[Chem. Pharm. Bull. 24(11)2871—2876(1976)]

UDC 547.793.04.08 : 615.31.076.9

Anticoccidials. I. Syntheses and Anticoccidial Activity of 2-Amino-5-aryl-1,3,4-oxadiazoles, 5-Alkoxy-3-aryl-1H-1,2,4-triazoles, and 3-Aryl-Δ^2-1,2,4-triazolin-5-ones

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(Received February 7, 1976)

A series of 2-amino-5-aryl-1,3,4-oxadiazoles, 5-alkoxy-3-aryl-1H-1,2,4-triazoles, and 3-aryl-Δ^2-1,2,4-triazolin-5-ones were prepared and their anticoccidial activity was tested.

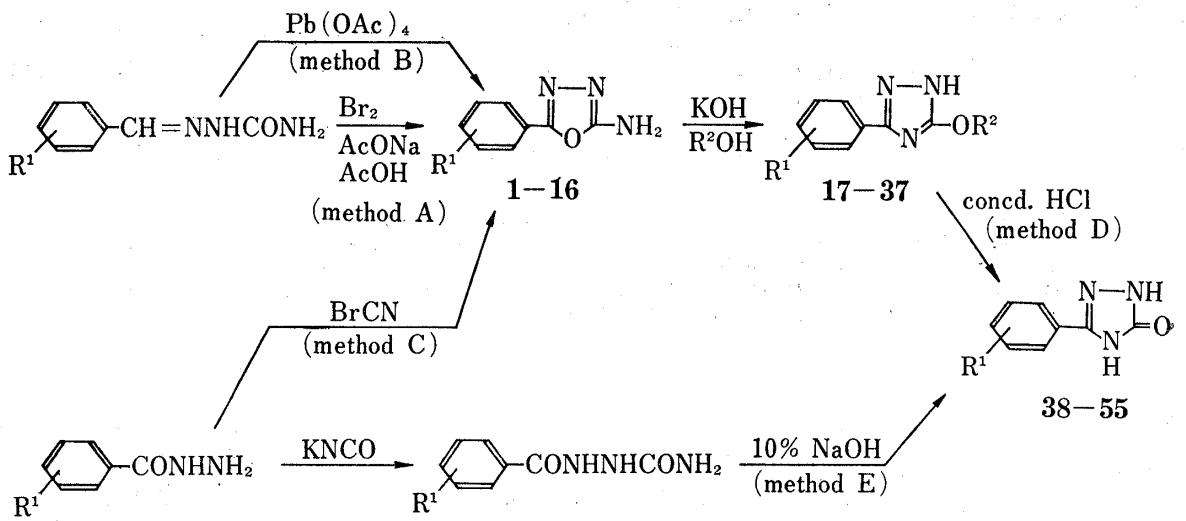
Among them, 5-(3,4-dichlorophenyl)- and 5-(2,4,5-trichlorophenyl)-2-amino-1,3,4-oxadiazoles, 3-(3,4-dichlorophenyl)- and 3-(2,4-dichlorophenyl)-5-ethoxy-1H-1,2,4-triazoles, and 3-(4-bromophenyl)-, 3-(4-chlorophenyl)-, and 3-(2,4-dichlorophenyl)-Δ^2-1,2,4-triazolin-5-ones showed moderate anticoccidial activity.

Although many compounds with anticoccidial activity have been reported in the literature over the last three decades and some of them have actually been used as anticoccidials in the poultry industry, the appearance of more effective and better tolerated drug for the prevention and control of coccidiosis is still required. In our program directed toward developing new anticoccidial agents, we have now synthesized 2-amino-5-aryl-1,3,4-oxadiazoles, 5-alkoxy-3-aryl-1H-1,2,4-triazoles, and 3-aryl-Δ^2-1,2,4-triazolin-5-ones and tested their anticoccidial activity.

Syntheses

Synthetic schemes used are summarized in Chart 1.

2-Amino-5-aryl-1,3,4-oxadiazoles (**1—16**) were readily prepared either by oxidative cyclization of benzaldehyde semicarbazones with bromine in glacial acetic acid containing anhydrous



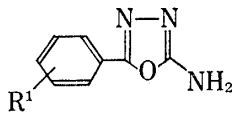
R^1: 4-Cl, 3-Cl, 2-Cl, 4-Br, 4-OCH_3, 4-CH_3, 3,4-Cl_2, 2-CH_3-4-Cl, 4-C_6H_5, 2-CH_3-4,5-$(OCH_3)_2$, 2,4-Cl_2, 2,4,5-Cl_3, 3-SO_2NH_2, 3-SO_2NHCH_3, 4-OH, 4-NH_2, 4-NO_2, H

R^2: CH_3, C_2H_5, *n*-C_4H_9

Chart 1

1) Location: *Juso-Honmachi, Yodogawa-ku, Osaka 532, Japan.*

Table I. 2-Amino-5-aryl-1,3,4-oxadiazoles



Compd. No.	R^1	Method	Recrystn. solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1} (C=N)	NMR (NH_2)
1	4-Cl	A	dioxane	81.8	273—274[a]	$C_8H_6ON_3Cl$	—	—	—	1660	6.97
2	3-Cl	A	EtOH	59.3	224—227[b]	$C_8H_6ON_3Cl$	49.12 (49.08)	3.09 (3.10)	21.48 (21.53)	1650 1680	7.33
3	2-Cl	A	dioxane–H_2O	32.1	157—159[c]	$C_8H_6ON_3Cl$	—	—	—	1640	7.33
4	4-Br	A	EtOH	53.5	282—284[d]	$C_8H_6ON_3Br$	—	—	—	1660	6.97
5	4-OCH_3	A	EtOH	70.0	257—258[e] (decomp.)	$C_9H_9O_2N_3$	—	—	—	1650	6.93
6	4-CH_3	A	EtOH	50.6	278—280[f]	$C_9H_9ON_3$	—	—	—	1655	7.00
7	3,4-Cl_2	A	dioxane–H_2O	60.0	235—237	$C_8H_5ON_3Cl_2$	41.77 (41.48)	2.19 (2.02)	18.27 (18.12)	1655	7.03
8	2-CH_3-4-Cl	A	EtOH–H_2O	74.4	182—185	$C_9H_8ON_3Cl$	51.57 (51.53)	3.85 (3.68)	20.04 (19.96)	1640	7.23
9	4-C_6H_5	A	dioxane–H_2O	61.0	290—292	$C_{14}H_{11}ON_3$	70.87 (70.30)	4.67 (4.59)	17.71 (17.24)	1650	7.33
10	2-CH_3-4,5-$(OCH_3)_2$	A	dioxane–H_2O	74.1	278—280	$C_{11}H_{13}O_3N_3$	56.16 (55.88)	5.57 (5.46)	17.86 (17.44)	1660	7.00
11	2,4-Cl_2	B	AcOEt–petr. ether	59.6	210—211[g]	$C_8H_5ON_3Cl_2$	—	—	—	1650	7.02
12	2,4,5-Cl_3	C	MeOH–H_2O	80.3	231—233	$C_8H_4ON_3Cl_3$	36.33 (36.35)	1.52 (1.44)	15.89 (15.92)	1650	7.02
13	3-SO_2NH_2	C	DMF[h]–H_2O	62.7	242—245	$C_8H_8O_3N_4S$	40.00 (39.49)	3.36 (3.55)	23.32 (22.95)	1650 1685	7.33
14	3-SO_2NHCH_3	C	DMF–H_2O	52.8	265—268	$C_9H_{10}O_3N_4S$	42.51 (42.48)	3.96 (3.67)	22.03 (21.71)	1655 1685	7.33
15	4-OH	B	DMF–H_2O	69.2	274—276[i]	$C_8H_7O_2N_3$	—	—	—	1650	7.12
		C	DMF–H_2O	35.0							
16	H	A	EtOH	55.5	246—248[j]	$C_8H_7ON_3$	—	—	—	1650	7.30

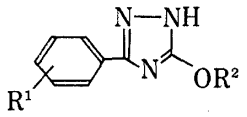
a) reported[2b] mp 270—272° *b*) H.L. Yale and K. Losee, *J. Med. Chem.*, **9**, 478 (1966), reported mp 245—246°. Gulf Research and Development Co., U.S. Patent 3808223 (1974) [*C. A.*, **81**, 13524*w* (1974)], reported mp 228—230° *c*) reported[8] mp 167—168° *d*) reported[2b] mp 275—276° *e*) reported[3b] mp 250—251° *f*) reported[2b] mp 265—267° *g*) reported[3b] mp 213—214° *h*) N,N-dimethylformamide *i*) reported[8] mp 288—290° *j*) reported[2b] mp 242°

sodium acetate (method A)[2] or with lead tetraacetate (method B),[2b] or by treatment of aroylhydrazines with cyanogen bromide (method C).[3] Alkaline treatment of **1**—**16** in alcohol gave 5-alkoxy-3-aryl-1H-1,2,4-triazoles (**17**—**35**, **37**). 4-Nitrophenyl derivative (**36**) was obtained by nitration of **37** with fuming nitric acid. The triazoles (**17**—**37**) were hydrolyzed with concentrated hydrochloric acid to yield the corresponding 3-aryl-Δ^2-1,2,4-triazolin-5-ones

2) *a*) F.L. Scott, T.M. Lambe, and R.N. Butler, *Tetrahedron Letters*, **1971**, 2669; *b*) *Idem*, *J. Chem. Soc. Perkin I*, **1972**, 1918.

3) *a*) H. Gehlen and K.-H. Uteg, *Arch. Pharm.*, **301**, 911 (1968); *b*) McNeil Lab. Inc., U.S. Patent 288339 (1959) [*C.A.*, **53**, 16157 g (1959)].

TABLE II. 5-Alkoxy-3-aryl-1H-1,2,4-triazoles



Compd. No.	R^1	R^2	Recrystn. solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
17	4-Cl	CH_3	MeOH–H_2O	33.4	197—198	$C_9H_8ON_3Cl$	51.57 (51.55)	3.85 (3.72)	20.04 (19.99)
18	4-Cl	C_2H_5	EtOH–H_2O	92.4	156—157[a]	$C_{10}H_{10}ON_3Cl$	53.70 (53.44)	4.51 (4.43)	18.79 (18.90)
19	3-Cl	C_2H_5	EtOH–H_2O	68.5	96— 97	$C_{10}H_{10}ON_3Cl$	53.70 (53.48)	4.51 (4.56)	18.79 (19.06)
20	2-Cl	C_2H_5	EtOH–H_2O	58.0	101—102	$C_{10}H_{10}ON_3Cl$	53.70 (53.71)	4.51 (4.32)	18.79 (18.82)
21	4-Br	CH_3	MeOH–H_2O	23.2	198—200	$C_9H_8ON_3Br$	42.54 (42.62)	3.17 (3.05)	16.54 (16.55)
22	4-Br	C_2H_5	EtOH–H_2O	80.0	144—145	$C_{10}H_{10}ON_3Br$	44.80 (44.64)	3.76 (3.50)	15.67 (15.50)
23	4-OCH_3	CH_3	MeOH–H_2O	13.1	170—172[b]	$C_{10}H_{11}O_2N_3$	58.53 (58.36)	5.40 (5.24)	20.48 (20.59)
24	4-OCH_3	C_2H_5	EtOH–H_2O	72.6	142—143[c]	$C_{11}H_{13}O_2N_3$	60.26 (60.20)	5.98 (5.83)	19.17 (19.01)
25	4-CH_3	CH_3	MeOH–H_2O	12.9	165—166	$C_{10}H_{11}ON_3$	63.48 (63.49)	5.86 (5.94)	22.21 (22.18)
26	4-CH_3	C_2H_5	EtOH–H_2O	76.1	141—143	$C_{11}H_{13}ON_3$	65.01 (64.99)	6.45 (6.29)	20.67 (20.76)
27	3,4-Cl_2	C_2H_5	EtOH–H_2O	84.5	161—163	$C_{10}H_9ON_3Cl_2$	46.54 (46.60)	3.51 (3.32)	16.28 (16.46)
28	2-CH_3-4-Cl	C_2H_5	$CHCl_3$-petr. ether	57.2	130—133	$C_{11}H_{12}ON_3Cl$	55.59 (55.95)	5.09 (5.09)	17.68 (16.93)
29	4-C_6H_5	C_2H_5	$CHCl_3$-petr. benzine	64.8	156—157	$C_{16}H_{15}ON_3$	72.43 (72.20)	5.70 (5.59)	15.84 (15.67)
30	2-CH_3-4,5-$(OCH_3)_2$	C_2H_5	EtOH–H_2O	55.9	163—165	$C_{13}H_{17}O_3N_3$	59.30 (58.89)	6.51 (6.61)	15.96 (15.77)
31	2,4-Cl_2	C_2H_5	EtOH–H_2O	79.8	130—131	$C_{10}H_9ON_3Cl_2$	46.54 (46.51)	3.51 (3.49)	16.28 (16.33)
32	2,4,5-Cl_3	C_2H_5	EtOH–H_2O	87.8	144—145	$C_{10}H_8ON_3Cl_3$	41.06 (40.96)	2.76 (2.63)	14.36 (14.41)
33	3-SO_2NH_2	C_2H_5	H_2O	42.8	103—106	$C_{10}H_{12}O_3N_4S\cdot H_2O$	41.95 (41.77)	4.93 (4.50)	19.57 (19.50)
34	3-SO_2NHCH_3	C_2H_5	MeOH–H_2O	93.3	74— 78	$C_{11}H_{14}O_3N_4S\cdot 1/2H_2O$	45.35 (45.70)	5.19 (5.11)	19.23 (19.36)
35	4-OH	n-C_4H_9	AcOEt	32.6	213—214	$C_{12}H_{15}O_2N_3$	61.79 (61.63)	6.48 (6.54)	18.01 (18.09)
36	4-NO_2	C_2H_5	MeOH–H_2O	63.5	160—163	$C_{10}H_{10}O_3N_4$	51.28 (51.07)	4.30 (4.11)	23.92 (24.20)
37	H	C_2H_5	EtOH–H_2O	74.2	113—114[d]	$C_{10}H_{11}ON_3$	—	—	—

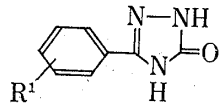
a) E. Hoggarth, *J. Chem. Soc.*, **1949**, 1918, reported mp 148° *b*) reported[a] mp 164° *c*) reported[a] mp 146° *d*) reported[a] mp 116—117°

(**38**—**52**, **54**, **55**) (method D). Compounds **52** and **53** were also obtained directly from the corresponding aroylsemicarbazides[4] by cyclization in alkaline solution (method E).

The structures of new compounds were established by the elemental analysis, infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy (Table I—III).[3a,5]

4) A. Dornow and S. Lüpfert, *Arch. Pharm.*, **288**, 311 (1955).
5) S. Kubota and M. Uda, *Chem. Pharm. Bull.* (Tokyo), **21**, 1343 (1973).

Table III. 3-Aryl-Δ^2-1,2,4-triazolin-5-ones



Compd. No.	R^1	Method	Recrystn. solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1} (C=O)	NMR (NH)
38	4-Cl	D	DMF	77.9	>300[a]	$C_8H_6ON_3Cl$	—	—	—	1710	11.65 12.05
39	3-Cl	D	EtOH	62.8	>300	$C_8H_6ON_3Cl$	49.12 (49.30)	3.09 (3.26)	21.48 (21.67)	1730	11.90 12.20
40	2-Cl	D	EtOH	38.4	>300[b]	$C_8H_6ON_3Cl$	49.12 (49.11)	3.09 (3.20)	21.48 (21.75)	1740	11.72
41	4-Br	D	EtOH	62.8	>300[c]	$C_8H_6ON_3Br$	40.03 (39.79)	2.52 (2.26)	17.50 (17.37)	1720	11.65 11.95
42	4-OCH_3	D	EtOH	75.6	>300[d]	$C_9H_9O_2N_3$	—	—	—	1720	11.42 11.76
43	4-CH_3	D	EtOH	78.4	>300[e]	$C_9H_9ON_3$	61.70 (61.91)	5.18 (5.26)	23.99 (24.04)	1720	11.52 11.86
44	3,4-Cl_2	D	DMF–H_2O	76.8	>300	$C_8H_5ON_3Cl_2$	41.77 (41.77)	2.19 (1.93)	18.27 (18.36)	1735	11.83 12.10
45	2-CH_3-4-Cl	D	DMF–H_2O	88.2	>300	$C_9H_8ON_3Cl$	51.57 (51.49)	3.85 (4.46)	20.04 (20.36)	1720	11.73
46	4-C_6H_5	D	DMF–EtOH	27.1	>270	$C_{14}H_{11}ON_3$	70.87 (70.83)	4.67 (4.57)	17.71 (17.64)	1750	11.68 12.05
47	2-CH_3-4,5-$(OCH_3)_2$	D	DMF–H_2O	76.4	291—293	$C_{11}H_{13}O_3N_3$	56.16 (56.07)	5.57 (5.55)	17.86 (17.83)	1680	11.50 11.65
48	2,4-Cl_2	D	DMF–H_2O	82.1	>300	$C_8H_5ON_3Cl_2$	41.77 (42.01)	2.19 (2.05)	18.27 (18.30)	1735	12.53
49	2,4,5-Cl_3	D	EtOH–H_2O	83.2	>300	$C_8H_4ON_3Cl_3$	36.33 (36.42)	1.52 (1.52)	15.89 (16.04)	1760	13.25
50	3-SO_2NH_2	D	DMF–H_2O	82.7	>300	$C_8H_8O_3N_4S$	40.00 (40.05)	3.36 (3.46)	23.32 (23.25)	1745	11.82 12.22
51	3-SO_2NHCH_3	D	DMF–H_2O	85.5	>300	$C_9H_{10}O_3N_4S$	42.51 (42.55)	3.96 (4.02)	22.03 (21.98)	1730	11.83 12.25
52	4-OH	D	MeOH–H_2O	93.1	>300[f]	$C_8H_7O_2N_3 \cdot H_2O$	49.23 (49.06)	4.65 (4.22)	21.53 (21.57)	1710	11.50 11.87
		E	EtOH–H_2O	17.2							
53	4-NH_2	E	EtOH–H_2O	12.5	>300	$C_8H_8ON_4$	54.54 (54.47)	4.58 (4.33)	31.80 (31.82)	1700 1720	11.33 11.62
54	4-NO_2	D	DMF	75.2	>300[g]	$C_8H_6O_3N_4$	46.61 (46.69)	2.93 (3.05)	27.18 (27.00)	1690	—
55	H	D	EtOH	70.6	>300[h]	$C_8H_7ON_3$	—	—	—	1750	11.58 11.94

a) reported[2b] mp 410—412° *b*) The mp of this compound was reported, without experimental details, as 202° by H.A. Offe, W. Siefken, and G. Domagk [*Z. Naturforsch.*, **7b**, 446 (1952)] *c*) reported[2b] mp 425—428° *d*) reported[2b] mp 347—349° *e*) reported[2b] mp 375—377° *f*) H. Gehlen and J. Schmidt, *Ann. Chem.*, **682**, 123 (1965), reported mp 340° (decomp.) *g*) C.-F. Kröger, R. Miethchen, H. Frank, M. Siemer, and S. Pilz, *Chem. Ber.*, **102**, 755 (1969), reported mp>360° *h*) reported[2b] 332—333°

Anticoccidial Activity

Nine-day-old male White Leghorn chicks, fed with the standard laboratory ration, were divided into experimental and control groups composed of 3 birds each and placed into battery cages. All medicated rations which contained the test compounds at a concentration of 0.0125% were fed *ad libitum* starting 24 hours before infection, and continuing for total 9 days. Ten-day-old chicks were inoculated orally to each birds with 50000 sporulated oocysts of *Eimeria tenella*.

Bloody droppings, mortality, weight gains, and cecal lesions were the parameter of activity. The presence of bloody droppings was examined on 4th, 5th, 6th, and 7th day

after infection. The surviving birds were sacrificed on 8th day after infection and autopsied and scored for gross pathological lesions of the ceca according to the system of Tsunoda and Ishii.[6]

Of all compounds (**1**—**55**) tested, compound **7**, **12**, **27**, **31**, **38**, **41**, and **48** exhibited moderate anticoccidial activity against *Eimeria tenella* but were less active than robenidine[1,3-bis(4-chlorobenzylideneamino)guanidine hydrochloride].[7] In Table IV biological data of the active compounds and robenidine were presented.

Table IV. Anticoccidial Activity

Compd. No.	Number of bloody dropping per bird				Mortality %	Cecal lesion					Weight gain %
	4[a]	5	6	7		ⅢⅢ	Ⅲ	Ⅱ	+	−	
7	0	0	0	0	0		3				76.5
12	0	0	0	0	0			3			84.6
27	0	0	0	0	0		2	1			81.5
31	0	0	0	0	0		2		1		93.4
38	0	0	0	0	0		2	1			92.9
41	0	0	0	0	0		3				76.9
48	0	0	0	0	0		3				79.9
Robenidine[b]	0	0	0	0	0					3	98.7
Infected unmedicated control	4.3	12.6	8.5	1.5	33.3	2					38.8
	3.3	13.3	7.5	4.0	66.6	1					38.5
	2.3	10.6	10.0	2.0	33.3	2					40.5
Uninfected unmedicated control	0	0	0	0	0					3	100.9
	0	0	0	0	0				1	2	106.9
	0	0	0	0	0				1	2	91.6

a) day after infection *b*) used at a concentration of 0.0033%

Experimental

All melting points are uncorrected and were measured with a Yanagimoto micro melting point apparatus (MP-S2). IR spectra were recorded with a Hitachi Model 215 Spectrophotometer. NMR spectra were measured with a Varian T-60 Spectrometer (60 MHz) in d_6-dimethylsulfoxide. Chemical shifts are expressed in ppm using tetramethylsilane as internal standard.

2-Amino-5-aryl-1,3,4-oxadiazoles (1—16)——Method A: Bromine (5.7 ml) in glacial AcOH (20 ml) was added dropwise to a stirred suspension of benzaldehyde semicarbazone (0.1 mole) and anhydrous sodium acetate (32.8 g) in glacial AcOH (120 ml). The mixture was stirred for few hours at room temperature and then poured into ice-water (1.5 liter). A white solid was collected, washed, and recrystallized.

Method B: Lead tetraacetate (2.5 g) was added during 10 min to a stirred suspension of benzaldehyde semicarbazone (5 mmole) in glacial AcOH (30 ml). The mixture was stirred for few hours at room temperature and the undissolved material was removed. The filtrate was poured into ice-water (300 ml) and the precipitates were collected, washed, and recrystallized.

Method C: Cyanogen bromide (1.06 g) in 50% MeOH (10 ml) was added dropwise to a stirred and ice-cooled suspension of aroylhydrazine (0.01 mole) in MeOH (30 ml). After stirring for 1 hr, the mixture was refluxed and allowed to cool to room temperature. The mixture was adjusted to pH 9 by addition of 28% NH_4OH. The precipitates were collected, washed, and recrystallized.

5-Alkoxy-3-aryl-1H-1,2,4-triazoles (17—35, 37)——A solution of 2-amino-5-aryl-1,3,4-oxadiazole (1 g) and KOH (1 g) in EtOH (30 ml) was refluxed for 5 hr. After cooling, the mixture was acidified with AcOH and concentrated. The precipitates which were separated by addition of H_2O were collected, washed, and recrystallized.

5-Ethoxy-3-(4-nitrophenyl)-1H-1,2,4-triazole (36)——Fuming HNO_3 (d=1.52) (10 ml) was added to **37** (2.84 g) and the mixture was stirred for 2 hr at room temperature and then for 1 hr at 50°. The mixture was poured into ice-water (100 ml) and the precipitates were collected, washed, and recrystallized to yield **36** (2.23 g).

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Aroylsemicarbazides——A hot solution of aroylhydrazine (10 mmole) in H_2O (20 ml) and AcOH (20 ml) was added to a stirred and ice-cooled solution of potassium cyanate (11 mmole) in H_2O (5 ml). The mixture was stirred overnight at room temperature. The precipitates were collected and washed with EtOH and ether to give the product. 4-Hydroxybenzoylsemicarbazide had mp 219—221° (lit.[8] mp 230°). *Anal.* Calcd. for $C_8H_9O_3N_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.52; H, 4.67; N, 21.15. 4-Aminobenzoylsemicarbazide had mp 230—232° (decomp.). *Anal.* Calcd. for $C_8H_{10}O_2N_4$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.25; H, 4.97; N, 28.27.

3-Aryl-Δ^2-1,2,4-triazolin-5-ones (38—55)——Method D: 5-Alkoxy-3-aryl-1H-1,2,4-triazole (1 g) was heated under reflux with concd. HCl (25 ml) for few hours. After cooling, the precipitates were collected, washed, and recrystallized.

Method E: After refluxing the solution of aroylsemicarbazide (25 mmole) in 10% NaOH (100 ml) for 10 hr, the undissolved material was removed while hot. The filtrate was acidified by addition of AcOH and cooled. The precipitates were collected, washed, and recrystallized.

Acknowledgement The authors are grateful to Assistant Prof. M. Ikeda, Faculty of Pharmaceutical Science, Osaka University, for his advice in preparation of this manuscript and to Prof. H. Shimazono, Miyazaki University, Drs. T. Miki, K. Sirakawa, Y. Hamada, and S. Yamatodani for their encouragement throughout this work. Thanks are also due to the members of Central Research Division who undertook the elemental analysis and NMR measurements.

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[Chem. Pharm. Bull. 24(11)2876—2880(1976)]

UDC 547.895.04 : 547.831.6.04

Heteroaromatic Analogs of Benzomorphan. III.[1] Synthesis of 1,2,3,4,5,6-Hexahydro-2,6-methano-3-methylpyrido[3,2-*d*]azocine

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(Received February 7, 1976)

6-Acetamido-5,6,7,8-tetrahydroquinoline N-oxide (VI) was derived to the 8-oxo derivative (IX) *via* the acetoxy compound (VII). Introduction of carboxymethyl group by a Wittig reaction of IX and catalytic hydrogenation afforded the amido ester (XI). The title compound (XVI) was synthesized from the amino acid ester (XII) by intramolecular cyclization and the subsequent lithium aluminum hydride reduction of the resulting lactam.

In the course of our study on analgesics, we were interested in the synthesis of heteroaromatic analogs of benzomorphan. Previously we reported the synthesis of 1,2,3,4,5,6-hexahydro-1,5-methanopyrido[2,3-*c*]azocine and -[3,2-*c*]azocine (I and II), and 1,2,3,4,5,6-hexahydro-2,6-methanopyrido[2,3-*d*]azocine (III) derivatives.[1,3] These compounds were synthesized by the formation of pyridine ring fused to the corresponding 2-azabicyclo[3.3.1]-nonane intermediates. This paper deals with the synthesis of 1,2,3,4,5,6-hexahydro-2,6-methano-3-methylpyrido[3,2-*d*]azocine (XVI) starting from a pyridine derivative.

According to the method for preparation of 5,6,7,8-tetrahydroquinoline derivative,[4] 4-acetamidocyclohexanone (IV) was heated with 3-aminoacrolein in triethylamine to give the

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