Studies on the Syntheses of Azole Derivatives. Part VII (1). Syntheses of 1-Phenyl-Δ^2-1,2,4-triazolin-5-one Derivatives [Studies on the Syntheses of Heterocyclic Compounds. CDXI (2)]

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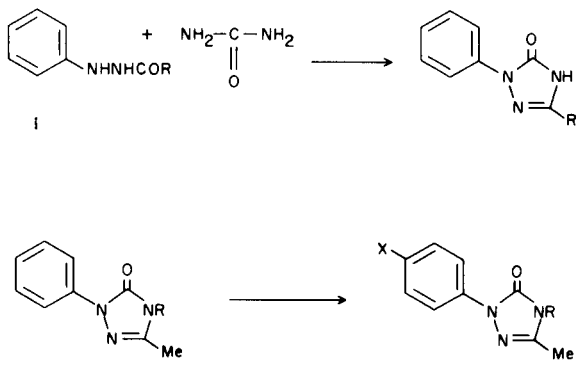
Received February 25, 1971

Bromination of 3-methyl-1-phenyl-Δ^2-1,2,4-triazolin-5-one (II) and its 4-phenyl derivative III afforded the corresponding 1-(*p*-bromophenyl) derivatives IV and V, respectively. Chlorination of the 4-phenyl derivative III gave 1-(*p*-chlorophenyl) derivative VI. In addition, 3-*N*-substituted-carbamoyl-1,2,4-triazolin-5-ones (XII, XIII, and XIV) were synthesized by the Schotten-Baumann reaction of 3-carboxy-1-phenyl-Δ^2-1,2,4-triazolin-5-one (XI) with various amines.

In the previous paper (4), the authors reported the syntheses of a series of 1,2,4-triazolin-5-ones by fusion of β-acylphenylhydrazine (I) with urea. Since some of the 1-phenyl-Δ^2-1,2,4-triazolin-5-one derivatives (4) were found to be effective against carrageenin induced edema in rats, we further investigated the syntheses of 1-phenyl-Δ^2-1,2,4-triazolin-5-ones with the purpose of testing the pharmacological activity. Herein we wish to report these results.

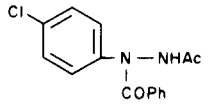
Chart 1



I

II: R = H
III: R = Ph

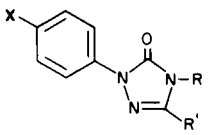
IV: R = H, X = Br
V: R = Ph, X = Br
VI: R = Ph, X = Cl



VIa

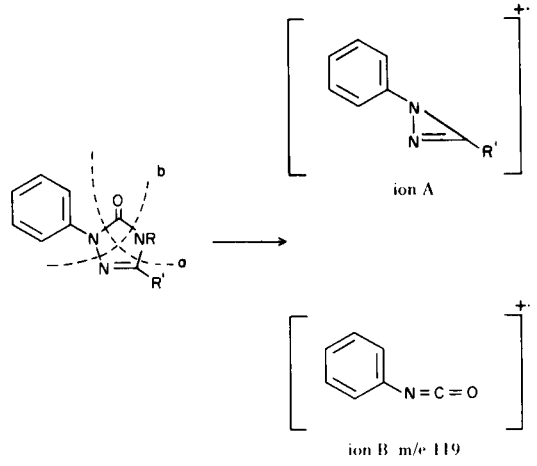
First the halogenation of 3-methyl-1-phenyl-Δ^2-1,2,4-triazolin-5-one (II) (4) and 3-methyl-1,4-diphenyl-Δ^2-1,2,4-triazolin-5-one (III) (4) was investigated. Bromination of II with bromine afforded 1-(*p*-bromophenyl)-Δ^2-1,2,4-triazolin-5-one (IV), whose NMR (DMSO-d_6) spectrum indicated the presence of a *p*-disubstituted aromatic ring giving signals at 7.54 and 7.83 ppm as AB type doublets (J = 9.0 Hz). Mass spectrum (M^+ and M + 2: m/e 253 and 255, respectively) and microanalysis of this compound supported the structure IV. Compound III was brominated in the same manner to give the monobrominated derivative V and bromination was found to occur on the N_1-benzene ring selectively. An NMR (DMSO-d_6) spectrum of this product showed a couple of AB type doublets (J = 9.0 Hz) at 7.61 and 7.90 ppm. The characteristic fragmentation pattern (5) of the 1,2,4-triazolin-5-one derivatives in the mass spectra started with the molecular ion of high intensity, followed by cleavage at *a* or *b* to ions A and B, respectively, as shown in Chart 2. Cleavage of the triazolin ring resulted in the loss of CONR producing the positively charged stable ion A. The origin of ion A by the illustrated pathway is confirmed by the observation of metastable ions. The mass numbers and relative intensities of the molecular ion peak (M^+), ion A, and ion B in the mass spectra of various kinds of 1,2,4-triazolin-5-one derivatives are recorded in Table I. The mass spectrum of the borminated compound V exhibited the molecular ion at m/e 329 (M + 2 at m/e 331), ion A (R′ = Me) at m/e 210, and ion B at m/e 197 (and 212, 199 due to ^{81}Br). Furthermore, a peak at m/e 132 (M^+ -$CONC_6H_4Br$) was not observed in its mass spectrum. These facts indicate that the bromine atom is situated at the *para*-position of the benzene ring at N_1.

TABLE I



	R′	R	X	M^+ m/e (%)	ion A	ion B
1	H	H	H	161 (70)	118 (20)	119 (10)
2	Me	H	H	175 (70)	132 (10)	119 (4)
3	$(CH_2)_3Me$	H	H	217 (70)	174 (18)	119 (15)
4	CH=CH-Me	H	H	201 (100)	158 (11)	119 (5)
5	CH=CH-Ph	H	H	263 (100)	220 (15)	119 (2)
6	Ph	H	H	237 (65)	194 (18)	119 (2)
7	Me	Ph	H	251 (80)	132 (22)	119 (18)
8	Me	H	^{81}Br	255 (100)	212 (10)	199 (1)
			Br	253 (100)	210 (10)	197 (1)
9	Me	Ac	H	217 (18)	132 (16)	119 (2)

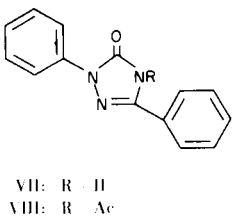
Chart 2



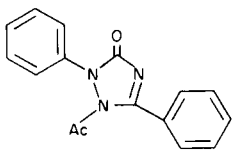
Treatment of III with sulfuryl chloride afforded the monochloro derivative VI, the structure of which was confirmed by comparison of spectroscopic data with those of the authentic specimen prepared from 1-acetyl-2-(*p*-chlorophenyl)-4-phenylsemicarbazide (VIa). Its NMR (DMSO-d_6) spectrum showed a couple of AB type doublets at 7.50 and 7.97 ppm and its mass spectrum showed a fragmentation pattern similar to that of V, indicating that chlorination also occurred at the *para*-position of the benzene ring at N_1. Consequently the N_1-phenyl group was found to be more active toward halogenation than the N_4-phenyl group.

Secondly, 1,3-diphenyl-Δ^2-1,2,4-triazolin-5-one (VII) was treated with acetic anhydride to afford the 4-acetyl derivative. Although there are three possible structures (VIII, IX, X) for the acetylated product, its mass spectrum indicated that VIII was the most likely structure. The fragmentation pattern was similar to that of a variety of 1-phenyl-3-substituted-Δ^2-1,2,4-triazolin-5-one and exhibited characteristic ions A and B at m/e 194 (R′ = C_6H_5) and 119, respectively.

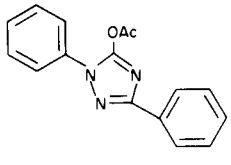
Chart 3



VII: R = H
VIII: R = Ac



IX

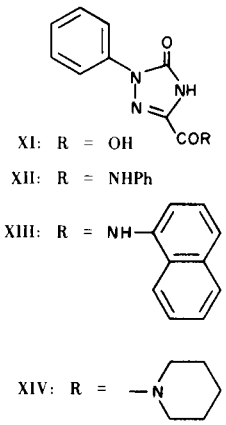


X

Finally, 3-carbamoyl-1-phenyl-Δ^2-1,2,4-triazolin-5-one derivatives and 5-carbamoyl-3-chloro-1-phenyl-1,2,4-triazole (XVII) were synthesized. Heating of the chloride, prepared from 3-carboxy-1-phenyl-Δ^2-1,2,4-triazolin-5-one

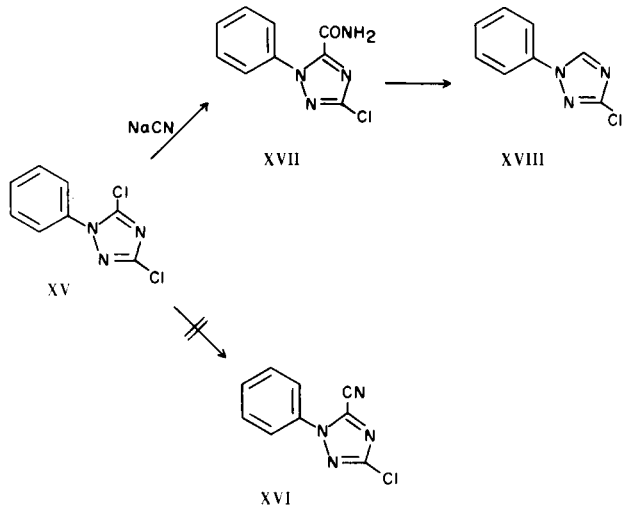
(XI) (6), with aniline, α-naphthylamine, and piperidine afforded the corresponding 3-carbamoyl derivatives XII, XIII, and XIV, respectively.

Chart 4



Furthermore, a novel reaction occurred on the attempted cyanation of 3,5-dichloro-1-phenyl-1,2,4-triazole (XV) (7). The treatment of XV with sodium cyanide afforded the 5-carbamoyl derivative XVII instead of the expected compound XVI. Conversion of XVII to 3-chloro-1-phenyl-1,2,4-triazole (XVIII) (8) confirmed the structure of XVII.

Chart 5



Pharmacological activity of all the above compounds is under investigation.

EXPERIMENTAL (9)

1-(*p*-Bromophenyl)-3-methyl-Δ^2-1,2,4-triazolin-5-one (IV).

To a stirred solution of 1 g. of 3-methyl-1-phenyl-Δ^2-1,2,4-triazolin-5-one (II) in 30 ml. of chloroform was added a solution of 2 g. of bromine in 15 ml. of chloroform. After the stirring had been continued for 3 hours, the mixture was worked up as usual to give 0.65 g. of IV as colorless needles, m.p. 263-264° (from ethanol). IR ν max (Nujol) cm^{-1}: 3200-2600 (NH), 1708 (C=O). NMR (DMSO-d_6) δ: 2.17 (3H, s, CH_3), 7.54 (2H, d, J = 9.0 Hz, C_3'-H and C_5'-H), 7.83 (2H, d, J = 9.0 Hz, C_2'-H and C_6'-H), 11.80 (1H, broad, NH). Mass (m/e): 253 (M^+, base peak), 255 (M + 2), 212, 210, 199, 197, 171, 169.

Anal. Calcd. for $C_9H_8BrN_3O$: C, 42.54; H, 3.16; N, 16.48. Found: C, 42.32; H, 3.13; N, 16.12.

1-(*p*-Bromophenyl)-3-methyl-4-phenyl-Δ^2-1,2,4-triazolin-5-one (V).

To a stirred solution of 1 g. of 3-methyl-1,4-diphenyl-Δ^2-1,2,4-triazolin-5-one (III) in 30 ml. of acetic acid was added dropwise a solution of 2.1 g. of bromine in 10 ml. of acetic acid. After the stirring had been continued for 4 hours, the mixture was poured into water and the precipitate was collected by filtration and recrystallized from ethanol to give 1.2 g. of V as colorless plates, m.p. 153-154°; IR ν max (Nujol) cm^{-1}: 1719 (C=O); NMR (DMSO-d_6) δ: 2.15 (3H, s, CH_3), 7.51 (5H, s, N_4-aromatic H), 7.61 (2H, d, J = 9.0 Hz, C_3'-H and C_5'-H at N_1-Ph), 7.90 (2H, d, J = 9.0 Hz, C_2'-H and C_6'-H); Mass (m/e): 329 (M^+), 331 (M + 2), 212, 210, 199, 197, 171, 169 (base peak).

Anal. Calcd. for $C_{15}H_{12}BrN_3O$: C, 54.56; H, 3.66; N, 12.72. Found: C, 54.28; H, 3.63; N, 12.65.

1-(*p*-Chlorophenyl)-3-methyl-4-phenyl-Δ^2-1,2,4-triazolin-5-one (VI).

(a) To a stirred solution of 0.5 g. of 3-methyl-1,4-diphenyl-Δ^2-1,2,4-triazolin-5-one (III) in a mixture of 5 ml. of acetic acid and 5 ml. of propionic acid was added a solution of 2.4 g. of sulfuryl chloride in 5 ml. of acetic acid. After the stirring had been continued for 5 hours, the mixture was poured into ice-water to give a precipitate, which was filtered off and recrystallized from ethanol to give 0.5 g. of VI as colorless prisms, m.p. 132-133°; IR ν max (Nujol) cm^{-1}: 1699 (C=O); NMR (DMSO-d_6) δ: 2.17 (3H, s, CH_3), 7.53 (5H, s, N_4-aromatic H), 7.50 (2H, d, J = 9.0 Hz, C_3'-H and C_5'-H at N_1-Ph-H), 7.97 (2H, d, J = 9.0 Hz, C_2'-H and C_6'-H at N_1-Ph-H); Mass (m/e): 284 (M^+), 286 (M + 2), 167, 165, 154, 152, 126, 124 (base peak).

Anal. Calcd. for $C_{15}H_{12}ClN_3O$: C, 63.05; H, 4.23; N, 14.71. Found: C, 63.01; H, 4.20; N, 14.82.

(b) A mixture of 3 g. of VIa and 60 ml. of 5% potassium hydroxide solution was refluxed for 45 minutes. After cooling, the crystals which separated were collected by filtration to give 1.8 g. of VI. Recrystallization from ethanol-water gave VI as colorless prisms, m.p. 132-133°, the spectroscopic data of which were identical with those of the chlorinated compound prepared from III.

1-Acetyl-2-(*p*-chlorophenyl)-4-phenylsemicarbazide (VIa).

A mixture of 10 g. of 1-acetyl-2-(4-chlorophenyl)hydrazine, 12 g. of phenyl isocyanate, and 200 ml. of benzene was refluxed for 0.5 hour. After cooling, the crystals which separated were collected by filtration and recrystallized from benzene to give 6.8 g. of VIa as colorless needles, m.p. 177-178°; ν max (Nujol) cm^{-1}: 3340 (NH), 1680 (C=O).

Anal. Calcd. for $C_{15}H_{14}ClN_3O$: C, 59.31; H, 4.65; N, 13.83. Found: C, 59.56; H, 4.66; N, 14.05.

4-Acetyl-1,3-diphenyl-Δ^2-1,2,4-triazolin-5-one (VIII).

A mixture of 0.2 g. of 1,3-diphenyl-Δ^2-1,2,4-triazolin-5-one (VII) and 3 ml. of acetic anhydride was refluxed for 2 hours. The usual treatment of the mixture, followed by recrystallization of

the crude product from ethanol, gave 0.2 g. of VIII as colorless needles, m.p. 143-144°; IR ν max (Nujol) cm^{-1}: 1739 (C=O); Mass (m/e): 279 (M^+), 194, 119, 91 (base peak).

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.06. Found: C, 68.87; H, 4.51; N, 15.03.

1-Phenyl-3-(*N*-phenylcarbamoyl)-Δ^2-1,2,4-triazolin-5-one (XII).

To a stirred suspension of 1 g. of 3-carboxyl-1-phenyl-Δ^2-1,2,4-triazolin-5-one (XI) in benzene was added 1.6 g. of phosphorus pentachloride and the mixture was heated on a water-bath for 1.5 hours. After the solvent had been evaporated, a solution of the remaining residue and 1 g. of aniline in benzene was heated at 70° for 1 hour. The precipitate was collected by filtration. The filtrate was washed with 5% hydrochloric acid, dried over sodium sulfate and evaporated to give the crude product which was combined with the above precipitate and recrystallized from ethanol to give 0.75 g. of XII as colorless needles, m.p. 281-282°; Mass (m/e): 280 (M^+, base peak), 119, 91.

Anal. Calcd. for $C_{15}H_{12}N_4O_2$: C, 64.27; H, 4.32; N, 19.99. Found: C, 64.32; H, 4.40; N, 19.70.

3-(α-Naphthylaminocarbonyl)-1-phenyl-Δ^2-1,2,4-triazolin-5-one (XIII).

A solution of 1.6 g. of 3-carbonyl-1-phenyl-Δ^2-1,2,4-triazolin-5-one (XI) in 20 ml. of benzene was treated with 1.6 g. of phosphorus pentachloride as above and a mixture of the crude acid chloride, 1.2 g. of α-naphthylamine, and 50 ml. of benzene was worked up as above. Recrystallization of the crude product from ethanol afforded 0.6 g. of XIII as colorless needles, m.p. 266-267°; Mass (m/e): 330 (M^+), 119, 91; IR ν max (Nujol) cm^{-1}: 3280, 3100-2600 (NH), 1708, 1669 (C=O).

Anal. Calcd. for $C_{19}H_{14}N_4O_2$: C, 69.08; H, 4.27; N, 16.96. Found: C, 69.15; H, 4.28; N, 16.98.

1-Phenyl-3-piperidinocarbonyl-Δ^2-1,2,4-triazolin-5-one (XIV).

The crude acid chloride, prepared from 1 g. of XI and 1.6 g. of phosphorus pentachloride as above, was treated with 1.5 g. of piperidine. After the usual work-up, the crude product was recrystallized from ethanol to give 0.55 g. of XIV as pale yellowish needles, m.p. 192-193°; IR ν max (Nujol) cm^{-1}: 3160-2600 (NH), 1703, 1640 (C=O); Mass (m/e): 272 (M^+), 119, 91.

Anal. Calcd. for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.60. Found: C, 61.62; H, 5.64; N, 20.64.

5-Carbamoyl-3-chloro-1-phenyl-1,2,4-triazole (XVII).

A mixture of 5 g. of 3,5-dichloro-1-phenyl-1,2,4-triazole, 6 g. of sodium cyanide, 50 ml. of ethanol, and 70 ml. of water was refluxed for 6 hours. After cooling, the precipitate was collected by filtration and recrystallized from ethanol-water to give 3.5 g. of XVII as colorless needles, m.p. 214-215°; IR ν max (Nujol) cm^{-1}: 3400, 3250 (NH_2), 1700 (C=O); Mass (m/e): 223 (M^+) and 225 (M + 2 due to ^{37}Cl).

Anal. Calcd. for $C_9H_7ClN_4O$: C, 48.55; H, 3.17; N, 25.17. Found: C, 48.61; H, 3.19; N, 25.02.

3-Chloro-1-phenyl-1,2,4-triazole (XVIII).

A solution of 0.5 g. of XVII in a mixture of 30 ml. of 20% potassium hydroxide and 10 ml. of ethanol was refluxed for 10 hours. After the solvent had been evaporated, the remaining aqueous solution was made neutral with 10% hydrochloric acid and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to give a solid, which was recrystallized from petroleum ether to afford 0.3 g. of XVIII as colorless needles, m.p. 75-76° (10) [lit. (8), m.p. 76°]; Mass (m/e): 179 (M^+) and 181 (M + 2 due to ^{37}Cl).

Anal. Calcd. for $C_8H_6ClN_3$: C, 53.50; H, 3.37; N, 23.48. Found: C, 53.65; H, 3.31; N, 23.67.

Acknowledgment.

We thank Vice-President S. Uehara and Director S. Ikawa, Taisho Pharmaceutical Co. Ltd., for their encouragement. We also thank Dr. I. Tanaka, Dr. T. Seki, and Dr. R. Yanase, Research Laboratory, Taisho Pharmaceutical Co. Ltd., for their kind suggestions and Mr. S. Hirata, Pharmaceutical Institute, Tohoku University, for mass spectral determinations.

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(9) Melting points are uncorrected. IR spectra were measured with a type EPI-3 Hitachi recording spectrometer, NMR spectra with a Hitachi R-20 spectrometer with tetramethylsilane as an internal reference, and mass spectra were measured with a Hitachi RMU-7 mass spectrometer operating at 80 eV.

(10) According to the literature (11), 5-chloro-1-phenyl-1,2,4-triazole showed m.p. 54° and, therefore, an alternative 5-chloro-structure should be excluded.

(11) A. Andreocci, *Atti della Reale Accademia dei Lindei (Rendiconti)*, (5), 6I, 221, 224 (1897) [*Beilstein*, 26, 21].