Tetrahedron Vol. 43, No. 18, pp. 4195 to 4202, 1987
Printed in Great Britain.

0040-4020/87 $3.00 + .00

SYNTHESIS OF 5-AMINO-4,5-DIHYDROPYRAZOLO [3,4-d] PYRIMIDIN-4-ONES AND RELATED ISOMERIC SYSTEMS. PART II. RING CLOSURE REACTIONS.

A. MAQUESTIAU * and J.-J. VANDEN EYNDE.

State University of Mons, Organic Chemistry Laboratory
B-7000 MONS (Belgium).

(*Received in UK* 10 *July* 1987)

Abstrat - Treatment of ethyl (heteroalkylidene)aminopyrazole-4-carboxylates with hydrazine hydrate generally provides a ready synthetic route to 5-amino-4,5-dihydropyrazolo [3,4-d] pyrimidin-4-ones, although ethyl 5-[(dimethylamino)alkylidene]aminopyrazole-4-carboxylates are unreactive.

On the other hand, reactions between aminopyrazole-4-carboxhydrazides and orthoesters or amide acetal are more versatile : we observed formation of isomeric 2-pyrazolyl-1,3,4-oxadiazoles, as major compounds, either from triethyl orthoacetate and 1-methyl-5-aminopyrazole-4-carboxhydrazide or from dimethylacetamide dimethyl acetal and various heterocyclic precursors. The ring closure mechanism is discussed.

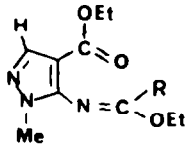
INTRODUCTION

In a preceding paper[1], we described reactions between aminopyrazole-4-carboxylic acids derivatives and orthoesters or amide acetals. We now wish to report the ring closure possibilities of the so obtained compounds.

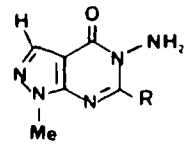
RESULTS AND DISCUSSION

Reactions between ethyl (heteroalkylidene)aminopyrazole-4-carboxylates and hydrazine hydrate.

Compounds 1-12 react with hydrazine hydrate in methanolic solution to yield the 5-amino-4,5-dihydropyrazolo [3,4-d] pyrimidin-4-ones 15-20 (ν(C=O) around 1700 cm^{-1}[2]. If reflux is needed to convert 2, 4 and 7, experimentally, we observed that the (dimethylamino)alkylidene derivatives 13 and 14 are stable towards hydrazine hydrate, both in boiling ethyleneglycol monomethylether and in refluxing methanol (scheme 1).

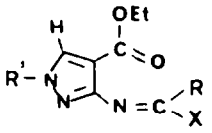


+ $NH_2NH_2.H_2O$ ⟶

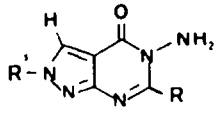


1, 2 15, 16

	R
1, 15	H
2, 16	Me



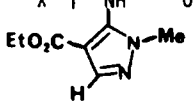
+ $NH_2NH_2.H_2O$ ⟶

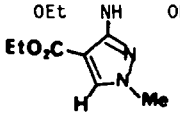


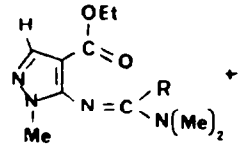
3-12 17-20

	R	R'
17	H	Me
18	Me	Me
19	H	H
20	Me	H

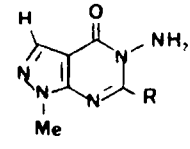
	3	4	5	6	7	8	9	10	11	12
R	H	H	Me	H	H	Me	H	Me	H	Me
R'	Me	Me	Me	H	H	H	Me	Me	H	H
X	NH	OH	OEt	NH	OH	OEt	$N(Me)_2$	$N(Me)_2$	$N(Me)_2$	$N(Me)_2$







+ $NH_2NH_2.H_2O$ ⟶ //

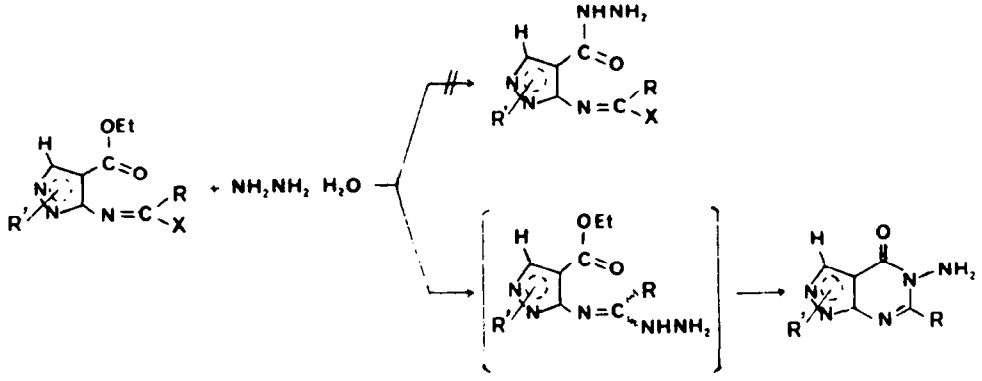


13, 14

	R
13	H
14	Me

Scheme 1

Two different pathways may explain the formation of 15-20 from 1-12 (scheme 2) : in the first step, hydrazine hydrate could attack either the carboethoxy function or the exocyclic N=C double bond. However, the former assumption can reasonably be ruled out as, in boiling methanol (1M ; 2 hours), hydrazine hydrate reacts neither with ethyl aminopyrazole-4-carboxylates, nor with 13 and 14.



Scheme 2

As for the second pathway, it is obvious that hydrazinolysis will be disfavoured by the presence of a strong electron donating group ($N(Me)_2$) on the imino bond[3] especially if this last is conjugated with the carboethoxy function (case of 13 and 14).

The NMR spectra of the 1- and 2-methyl-4,5-dihydropyrazolo [3,4-d] pyrimidin-4-ones exhibit rather different patterns in the region 8-10 ppm (in the case of 15, 17, 19, assignment of the position of H-3 is established by comparison with the spectra of the 6-methyl derivatives). From figure 1, it appears that, in DMSO solution, the tautomeric substance 19 exists as a mixture of the two potential tautomers. In TFA solution, 19 exists as a 2H-derivative and the large downfield shift (ca. 1 ppm) observed for H(6) indicates that protonation occurs on the 6-membered ring[4,5].

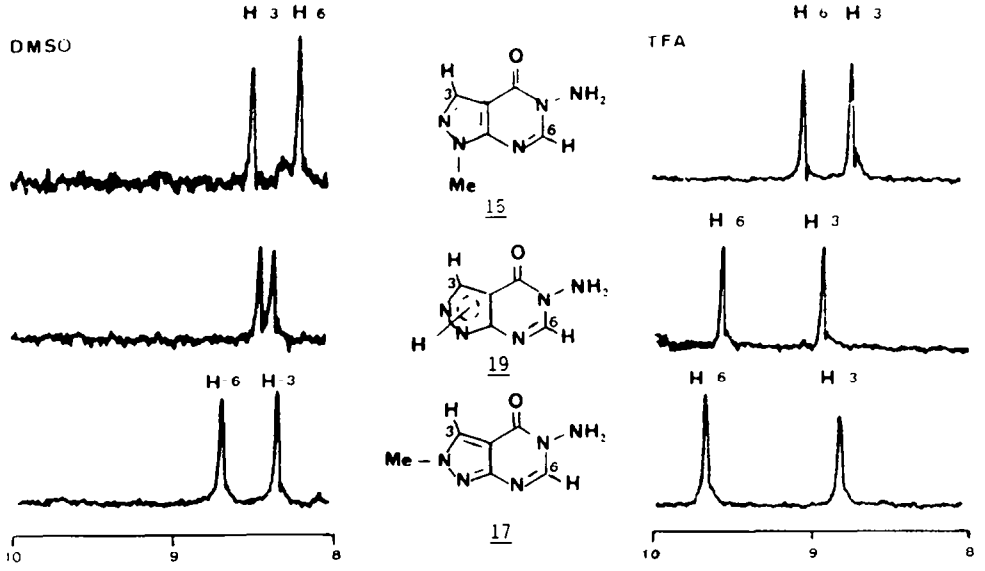
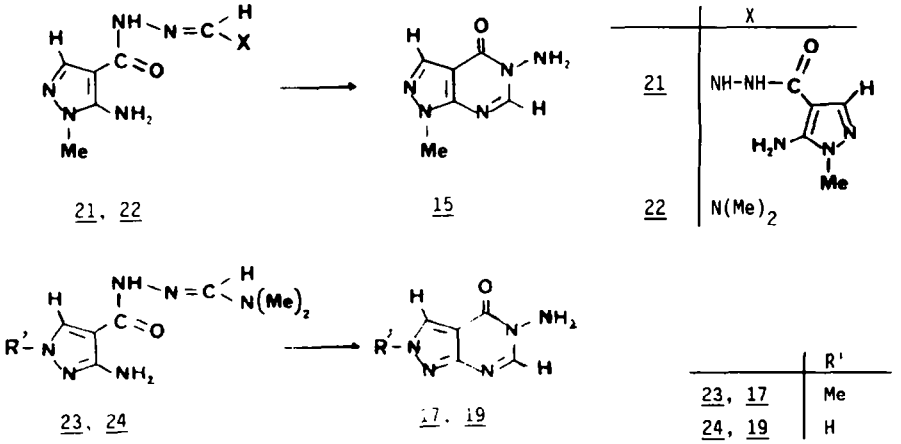


Figure 1 : NMR spectra of compounds 15, 17 and 19 in DMSO (left) and TFA (right).

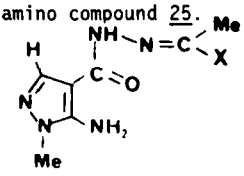
Intramolecular cyclization of β-heteroalkylidene aminopyrazole-4-carboxhydrazides.

All the compounds 21-30 cyclize when heated in a refluxing mixture of methanol-acetic acid (5 %). But it clearly appears that both the nature of the heteroalkylidene substituents and the position of the amino group on the precursors represent driving forces in the cyclization processes. Thus, heteromethylene derivatives (21-24) always cyclize to 5-amino-4,5-dihydropyrazolo [3,4-d] pyrimidin-4-ones (scheme 3).

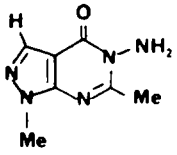


Scheme 3

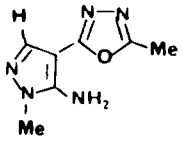
Starting from heteroethylidene derivatives (25 - 30 ; scheme 4), either 5-amino-4,5-dihydro-6-methylpyrazolo [3,4-d] pyrimidin-4-ones or 5-methyl-2-pyrazolyl-1,3,4-oxadiazoles (no carbonyl absorption in the I.R. spectra[2]) may be obtained. Oxadiazole formation is exclusive in the presence of a dimethylamino group on the precursors (26, 29, 30) and is largely favoured in the case of the 5-amino compound 25.



25, 26



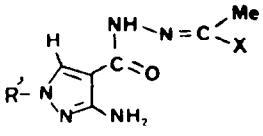
16



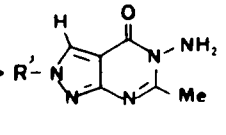
31

	X
25	OEt
26	$N(Me)_2$

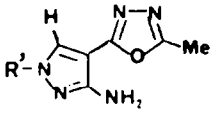
X	Yield
OEt	16 ≈ 10 %
$N(Me)_2$	16 < 5 %



27-30



18, 20



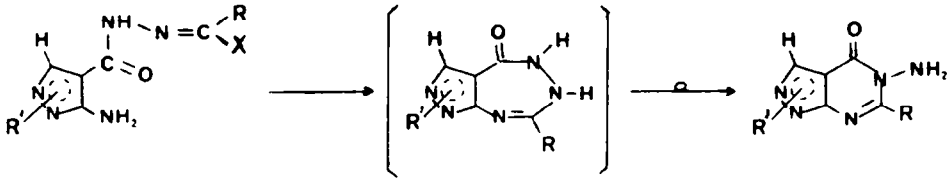
32, 33

	R'	X
27	Me	OEt
28	H	OEt
29	Me	$N(Me)_2$
30	H	$N(Me)_2$
18 , 32	Me	
20 , 33	H	

X	Yield
OEt	18, 20 ≈ 85 %
$N(Me)_2$	18, 20 < 5 %

Scheme 4

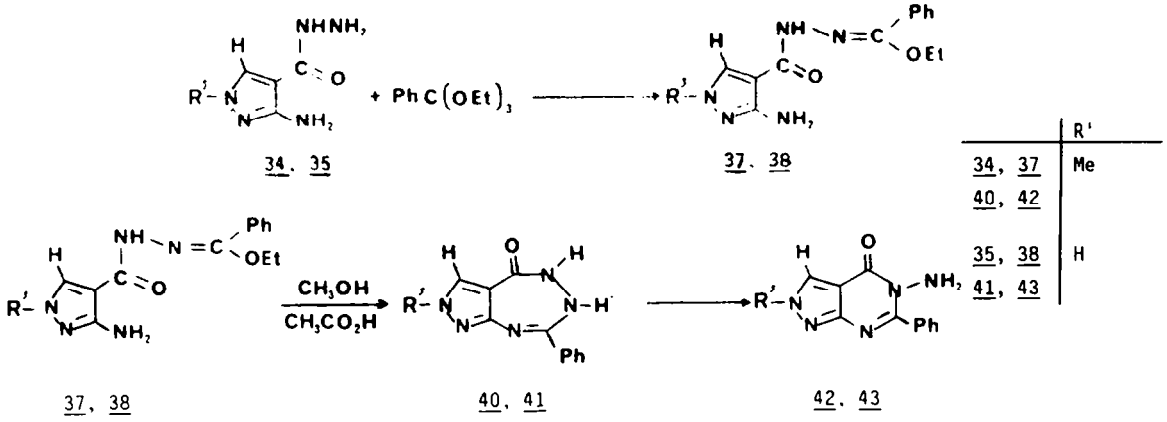
To account for the obtention of dihydropyrazolo [3,4-d] pyrimidin-4-ones 15-20, from 21-30, we propose a mechanism quite similar to the one suggested by Scheiner[2] in a related series : the amino group attacks the carbon atom on the exocyclic N=C double bond to yield dihydropyrazolotriazepinones (scheme 5) which then rearrange into dihydropyrazolopyrimidinones (the isomerization processes are exhaustively described by Scheiner[2]).



Scheme 5

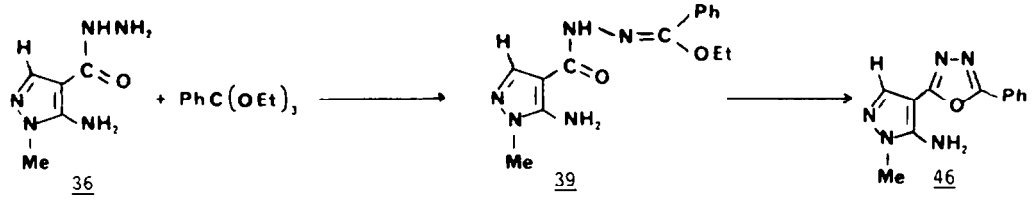
To provide a chemical proof of the proposed mechanism, we prepared derivatives 37-39 (from the hydrazides 34-36 and triethyl orthobenzoate - schemes 6 and 7) and we studied their behaviour in a refluxing mixture of methanol-acetic acid (5 %). So, we observed that 37 and 38 readily cyclize to dihydropyrazolotriazepinones 40 and 41. But, prolonged heating induces conversion to the dihydropyrazolopyrimidinones 42 and 43 (scheme 6). This suggests that cyclizations effectively proceed via transient fused dihydrotriazepinones, yet, the rate of isomerization of the seven-membered ring

governs the possibility to isolate them. This possibility is greatly enhanced by the presence of the bulky[2] and deactivating[6] phenyl group at the 7-position.



Scheme 6

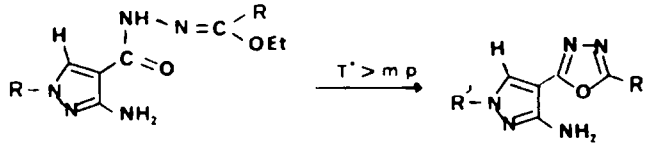
On the other hand, 39 cyclises into pyrazolyloxadiazole 46 (scheme 7). This observation also agrees with the proposed mechanism. Indeed, ring closure into oxadiazole is a competitive reaction and is favoured when the amino group is less nucleophilic (because of conjugation with a carbonyl function : cf. precursors 25, 26 and 39) and/or when the carbon atom of the exocyclic N=C double bond is highly deactivated (because it bears a strong electron donating group[3] : cf. precursors 26, 29 and 30).



Scheme 7

Scheiner[2] also emphasized that, starting from anthranilic hydrazide and orthoesters, use of non-polar solvents favours cyclizations to oxadiazoles (reflecting the less polar nature of such a process), while non-hydroxylic polar solvents minimize the yields of fused dihydropyrimidinones (because isomerization is slowed down).

For our compounds, we observed that 27, 28, 37 and 38 (scheme 8) preferentially cyclize into oxadiazoles (ca. 80 %) when they are heated at temperatures slighty above their melting point. Such experiments may be compared to reactions carried out in a non-polar solvent. However, use of boiling N,N-dimethylformamide to perform cycliszations (but also the one-step reactions of the hydrazides 34-36 with orthoesters) does not alter the nature of the final products, except that dihydropyrazolotriazepinones 40 and 41 isomerize more slowly. Mention should be made that, even in this solvent, it was impossible to isolate the fused dihydrotriazepinones involved in the preparation of the dihydropyrazolopyrimidinones 15-20.



	R'	R
27, 32	Me	Me
28, 33	H	Me
37, 44	Me	Ø
38, 45	H	Ø

27, 28, 37, 38 — 32, 33, 44, 45

Scheme 8

CONCLUSIONS

The four following strategies were proposed to prepare 5-amino-4,5-dihydropyrazolo [3,4-d] pyrimidin-4-ones :

- introduction of a heteroalkylidene moeity on the amino group of aminopyrazole-4-carboxylates by means of i) an orthoester or ii) an amide acetal and subsequent treatment of the so obtained compounds with hydrazine hydrate ;
- reactions between aminopyrazole-4-carboxhydrazides and iii) orthoesters or iv) amide acetals.

The results of our investigations indicate the feasibility and the limitations of these strategies.

Thus, way i is of wide applicability and provides 5-amino-4,5-dihydropyrazolo [3,4-d] pyrimidin-4-ones in good yields. Replacement of the orthoester by the corresponding amide acetal (way ii) is unfavourable only when starting from 1-substituted-5-aminopyrazole-4-carboxylates.

Ways iii and iv are more versatile as they may lead to either 5-amino-4,5-dihydropyrazolo [3,4-d] pyrimidin-4-ones or 2-(aminopyrazolyl)-1,3,4-oxadiazoles. Formation of the former derivatives is always observed with triethyl orthoformate and N,N-dimethylformamide dimethyl acetal ; it is also the favoured process starting from 3-aminopyrazole-4-carboxhydrazides and triethyl orthoacetate or triethyl orthobenzoate. On the other hand, reactions performed with N,N-dimethylacetamide dimethyl acetal or from 5-aminopyrazole-4-carboxhydrazide and triethyl orthoacetate or triethyl orthobenzoate preferentially afford 2-(aminopyrazolyl)-1,3,4-oxadiazoles.

Finally, early work-up procedures allow the isolation of 5,6-dihydro-4H-pyrazolo [3,4-e]-1,2,4-triazepin-4-ones during the reactions between triethyl orthobenzoate and 3-aminopyrazole-4-carboxhydrazides. Such fused derivatives are also supposed to form when starting from other orthoesters, but they could not be trapped.

EXPERIMENTAL

All melting points are uncorrected. The I.R. spectra were recorded on a Perkin-Elmer 577 spectrophotometer, NMR spectra on a Varian EM-360 L spectrometer (TMS as internal reference) and mass spectra on a Varian 311 A spectrometer.

Compound 1[7], 2-6[1], 7[8], 8-10[1], 11[9-11], 12[9,10], 13[1], 14[1], 15[7], 17[1], 19[12], 20[12], 21-30[1], 34[1], 35[13], 36[7], 41[2], 43[12] and 45[12] are described.

Action of hydrazine hydrate on ethyl pyrazole-4-carboxylates derivatives - general procedure.

A solution of 10 mmoles of the ethyl pyrazole-4-carboxylate derivative and 12 mmoles of hydrazine hydrate in 10 ml of methanol was stirred at room temperature[7] for several hours. The precipitate was collected and recrystallized from the appropriate solvent.

- 5-amino-4,5-dihydro-1,6-dimethylpyrazolo [3,4-d] pyrimidin-4-one (16). Yield : 60 % (reaction carried out in refluxing methanol for 1 h) ; m.p. (CH_3OH) : 165-6°C.

  I.R. (KBr) : 3400, 3320, 3210 (N-H), 1710 (C=O) cm^{-1} ; $m^{+\cdot}$ = 179 u.m.a.

  N.M.R. (DMSO d_6-δ) : 8.0 (s, 3-H), 5.5 (br, NH_2), 3.6 (s, N-CH_3), 2.6 (s, CH_3) ppm.

  $C_7H_9N_5O$ (179.2). Calc. C 46.92, H 5.06, N 39.09 ; Found C 47.34, H 5.77, N 39.48.

- 5-amino-4,5-dihydro-2,6-dimethylpyrazolo [3,4-d] pyrimidin-4-one (18). Yield : 60 % from 5 (methanol must be evaporated to isolate 18) ; 80 % from 10 ; m.p. (CH_3OH) : 147-8°C.

  I.R. (KBr) : 3400, 3340, 3200 (N-H), 1700 (C=O) cm^{-1} ; $M^{+\cdot}$ = 179 u.m.a.

N.M.R. (DMSO D_6-δ) : 8.4 (s, 3-H), 5.5 (br, NH_2), 3.6 (s, N-CH_3), 2.5 (s, CH_3) ppm.

$C_7H_9N_5O$ (179.2) Calc. C 46.92, H 5.06, N 39.09 ; Found C 47.44, H 5.58, N 38.85

Intramolecular cyclization of pyrazole-4-carboxhydrazides derivatives - general procedure.

A suspension of 10 mmoles of the pyrazole-4-carboxhydrazide derivative in 10 ml of methanol containing 0.5 ml of acetic acid was refluxed for 1 h. After cooling, the precipitate was collected.

- 2-(5-amino-1-methyl-4-pyrazolyl)-5-methyl-1,3,4-oxadiazole (31). Yield : 90 % from 26 (structure reported by Wamhoff[7] is probably in error) ; m.p. (CH_3OH) : 187-9°C.

  I.R. (KBr) : 3460, 3360 (N-H) cm^{-1} ; $M^{+\cdot}$ = 179 u.m.a.

  N.M.R. (DMSO d_6-δ) : 7.5 (s, 3'-H), 6.1 (br, NH_2), 3.5 (s, N-CH_3), 2.5 (s, CH_3) ppm.

  $C_7H_9N_5O$ (179.2) Calc. C 46.92, H 5.06, N 39.09 ; Found C 46.74, H 5.74, N 39.52.

- 2-(3-amino-1-methyl-4-pyrazolyl)-5-methyl-1,3,4-oxadiazole (32). Yield : 85 % from 29 ; m.p. (CH_3OH) : 166-7°C.

  I.R. (KBr) : 3450, 3300 (N-H) cm^{-1} ; $M^{+\cdot}$ = 179 u.m.a.

  N.M.R. (DMSO d_6-δ) : 8.0 (s, 5'-H), 5.3 (br, NH_2), 3.6 (s, N-CH_3), 2,5 (s, CH_3) ppm.

  $C_7H_9N_5O$ (179.2) Calc. C 46.92, H 5.06, N 39.09 ; Found C 47.78, H 5.32, N 39.61.

- 2-[3(5)amino-4-pyrazolyl]-5-methyl-1,3,4-oxadiazole (33). Yield : 85 % from 30 ; m.p. (CH_3OH) : 228-9°C.

  I.R. (KBr) : 3400, 3300, 3180 (N-H) cm^{-1} ; $M^{+\cdot}$ = 165 u.m.a.

  N.M.R. (DMSO d_6-δ) : 12.2 (br, NH), 7.6 (s, 3'(5')-H), 5.6 (br, NH_2), 2.5 (s, CH_3) ppm.

  $C_6H_7N_5O$ (165.2) Calc. 43.64, H 4.27, N 42.41 ; Found C 44.36, H 4.65, N 42.41.

- β-(ethoxybenzylidene) 3-amino-1-methylpyrazole-4-carboxhydrazide (37). A suspension of 34 (10 mmoles) and triethyl orthobenzoate (12 mmoles) in 10 ml of acetonitrile was refluxed for 6 h.The solvent was evaporated under reduced pressure. Yield : 80 % ; m.p. ($CH_3CO_2C_2H_5$) : 160-2°C.

  I.R. (KBr) : 3420, 3280, 3160 (N-H), 1620 (C=O) cm^{-1} ; $M^{+\cdot}$ = 287 u.m.a.

  N.M.R. (DMSO d_6-δ) : 8.3 (s, 5-H), 7.8-7.4 (m, Ar), 5.5 (br, NH_2), 4.1. (q, CH_2, J = 7 Hz), 3.7 (s, N-CH_3), 1.2 (t, CH_3) ppm.

  This product was used without further purification.

- β-(ethoxybenzylidene) 3(5)-aminopyrazole-4-carboxhydrazide (38). Prepared from 35 as described for 37. Yield : 60 % ; m.p. (petroleum ether ; 40-60°C) : 105-6°C.

  I.R. (KBr) : 3420 , 3300, 3200 (N-H), 1620 (C=O) cm^{-1} ; $M^{+\cdot}$ = 273 u.m.a.

  N.M.R. (DMSO d_6-δ) : 12.5 (br, N-H), 9.8 (br, N-H), 8.2 (s, 5(3)-H), 7.8-7.3 (m, Ar), 6.0 (br, NH_2), 4.0 (q, CH_2, J = 7 Hz), 1.2 (t, CH_3) ppm.

  This product was used without further purification.

- β-(ethoxybenzylidene) 5-amino-1-methylpyrazole-4-carboxhydrazide (39). Prepared from 36 as described for 37. Yield : 85 % ; m.p. ($CH_3CO_2C_2H_5$) : 132-4°C.

  I.R. (KBr) : 3400, 3280 (N-H) cm^{-1} ; $M^{+\cdot}$ = 287 u.m.a.

  N.M.R. (DMSO d_6-δ) : 10.8 (br, NH), 8.0 (s, 3-H), 7.8-7.2 (m, Ar), 6.4 (br, NH_2), 4.1 (q, CH_2, J = 7 Hz), 3.6 (s, N-CH_3), 1.2 (t, CH_3) ppm.

  This product was used without further purification.

- 5,6-dihydro-2-methyl-7-phenyl-4H-pyrazolo [3,4-e]-1,2,4-triazepin-4-one (40). One-step synthesis: a suspension of 34 (10 mmoles) and triethyl orthobenzoate (12 mmoles) in 10 ml of methanol containing 0.5 ml of acetic acid was refluxed[2] for 3h. After cooling, the precipitate was collected. Yield : 70 % ; m.p. (CH_3OH) : 235-6°C.

  I.R. (KBr) : 3220 (N-H), 1660 (C=O) cm^{-1} ; $M^{+\cdot}$ = 241 u.m.a.

  N.M.R. (DMSO d_6-δ) : 9.4 (br, N-H), 9.3 (br, N-H), 8.0 (s, 3-H), 7.7-7.3 (m, Ar), 3.6 (s, N-CH_3) ppm.

  $C_{12}H_{11}N_5O$ (241.3) Calc. C 59.74, H 4.60, N 29.03 ; Found C 60.09, H 5.28, N 29.18.

- 5-amino-4,5-dihydro-2-methyl-6-phenylpyrazolo [3,4-d] pyrimidin-4-one (42). One-step synthesis : prepared as described for 40. Reaction time : 10 h. Yield : 80 % ; m.p. (CH_3OH) : 172-3°C.

  I.R. (KBr) : 3400, 3300 (N-H), 1680 (C=O) cm^{-1} ; $M^{+\cdot}$ = 241 u.m.a.

  N.M.R. (DMSO d_6-δ) : 8.7 (s, 3-H), 7.9-7.2 (m, Ar), 5.5 (br, NH_2), 4.1 (s, N-CH_3).

  $C_{12}H_{11}N_5O$ (241.3) Calc. C 59.74, H 4.60, N 29.03 ; Found C 59.33, H 5.08, N 29.62.

- 2-(3-amino-1-methyl-4-pyrazolyl)-5-phenyl-1,3,4-oxadiazole (44). Prepared by short heating of 37 at a temperature slighty above its melting point. Yield : 80 % ; m.p. (CH_3OH) : 184-5°C.

  I.R. (KBr) : 3420, 3300 (N-H) cm^{-1} ; $M^{+\cdot}$ = 241 u.m.a.

  N.M.R. (DMSO d_6-δ) : 8.3 (s, 5'-H), 8.2-7.2 (m, Ar), 5.5 (br, NH_2), 3.8 (s, N-CH_3).

  $C_{12}H_{11}N_5O$ (241.3) Calc. C 59.74, H 4.60, N 29.03 ; Found C 60.43, H 4.85, N 29.12.

- 2-(5-amino-1-methyl-4-pyrazolyl)-5-phenyl-1,3,4-oxadiazole (46). One-step synthesis : prepared from 36 as described for 40. Reaction time : 5 h ; the solvent was evaporated under reduced pressure. Yield : 85 % ; m.p. (CH_3OH) : 195-6°C.

  I.R. (KBr) : 3400, 3280 (N-H) cm^{-1} ; $M^{+\cdot}$ = 241 u.m.a.

  N.M.R. (DMSO d_6-δ) : 8.2-7.3 (m, Ar and 3'-H), 5.6 (br, NH_2), 3.8 (s, N-CH_3).

  $C_{12}H_{11}N_5O$ (241.3) Calc. C 59.74, H 4.60, N 29.03 ; Found C 60.09, H 4.90, N 29.63.

REFERENCES

1. A. MAQUESTIAU and J.-J. VANDEN EYNDE, this journal, preceding paper.
2. P. SCHEINER, L. FRANK, I. GUISTI, S. ARWIN, S. PEARSON, F. EXCELLENT and A. HARPER, J. Heterocycl. Chem., 21, 1817 (1984).
3. F. THERON, Bull. Soc. Chim. Fr., 278 (1969).
4. Y. INOUE, N. FURUTACHI and K. NAKANISHI, J. Org. Chem., 31, 175 (1966).
5. R. WAGNER and W. von PHILIPSBORN, Helv. Chim. Acta, 53, 299 (1970).
6. R. LAYER, Chem. Rev., 63, 489 (1963).
7. H. WAMHOFF, M. ERTAS and S. ATTA, Justus Liebigs Ann. Chem., 1910 (1985).
8. P. FINDLANDER and E. PEDERSEN, Arch. Pharm., 318, 452 (1985).
9. V. GRANIK, E. SOCHNEVA and I. PERSIANOVA, Khim. Geterotsikl. Soedin., 379 (1978) ; C.A., 89, 43228 k (1978).
10. V. GRANIK, E. SOCHNEVA, N. SOLOV'EVA, G. SHVARTS, R. SYUBAEV and M. MASHKOVSKII, Khim.-Farm. Zh., 14, 36 (1980) ; C.A., 93, 220653 a (1980).
11. M. TISLER, B. STANOVNIK and Z. ZRIMSEK, Heterocycles, 17, 405 (1982).
12. P. SCHEINER, S. ARWIN, M. ELICIAN and J. TU, J. Heterocycl. Chem., 22, 1435 (1985).
13. Brevet, C.A., 54, 16467 c (1960).