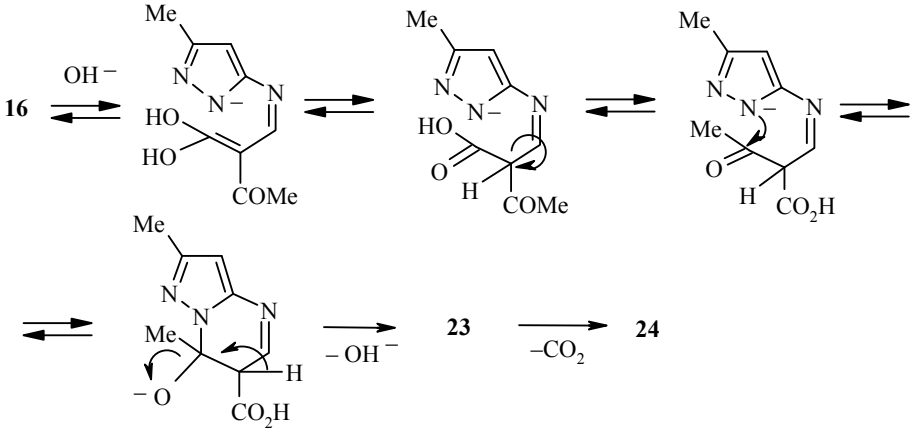
A possible scheme for the conversion of compounds **6-11** is given below.



In the recyclization process using hydroxide ion there evidently occurs opening of the pyrimidine ring at the N–C(7) bond, subsequent rotation around the C(5)–C(6) bond and a repeated cyclization involving a nucleophilic attack of a triazole ring nitrogen atom such that a carbon of the ester group is included in the newly formed pyrimidine ring while the C(7) atom (which was in the pyrimidine ring) proves to be outside the heterocycle. The relatively low yield of the rearrangement product in the case of recyclization of triazolopyrimidine **11** is possibly related to the lowering of the electron density at the N(1) atom in the intermediate due to the (-M) effect of the N(3) triazole ring atom.



We have previously reported that prolonged refluxing of the 6-ethoxycarbonyl-7-methyl-2-phenyl- or 6-acetyl-7-hydroxy-2-phenylpyrazolo[1,5-*a*]pyrimidines in a 12% aqueous alcoholic solution of potassium hydroxide causes rearrangement to give in both cases 7-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine [5]. The formation of the latter indirectly points to the occurrence of a repeated, two-stage rearrangement of both starting compounds to the 6-carboxy-7-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine which undergoes decarboxylation under these reaction conditions. We have also recorded similar recyclizations in the case of the corresponding



2-methyl derivatives **6** and **16**. Moreover, under these conditions (in contrast to those reported before) we have been able to separate and to identify the product of the noted two-stage C–C recyclization as the 6-carboxy-2,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**23**) and the final reaction product, i.e. the 2,7-dimethylpyrazolo-[1,5-*a*]pyrimidine (**24**). Separation of the 6-carboxy-2,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**23**) is a direct, rather than indirect, proof of the existence of a two-stage C–C recyclization.

TABLE 2. ^{1}H and ^{13}C NMR Spectra of the Condensed Pyrimidines **6-24**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
6*	1.44 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 2.56 (3H, s, 2-CH_3); 3.20 (3H, s, 7-CH_3); 4.44 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 6.55 (1H, s, H-3); 8.91 (1H, s, H-5)
7	1.47 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 3.28 (3H, s, 7-CH_3); 4.47 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 7.30 (1H, s, H-3); 7.37-7.41 (2H, m, C_6H_4); 7.53 (1H, m, C_6H_4); 7.97 (1H, m, C_6H_4), 8.99 (1H, s, H-5)
8	1.44 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 3.26 (3H, s, 7-CH_3); 4.46 (2H, q, *J* = 7.1, OCH_2); 7.30 (1H, s, H-3); 7.41-7.79 (4H, m, C_6H_4); 8.99 (1H, s, H-5)
9	1.40 (0.6H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 2.45 (0.6H, s, CH_3); 4.34 (0.4H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 6.19 (0.2H, s, H-3); 8.13 (0.2H, br. s, NH_2) and 8.36 (0.2H, br. s, NH_2); 8.53 (0.2H, s, H-5)
11	1.35 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 4.21 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 8.18 (1H, br. s, H-2); 8.61 (1H, d, *J* = 13.5, H-5); 11.35 (1H, d, *J* = 13.5, NH); 13.65 (1H, br. s, NH)
12	1.47 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 2.67 (3H, s, 2-CH_3); 3.37 (3H, s, 7-CH_3); 4.45 (3H, s, N-CH_3); 4.51 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 7.33 (1H, s, H-3); 9.78 (1H, s, H-5)
13	1.51 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 1.65 (3H, t, *J* = 7.1, $NCH_2C\underline{H}_3$); 2.65 (3H, s, 2-CH_3); 3.35 (3H, s, 7-CH_3); 4.50 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 4.91 (2H, q, *J* = 7.1, $NC\underline{H}_2CH_3$); 7.43 (1H, s, H-3); 9.84 (1H, s, H-5)
14a and **14b**	1.33 and 1.37 (3H, t, *J* = 7.1, CH_3); 4.21 and 4.28 (2H, q, *J* = 7.1, OCH_2); 6.32 and 6.64 (1H, d, *J* = 2.1, H-4); 7.26-7.42 (3H, m, C_6H_5) and 7.64-7.69 (2H, m, C_6H_5); 8.27 and 8.57 (1H, d, *J* = 13.8, =C<u>H</u>NH); 10.75 (1H, d, *J* = 13.8, =CHN<u>H</u>); 12.82 and 12.94 (1H, d, *J* = 2.1, NH)
15a and **15b**	1.31 and 1.35 (2.4H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 2.23 and 2.25 (2.4H, s, CH_3); 4.19 and 4.25 (1.6H, q, *J* = 7.1, OCH_2); 5.74 and 5.95 (0.8H, br. s, H-4 pyrazole); 8.14 and 8.49 (0.8H, d, *J* = 13.8, =C<u>H</u>NH); 10.56 and 10.62 (0.8H, d, *J* = 13.8, =CHN<u>H</u>); 11.98 and 12.12 (0.8H, br. s, NH)
16	2.49 (3H, s, 2-CH_3); 3.13 (3H, s, $COCH_3$); 6.41 (1H, s, H-3); 7.00 (1H, br. s, OH); 8.79 (1H, s, H-5)
17	3.23 (3H, s, CH_3); 5.8-6.3 (1H, br. s, OH); 7.17 (1H, s, H-3); 7.38 (2H, m, C_6H_4); 7.51 (1H, m, C_6H_4); 7.98 (1H, m, C_6H_4); 8.90 (1H, s, H-5)
18	3.22 (3H, s, CH_3); 7.17 (1H, s, H-3); 7.40-7.97 (4H, m, C_6H_4); 8.91 (1H, s, H-5); 12.4-13.3 (1H, br. s, OH)
19	8.34 (1H, s, H-2); 8.62 (1H, br. s, NH); 8.83 (1H, s, H-5); 8.88 (1H, br. s, NH); 12.4-13.4 (1H, br. s, OH)
20	2.55 (3H, s, 2-CH_3); 2.97 (3H, s, $COCH_3$); 6.57 (1H, s, H-3); 8.68 (1H, s, H-5)
21*[2]	2.41 (3H, s, CH_3); 6.18 (1H, s, H-3); 8.03 (1H, br. s, NH); 8.43 (1H, br. s, NH); 8.55 (1H, s, H-5); 11.0-13.0 (1H, br. s, OH)
22	6.78 (1H, s, H-3); 7.4-8.0 (5H, m, C_6H_5); 8.18 (1H, br. s, NH); 8.58 (1H, br. s, NH); 8.59 (1H, s, H-5); 11.4-13.1 (1H, br. s, OH)
23	2.49 (3H, s, 2-CH_3); 3.13 (3H, s, 7-CH_3); 6.41 (1H, s, H-3); 8.79 (1H, s, H-5); 12.92 (1H, br. s, COOH)
24	2.48 (3H, s, 2-CH_3); 2.72 (3H, d, *J* = 0.9, 7-CH_3); 6.37 (1H, s, H-3); 6.68 (1H, dq, *J* = 4.2, *J* = 0.9, H-6); 8.24 (1H, d, *J* = 4.2, H-5)

* ^{13}C spectrum, δ, ppm: 14.43 ($\underline{C}H_3CH_2O$); 14.99 (2-CH_3); 15.19 (7-CH_3); 61.54 (OCH_2); 97.76 (C-3); 109.89 (C-2); 149.51 (C-*ipso*); 149.78 (C-5); 150.98 (C-7); 157.38 (C-6); 165.10 (COO).

*[2] ^{13}C spectrum, δ, ppm: 14.11 (CH_3); 89.88 (CO–<u>C</u>); 95.94 (=CH); 148.70 (C-7); 149.53 (C-4); 150.34 (N=CH), 154.36 (C-2); 167.99 (CO).

The formation of compounds **23** and **24** from pyrazolopyrimidines **6** and **16** can be explained by the occurrence of a series of successive reactions which include the opening of the pyrimidine ring, its cyclization, and then decarboxylation. The scheme given below shows The scheme for the transformation of the acetyl derivative **16** is given above. According to the scheme reported previously the transformation of compound **6** to compounds **23** and **24** initially forms the acetyl derivative **16** (C–C recyclization) but in this case a normal hydrolysis of the ester group is not excluded. Compound **16** then again undergoes rearrangement to the final compounds **23** and **24**.

EXPERIMENTAL

IR spectra were obtained on a UR-20 spectrometer using vaseline oil. ^{1}H and ^{13}C NMR spectra were recorded at the Molecular Structure Research Center, National Academy of Sciences of Armenia (US CRDF RESC 17-5 program) on a Varian Mercury 300 instrument (300 and 75 MHz respectively) using $CDCl_3$ (compounds **6-8**), DMSO-d_6 (compounds **9-19**, **21-24**) or D_2O (compound **20**) with TMS as standard. The sample temperature was 303 K. Mass spectra were recorded on an MK-1321 spectrometer with direct insertion of the sample into the ion source and an ionization energy of 70 eV. TLC was performed on Silufol UV-254 plates and revealed using iodine vapor and the Ehrlich reagent.

5-Amino-3-methylpyrazole (**1**) and 5-amino-1,2,4-triazole (**5**) used in the synthesis of the azolopyrimidines were obtained from the Aldrich company and the 5-amino-3-phenylpyrazole (**2**), 5-amino-3-(*o*-chlorophenyl)pyrazole (**3**), and 5-amino-3-(*o*-bromophenyl)pyrazole (**4**) were prepared by method [6].

The physicochemical and spectroscopic characteristics of the compounds synthesized are given in Tables 1 and 2.

6-Ethoxycarbonyl-2,7-dimethylpyrazolo[1,5-*a*]pyrimidine (6). A solution of ethyl ethoxymethyleneacetoacetate (18.6 g, 100 mmol) in ethanol (20 ml) was added to a solution of 5-amino-3-methylpyrazole (9.7 g, 100 mmol) in ethanol (30 ml). Over 3-5 min the temperature of the reaction mixture increased. It was then refluxed for 15 min, cooled, and the precipitate formed was filtered off to give the product (18.8 g, 86%) as shining white crystals of the pyrazolo[1,5-*a*]pyrimidine **6**.

2-(*o*-Chlorophenyl)-6-ethoxycarbonyl-7-methylpyrazolo[1,5-*a*]pyrimidine (7). A mixture of 5-amino-3-(*o*-chlorophenyl)pyrazole (1.4 g, 7 mmol), ethyl ethoxymethyleneacetoacetate (1.5 g, 8 mmol), and absolute ethanol (10 ml) was refluxed for 1 h. The precipitate formed on cooling was filtered off to give compound **7** (1.4 g, 63%).

2-(*o*-Bromophenyl)-6-ethoxycarbonyl-7-methylpyrazolo[1,5-*a*]pyrimidine (8). A mixture of ethyl ethoxymethyleneacetoacetate (0.85 g, 4.5 mmol), 5-amino-3-(*o*-bromophenyl)pyrazole (1.0 g, 4.2 mmol), and absolute alcohol (10 ml) was refluxed for 1 h. The precipitate formed on cooling was filtered off to give the pyrazolo[1,5-*a*]pyrimidine **8** (0.9 g, 60%).

7-Amino-6-ethoxycarbonyl-2-methylpyrazolo[1,5-*a*]pyrimidine (9). A solution containing 5-amino-3-methylpyrazole (2.0 g, 20 mmol) in absolute ethanol (20 ml) was added to a solution of ethyl ethoxymethylenecyanoacetate (3.4 g, 20 mmol) in absolute ethanol (5 ml). An increase in temperature of 10-15ºC was observed almost at once. The solution was refluxed for 15 h. After cooling, the precipitate was filtered off to give 3.4 g (77%) of a mixture of compound **9** and ethyl 2-cyano-3-(5-methylpyrazol-3-yl)aminopropenoate (**15**). IR spectrum, ν, cm^{-1}: 1500, 1570, 1625, 1630, 1678 (C=C and C=N), 1710 (C=O), 2210 (cyano), 3200 (NH). Mass spectrum, *m/z* (I_{rel}, %): 221 $[M^{+}+1]$ (16), 220 $[M]^{+}$ (100), 193 (15), 192 (16), 186 (17), 175 (23), 174 (69), 148 (12), 120 (15).

Ethyl 2-Cyano-3-(5-phenylpyrazol-3-yl)aminopropenoate (14). Similarly as above. A solution containing 5-amino-3-phenylpyrazole (4.0 g, 25 mmol) in absolute ethanol (30 ml) was added to a solution of

ethyl ethoxymethylenecyanoacetate (4.2 g, 25 mmol) in absolute ethanol (5 ml). Formation of a precipitate was noted almost at once. The precipitate was filtered off to give compound **14** (5.25 g, 75%) which was recrystallized from ethanol. IR spectrum, ν, cm^{-1}: 1565 and 1583, 1630, 1675 (C=C and C=N), 1703 (C=O), 2220 (CN), 3270 (NH). Mass spectrum, *m/z* (I_{rel}, %): 283 [M^++1] (20), 282 [M^+] (100), 237 (20), 236 (58), 210 (33), 209 (30), 182 (11).

7-Amino-6-ethoxycarbonyl-1,2,4-triazolo[1,5-*a*]pyrimidine (11). A solution containing 5-amino-1,2,4-triazole (1.8 g, 20 mmol) in absolute ethanol (35 ml) was added to a solution of ethyl ethoxymethylenecyanoacetate (3.4 g, 20 mmol) in absolute ethanol (5 ml). The mixture was refluxed for 5 h. The precipitate formed after cooling was filtered off and washed with cold alcohol to give compound **11** (2.86 g, 69%) which was recrystallized from ethanol.

6-Ethoxycarbonyl-2,4,7-trimethylpyrazolo[1,5-*a*]pyrimidinium Iodide (12). A mixture of the pyrazolo[1,5-*a*]pyrimidine **6** (2 g, 9 mmol) and methyl iodide (4 ml, 9.12 g, 64 mmol) was heated in a sealed ampule for 5 h. The crystals formed were filtered off, washed with hexane, and dried to give the iodide **12** (3.1 g, 95%).

6-Ethoxycarbonyl-4-ethyl-2,7-dimethylpyrazolo[1,5-*a*]pyrimidinium Iodide (13). Similarly to the above. A mixture of the pyrazolo[1,5-*a*]pyrimidine **6** (1.8 g, 8 mmol) and ethyl iodide (5 ml, 9.66 g, 62 mmol) was heated in a sealed ampule on a water bath for 8 h. The crystals formed were filtered off, washed with hot hexane, and dried to give the iodide **13** (2.3 g, 75%).

6-Acetyl-7-hydroxy-2-methylpyrazolo[1,5-*a*]pyrimidine (16). A solution of potassium hydroxide (1.0 g) in ethanol (10 ml) was added to a solution of the 6-ethoxycarbonyl derivative **6** (1.1 g, 5 mmol) in ethanol (5 ml). The color changed from yellow to blue after addition of alkali and crystals of the potassium salt of the product began to precipitate from the solution. The crystals were filtered off, dissolved in water, and acidified to pH 5-6. The precipitate was then filtered off and washed with water and acetone to give the 6-acetyl derivative **16** (0.88 g, 93%).

6-Acetyl-2-(*o*-chlorophenyl)-7-hydroxypyrazolo[1,5-*a*]pyrimidine (17). A solution of compound **7** (1.26 g, 4 mmol) in ethanol (15 ml) was added to a solution of KOH (2.0 g, 36 mmol) in aqueous ethanol (70%, 15 ml). After stirring for several minutes a precipitate began to appear. The mixture was refluxed for 1 h, cooled, and acidified with dilute hydrochloric acid (1:) to pH 5-6 to give compound **17** (0.65 g, 57%).

6-Acetyl-2-(*o*-bromophenyl)-7-hydroxypyrazolo[1,5-*a*]pyrimidine (18). Analogously to the above. A solution of compound **8** (1.44 g, 4 mmol) in ethanol (15 ml) was added to a solution of KOH (2.0 g, 36 mmol) in 70% aqueous ethanol (15 ml). A dark-violet coloration was produced instantaneously and this then disappeared. The solution was acidified with dilute hydrochloric acid to pH 6-7 and the precipitate formed was filtered off and washed on the filter with water to give grayish crystals of compound **18** (1.0 g, 76%) which were recrystallized from ethanol.

6-Carbamoyl-7-hydroxy-1,2,4-triazolo[1,5-*a*]pyrimidine (19). A solution of sodium hydroxide (0.4 g, 10 mmol) in ethanol (5 ml) was added to a suspension of compound **11** (1.04 g, 5 mmol) in ethanol (10 ml) and refluxed for 5 h. The precipitate formed after cooling was filtered off, dissolved in water, and acidified using dilute hydrochloric acid to pH 5-6. The precipitate then produced was filtered off and washed with cold water to give the triazolo[1,5-*a*]pyrimidine **19** (0.45 g, 51%).

Sodium Salt of 6-Acetyl-7-hydroxy-2-methylpyrazolo[1,5-*a*]pyrimidine (20). A solution of sodium ethylate (prepared from sodium (0.21 g, 9 mmol) and absolute alcohol (5ml)) was added to a suspension of 6-acetyl-7-hydroxy-2-methylpyrazolo[1,5-*a*]pyrimidine **16** (1.7 g, 9 mmol) in absolute alcohol (10 ml). The mixture was left for several hours at room temperature and the precipitate was filtered off to give the sodium salt of **20** (1.7 g, 90%).

6-Carbamoyl-7-hydroxy-2-methylpyrazolo[1,5-*a*]pyrimidine (21). A solution of sodium hydroxide (1.0 g, 25 mmol) in absolute ethanol (5 ml) was added to a solution of a mixture of compound **9** and the acyclic

cyano derivative **15** (0.5 g, 2.2 mmol) in absolute ethanol (15 ml) and refluxed for 10 min. The solution changed color and a precipitate was formed. Solvent was evaporated and the residue was washed with absolute benzene. The precipitate remaining was filtered off, dissolved in water, and acidified using dilute hydrochloric acid (1:1) to pH 4. The precipitate was filtered and washed with cold water to give the pyrazolo[1,5-a]pyrimidine **21** (0.36 g, 86%).

6-Carbamoyl-7-hydroxy-2-phenylpyrazolo[1,5-*a*]pyrimidine (22). A solution of potassium hydroxide (2.0 g, 36 mmol) in ethanol (20 ml) was added to a solution of the cyano derivative **14** (2.0 g, 7 mmol) in ethanol (15 ml) and refluxed for 15 min. A change in color was noted and a precipitate was formed which was filtered off, dissolved in water, and acidified with dilute hydrochloric acid (1:1) to pH 5-6. The precipitate formed was filtered off and washed with cold water to give compound **22** (1.65 g, 94%).

6-Carboxy-2,7-dimethylpyrazolo[1,5-*a*]pyrimidine (23) and 2,7-Dimethylpyrazolo[1,5-*a*]pyrimidine (24). A. A solution of potassium hydroxide (1.2 g, 20 mmol) in water (5 ml) was added to a solution of the 6-ethoxycarbonyl derivative **6** (1.1 g, 5 mmol) in ethanol (5 ml) and refluxed for 20 h. Solvent was evaporated to dryness and the residue was washed twice with benzene collecting the benzene extracts. Removal of the benzene gave compound **24** (0.27 g, 37%). The residue formed after treatment of the reaction mixture with benzene was dissolved in water (5 ml) and acidified using hydrochloric acid to pH 4-5. The crystals formed were filtered off and recrystallized from benzene to give compound **23** (0.46 g, 48%).

B. Similarly to the above, refluxing a mixture of the 6-acetyl derivative **16** (0.96 g, 5 mmol) and potassium hydroxide (1.68 g, 30 mmol) in aqueous alcohol solution (13 ml) for 30 h. Treatment with benzene then gave compound **24** (0.43 g, 58%) and the acid **23** (0.24 g, 25%). According to melting point, chromatographic mobility, and ^{1}H NMR spectrum the sample obtained agreed with that prepared by the counter synthesis of ester **6** using method A.

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