Studies on the Syntheses of Azole Derivatives. Part III (1). Syntheses of 1-Phenyl-Δ^2-1,2,4-triazolin-5-one and 4-Phenyl-Δ^2-1,3,4-oxadiazolin-5-one Derivatives by Fusion of 1-Phenyl-2-acylhydrazine with Urea

Tetsuji Kametani (2), Kaoru Sota, and Masahisa Shio

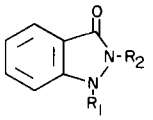
Pharmaceutical Institute, Tohoku University (2) and Research Laboratory, Taisho Pharmaceutical Co., Ltd.

Fusion of 1-phenyl-2-acylhydrazine (III) with urea gave Δ^2-1,2,4-triazolin-5-one and Δ^2-1,3,4-oxadiazolin-5-one derivatives together with various by-products. Furthermore, various derivatives were synthesized for the purpose of examination in a pharmacological screening test.

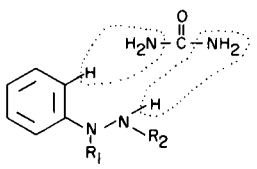
In the preceding paper (1) the syntheses of *N*-monosubstituted-3-oxoindazole derivatives were examined as one of the synthetic studies on azole derivatives. For the purpose of synthesizing *N*-monoacylindazolone from the biological point of view, fusion of 1-phenyl-2-acetylhydrazine with urea has been investigated and these results are hereby reported.

With regard to the syntheses of the indazolone skeleton having a monoacyl group at either the 1- or 2-position, only one example, that of selective hydrolysis of 1,2-diacetylindazolone (Ia) under reflux with water to give 1-acetylindazolone (Ib), has been reported (3). Therefore, if the reaction of 1-phenyl-1-acylhydrazine (II) or 1-phenyl-2-acylhydrazine (III) with urea proceeds as shown in Scheme I (4), formation of 1-acyl-(Ic) and 2-acylindazolone would be expected.

SCHEME I



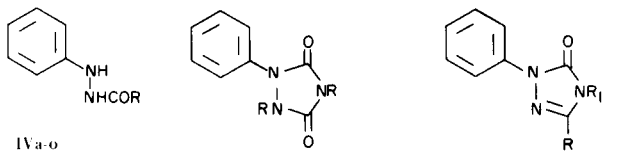
Ia: $R_1 = R_2 = COMe$
Ib: $R_1 = COMe$, $R_2 = H$
Ic: R_1 COR, $R_2 = H$
Id: $R_1 = H$, $R_2 = COR$



II: $R_1 = COR$, $R_2 = H$
III: $R_1 = H$, $R_2 = COR$

Fusion of 1-phenyl-2-acetylhydrazine (IVa) with one molar equivalent of urea was carried out at 170-180° for 3 hours and then at 270-280° for 3 minutes to give a reaction mixture, which was separated into two parts, one insoluble and the other soluble in ether. The former substance was found to be 1-phenyl-Δ^2-1,2,4-triazolidin-3,5-dione (V). The latter one was chromatographed on alumina yielding five compounds, namely acetamide, 3-methyl-1-phenyl-Δ^2-1,2,4-triazolin-5-one (VIa), 3-methyl-1,4-diphenyl-Δ^2-1,2,4-triazolin-5-one (VII), 3-methyl-1-phenyl-1,2,4,6,8-pentaazaoct-2-one-5,7-dione (IX) and 2-methyl-4-phenyl-Δ^2-1,3,4-oxadiazolin-5-one (Xa) but the expected 2-acetylindazolone was not formed. Both compound V (5) and VIa (6), which were soluble in alkaline solution, were heated with acetic anhydride. Compound V gave 2-acetyl- and 2,4-diacetyl-1-phenyl-Δ^2-1,2,4-triazolidin-3,5-dione (7), whereas only 4-acetyl-3-methyl-1-phenyl-Δ^2-1,2,4-triazolin-5-one was formed from compound VIa. The structure of 3-methyl-1,4-diphenyl-Δ^2-1,2,4-triazolin-5-one (VII) was based on the following evidence. The ir spectrum (nujol) showed an absorption band due to carbonyl C=O at 1710 cm^{-1}, which was similar to those of VIa at 1700 cm^{-1} and 3-methyl-4-(γ-dimethylaminopropyl)-Δ^2-1,2,4-triazolin-5-one (VIII) at 1705 cm^{-1}. The nmr spectrum (deuteriochloroform) showed two phenyl and one methyl protons. Furthermore, compound VII was found to be identical with an authentic sample prepared according to Gehlen's method (8). The structure of IX had the molecular formula, $C_{10}H_{13}N_5O_2$ and, upon heating at 300-320°, compound VIa was formed quantitatively with an evolution of ammonia gas. The uv spectrum of IX showed absorption maxima at 249 and 280 mμ which were similar to those of VIa. Moreover, the ir spectrum (nujol) showed the NH absorption at 3450, 3300, 3220, 3000, carbonyl band at 1710, 1680 and an absorption due to C=N group at 1630 cm^{-1}. These facts support the structure of IX. The compound (Xa) (9), identical with an authentic sample, showed a strong luminescence and its ir (ν C=O (nujol), 1776 cm^{-1}) and nmr spectra also supported its structure.

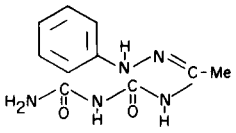
SCHEME 2



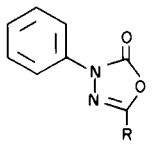
IVa-o

V: R = H
Va: R = COMe

VIa: R = Me, R_1 = H
VIp: R = Me, R_1 = COMe
VII: R = Me, R_1 = 
VIII: R = Me, R_1 = $-(CH_2)_3N(Me)_2$



IX



Xa: R = Me
Xo: R = 

The ratio of formation of V as a main product against VIa was examined in order to increase the yield and possible selective synthesis of both compounds. The results showed that fusion of IVa with 2-3 molar equivalents of urea at 170-180° for 3 hours and then at 270-280° for 5 minutes (method B) gave V predominantly in 73% yield and fusion with 2 molar equivalents of urea (method C) afforded VIa in 65% yield as shown in Table I. On the other hand, heating of equal molar equivalents of both compounds (method A) gave poor yields. Furthermore, in the latter case (method C), use of 3 molar equivalents of urea decreased the yield of VIa, and a polymer, which had the molecular formula $(CHNO)_n$, m.p. >350° (10), and was insoluble in almost all the organic solvents, was also formed as a colorless powder. When the fusion of urea itself was performed at 300° this polymer was again obtained. On the other hand, the fusion of IVa with urea at 190-200° for 45 minutes gave 1-phenylsemicarbazide (XI) (11).

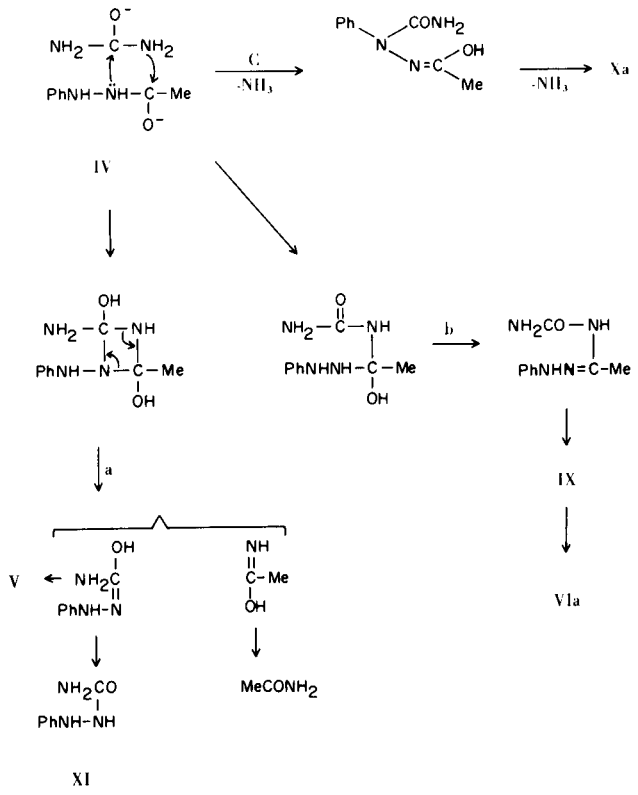
Perhaps the simplest mechanism for formation of these compounds would proceed *via* the routes, a, b, and c as shown in Scheme 3. The temperature seems to determine whether the above reaction would proceed by way of route a with deacylation or by route b with dehydration. The mechanism for the formation of VII was not studied.

TABLE I

The Reaction of 2-Acetyl-1-phenylhydrazine (IV) with Urea under Various Conditions

	Molecular Ratio		Reaction		Yield (%)	
	IV	Urea	Temp. (°C)	Time	V	VIa
	1	1	140-150	3 hr.	0	0
A	1	1	170-180	3 hr.	9	0
	1	1	190-200	3 hr.	10	0
	1	1	170-180	3 hr	26	10
			270-280	3 min.		
	1	1	170-180	3 hr.	35	14
			270-280	5 min.		
B	1	2	170-180	3 hr.	71	16
			270-280	5 min.		
	1	3	170-180	3 hr.	73	18
			270-280	5 min.		
	1	1	270-280	30 min.	12	4
	1	1	310-320	5 min.	trace	32
	1	2	280-300	20 min.	27	54
C	1	2	310-320	5 min.	trace	65
	1	3	310-320	5 min.	39	35
	1	3	310-320	10 min.	11	43
	1	3	310-320	20 min.	trace	19

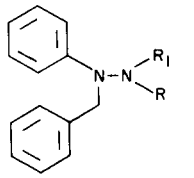
SCHEME 3



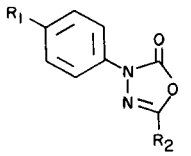
Finally, since these attempts to obtain the indazolone derivative were unsuccessful, 1-benzyl-2-acetyl- (XIIa) and 1-benzyl-2,2-diacetylphenylhydrazine (XIIb) were similarly treated resulting in the formation of a small amount of 1-phenyl-Δ^2-1,2,4-triazolidin-3,5-dione. Starting material was recovered almost quantitatively especially in the former case. Acetylation of compound XIIb gave the monoacetyl derivative (XIIa) quantitatively. Whereas in the reaction of 1-benzyl-2-benzoylphenylhydrazine (XIIc) with urea to give 2,4-diphenyl-Δ^2-1,3,4-oxadiazolin-5-one (Xo) (9), no product was formed.

Furthermore, various triazolinone (VIa-o) and oxadiazolinone derivatives (Xa-o) were synthesized by the best methods described above in order to test the physiological activity (12a-d). The reaction conditions and yields of these compounds are summarized in Table II and characterized in Tables III and IV. Table V gives the data of the bromo- and nitro-derivatives (XIII) of those oxadiazolinones, which could not be confirmed as X due to difficulty of crystallization.

SCHEME 4



XIIa: R = H, R_1 = COMe
XIIb: R = R_1 = COMe
XIIc: R = H, R_1 = COPh



XIII

TABLE II

Fusion of 2-Acylphenylhydrazine (IVa-o) with Urea

No.	x	R	IVx (g.)	Yield (%) Condition (a) A V	A VIx	A Xx	B V	B VIx	B Xx
1	a	$-CH_3$	2.2	71	16	trace	trace	65	2
2	b	$-H$	1.4	68	21	0	11	80	0
3	c	$-CH_2CH_3$	1.6	33	18	trace	trace	52	4
4	d	$-(CH_2)_2CH_3$	1.8	41	21	trace	22	50	5
5	e	$-(CH_2)_3CH_3$	1.9	41	41	3	25	52	4
6	f	$-(CH_2)_4CH_3$	2.0	43	25	5	18	50	5
7(b)	g	$-C_6H_{11}$	2.2	44	36	4	4	43	10
8	h	$-CH(CH_3)_2$	1.8	46	42	7	27	50	20
9	i	$-CH_2CH(CH_3)_2$	1.9	27	39	12	23	50	20
10	j	$-(CH_2)_2CH(CH_3)_2$	2.0	23	49	6	17	50	13
11(c)(d)	k	$-C(CH_3)_3$	1.9	18	25	45	9	34	45
12(c)	l	$-CH(C_2H_5)_2$	2.0	----	----	----	10	45	36
13(e)	m	$-CH=CH-CH_3$	3.4	0	61	0	0	78	0
14(e)	n	$-CH=CH-C_6H_5$	2.4	0	15	trace	0	69	27
15(e)	o	$-C_6H_5$	2.2	9	37	35	2	46	43

(a) The method A: A mixture of IVx with 2 molar equivalents of urea was heated at 170-180° for 3 hours and then at 310-320° for 5 minutes; the method B: The above mixture was heated at 310-320° for 5 minutes. (b) In this case since the melting point of the starting material (IVg) was higher, the mixture was heated at 190-200° for 3 hours and then at 310-320° for 5 minutes in case of the method A. (c) Using method B, the mixture was heated at 330-340° for 7 minutes. (d) The starting material (IVk) was recovered in 24% yield in case of the method A. (e) Because of the higher melting points of IVm-o, the mixtures were heated at 200-210° for 3 hours and then at 310-320° for 5 minutes (cf. IVm, m.p. 190°; IVn, m.p. 187-188°; IVo, m.p. 168°).

TABLE III

3-Substituted-1-phenyl-Δ^2-1,2,4-triazolin-5-one (VI)

	R	M.p. (°C) Appearance	Formula	Analyses Calcd. C	Analyses (Found) H	Analyses (Found) N	IR (Nujol) cm^{-1} ν NH	IR (Nujol) cm^{-1} ν C=O	NMR (a) (ppm) (C_2–H and C_6–H of *N*-phenyl group)
VIb	–H	183-184 (EtOH) Colorless prisms [lit. (13), 179-181]	$C_8H_7N_3O$	---			3160-2600	1685	7.90
VIc	$-CH_2CH_3$	122-123 (EtOH) colorless needles [lit. (8), 122-123]	$C_{10}H_{11}N_3O$	---			3200-2600	1713	7.96
VId	$-(CH_2)_2CH_3$	145-146 (AcOEt) colorless needles [lit. (8), 146]	$C_{11}H_{13}N_3O$	---			3140 (broad)	1710	7.97
VIe	$-(CH_2)_3CH_3$	120-121 (AcOEt) colorless needles	$C_{12}H_{15}N_3O$	66.41 (66.43	6.97 6.88	19.37 19.45)	3180-2650	1711	7.97
VIf	$-(CH_2)_4CH_3$	95-96 (petr. benzin) colorless needles	$C_{13}H_{17}N_3O$	67.50 (67.46	7.41 7.25	18.19 18.08)	3180-2650	1710	7.98
VIg	$-C_6H_{11}$	196-197 (AcOEt) colorless needles [lit. (14), 196-197]	$C_{14}H_{17}N_3O$	---			3200-2600	1715	7.98
VIh	$-CH(CH_3)_2$	175-176 (AcOEt) colorless needles	$C_{11}H_{13}N_3O$	65.08 (64.86	6.46 6.24	20.70 20.71)	3180-2600	1715	7.98
VIi	$-CH_2CH(CH_3)_2$	146-147 (petr. benzin) colorless needles [lit. (8), 149-151]	$C_{12}H_{15}N_3O$	---			3200-2600	1714	7.98
VIj	$-(CH_2)_2CH(CH_3)_2$	117-118 (petr. benzin) colorless needles	$C_{13}H_{17}N_3O$	67.50 (67.79	7.41 7.36	18.19 18.62)	3180-2680	1715	7.98
VIk	$-C(CH_3)_3$	208-209 (EtOH) colorless needles	$C_{12}H_{15}N_3O$	66.34 (66.48	6.96 6.86	19.34 19.41)	3250-2650	1717	8.15
VIl	$-CH(C_2H_5)_2$	153-154 (AcOEt) colorless needles	$C_{13}H_{17}N_3O$	67.50 (67.81	7.41 7.31	18.17 18.22)	3180-2650	1718	8.05
VIm	$-CH=CH-CH_3$	185-186 (AcOEt) colorless needles [lit. (14), 188]	$C_{11}H_{11}N_3O$	---			3150-2670	1705	7.97
VIn	$-CH=CH-C_6H_5$	227-228 (AcOEt) colorless needles	$C_{16}H_{13}N_3O$	72.98 (72.86	4.98 4.91	15.96 16.18)	3150-2650	1718	8.10
VIo	$-C_6H_5$	229-230 (EtOH) colorless needles [lit. (15), 229-230]	$C_{14}H_{11}N_3O$	---			3200-2600	1718	8.13

(a) Deuteriochloroform (2H, quarter, J = 9.0, 2.5 cps). (b) Sweep width, 300 Hz.

TABLE IV

2-Substituted-4-phenyl-Δ^2-1,3,4-oxadiazolin-5-one (X)

	R	M.p. (°C) Appearance	Formula	Analyses Calcd. (Found) C	H	N	IR (Nujol) cm^{-1} ν C=O	NMR (a) (ppm) (Two protons of C_2 and C_6 in phenyl ring)
Xc	$-CH_2CH_3$	62-63 (petr. ether) colorless prisms [lit. (9), 62-63]	$C_{10}H_{10}N_2O_2$	---	---	---	1796	7.84
Xd	$-(CH_2)_2CH_3$	58-59 (petr. benzin) colorless prisms	$C_{11}H_{12}N_2O_2$	64.76 (76.87	5.93 5.89	13.78 13.88)	1780	7.84
Xe	$-(CH_2)_3CH_3$	36-37 (petr. ether) colorless prisms	$C_{12}H_{14}N_2O_2$	66.03 (65.96	6.47 6.40	12.84 13.01)	1789	7.84
Xg	$-C_6H_{11}$	108-109 (petr. benzin) colorless prisms	$C_{14}H_{16}N_2O_2$	68.91 (69.09	6.61 6.56	11.48 11.42)	1795	7.86
Xk	$-C(CH_3)_3$	60-61 (petr. benzin) colorless prisms	$C_{12}H_{14}N_2O_2$	66.03 (66.15	6.47 6.50	12.84 12.72)	1785	7.90
Xn	$-CH=CH-C_6H_5$	106-107 (EtOH) yellow prisms	$C_{16}H_{12}N_2O_2$	72.71 (72.70	4.58 4.51	10.60 10.67)	1788	7.85
Xo	$-C_6H_5$	110-111 (EtOH) colorless prisms [lit. (9), 113-114]	$C_{14}H_{10}N_2O_2$	70.65 (70.58	4.26 4.51	11.76 12.00)	1783	7.95 (b)

(a) Deuteriochloroform (2H, quartet, J = 9.0, 2.5 cps). (b) Sweep width, 300 Hz.

TABLE V

Characterization of 2-Substituted-4-(4-bromo- or 4-nitrophenyl)-Δ^2-1,3,4-oxadiazolin-5-one (XIII)

Compound	R_1	R_2	Yield (%)	M.p. (°C) or b.p. Appearance	Formula	Analyses Calcd. (Found) C	H	N	NMR (a) (ppm) N–C_6H_4–R_1	
XIIIa	Br	$-(CH_2)_3CH_3$	81.7	76-77 (EtOH) colorless scales	$C_{12}H_{13}BrN_2O_2$	48.53 (48.61	4.41 4.28	9.43 9.64)	7.47	7.73
XIIIb	Br	$-(CH_2)_4CH_3$	79.4	61-62 (petr. ether) colorless scales	$C_{13}H_{15}BrN_2O_2$	50.20 (50.16	4.86 4.68	9.01 9.01)	7.49	7.73
XIIIc	Br	$-CH(CH_3)_2$	73.5	64-65 (petr. ether) colorless prisms	$C_{11}H_{11}BrN_2O_2$	46.68 (46.21	3.92 3.87	9.90 10.14)	7.45	7.72
XIIId	Br	$-CH_2CH(CH_3)_2$	88.2	65-66 (petr. ether) colorless scales	$C_{12}H_{13}BrN_2O_2$	48.49 (48.34	4.41 4.37	9.43 9.31)	7.50	7.76
XIIIe	Br	$-CH(C_2H_5)_2$	70.3	147-148 (0.25 mm. Hg) colorless oil	$C_{13}H_{15}BrN_2O_2$	50.20 (50.01	4.86 4.83	9.01 9.11)	7.54	7.83
XIIIf	NO_2	$-CH_2CH(CH_3)_2$	75.1	72-73 (petr. ether-EtOH) colorless prisms	$C_{12}H_{13}N_3O_4$	54.75 (54.82	4.98 4.87	15.96 16.32)	8.01	8.30
XIIIg	NO_2	$-(CH_2)_2CH(CH_3)_2$	76.8	64-65 (MeOH) colorless prisms	$C_{13}H_{15}N_3O_4$	56.31 (56.49	5.45 5.38	15.16 15.19)	8.07	8.36

(a) Deuteriochloroform (2H, doublet, J = 9.0 cps).

The physiological activity of seven triazolinone derivatives (VI) and their effects on carrageenin-induced edema in rats were examined as shown in Table VI.

TABLE VI

Effect of 1-Phenyl-Δ^2-1,2,4-triazolin-5-one Derivatives on Carrageenin-Induced Edema in Rats

Compound	Rats	Dose (mg./kg.)	Inhibition (%) 3 (hours)	5
VIa	6	30	13.5	2.1
VIe	6	30	-69.7	-44.4
VIh	6	30	-66.2	-2.4
VIi	6	30	-8.7	8.3
VIj	6	30	-50.0	-44.4
VIg	6	30	9.6	2.0
VIo	6	30	8.0	2.5

EXPERIMENTAL (16)

Fusion of 2-Acetyl-1-phenylhydrazine (IVa) with Urea.

(a) A mixture of 6.5 g. (0.043 mole) of IVa and 2.6 g. (0.043 mole) of urea was heated at 170-180° (bath temperature) for 3 hours and then at 270-280° for 3 minutes with evolution of ammonia gas. After cooling, the reaction mixture was triturated with ether-ethanol (10:1) to precipitate the crystals, which were collected and recrystallized from ethanol to give 1.95 g. (25.5%) of 1-phenyl-Δ^2-1,2,4-triazolidin-3,5-dione (V) as colorless scales, m.p. 260-261° [lit. (5), m.p. 262-263°]; ir ν max (nujol), cm^{-1}, 3150, 3050 (NH), 1755, 1700 (C=O); uv λ max (ethanol), mμ (log ϵ) 250 (4.03). Evaporation of the above filtrate *in vacuo* gave a residue, which was separated by chromatography on alumina as follows to give four fractions (17). The first benzene eluate gave an oil which was extracted with hot petroleum ether to give 0.01 g. of 3-methyl-1,4-diphenyl-Δ^2-1,2,4-triazolin-5-one (VII) as colorless prisms, m.p. 106-107° [lit. (10), m.p. 108°]; ir (nujol) cm^{-1} 1700 (C=O); nmr (ppm in deuteriochloroform), 2.12 (3H, singlet, CH_3), 7.98 (4H, quartet, J = 8.0 and 2.5 cps, C_2H, $C_2'H$, C_6H, $C_6'H$), 7.17-7.55 (6H, multiplet, C_3H, C_4H, C_5H, $C_3'H$, $C_4'H$, $C_5'H$); uv λ max (ethanol), mμ (log ϵ) 248 (4.59), 280 (3.32).

The residue, which was insoluble in the hot petroleum ether above, was chromatographed on alumina using benzene as an eluant. Removal of the first eluate (18) gave a syrup, which was recrystallized from ethanol to afford 0.06 g. of 2-methyl-4-phenyl-Δ^2-1,3,4-oxadiazolin-5-one (Xa) as colorless prisms, m.p. 91-94° [lit. (9), m.p. 93-94°]; ir ν max (nujol), cm^{-1} 1776 (C=O); nmr (ppm in deuteriochloroform), 2.37 (3H, singlet, CH_3), 7.82 (2H, quartet, J = 8.0 and 2.5 cps, C_2H, C_6H), 7.17-7.58 (3H, multiplet, C_3H, C_4H, C_5H); uv λ max (ethanol), mμ (log ϵ) 241 (4.19), 271 (2.95), 279 (2.71).

Evaporation of the second benzene eluate gave a colorless powder, which was recrystallized from benzene to afford 1.9 g. (30%) of the starting material (IVa). The filtrate gave 0.35 g. of acetamide, whose ir spectrum was identical with that of an authentic sample.

The third fraction eluated with chloroform gave a solid, which recrystallized from ethanol to give 0.8 g. (10.4%) of 3-methyl-1-phenyl-Δ^2-1,2,4-triazolin-5-one (VIa) as colorless needles, m.p. 165-166° [lit. (6), m.p. 168-170°]; ir ν max (nujol), cm^{-1} 3180-2605 (NH), 1700 (C=O); nmr (ppm in deuteriochloroform), 2.23 (3H, singlet, CH_3), 7.90 (2H, quartet, J = 8.0 and 2.5 cps, C_2H, C_6H), 7.15-7.57 (3H, multiplet, C_3H, C_4H, C_5H), 12.32 (1H, broad, NH); uv λ max (ethanol), mμ (log ϵ) 249 (4.17), 280 (2.98).

The fourth fraction eluated with ethanol gave a solid, which was recrystallized from ethanol to give 0.1 g. of 3-methyl-1-phenyl-1,2,4,6,8-pentaazaoct-2-ene-5,7-dione (IX) as colorless needles, m.p. 174-175°; ir ν max (nujol), cm^{-1} 3450, 3300, 3220, 3000 (NH), 1710, 1680 (C=O), 1630 (C=N); uv λ max (ethanol) mμ (log ϵ) 249 (4.22), 280 (2.93).

Anal. Calcd. for $C_{10}H_{13}N_5O_2$: C, 51.05; H, 5.57; N, 29.77. Found: C, 51.43; H, 5.85; N, 29.68.

(b) A mixture of 2.2 g. (0.015 mole) of IVa and 1-3 molar equivalents of urea shown in Table I was heated under various conditions and the reaction mixture was worked up according to the above method (a) to give V and VIa.

In some cases the ether-soluble substance was dissolved in a small amount of dilute sodium hydroxide solution to remove insoluble material. The alkaline solution was acidified with concentrated hydrochloric acid to precipitate the crystals, which were collected, washed, and dried to give VIa.

Formation of 1-Phenylsemicarbazide (XI).

A mixture of 2.2 g. of IVa and 0.9 g. (one molar equivalent) of urea was heated at 190-200° for 45 minutes. After addition of ether, an insoluble substance was collected and recrystallized from a small amount of water. The filtrate was saturated with sodium chloride to give the crystals, which were chromatographed on alumina using benzene-ethanol (9:1), to give XI as colorless needles, m.p. 171-172° (ethanol) [lit. (19), m.p. 172°], which were identical to an authentic sample by mixed melting point test and ir spectral comparison. In this case, compound IVa and acetamide were also obtained from the first eluate.

Fusion of 3-Methyl-1-phenyl-1,2,4,6,8-pentaazaoct-2-ene-5,7-dione (IX).

Fusion of 0.5 g. of IX at 300-320° with an evolution of ammonia gas, followed by recrystallization from ethanol, gave 0.37 g. of VIa as colorless needles, m.p. 165-166°, whose ir spectrum was identical with that of an authentic sample.

2,4-Diacetyl-1-phenyl-Δ^2-1,2,4-triazolidin-3,5-dione (Va).

A mixture of 0.3 g. of V and 20 ml. of acetic anhydride was heated at 180-190° for 3 hours in a sealed tube. After cooling, the reaction mixture was mixed with 30 ml. of water. Collection of the solid, followed by recrystallization from ethanol, gave 0.3 g. (60%) of Va as colorless needles, m.p. 161-162° [lit. (7), m.p. 162-163°]; ir ν max (nujol), cm^{-1} 1820, 1765, 1720 (C=O); nmr (ppm in deuteriochloroform), 2.62 and 2.67 (3H each, two singlets, 2 x $COCH_3$), 7.34 (5H, singlet, aromatic protons).

4-Acetyl-3-methyl-1-phenyl-Δ^2-1,2,4-triazolin-5-one (VIp).

The usual acetylation of 0.5 g. of VIa with acetic anhydride gave 0.45 g. (72%) of the acetyl derivative (VIp) as colorless needles, m.p. 95-96° (from ethanol); ir ν max (nujol), cm^{-1} 1735, 1705 (sh) (C=O); nmr (ppm in deuteriochloroform), 2.58 and 2.73 (3H each, two singlets, CH_3 and $COCH_3$), 7.88 (2H, quartet, J = 7.5, 2.5 cps, C_2H, C_6H), 7.18-7.57 (3H, multiplet, C_3H, C_4H, C_5H).

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: N, 19.35. Found: N, 19.54.

3-Methyl-4-(γ-dimethylaminopropyl)-1-phenyl-Δ^2-1,2,4-triazolin-5-one (VIII) Hydrochloride.

To a refluxing mixture of 1 g. of VIa and one molar equivalent of sodium methoxide in 50 ml. of dry xylene was added dropwise a solution of 0.9 g. of γ-dimethylaminopropyl chloride in 10 ml. of xylene within 1 hour, and the refluxing was then continued for 2 hours. After the reaction mixture had been washed with water and extracted with 2 *N* hydrochloric acid solution, the resulting acidic extract was made basic with dilute sodium hydroxide solution and extracted with ether. The extract was washed with water, dried and evaporated to give an oil, which was chromatographed on alumina using benzene as an eluant. The first eluate (19) gave 1.2 g. of VIII as a colorless oil; ir ν max (liquid) cm^{-1} 1705 (C=O), whose hydrochloride was recrystallized from ethanol-ether to afford 1.0 g. (62%) as colorless needles, m.p. 156-157°.

Anal. Calcd. for $C_{14}H_{21}ClN_4O$: C, 56.65; H, 7.13; N, 18.87. Found: C, 56.61; H, 7.35; N, 18.72.

2,4-Diphenyl-Δ^2-1,3,4-oxadiazolin-5-one (Xo).

A mixture of 1.5 g. of 2-benzoyl-1-benzylphenylhydrazine (XIIc) and 0.6 g. of urea was heated at 300-310° in a metal-bath for 7 minutes. After cooling the chloroform was added and an insoluble substance was removed by filtration while warm. After evaporation of the chloroform extract, the residue was chromatographed on alumina. The benzene eluate gave 0.95 g. of colorless prisms, m.p. 110-111° [lit. (9), m.p. 113-114°], ir ν max (nujol), cm^{-1} 1783 (C=O).

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.65; H, 4.26; N, 11.76. Found: C, 70.53; H, 4.43; N, 11.78.

The Representative Reaction of 2-Valeryl-1-phenylhydrazine (IVe) with Urea as One Example under the Conditions Shown in Table II.

(a) A mixture of 1.9 g. (0.01 mole) of IVe and 1.2 g. (0.02 mole) of urea was heated at 170-180° (bath temperature) for 3 hours and then at 310-320° for 5 minutes. After cooling, the resulting reddish brown viscous syrup was refluxed with 30 ml. of chloroform on a water-bath and an insoluble substance began to separate. After cooling at room temperature, the precipitate was collected and washed with a small amount of chloroform to afford 762 mg. of a colorless powder, to which was added 50 ml. of ethanol. After reflux of the preceding mixture on a water-bath, an insoluble polymer (55 mg.), m.p. >350° was removed by filtration. Evaporation of the ethanolic filtrate gave 700 mg. (41.2%) of a colorless powder, m.p. 259-260.5°, which was recrystallized from ethanol to give 1-phenyl-Δ^2-1,2,4-triazolidin-3,5-dione (V) as colorless scales, m.p. 260-261°, identical with an authentic sample.

Removal of the above chloroform extract gave 800 mg. of a syrup, which was chromatographed on silica gel (100-200 mesh) using benzene as an eluant. The first eluate [benzene-chloroform (1:1); detected with ultraviolet irradiation (λ = 3650 Å); the strongly luminescent substance in the colorless column was collected] gave 69 mg. (3.3%) of colorless crystals, which were recrystallized from petroleum ether to afford 2-butyl-4-phenyl-Δ^2-1,3,4-oxadiazolin-5-one (Xe) as colorless prisms, m.p. 36-37°; ir ν max (nujol), cm^{-1} 1789 (C=O); nmr (ppm in deuteriochloroform), 7.84 (2H, quartet, J = 9.0, 2.5 cps, C_2H, C_6H), 7.1-7.6 (3H, multiplet, C_3H, C_4H, C_5H), 2.60 (2H, triplet, J = 7.2 cps, $C_2-CH_2CH_2-$).

Evaporation of the second chloroform eluate gave 854 mg. (40.8%) of a pale brown powder, which was recrystallized from ethyl acetate to give 3-butyl-1-phenyl-Δ^2-1,2,4-triazolin-5-one (VIe) as colorless needles, m.p. 120-121°; ir ν max (nujol), cm^{-1} 3180-2650 (NH), 1711 (C=O); nmr (ppm in deuteriochloroform), 7.97 (2H, quartet, J = 9.0, 2.5 cps, C_2H, C_6H), 7.1-7.6 (3H, multiplet, C_3H, C_4H, C_5H), 2.56 (2H, triplet, J = 7.2 cps, $-CH_2CH_2-$), 12.12 (1H, broad, NH).

Removal of the third eluate [chloroform and chloroform-ethanol (3:1)] gave 450 mg. of a colorless powder, whose recrystallization from ethanol gave valeramide as colorless needles, m.p. 115-116° [lit. (20), m.p. 114-116°].

(b) A mixture of 1.9 g. (0.01 mole) of IVe and 1.2 g. (0.02 mole) of urea was heated in a metal-bath (330°); the temperature was then lowered to 310-320° for 5 minutes, and the mixture was worked up according to the method (a) to give 420 mg. (25.1%) of V, 92 mg. (4.3%) of Xe and 1.1 g. (52.4%) of VIe.

2-Substituted-4-(4-bromophenyl)-Δ^2-1,3,4-oxadiazolin-5-one (XIII: R_1 = Br.).

The following experiment is described as a representative example. To a stirred solution of 500 mg. of 2-isobutyl-4-phenyl-Δ^2-1,3,4-oxadiazolin-5-one (Xi) [colorless oil, ir ν max (liquid), cm^{-1} 1788 (C=O)] in 40 ml. of chloroform was added dropwise a solution of 500 mg. of bromine in 2 ml. of chloroform at room temperature and the stirring was continued for 3 hours. The reaction mixture was washed with water, saturated sodium bicarbonate, 5% sodium thiosulfate and water, dried over sodium sulfate, and evaporated to give 600 mg. (88.2%) of a colorless solid which recrystallized from petroleum ether to give 4-(4-bromophenyl)-2-isobutyl-Δ^2-1,3,4-oxadiazolin-5-one [XIIId: R_1 = Br, R_2 = $CH_2CH(CH_3)_2$] as colorless scales, m.p. 65-66°.

Data for other compounds synthesized are summarized in Table V.

2-Substituted-4-(4-nitrophenyl)-Δ^2-1,3,4-oxadiazolin-5-one (XIII: R_1 = NO_2).

The following experiment was carried out as a representative example. To a solution of 600 mg. of 2-isoamyl-4-phenyl-Δ^2-1,3,4-oxadiazolin-5-one (Xj) [colorless oil, ir ν max (liquid), cm^{-1}; 1786 (C=O)] in 2 g. of acetic acid was added dropwise 2 g. of fuming nitric acid with cooling. After heat evolution had ceased, the mixture was set aside at room temperature overnight. The reaction mixture was poured into 50 ml. of ice-water and the crystals which separated were collected and recrystallized from methanol to give 550 mg. (76.8%) of 2-isoamyl-4-(4-nitrophenyl)-Δ^2-1,3,4-oxadiazolin-5-one [XIIIg: R_1 = NO_2, R_2 = $-(CH_2)_2CH(CH_3)_2$] as pale yellow prisms, m.p. 64-65°.

The other examples are summarized in Table V.

Investigation of the Effect on Plantar Edema Induced by Carrageenin in the Rat (21).

Six male rats of Wistar strain were used as one group. After the samples tested had been dissolved in 0.1 *N* sodium hydroxide aqueous solution, the *p*H of the resulting solution was adjusted to 10 with 0.1 *N* hydrochloric acid. The solutions were diluted with physiological saline.

Thirty mg. of the sample per 1 kg. of body weight were injected subcutaneously into the dorsum of the experimental rats, whereas only the corresponding volume of physiological saline was injected into the control group. After 1 hour, 0.1 ml. of a carrageenin suspension [0.1% (w/v) in physiological saline, sterilized by heating at 120° for 10 minutes in an autoclave] was injected subcutaneously on the right foot pad of the rat.

Before and after carrageenin injection, the foot volume was measured (22) and the edema volume was determined by the

difference between two measured values. Inhibition ratios (%) in comparison with the control group on a carrageenin-induced edema are shown in Table VI.

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