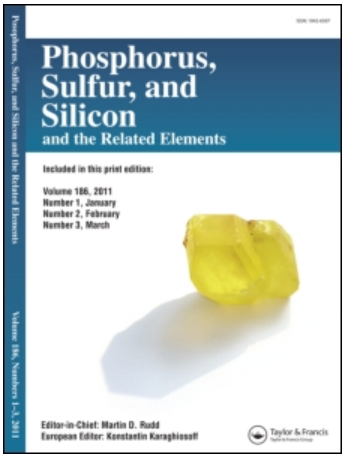


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF TRICYCLIC COMPOUNDS WITH THIOPYRIDONE RINGS

Kh. M. Hassan[a]; G. M. El-Naggar[a]; A. M. El-Khawaga[a]; A. M. Kamal El-Dean[a]
[a] Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

To cite this Article Hassan, Kh. M. , El-Naggar, G. M. , El-Khawaga, A. M. and El-Dean, A. M. Kamal(1989) 'SYNTHESIS OF TRICYCLIC COMPOUNDS WITH THIOPYRIDONE RINGS', Phosphorus, Sulfur, and Silicon and the Related Elements, 45: 3, 261 — 267
To link to this Article: DOI: 10.1080/10426508908045027
URL: http://dx.doi.org/10.1080/10426508908045027

Phosphorus, Sulfur, and Silicon, 1989, Vol. 44, pp. 261–267
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHESIS OF TRICYCLIC COMPOUNDS WITH THIOPYRIDONE RINGS

Kh. M. HASSAN, G. M. EL-NAGGAR, A. M. EL-KHAWAGA and A. M. KAMAL EL-DEAN*

Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt.

(Received December 6, 1988; in final form February 7, 1989)

Reaction of 3,4-trimethylene-6-amino-5-ethoxycarbonylthiopyrane-2-thione (**1**) with hydrazine hydrate gave the corresponding o-diaminocyclopentapyridine-2-thione (**2**). Ring closure of **2** with some reagents, namely, formic acid, aromatic aldehydes, carbon disulphide, phenacyl bromide, ethyl chloroformate, ethyl chloroacetate, nitrosylsulfuric acid, and pyruvic acid gave tricyclic compounds (2–14) by direct or indirect pathways, respectively.

Key words: Cyclopentapyridonecarboxylates; 1,2-diamino thio-pyridone carboxylates; triazolo thiopyridone; triazinothiopyridone.

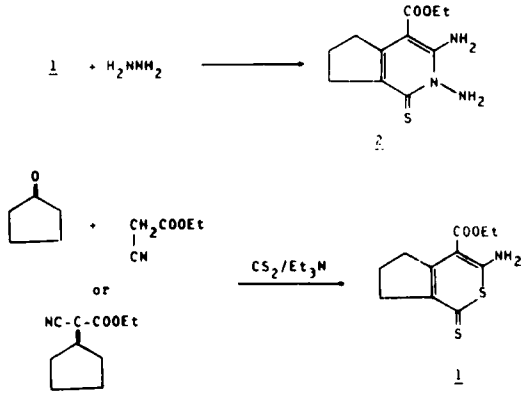
Several annelated pyridines isolated from natural sources have found broad spectrum of clinical applications. Members of this class were found to be active in protection against gasteric erosions,[1] and useful as a coronary vasodilator and blood pressure heightening agents.[2] Also, they have proved useful as antituberculostatic, antiviral, fungicidal, insecticidal and pesticidal agents.[3,4] Moreover, they were used for inhibition of aldose reductase activity and cataract formation in diabetes.[5]

The above findings promoted our interest to survey the chemistry of the o-diamino compound **2** and its uses as raw starting material for synthesis of tricyclic compounds, namely, triazino, triazolo and tetrazolo cyclopentapyridine derivatives.

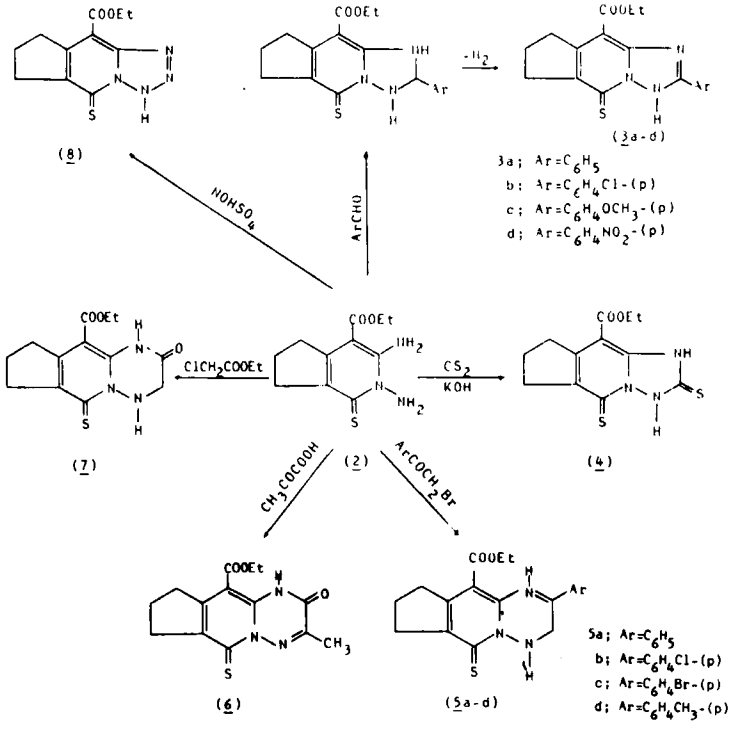
RESULTS AND DISCUSSION

In this work the light is shed on the chemistry of the highly active, thiopyranethione (**1**) through its utilization as a precursors for the synthesis of several hitherto unreported tricyclic compounds with a condensed thiopyridone ring. Many of these compounds are either isosteres or structurally related to some biologically active compounds and are serve as useful models for studying the transmission of substituent–induced electronic effects across the thiopyridone ring.

Thus, treatment of cyclopentanone with ethyl cyanoacetate and CS_2 or ethyl cyclopentylidenecyanoacetate with CS_2 afforded 3,4-trimethylene-6-amino-5-ethoxycarbonyl-2(1H) thiopyranethione (**1**). Interaction of **1** with hydrazine hydrate in boiling ethanol giving the corresponding ethyl 4,5,6,7-tetrahydro-1,2-diamino-7-thioxocyclopenta[c]pyridine-3-carboxylate **2** in a good yield.

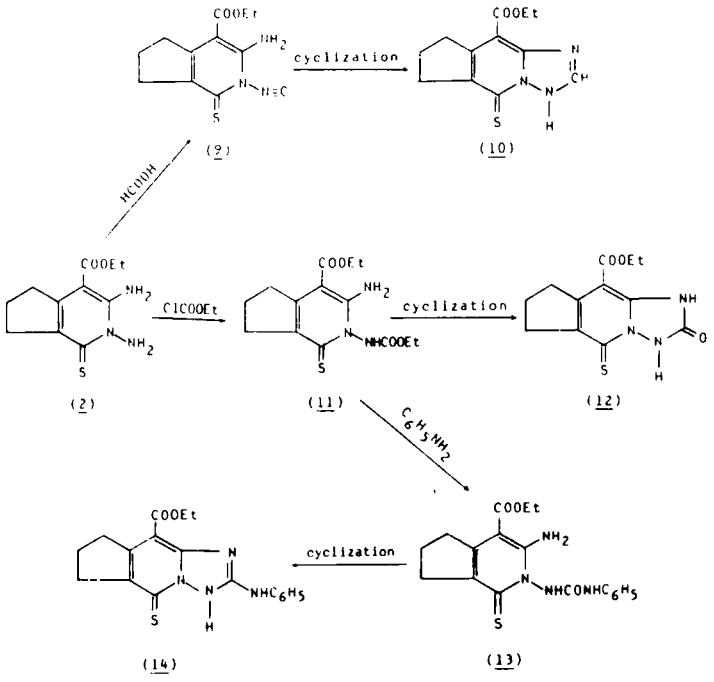


It was of interest to us to explore the new o-diamino compound **2** in its reaction with some reagents for building up a third angular ring. Thus, reaction of 2 with aromatic aldehydes, CS_2 in KOH, phenacyl bromide, pyruvic acid, ethyl chloroacetate or nitrosyl-sulfuric acid lead to direct ring closure to give the corresponding tricyclic compounds (**3–8**), respectively (Scheme 1).



SCHEME 1

However, in the case of reaction of compound **2** with formic acid ethyl chloroformate ring closure occurred indirectly with the separation of some intermediates giving the corresponding compounds (9–14), respectively (Scheme 2).



SCHEME 2

EXPERIMENTAL

All melting points are uncorrected and were determined on a Gallen-Kamp melting point apparatus, IR spectra were taken on Pye-Unicam infrared spectrophotometer using the KBr wafer technique. NMR spectra were recorded by 90 MHz Varian NMR spectrometer and NT-200 NMR spectrometer. Mass spectra were determined on Dupont 21-492B mass spectrometer. Elemental analysis was carried out on the Perkin-Elmer 240C micro analyser.

3,4-Trimethylene-6-amino-5-ethoxycarbonyl-2(1H)thiopyranethione(**1**). To a mixture of (16.9 g, 0.1 mole) ethyl cyclopentylidine cyanoacetate 20 ml carbon disulphide and dimethylformamide (5 ml) in methanol (30 ml) triethylamine (5 ml) was added dropwise. The mixture was stirred at room temperature until the product starts to precipitate. The reaction was left over night. The solid product was separated by filtration and recrystallized from ethanol to give orange crystals of compound **1**.

Ethyl 4,5,6,7-tetrahydro-1,2-diamino-7-thioxocyclopenta[c]pyridine-3-carboxylate (**2**). A mixture of compound **1** (2.5 gm, 0.01 mole) and hydrazine hydrate (2 ml) in 30 ml ethanol was refluxed until evolution of H_2S gas ceased. The reaction mixture was cooled, and the solid product was collected and recrystallized from ethanol to produce yellow needles of compound **2**.

Ethyl 5,6,7,8-tetrahydro-2-aryl-5-thioxo-3H-cyclopenta[d][1,2,4]-triazolo[1,5-a]pyridine-9-carboxylate (3a–d). General procedure: To a mixture of compound **2** (0.01 mole) and aryl aldehyde (0.01 mole) in 30 ml ethanol, few drops of piperidine was added. The mixture was refluxed for 6 hours, then allowed to cool, the solid product was separated by filtration, washed by ethanol, and recrystallized from acetic acid.

Ethyl 2,3,5,6,7,8-hexahydro 2,5-dithioxo-1H-cyclopenta[d][1,2,4]-triazolo[1,5-a]pyridine-9-carboxylate (**4**). To a mixture of compound **2** (2.5 gm, 0.01 mole), and carbon disulphide in ethanol 30 ml, potassium hydroxide solution (1 gm in 2 ml water) was added. The mixture was refluxed on a water bath for 5 hours, then allowed to coll, and acidified by HCl. The solid product was collected and recrystallized from ethanol as golden yellow crystals.

Ethyl 3,4,6,7,8,9-hexahydro-2-aryl-6-thioxocyclopenta[d]pyrido[1,2-b][1,2,4]triazine-10-carboxylate (**5a–d**). *General procedure*: A mixture of compound 2 (2.5 gm, 0.01 mole), and phenacyl bromide and its derivatives (0.01 mole) in 30 ml ethanol was refluxed for 5 hours. The reaction mixture was allowed to cool, the solid product was filtered off, washed with dilute sod carbonate solution and recrystallized fro the suitable solvent..

Ethyl 1,2,6,7,8,9-hexahydro-2-oxo-6-thioxocyclopenta[d]pyrido[1,2,-b][1,2,4]triazine-10-carboxylate (**6**). To a solution of compound **2** (2.5 gm, 0.01 mole) in 10 ml acetic acid aqueous solution of sodium pyruvate (1.1 gm in 2 ml water) was added. The mixture was stirred for 3 hours, then refluxed for one hour, and finally it was poured into cold water. The solid product was filtered off and recrystallized from ethanol to give yellow crystals of compound **6**.

Ethyl 1,2,3,4,6,7,8,9-octahydro-6-thioxocyclopenta[d]pyrido[1,2-b][1,2,4]triazine-10-carboxylate (**7**). To solution of compound **2** (1.7 gm 0.005 mole) and ethyl bromoacetate (0.005 mole) in ethanol 30 ml, sodium acetate (2 gm) was added, the mixture was refluxed for 12 hours, then the reaction mixture

TABLE I

Physical data of compounds (1–14).

Compound	M.P. (Solvent)	% Yield	Molecular formula		Elemental analysis C	H	N	S	Br	Cl
1	195 (ethanol)	78	$C_{11}H_{13}NO_2S_2$	Calcd.	51.72	5.13	5.50	25.10	—	—
				Found.	52.08	5.34	5.48	25.38	—	—
2	128–30 (ethanol)	85	$C_{11}H_{15}N_3O_2S$	Calcd.	52.15	5.96	16.58	12.65	—	—
				Found.	52.35	6.22	14.42	15.58	—	—
3a	210–12 (acetic acid)	78	$C_{18}H_{17}N_3O_2S$	Calcd.	63.71	5.01	12.38	9.34	—	—
				Found.	64.05	5.21	12.71	9.14	—	—
3b	170 (acetic acid)	82	$C_{18}H_{16}ClN_3O_2S$	Calcd.	57.83	4.28	11.24	8.56	—	9.50
				Found.	58.08	4.42	10.96	8.77	—	9.68
3c	290 (acetic acid)	68	$C_{19}H_{19}N_3O_3S$	Calcd.	61.78	5.14	11.38	8.67	—	—
				Found.	62.08	5.35	11.19	8.35	—	—
3d	160 (acetic acid)	68	$C_{18}H_{16}N_4O_4S$	Calcd.	56.25	4.16	14.58	8.33	—	—
				Found.	56.62	4.37	14.32	8.11	—	—
4	245 (decomp.) (ethanol)	86	$C_{12}H_{13}N_3O_2S_2$	Calcd.	48.81	4.40	14.23	21.69	—	—
				Found.	49.08	4.53	14.02	21.58	—	—
5a	260.2 (ethanol)	80	$C_{19}H_{19}N_3O_2S$	Calcd.	64.85	5.38	11.89	9.06	—	—
				Found.	64.80	5.52	11.77	8.82	—	—
5b	255 (acetic acid)	78	$C_{19}H_{18}ClN_3O_2S$	Calcd.	58.83	4.64	10.83	8.25	—	9.16
				Found.	59.12	4.85	10.68	8.15	—	8.96
5c	270–2 (acetic acid)	78	$C_{19}H_{18}BrN_3O_3S$	Calcd.	52.77	4.16	9.72	7.40	18.51	—
				Found.	52.98	4.32	10.02	7.12	18.32	—
5d	237 (ethanol)	70	$C_{20}H_{21}N_3O_2S$	Calcd.	65.39	5.72	11.44	8.71	—	—
				Found.	65.52	5.93	11.31	8.52	—	—
6	197–99 (ethanol)	70	$C_{14}H_{15}N_3O_3S$	Calcd.	55.08	4.91	13.77	10.49	—	—
				Found.	55.31	5.12	13.58	10.42	—	—
7	260 (ethanol)	75	$C_{13}H_{15}N_3O_3S$	Calcd.	53.24	5.11	14.33	10.92	—	—
				Found.	53.51	5.23	14.12	11.08	—	—
8	175–6 (ethanol)	65	$C_{11}H_{12}N_4O_2S$	Calcd.	50.00	4.54	21.21	12.12	—	—
				Found.	50.32	4.65	20.98	11.89	—	—
9	160 (ethanol)	78	$C_{12}H_{13}N_3O_2S$	Calcd.	54.75	4.94	15.96	12.16	—	—
				Found.	55.00	5.08	15.78	12.02	—	—
10	240 (ethanol)	72	$C_{12}H_{13}N_3O_2S$	Calcd.	54.75	4.94	15.96	12.16	—	—
				Found.	54.94	4.59	16.22	11.89	—	—
11	250–51 (ethanol)	85	$C_{14}H_{19}N_3O_4S$	Calcd.	51.69	5.84	12.92	9.84	—	—
				Found.	51.82	5.72	13.80	10.12	—	—
12	270 (acetic acid)	60	$C_{12}H_{13}N_3O_3S$	Calcd.	51.61	4.65	15.05	11.46	—	—
				Found.	51.83	4.71	14.83	11.18	—	—
13	240 (acetic acid)	60	$C_{18}H_{20}N_4O_3S$	Calcd.	58.06	5.37	15.05	8.60	—	—
				Found.	58.29	5.22	14.87	8.72	—	—
14	230–2 (ethanol	85	$C_{18}H_{18}N_4O_2S$	Calcd.	61.01	5.08	15.81	9.03	—	—
				Found.	61.27	4.88	16.04	8.80	—	—

TABLE II

Spectral data of compounds (1–14).

Compound (solvent)	IR	^{1}H-NMR	M.S. (M^+)
1 ($CDCl_3$)	3330, 3200 cm^{-1} (NH_2) and 1680 cm^1 (C=O).	δ1.3(t, 3H, CH_3), 4.2(q, 2H, CH_2) of ester group, δ1.9(m, 2H, βCH_2) δ2.9, δ3.2(2t, 4H, 2αCH_2) of cyclopentane ring, and at 8.7(s, 2H, NH_2)	255
2 (C_5D_5N)	3410, 3310 cm^{-1} ($2NH_2$)	δ1.3(t, 3H, CH_3), δ4.25(q, 2H, CH_2) of ester group, δ1.85 (m, 2H, βCH_2), δ3.1(m, 4H, 2αCH_2) of cyclopentane ring, δ7.3 (s, 2H, NH_2) and δ8.8(s, 2H, NH_2).	253
3a (C_5D_5N)	3400 cm^{-1} (NH), 1700 cm^{-1} (C=O) and 1660 cm^{-1} (C=N).	δ1.3(t, 3H, CH_3), δ4.4(q, 2H, CH_2) of ester group, δ1.9(m, 2H, βCH_2), δ3.25(q, 4H, 2αCH_2) of cyclopentane ring, δ7.4, δ8.35(2m, 5H, Ar-H).	339
3b	3380 cm^{-1} (NH) and 1680 cm^{-1} (C=O).	—	—
3c	3400 cm^{-1} (NH and 1710 cm^{-1} (C=O).	—	—
3d	3400 cm^{-1} (NH) and 1710 cm^{-1} (C=O).	—	—
4 (tri fluoro-acetic acid)	3470, 3300 cm^{-1} (2NH), 1700 cm^{-1} (C=O) and 1250 cm^{-1} (C=S).	δ1.55(t, 3H, CH_3), δ4.5(q, 2H, CH_2) of ester group, δ2.45(m, 2H, βCH_2), δ3.05, δ3.55(2t, 4H, 2αCH_2) of cyclopentane ring and δ8.5(s, 2H, 2NH).	—
5a	3300 cm^{-1} (NH) and 1700 cm^{-1} (C=O).	δ1.55(t, 3H, CH_3), δ4.5(q, 2H, CH_2) of ester group, δ2.2(m, 2H, βCH_2), δ2.95, δ3.45(2t, 4H, 2αCH_2) of cyclopentane ring, δ4.2(s, 2H, CH_2) of triazine ring and δ7.3 (m, 5H, Ar-H).	253
5b	3300 cm^{-1} (NH) and 1700 cm^{-1} (C=O).	—	—
5c	3250 cm^{-1} (NH) and 1700 cm^{-1} (C=O).	—	—
5d (tri fluoro-acetic acid)	3300 cm^{-1} (NH) and 1700 cm^{-1} (C=O).	δ1.55 (t, 3H, CH_3), δ4.55(q, 2H, CH_2) of ester group, δ2.4(t, 2H, βCH_2), δ3.0, δ3.5(2t, 4H, 2CH_2) of cyclopentane ring, δ4.1(s, 2H, CH_2) of triazine ring, δ2.3(s, 3H, CH_3) of Ph-CH_3 and δ7.4, δ7.9(2d, 4H, Ar-H).	—
6 ($CDCl_3$)	3420 cm^{-1} (NH), 1670–1710 cm^{-1} (C=O) and 1610 cm^{-1} (C=N).	δ1.3(t, 3H, CH_3), δ4.2(q, 2H, CH_2) of ester group, δ1.9(m, 2H, βCH_2), δ2.9, δ3.2(2t, 4H, 2αCH_2) of cyclopentane ring, δ4.4(s, 3H, CH_3) and δ7.8(s, 1H, NH).	—
7	3340 cm^{-1}, 3200 cm^{-1} (2NH), 1720 cm^{-1}, 1680 cm^{-1} (2C=O).	δ1.3(t, 3H, CH_3), δ4.3(q, 2H, CH_2) of ester group, δ2.1(m, 2H, βCH_2), δ2.9, δ3.2(2t, 4H, 2αCH_2) of cyclopentane ring, δ3.7(s, 2H, CH_2) of triazine ring and δ9.1(s, 2H, 2NH).	—
8 (C_5D_5N)	1700 cm^{-1} (C=O) and showed the disappearance of band characteristic of (NH_2).	δ1.2(t, 3H, CH_3), δ4.3(q, 2H, CH_2) of ester group, δ1.85(m, 2H, βCH_2), δ2.7, δ2.9(2t, 4H, 2αCH_2) of cyclopentane ring and δ6.1(s, 1H, NH).	—
9 ($CDCl_3$)	3500, 3400 cm^{-1}(NH_2), 2220 cm^{-1} (NC), and	δ1.35(t, 3H, CH_3), δ4.35(q, 2H, CH_2) of ester group, δ2.15(m, 2H, βCH_2), δ2.7, δ3.1(2m, 4H, 2αCH_2) of cyclopentane ring and δ6.4(s, 2H, NH_2).	263

TABLE II
(Cont'd)

Compound (solvent)	IR	^{1}H-NMR	M.S. (M^+)
10	3300 cm^{-1} (NH), 1700 cm^{-1} (C=O) and showed the disappearance of bands characteristic of (NH_2) and (NC)	—	—
11 (C_5D_5N)	3480, 3230 cm^{-1} (NH, NH) and 1800–1680 cm^{-1} (C=O).	δ1.1, δ1.3(2t, 6H, $2CH_3$), δ4.25(q, 4H, $2CH_2$) of 2 ester group, δ1.8(m, 2H, βCH_2), δ3.1(m, 4H, $2\alpha CH_2$) of cyclopentane ring, δ9.6(s, 2H, NH_2) and δ12.0(s, 1H, NH).	325
12 (tri fluoro-acetic acid)	3480, 3230 cm^{-1} (2NH) and 1800–1680 cm^{-1} (2C=O).	δ1.4(t, 3H, CH_3), δ4.5(q, 2H, CH_2) of ester group, δ2.4(m, 2H, βCH_2) δ3.1, δ3.5(2t, 4H, $2\alpha CH_2$) of cyclopentane ring and δ10.1(s, 2H, NH_2).	—
13 DMSO-d_6	3500–3100 cm^{-1} (NH_2 and NH), 1780–1680 cm^{-1} (C=O).	δ1.3(t, 3H, CH_3), δ4.15(q, 2H, CH_2) of ester group, δ1.85(m, 2H, βCH_2), δ2.7, δ3.15(2t, 4H, $2\alpha CH_2$) of cyclopentane ring and δ7.2(m, 5H, Ar-H).	
14 (C_5D_5N)	3500, 3300 cm^{-1} (2NH) and 1720 cm^{-1} (C=O).	δ1.25(t, 3H, CH_3), δ4.15(q, 2H, CH_2) of ester group, δ1.8(m, 2H, βCH_2), δ2.00, δ2.9(2m, 4H, $2\alpha CH$) of cyclopentane ring, δ9.8 (s, 1H, NH) and δ10.8(s, 1H, NH).	321

was allowed to cool. The solid product was collected, and recrystallized from ethanol as yellowish white crystals of compound **7**.

Ethyl 5,6,7,8-tetrahydro-5-thioxo-3H-cyclopenta[d]tetrazolo[1,5-a]-pyridine-9-carboxylate (**8**). To a solution of compound **2** (2.5 gm, 0.01 mole) in 15 ml acetic acid, nitrosylsulfuric acid (0.012 mole) was added. The reaction mixture was stirred at room temperature until complete dissolution had occurred. After standing for 5 hours, the reaction mixture was poured into ice/water. The resulting precipitate was filtered off, washed well with water and recrystallized from ethanol to give orange crystals of compound **8**.

Ethyl 4,5,6,7-tetrahydro-2-amino-1-isocyanato-7-thioxocyclopenta[c]pyridine-3-carboxylate (**9**). A sample of compound **2** and 10 ml formic acid was refluxed for 6 hours. The reaction mixture cooled, poured into water and the solid product was collected. Recrystallization from ethanol gave white crystals of compound **9**.

Ethyl 5,6,7,8-tetrahydro-5-thioxo-3H-cyclopenta[d][1,2,4]triazolo[1,5-a]pyridine-9-carboxylate (**10a**). To a solution of compound **9** (1.3 gm, 0.005 mole) in 30 ml ethanol, anhydrous potassium carbonate (1 gm) was added. The mixture was refluxed for 5 hours, then allowed to cool and poured into cold water. The solid product was collected and recrystallized from ethanol to give yellowish white crystals of compound **10**.

Ethyl 4,5,6,7-tetrahydro-2-amino-1-ethoxycarbonylamino-7-thioxocyclopenta[c]pyridine-3-carboxylate (**11**). To a solution of compound **2** (2.5 gm, 0.01 mole) in 30 ml ethanol, ethyl chloroformate (3 ml) was added. The mixture was refluxed in a water bath for 4 hours, then the reaction mixture was allowed to cool. The solid product was filtered off, washed well with ethanol and recrystallized from ethanol to give yellowish green crystals of compound **11**.

Ethyl 2,3,5,6,7,8-hexahydro-2-oxo-5-thioxo-1H-cyclopenta[d]-[1,2,4]triazolo[1,5-a]pyridine-9-car-boxylate (**12**). To a solution of compound **11** (1.6 gm, 0.0005 mole) in 30 ml acetic acid, fused sodium acetate (2 gm) was added. The mixture was refluxed for 6 hours, allowed to cool, and poured into cold

water. The solid product was separated by filtration and recrystallized from acetic acid as greenish white crystals of compound **12**.

N(2-amino-3-ethoxycarbonyl-4,5,6,7-tetrahydro-7-thioxocyclopenta[c]pyridinyl)N'-phenylurea (**13**). A mixture of compound **11** (1.8 gm, 0.005 mole) and aniline (0.01 mole) was refluxed for 1 hour, then it was allowed to cool. Ethanol (20 ml) was added, the mixture was refluxed for 2 hours, then allowed to cool. The solid product was collected and recrystallized from acetic acid to give white crystals of compound (**13**).

Ethyl 5,6,7,8-tetrahydro-2-phenylamino-5-thioxo-3H-cyclopenta[d]-[1,2,4]triazolo[1,5-a]pyridine-9-carboxylate (**14**). Method (a): A mixture of compound **2** (2.5 gm, 0.01 mole) and phenyl isocyanate (1.2 gm, 0.01 mole) in dry benzene was refluxed for 2 hours on a water bath, then the reaction mixture was allowed to cool. The solid product was collected. On crystallization from ethanol gave yellow crystals of compound **14** in 80% yield, m.p. 230°C.

Method (b): A sample of compound 8 was heated above its melting point for one hour, then ethanol 30 ml was added, and refluxed for another one hour, then was allowed to cool. The solid product was collected and recrystallized from ethanol to give compound **14**.

REFERENCES

1. D. E. Beattie, R. Crossley, A. C. W. Curran, G. T. Dioxon, D. G. Hill, A. E. Lawrence and R. G. Shephered, *J. Med. Chem.*, **20,** 714 (1977).
2. Tanabe Seiyaka Co., Ltd., Japan Patent, 7200811 (1972), *C.A.*, **76,** 140574 (1972).
3. C. A. Hoechst, German Patent, 2432635 (1976), *C.A.*, **84,** 150525y (1976).
4. *Ibid,* 2361436 (1975), *C.A.* **83**; 114227y (1975).
5. Pfizer Inc., German Patent, 2746244 (1978), *C.A.*, **89,** 24308v (1978).