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Ring-Opening Reactions of Triazolo- and Tetrazolo-Pyridopyrimidines or Quinazolines with some Carbon Nucleophiles

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Syntheses of some new pyridotriazolo- and pyridotetrazolopyrimidines are described. These tricyclic systems and tetrazoloquinazoline react with some carbon nucleophiles, generated from compounds with reactive methylene groups, exclusively at position 2 of the fused pyrimidine ring to give the corresponding open-chain enamines.

(Keywords: Cyclization with C—N *or* N—N *bond formation; Tricyclic azaheterocyclic compounds; Substituted pyridines)*

Ringöffnungsreaktionen von Triazolo- und Tetrazolo-Pyridopyrimidinen oder Chinazolinen unter dem Einfluß einiger Carbanionen als Nucleophile

Die Synthesen von einigen neuen Pyridotriazolo- und Pyridotetrazolopyrimidine werden beschrieben. Diese tricyclischen Verbindungen sowie Tetrazolochinazolin reagieren mit einigen Carbanionen, die aus Verbindungen mit reaktiven Methylengruppen entstehen, ausschließlich in Stellung 2 des kondensierten Pyrimidinringes, wobei die entsprechenden offenkettige Enamine entstehen.

Introduction

We have recently described the preparation of some azolopyridopyrimidines[1,2]. It was of interest to examine these systems as model pyrimidines with blocked positions 4, 5, 6 (and 3) in order to determine the succeptibility of position 2 for attack of nucleophiles and eventual ring opening involving the N1—C2 bond.

Results and Discussion

Previously we have described the syntheses of three isomeric pyridopyrimidines and we are now describing the synthesis of derivatives of the fourth isomeric system, pyrido[4,3—*d*]pyrimidine. 3-Methyl-4-nitropyridine 1-oxide (**1**) was reduced with hydrogen in the presence of palladized carbon to give, after acetylation, 4-acetylamino-3-methylpyridine (**2**) in yield over 80%. This approach represents a better method than the previously described reduction with iron and acetic acid where the same compound could be obtained in 47% yield[3]. Upon oxidation of the methyl group and esterification of the corresponding nicotinic acid, the hydrazide **3** was obtained in the usual manner[3]. The latter was converted into the corresponding acylazide **4** in the usual manner, and reduction with hydrogen sulfide afforded 4-aminonicotinamide (**5**) in almost quantitative yield. Although the synthesis of this amide has been described from ethyl 4-aminonicotinate and liquid ammonia[3], we were unable to repeat this synthesis with a satisfactory result. Treatment of the amide **5** with N,N-dimethylformamide and $POCl_3$ afforded the nitrile with simultaneous conversion of the amino into the amidine function (**6**). The latter compound could be transformed with hydroxylamine hydrochloride at room temperature in excellent yield into 4-aminopyrido[4,3—*d*]pyrimidine 3-oxide (**7**). The attempted crystallization of the crude separated product from N,N-dimethylformamide afforded another compound with the same elemental analysis and molecular weight. By NMR spectra correlation it could be established that compound **7** was transformed into compound **8** in a *Dimroth* type rearrangement. If, however, the crude bicyclic N-oxide **7** was first suspended in water and thereafter crystallized from N,N-dimethylformamide, the pure compound **7** could be obtained. By this procedure the by-products which cause rearrangement (hydroxylamine hydrochloride, dimethylamine hydrochloride) were eliminated. That the rearrangement is catalyzed by these by-products and not by N,N-dimethylformamide could be demonstrated by heating the pure compound **7** in *DMF*: after 30 minutes no rearranged product could be detected in the reaction mixture. After addition of catalytic amounts of hydroxylamine hydrochloride rearrangement of compound **7** into **8** is completed within a few minutes.

For the synthesis of the isomeric pyrido-s-triazolopyrimidines **14** and **15** 4-hydrazinopyrido[3,2—*d*]pyrimidine (**12**) was prepared from the corresponding 4-chloro compound **11**, which was obtained by a new procedure from pyrido[3,2—*d*]pyrimidin-4-(3*H*)one (**10**). The hydrazino compound, when treated at room temperature with diethoxymethyl acetate afforded the tricyclic system **14**, whereas in boiling triethyl orthoformate and glacial acetic acid the isomeric tricyclic system **15** could

Me
NO2
1
Me
NHCOMe
2
CONHNH2
NH2
3
CON3
NH2
4
CONH2
NH2
5
CN
N=CHNMe2
6
NRR1
7 : RR1 = H, H
9 : RR1 = =CHNMe2
NHOH
8

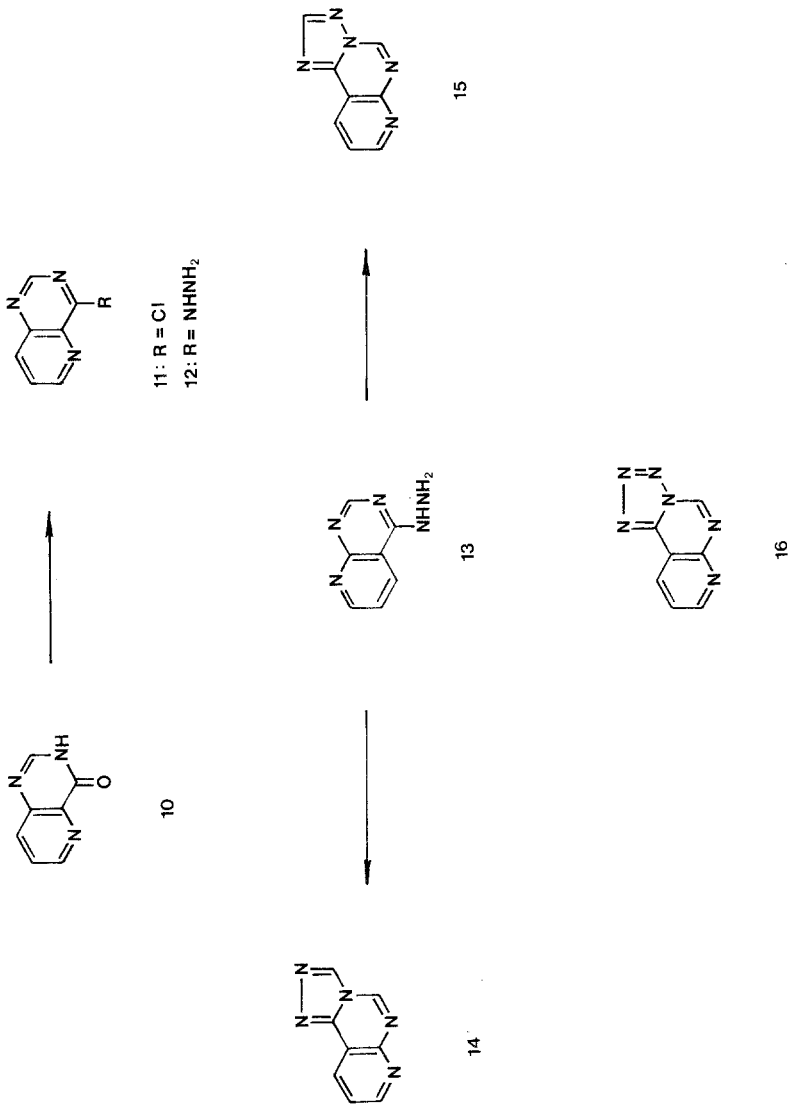
Table 1. *Products from ring-opening reactions of triazolo- or tetrazolopyridopyrimidines or quinazolines and reactive methylene compounds*

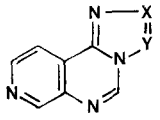
No.	Reaction time (room temp.)	Yield %	Solvent for crystallization	M.p. °C
25	1 h	60	ethanol	175–178[a]
26	15 min	30	ethanol	193–197 (dec.)
27	1 h	45[b]	$CHCl_3$/*n*-hexane	115–121[c]
28	1.5 h	54	ethanol	194 (dec.)
29	1.25 h	88	ethanol	150–152
30	40 min	80[b]	*n*-propanol	159–176 (dec.)
31	1.5 h	78[d]	ethanol/*DMF*	> 260
32	1 h	72	ethanol/*DMF*	222–224 (dec.)
33	1.25 h	71[b,d]	ethanol	198–201
34	1.5 h	78[d]	ethanol/*DMF*	221–223 (dec.)
35	2.5 h	94[d]	ethanol	166–168
36	1.5 h	95[d]	ethanol	183–210 (dec.)
37	1 h	52	ethanol/*DMF*	249–250
38	1 h	77	ethanol/*DMF*	238
39	2 h	77	ethanol/*DMF*	188–192
40	1.5 h	87	ethanol/*DMF*	> 250 (dec.)
41	1 h	53	ethanol/*DMF*	> 265
42	30 min	89	ethanol	206–208[e]
43	3.5 h[f]	50	ethanol	238–240
44	12 h	62	ethanol/*DMF*	245–255 (dec.)
45	2 h[f]	56[b]	ethanol	199–203 (dec.)
46	5 h	69	ethanol/*DMF*	269–271 (dec.)
47	1.5 h	86	ethanol/*DMF*	295 (dec.)
48	2.5 h	35	*DMF*	249–255
49	2.75 h	62	ethanol/*DMF*	> 235 (dec.)
50	4 h	68	ethanol	218–221

[a] At m.p. new crystals with m.p. 195–210 °C are formed.
[b] Isolated after extraction with $CHCl_3$.
[c] At m.p. new crystals with m.p. 140 °C are formed.
[d] Mixture of *Z* and *E* isomers.
[e] At m.p. new crystals were formed and decomposed at 245 °C.
[f] Under reflux.

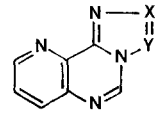
be obtained. The easy isomerization of **14** into **15** could be achieved thermaly upon sublimation *in vacuo*. Both systems are easily differentiated by their NMR spectra, i.e. the signal for H-3 in **14** appears at δ 9.39 whereas that for H-2 of compound **15** at 8.69 ppm.

Ring opening of the tricyclic pyridotriazolopyrimidines under the influence of carbon nucleophiles occurs very easily (usually at room temperature, see Tab. 1), to give the unsaturated azolosubstituted pyridines or benzenes. For example, both isomeric pyrido-s-

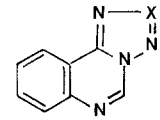

11: R = Cl
12: R = NHNH2
10
13
14
15
16



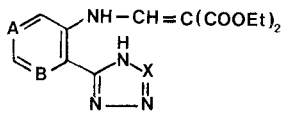
	X	Y
17:	N	CH
18:	CH	N
19:	N	N



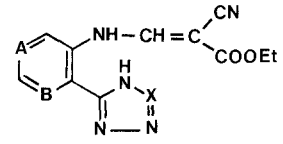
	X	Y
20:	N	CH
21:	CH	N
22:	N	N



	X
23:	CH
24:	N

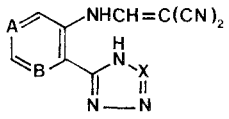


	A	B	X
25:	N	CH	CH
26:	N	CH	N
27:	CH	N	CH
28:	CH	N	N
29:	CH	CH	CH
30:	CH	CH	N

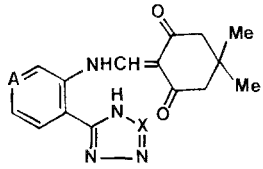


	A	B	X
31:	N	CH	CH
32:	N	CH	N
33:	CH	N	CH
34:	CH	N	N
35:	CH	CH	CH
36:	CH	CH	N

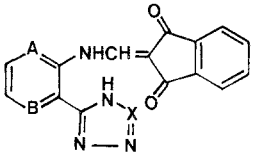
triazolopyrimidines, **17** and **18**, afforded the same products when treated either with diethyl malonate (**25**), ethyl cyanoacetate (**31**, as a mixture of *E* and *Z* isomers as evidenced from NMR), malonodinitrile (**37**) or 5,5-dimethylcyclohexane-1,3-dione (**43**). When we compare the reactivity of these isomeric triazolo systems with the corresponding tetrazolo analogue **19**, it follows that **26** was formed at a higher rate, compounds **32** and **38** with a comparable rate, whereas reaction with 5,5-dimethylcyclohexane-1,3-dione afforded compound **44** at a much lower rate. It should be mentioned that in another isomeric system, e.g. **14** vs. **16** the tetrazolo



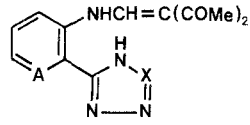
	A	B	X
37:	N	CH	CH
38:	N	CH	N
39:	CH	N	CH
40:	CH	N	N
41:	CH	CH	CH
42:	CH	CH	N



	A	X
43:	N	CH
44:	N	N
45:	CH	N



	A	B	X
46:	CH	N	CH
47:	CH	N	N
48:	N	CH	N



	A	X
49:	N	N
50:	CH	N

isomer reacted more readily than the triazolo system[1] and similar evidence came also from the experiment with 1,3-indanedione to give compound **48**.

Comparable results were observed with either the isomeric triazolo systems **20** or **21** which gave the same products after ring opening (**27**, **33**, **39** or **46**) or with the tetrazolo isomer **22** which gave compounds **28** and **34**.

That the pyridine ring nitrogen does not exert any significant influence upon the reactivity of the pyridine ring for ring opening could be demonstrated in the case of quinazoline analogs **23** and **24** which were treated in the same manner. It should be mentioned that **30** could be also prepared from 5-(2′-aminophenyl)tetrazole and diethyl ethoxymethylenemalonate.

Acknowledgement

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Experimental

Melting points were determined on a *Kofler* hot plate m.p. apparatus. ^{1}H-NMR spectra were recorded on a JEOL JNM C-60 HL spectrometer (*TMS* as internal standard, δ values in ppm) and mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6 L spectrometer. Elemental analyses (C, H, N) are in agreement with the formulas for all described compounds.

4-Acetylamino-3-methylpyridine (**2**)

A mixture of 50 g 4-nitro-3-methylpyridine 1-oxide[3] (**1**), 150 ml of ethanol and 4 g of 10% palladium on charcoal was hydrogenated at a pressure of 300 kPa until the consumption of hydrogen ceased (about 3 h). The solvent was evaporated and the residue suspended in 150 ml of glacial acetic acid. After addition of 1 g of palladized charcoal (5%) the mixture was kept in an atmosphere of hydrogen at 300 kPa for 72 h. The catalyst was filtered and the solution evaporated. The oily residue was treated with 175 ml of acetic anhydride and the mixture was heated under reflux for 0.5 h. The reaction mixture was evaporated and the oily residue was distilled *in vacuo* at 150–200 °C/120 Pa to give 40–43 g (82–88%) of the product (**2**), identical in all respects with an authentic specimen.

4-Aminonicotinoyl azide (**4**)

A solution of 1.53 g 4-aminonicotinoyl hydrazide[3] (**3**) in 15 ml of 2*N* hydrochloric acid was cooled to 0 °C and under stirring a solution of 0.74 g $NaNO_2$ in 10 ml water was added. After stirring for 10 min the reaction mixture was neutralized with solid $NaHCO_3$ and extracted with $CHCl_3$ to give upon evaporation of the solvent 1.49 g (91%) of the crude azide, m. p. 100–130 °C, with formation of new crystals with m.p. 305–312 °C. $C_6H_5N_5O$. MS (*m/e*): 163 (M^+). NMR (*DMSO-d*$_6$): 6.66 (d, H5), 7.54 (broad s, NH_2), 8.06 (d, H6), 8.57 (s, H2), $J_{5,6} = 6.2$ Hz.

4-Aminonicotinamide (**5**)

In a suspension of 8.9 g 4-aminonicotinoyl azide (**4**) in 500 ml of ethanol hydrogen sulfide was introduced for 1 h at room temperature. Upon addition of charcoal and filtration, the filtrate was evaporated to give 7.4 g (99%) of crude amide which can be used straightforward for further transformations. M.p. 225–230 °C, identical with an authentic specimen (Lit.[3] 228–230 °C).

4-(N,N-Dimethylaminomethyleneamino)nicotinonitrile (**6**)

To a stirred suspension of 3 g 4-aminonicotinamide (**5**) in 45 ml anhydrous N,N-dimethylformamide 4.5 ml of $POCl_3$ were added. The reaction mixture was stirred at 60–70 °C for 3 h and left overnight at room temperature. Upon evaporation to a pasty residue 100 g of ice were added and neutralized with solid $NaHCO_3$. After 150 ml water was added the mixture was extracted five times with 60 ml $CHCl_3$. Upon evaporation of the solvent, the oily residue was treated with diethyl ether and upon standing on ice the product crystallized (2.57 g, 67%), m.p. 98–106 °C (from $CHCl_3$ and *n*-hexane). $C_9H_{10}N_4$. MS (*m/e*): 174 (M^+). NMR ($CDCl_3$): 3.09 (s, *Me*), 6.74 (d, H5), 6.65 (broad s, N=CH—), 8.32 (d, H6), 8.52 (s, H2), $J_{5,6} = 6.0$ Hz.

4-Aminopyrido[4,3—d]pyrimidine 3-Oxide (**7**)

1 g of the above compound (**6**), 0.439 g hydroxylamine hydrochloride, and 18 ml *Me*OH were stirred at room temperature for 24 h. The separated product was suspended in 10 ml water and filtered after 10 min. The bicyclic product (**7**) (0.84 g, 90%) was crystallized from N,N-dimethylformamide, 240–260 °C with sublimation and thereafter m.p. 271–273 °C. $C_7H_6N_4O$. MS (*m/e*): 162 (M^+). NMR (*DMSO-d*$_6$, 145 °C): 7.46 (dd, H8), 8.53 (d, H7), 8.74 (s, H2), 9.45 (d, H5), $J_{7,8} = 5.85$, $J_{5,8} = 0.75$ Hz.

4-Hydroxyaminopyrido[4,3—d]pyrimidine (**8**)

A mixture of 1.74 g of the amidine (**6**), 0.695 g hydroxylamine hydrochloride and 30 ml *Me*OH was stirred at room temperature for 24 h. The product was filtered and crystallized from N,N-dimethylformamide (0.9 g, 55%), m.p. 274–277 °C. $C_7H_6N_4O$. MS (*m/e*): 162 (M^+). NMR (*DMSO-d*$_6$, 145 °C): 6.99 (d, H8), 7.51 (s, H2), 8.34 (d, H7), 8.80 (s, H5), $J_{7,8} = 5.55$ Hz.

4-(N,N-Dimethylaminomethyleneamino)pyrido[4,3—d]pyrimidine 3-Oxide (**9**)

A mixture of 0.49 g 4-aminopyrido[4,3—*d*]pyrimidine 3-oxide (**7**) and 3 ml N,N-dimethylformamide dimethyl acetal was stirred at room temperature for 18 h. The separated product (0.596 g, 91%) was crystallized from 1,2-dimethoxyethane, m.p. 171–176 °C with formation of new crystals with m.p. 182 °C. $C_{10}H_{11}N_5O$. MS (*m/e*): 217 (M^+). NMR ($CDCl_3$): 3.24 (s, *Me*), 7.51 (dd, H8), 8.61 (d, H7), 8.77 (s, H2), 9.63 (d, H5), 10.53 (broad s, CH), $J_{7,8} = 5.85$, $J_{5,8} = 0.81$ Hz.

4-Chloropyrido[3,2—d]pyrimidine (**11**)

1 g of powdered pyrido[3,2—*d*]pyrimidin-4(3*H*)one[4] (**10**) was suspended in 25 ml $CHCl_3$ and treated with 2 drops of N,N-dimethylformamide and 2 ml of oxalyl chloride. The reaction mixture was heated under reflux for 5 h, evaporated and the residue dissolved in 80 ml $CHCl_3$ and shaken with a saturated aqueous Na_2CO_3 solution. The $CHCl_3$ layer was dried and evaporated to give the chloro derivative (**11**) (1.1 g, 98%), m.p. 136–139 °C (dec.) (Lit.[3] 148–150 °C, dec.).

4-Hydrazinopyrido[3,2—d]pyrimidine (**12**)

A solution of 8.6 g of the chloro compound **11** in 50 ml ethanol was treated with 15 ml of 80% hydrazine hydrate and the mixture was heated under reflux for

30 min. Upon cooling the hydrazino compound separated and was crystallized from ethanol (1.2 g, 14%), m.p. 194–197 °C (Lit.[5] 206 °C).

Pyrido[2,3—d]-s-triazolo[3,4—f]pyrimidine (**14**)

A mixture of 0.2 g 4-hydrazinopyrido[2,3—*d*]pyrimidine[6] (**13**) and 2 ml of diethoxymethyl acetate was stirred at room temperature for 2 days. The separated product was crystallized from a mixture of $CHCl_3$ and *n*-hexane (0.195 g, 91%), m.p. 170–200 °C with formation of new crystals and m.p. 239–248 °C (Lit.[5], 140 °C). $C_8H_5N_5$. MS (*m/e*): 171 (M^+). NMR (*DMSO-d*$_6$): 7.72 (dd, H9), 8.86 (dd, H10), 8.99 (dd, H8), 9.39 (s, H3), 9.42 (s, H5), $J_{8,9} = 4.6$, $J_{9,10} = 8.2$, $J_{8,10} = 2.1$ Hz.

Pyrido[2,3—d]-s-triazolo[5,1—f]pyrimidine (**15**)

A mixture of 0.8 g 4-hydrazinopyrido[2,3—*d*]pyrimidine[6] (**13**), 10 ml of triethyl orthoformate and 2 ml of glacial acetic acid was heated under reflux for 6.5 h. Upon cooling the product was separated (0.47 g, 55%) and for analysis sublimed, m.p. 249–251 °C. The same compound is also obtained after sublimation of the isomeric **14** at 180 °C/40 Pa. $C_8H_5N_5$. MS (*m/e*): 171 (M^+). NMR (*DMSO-d*$_6$): 7.77 (dd, H9), 8.69 (s, H2), 8.84 (dd, H10), 9.08 (dd, H8), 9.78 (s, H5), $J_{8,9} = 4.6$, $J_{9,10} = 8.2$, $J_{8,10} = 2.0$ Hz.

Reaction between Pyrido[3,4—d]-s-triazolo[3,4—f]pyrimidine (**17**) *or Pyrido[3,4—d]-s-triazolo[5,1—f]pyrimidine* (**18**) *and Reactive Methylene Compounds. General Procedure*

0.5 mmol of the corresponding reactive methylene compound was dissolved in a solution of sodium ethoxide in ethanol, prepared from 0.5 mmol of sodium and 5 ml of absolute ethanol. Thereafter the corresponding heterocyclic compound (0.5 mmol) was added and after standing at room temperature the solvent was evaporated, 10 ml water were added, the mixture was acidified with hydrochloric acid 1:1 and the separated product filtered. The following compounds were prepared in this manner: **25** ($C_{15}H_{17}N_5O_4$), **31** ($C_{13}H_{12}N_6O_2$), **37** ($C_{11}H_7N_7$), and **43** ($C_{16}H_{17}N_5O_2$) (see Table 1).

Reaction between Pyrido[3,4—d]tetrazolo[5,1—f]pyrimidine (**19**)

and carbon nucleophiles was performed in a similar manner and afforded the following products: compound **26** ($C_{14}H_{16}N_6O_4$), **32** ($C_{12}H_{11}N_7O_2$), **38** ($C_{10}H_6N_8$), and **44** ($C_{15}H_{16}N_6O_2$). By ring opening reactions of either pyrido[3,2—*d*]-s-triazolo[3,4—*f*]pyrimidine (**20**) or pyrido[3,2—*d*]-s-triazolo[5,1—*f*]pyrimidine (**21**) the following compounds were obtained: **27** ($C_{15}H_{17}N_5O_4$), **33** ($C_{13}H_{12}N_6O_2$), **39** ($C_{11}H_7N_7$), and **46** ($C_{17}H_{11}N_5O_2$). From pyrido[3,2—*d*]tetrazolo[5,1—*f*]pyrimidine (**22**) compounds **28** ($C_{14}H_{16}N_6O_4$) and **34** ($C_{12}H_{11}N_7O_2$) were obtained and from s-triazolo[2,3—*c*]quinazoline (**23**) or tetrazolo[1,5—*c*]quinazoline (**24**) compounds **29** ($C_{16}H_{18}N_4O_4$), **35** ($C_{14}H_{13}N_5O_2$), **41** ($C_{12}H_8N_6$), **30** ($C_{15}H_{17}N_6O_4$), and **36** ($C_{13}H_{12}N_6O_2$) were prepared (see Table 1).

Compound **30** could be prepared also in the following manner: A mixture of 0.161 g of 5-(2′-aminophenyl)tetrazole and 0.216 g of diethyl ethoxymethylenemalonate in 3 ml toluene was heated under reflux for 2 h and upon cooling the separated product was filtered. Yield 0.15 g (45%). The compound was identical in all respects with the product obtained by ring opening reaction of **24** with diethyl malonate.

2-[(1,3-Dioxoindanylidene-2)methylamino]-3-(tetrazolyl-5')pyridine (**48**)

This compound was prepared in a similar manner from the tricycle **16** and 1,3-indanedione in 52% yield, m.p. 270° (dec.) (from N,N-dimethylformamide). $C_{16}H_{10}N_6O_2$. MS (*m/e*): 318 (M^+). NMR (*DMSO-d_6*, 150 °C): 8.37 (dd, H4), 7.29 (dd, H5), 8.46 (dd, H6), 7.68 (s, H4, H5, H6, H7), 8.86 (s, NHC**H**), $J_{4,5} = 7.8$, $J_{5,6} = 4.5$, $J_{4,6} = 1.8$ Hz.

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