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Reaction of Biguanides and Related Compounds. XIII.[1] Benzilic Acid Rearrangement. The Reactions of 1,2-Cyclohexanedione and 9,10-Phenanthrenequinone with Arylbiguanides and N-Amidino-O-alkylisoureas[2]

Mitsuru Furukawa, Takatoshi Yoshida, and Seigoro Hayashi

Faculty of Pharmaceutical Sciences, Kumamoto University[3]

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Benzilic acid rearrangements of 1,2-cyclohexanedione (I) and 9,10-phenanthrenequinone (II) are described: The base-catalysed condensation of I with arylbiguanides (III) and with N-amidino-O-alkylisoureas (IV) gave 2-arylguanidylidene-4-oxo-1,3-diazaspiro[4.4]-nonanes (V) and 2-alkoxyamidinylidene-4-oxo-1,3-diazaspiro[4.4]nonanes (X) respectively. Analogously, the reaction of II with III and with IV afforded 2-arylguanidylidene-5-fluorenylidene-4-oxoimidazolidines (XI) and 2-alkoxyamidinylidene-5-fluorenylidene-4-oxoimidazolidines (XII) respectively.

Toi[4] reported that arginine reacts with 1,2-cyclohexanedione in basic conditions to give N^5-(4-oxo-1,3-diazaspiro[4.4]non-2-ylidene)-ornithine. Later, the same reaction with a decreased concentration of the base is shown by Anzai[5] to afford N^5-(1-hydroxy-5-oxo-2,4-diazabicyclo[4.3.0]non-2-ylidene)-ornithine together with N^5-(4-oxo-1,3-diazaspiro[4.4]non-2-ylidene)-ornithine. The proportion of the products is dependent upon the base concentration. A similar rearrangement is also observed in the reaction of 1,2-cyclohexanedione with guanidine in alkaline solution.[5] Such rearrangements of α-diketone similar to the benzilic acid rearrangement are known in the reactions of benzil with guanidines,[6] biguanides,[7] and N-amidino-O-alkylisoureas.[8] However, little has been known relating to the benzilic acid rearrangement of 1,2-cyclohexanedione with ring contraction, except that 1,2-cyclohexanedione is transformed to 1-hydroxycyclopentanecarboxylic acid[9] on heating in a concentrated sodium hydroxide solution. We wish now to report the same rearrangement in the reactions of 1,2-cyclohexanedione (I) or 9,10-phenanthrenequinone (II) with arylbiguanides (III) or with N-amidino-O-alkylisoureas (IV).

Reactions of 1,2-Cyclohexanedione (I) with Arylbiguanides (III) and N-Amidino-O-alkylisoureas (IV)

When I was heated with an equivalent amount of III in ethanol for 20 min under reflux and then the reaction mixture was concentrated by partial evaporation, a product was obtained in 30—50% yield, as the only product isolated. The reaction proceeded more readily at

1) Part XII: M. Furukawa, T. Yoshida, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 2875 (1974).
2) A part of this paper has been reported in a preliminary form: see M. Furukawa, T. Yoshida, and S. Hayashi, *Synthesis*, **1974**, 132.
3) Location: *Oe-hon Machi, Kumamoto, 862, Japan.*
4) K. Toi, F. Bynum, E. Norris, and H.A. Itano, *J. Biol. Chem.*, **242**, 1036 (1967).
5) K. Anzai, *Bull. Chem. Soc. Japan*, **42**, 3314 (1969).
6) H.W. Carhart and P.C. Teague, *Chem. Abstr.*, **47**, 1733 (1953); H. Adkins, J.E. Castle, and E.E. Royals, *ibid.*, **48**, 2117 (1954); M. Lempert-Sreter, V. Solt, and K. Lempert, *ibid.*, **59**, 10022 (1963); K. Lempert and M. Lempert-Sreter, *Chem. Ber.*, **94**, 796 (1961); R.G. Nevile, *J. Org. Chem.*, **23**, 1588 (1958).
7) M. Furukawa, Y. Fujino, Y. Kojima, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 521 (1972).
8) M. Furukawa, K. Matsuoka, T. Yoshida, Y. Kojima, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 1 (1974).
9) O. Wallach, *Ann. Chem.*, **437**, 174 (1924).

room temperature in the presence of sodium ethoxide catalyst in a similar yield. The elemental analysis of the product corresponded to that of the condensation product of the molecular equivalents of I and III with elimination of water. It was confirmed by the molecular determination by mass spectrometry, in which the molecular ion peak was observed as the most abundant peak. The infrared (IR) spectrum of the product exhibited a characteristic absorption assignable to a carbonyl group at 1700—1710 cm^{-1}. The frequency of the carbonyl absorption was quite similar to that of 2-arylguanidylidene-5,5-diphenyl-4-oxoimidazolidine.[7] The ultraviolet (UV) spectrum showed the maximum absorption band near 220 nm and the absorption pattern was quite similar to that of 2-arylguanidylidene-5,5-diphenyl-4-oxoimidazolidine. The nuclear magnetic resonance (NMR) spectrum (C_5D_5N) showed an eight-proton multiplet at 1.70—2.50 δ corresponding to the cyclopentylidene ring. On the basis of these results, it is reasonable to conclude that 2-arylguanidylidene-4-oxo-1,3-diazaspiro-[4.4]nonane (V) is the most likely for the structure of the product. The results are summarized in Table I.

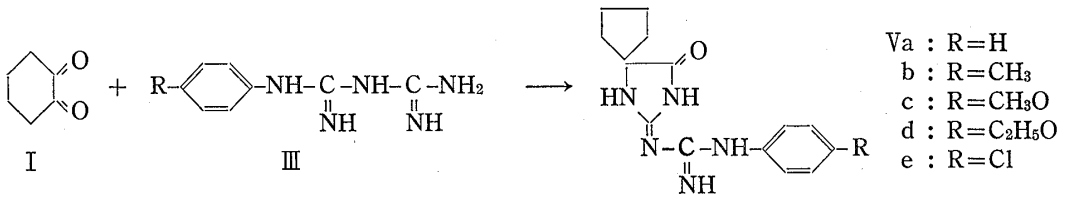

Chart 1

TABLE I. 2-Arylguanidylidene-4-oxo-1,3-diazaspiro[4.4]nonane (V)

No.	Yield (%)	mp (decomp) (°C)	Formula	Analysis (%) Found (Calcd.) C	H	N	IR cm^{-1} (KBr) $\nu_{C=O}$
Va	33	250—251	$C_{14}H_{17}ON_5$	61.95 (61.97)	6.68 (6.32)	25.56 (25.81)	1710
Vb	40	254—255	$C_{15}H_{19}ON_5$	63.42 (63.14)	6.84 (6.71)	24.04 (24.55)	1705
Vc	41	251—252	$C_{15}H_{19}O_2N_5$	59.81 (59.78)	6.61 (6.36)	23.10 (23.24)	1705
Vd	52	229—230	$C_{16}H_{21}O_2N_5$	61.06 (60.93)	6.80 (6.71)	21.93 (22.21)	1710
Ve	47	263—264	$C_{14}H_{16}ON_5Cl$	55.14 (54.99)	5.34 (5.27)	23.20 (22.91)	1710

The formation of V can be reasonably explained by assuming a molecular rearrangement, in which the cyclohexane ring undergoes 1,2-shift similar to benzilic acid rearrangement. The rearrangement starts with the addition of the amino nitrogen atom of III onto the carbonyl carbon atom of I to form VI. Because of the parallel inductive effects of the two negative oxygen function in VII, an anionotropic migration of a C-C bond in the cyclohexane ring results and forms the anion VIII which is stabilized by the formation of IX followed by the intramolecular cyclization to V.

The similar rearrangement reaction was observed in the reaction between I and IV under the similar conditions in the presence of a catalytic amount of sodium ethoxide to give 2-alkoxyamidinylidene-4-oxo-1,3-diazaspiro[4.4]nonanes (X) in about 50% yield. The reaction readily proceeded at room temperature, accompanying the slight elevation of the temperature of the reaction mixture. In the absence of the catalyst, however, no crystalline product was obtained even by heating for a prolonged reaction time. The exchange of the methoxy

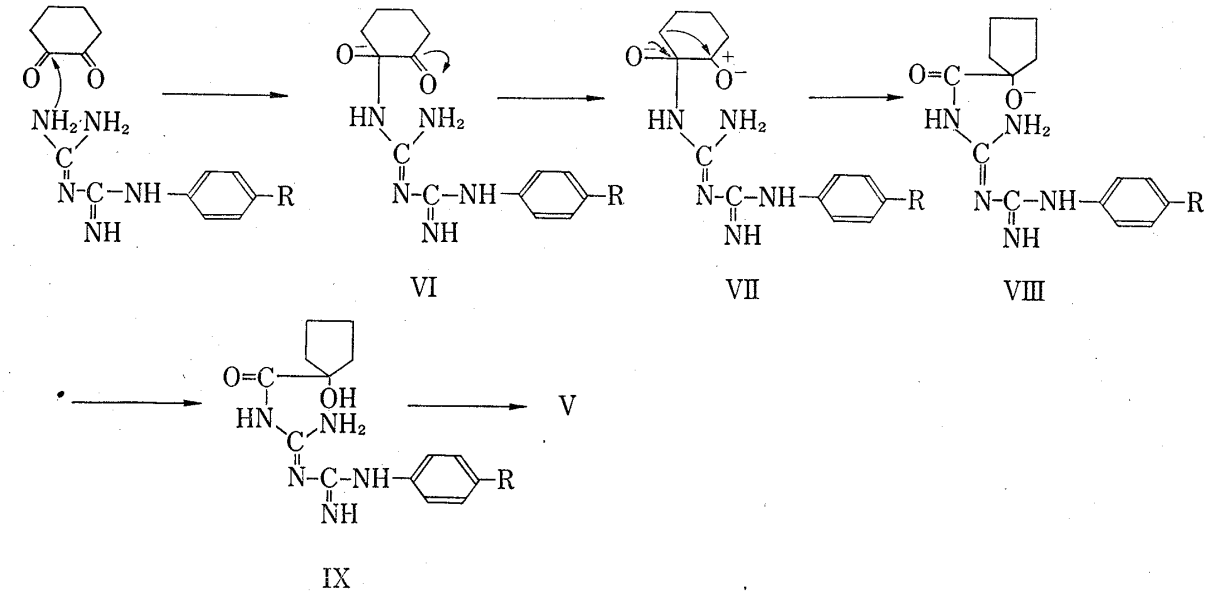

Chart 2

group of the product into the ethoxy group, arising from ethanol used as the reaction solvent, was observed only in the case of IVa. Of course, such a exchange reaction can be avoided by using methanol as the solvent. The IR spectrum of X exhibited the absorption assignable to a carbonyl group near 1660 cm^{-1}. The NMR spectrum (C_5D_5N) showed the eight-proton multiplet at 1.60—2.50 δ corresponding to the cyclopentylidene ring. The UV spectrum indicated a maximum absorption band at 230—240 nm and the absorption pattern was quite similar to that of V. The mass spectrum exhibited the molecular ion peak as the most abundant peak and the experimental elemental analysis gave a satisfactory agreement with that of X. All of the compounds obtained are summarized in Table II.

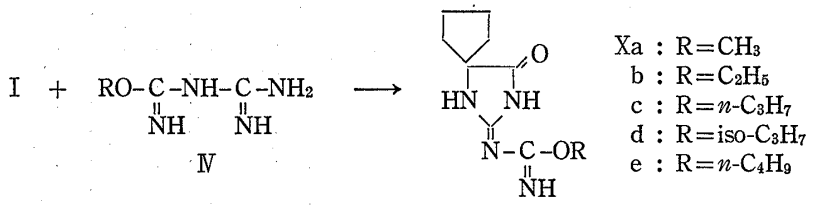

Chart 3

Table II. 2-Alkoxyamidinylidene-4-oxo-1,3-diazaspiro [4.4] nonane (X)

No.	Yield (%)	mp (decomp) (°C)	Formula	Analysis (%) Found (Calcd.) C	H	N	IR cm^{-1} (KBr) $\nu_{C=O}$
Xa	52	202—203	$C_9H_{14}O_2N_4$	51.92 (51.42)	6.65 (6.71)	26.42 (26.65)	1665
Xb	51	213—214	$C_{10}H_{16}O_2N_4$	53.83 (53.55)	7.00 (7.19)	25.02 (24.99)	1668
Xc	42	205—206	$C_{11}H_{18}O_2N_4$	55.14 (55.44)	7.48 (7.61)	23.41 (23.52)	1665
Xd	54	232—233	$C_{11}H_{18}O_2N_4$	55.50 (55.44)	7.89 (7.61)	23.54 (23.52)	1658
Xe	55	197—198	$C_{12}H_{20}O_2N_4$	57.14 (57.11)	7.65 (7.99)	22.13 (22.21)	1660

Reactions of 9,10-Phenanthrenequinone (II) with Arylbiguanides (III) and N-Amidino-O-alkylisoureas (IV)

Compound II is known to react specifically with arginine and with arginyl peptides to form the highly fluoresent 2-amino-1H-phenanthro[9,10-*d*]imidazole.[10] On the other hand, we found that II underwent a benzilic acid transformation similar to the case of I with III and with IV.

When equimolar quantities of II and III were heated in ethanol in the presence of a catalytic amount of sodium ethoxide under reflux, 2-arylguanidylidene-5-fluorenylidene-4-oxoimidazolidines (XI) were obtained in moderate yields. Analogously, the heating of II with an equivalent amount of IV under the similar conditions gave 2-alkoxyamidinylidene-5-fluorenylidene-4-oxoimidazolidines (XII). The results are summarized in Table III.

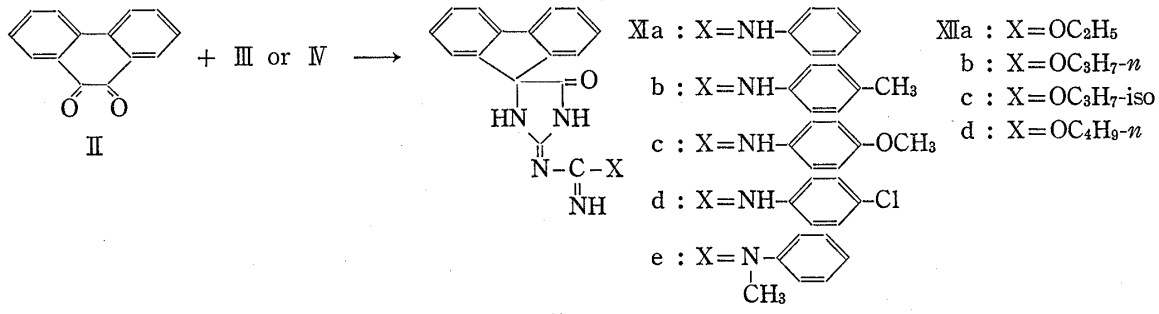

Chart 4

TABLE III. 2-Arylguanidylidene-5-fluorenylidene-4-oxoimidazolidine (XI) and 2-Alkoxyamidinylidene-5-fluorenylidene-4-oxoimidazolidine (XII)

No.	Yield (%)	mp (decomp) (°C)	Formula	Analysis (%) Found (Calcd.) C	H	N	IR cm^{-1} (KBr) $\nu_{C=O}$
XIa	71	172—174	$C_{22}H_{17}ON_5$	72.31 (71.92)	4.79 (4.66)	18.91 (19.06)	1690
XIb	59	169—171	$C_{23}H_{19}ON_5$	71.96 (72.42)	5.32 (5.02)	18.02 (18.36)	1690
XIc	50	184—185	$C_{23}H_{19}O_2N_5$	69.15 (69.51)	5.15 (4.82)	17.48 (17.62)	1685
XId	46	187—188	$C_{22}H_{16}ON_5Cl$	65.75 (65.83)	4.01 (4.17)	17.43 (17.18)	1690
XIe	51	203—204	$C_{23}H_{19}ON_5$	72.57 (72.42)	5.21 (5.02)	17.96 (18.36)	1690
XIIa	56	228	$C_{18}H_{16}O_2N_4$	67.63 (67.48)	4.78 (5.03)	17.09 (17.49)	1693
XIIb	36	209	$C_{19}H_{18}O_2N_4$	68.38 (68.24)	5.13 (5.42)	17.09 (16.76)	1700
XIIc	95	220	$C_{19}H_{18}O_2N_4$	68.43 (68.24)	5.46 (5.42)	16.82 (16.76)	1695
XIId	15	233	$C_{20}H_{20}O_2N_4$	69.24 (68.95)	6.01 (5.79)	16.39 (16.08)	1680

The mass spectra of XI and XII respectively showed the corresponding molecular ion peaks as the most abundant peak. The IR spectra of XI and XII exhibited the absorption assignable to the carbonyl group near 1690 cm^{-1}. The UV spectrum of X indicated the maximum absorption band near 245 nm and the absorption pattern was quite similar to that of 2-arylguanidylidene-5,5-diphenyl-4-oxoimidazolidine.

10) S. Yamada and H.A. Itano, *Biochem. Biophys. Acta.*, **130**, 538 (1966).

The mechanism for this rearrangement with ring contraction can be reasonably explained similarly to the case of I.

Generally, II shows the typical reactions of a 1,2-diketone and it is well known to undergo a benzilic acid transformation with aqueous caustic alkali with the formation of biphenyleneglycollic acid. Therefore, the result that the reaction of III or IV with II was quite similar to that with I was just as expected. On the other hand, arginine shows a exclusively quite different behavior toward II,[10] though similar results are obtained with I and benzil.[11] The difference of the reactivity is difficult to explain reasonably.

Experimental[12]

2-Arylguanidylidene-4-oxo-1,3-diazaspiro[4.4]nonane (V)——General Procedure: To a solution of arylbiguanide (5 mmole) in EtOH (20 ml) was added dropwise with stirring 1,2-cyclohexanedione (5 mmole) at room temperature. The mixture was heated for 20 min under reflux and concentrated by partial evaporation under reduced pressure. The precipitates thus deposited on cooling were collected by filtration, washed with a small amount of cold EtOH, and recrystallized from EtOH to give colorless prisms.

2-*p*-Methoxyphenylguanidylidene-4-oxo-1,3-diazaspiro[4.4]nonane (Vc)——A solution of sodium ethoxide prepared by dissolving metallic sodium (0.115 g, 5 mg-atom) in EtOH (10 ml) was added with stirring into a hot solution of *p*-methoxyphenylbiguanide hydrochloride (1.22 g, 5 mmole) in EtOH (20 ml). The precipitates of NaCl were removed by filtration and 1,2-cyclohexanedione (0.57 g, 5 mmole) was added, drop by drop, with stirring into the filtrate at room temperature. The mixture was heated for 20 min under reflux and the precipitates thus deposited during heating were collected by filtration after cooling. The filtrate was concentrated by partial evaporation under reduced pressure and the precipitates were collected by filtration. The combined precipitates were recrystallized from EtOH to give colorless prisms (0.62 g, 41%), mp 251—252°. NMR (C_5D_5N): δ 1.70—2.50 (m, 8H, cyclopentylidene CH_2), 3.67 (s, 3H, OCH_3), 7.00 (d, J=9 Hz, 2H, arom-H), 7.57 (d, J=9 Hz, 2H, arom-H), 7.93 (bs, 2H, NH), 8.74 (bs, 2H, NH). Mass Spectrum *m/e*: 301 (M^+).

2-Alkoxyamidinylidene-4-oxo-1,3-diazaspiro[4.4]nonane (X)——General Procedure: To a solution of sodium ethoxide prepared by dissolving metallic sodium (6 mg-atom) in EtOH (10 ml) was added with stirring powdered N-amidino-O-alkylisourea hydrochloride (5 mmole) at room temperature. The precipitated NaCl was filtered off and 1,2-cyclohexanedione (5 mmole) was added dropwise with stirring into the filtrate. The mixture was allowed to stand for 15 min at room temperature and then heated for 20 min under reflux. After completion of the reaction, the mixture was concentrated by partial evaporation under reduced pressure and the precipitates deposited on cooling were collected by filtration and washed with a small amount of EtOH. Recrystallization from EtOH gave colorless plates.

2-Methoxyamidinylidene-4-oxo-1,3-diazaspiro[4.4]nonane (Xa)——To a solution of sodium methoxide prepared by dissolving sodium (0.13 g, 6 mg-atom) in MeOH (10 ml) was added with stirring powdered N-amidino-O-methylisourea hydrochloride (0.76 g, 5 mmole) at room temperature. The precipitates thus deposited were filtered off and 1,2-cyclohexanedione (0.57 g, 5 mmole) was added, drop by drop, with stirring into the filtrate. The mixture was allowed to stand for 15 min at room temperature and then heated for 20 min under reflux. After completion of the reaction, the mixture was concentrated by partial evaporation under reduced pressure. The precipitates deposited on cooling were collected by filtration, washed with a small amount of MeOH, and recrystallized from MeOH to give colorless plates (0.55 g, 52%), mp 202—203°. NMR (C_5D_5N): δ 1.60—2.50 (m, 8H, cyclopentylidene CH_2), 3.82 (s, 3H, OCH_3). Mass Spectrum *m/e*: 210 (M^+).

2-Arylguanidylidene-5-fluorenylidene-4-oxoimidazolidine (XI)——General Procedure: A solution of arylbiguanide (2.5 mmole) and 9,10-phenanthrenequinone (2.5 mmole) in EtOH (70 ml) was heated for 3 hr under reflux and the mixture was then concentrated by partial evaporation. The precipitates thus deposited were collected by filtration, washed with EtOH, and recrystallized from AcOEt to give light yellow prisms. The detailed data were summarized in Table III.

2-Alkoxyamidinylidene-5-fluorenylidene-4-oxoimidazolidine (XII)——General Procedure: Powdered N-amidino-O-alkylisourea (2.5 mmole) was added with stirring into an ethanolic solution of sodium ethoxide

11) K. Toi, E. Bynum, E. Norris, and H.A. Itano, *J. Biol. Chem.*, **240**, 3455 (1965).

12) All the melting points are uncorrected. IR spectra were measured on a JASCO IRA-1 Grating Infrared Spectrometer. UV spectra were obtained with a Hitachi 124 Spectrophotometer. Mass spectra were determined at 75 eV on a JEOL JMS-O1SG Mass Spectrometer. NMR spectra were determined at 60 MHz on a JEOL High Resolution NMR Instrument C-60H, using tetramethylsilane as the internal standard. The chemical shifts were expressed in δ values (s: singlet, bs: broad singlet, d: doublet, m: multiplet).

prepared by dissolving metallic sodium (3 mg-atom) in EtOH (10 ml) at room temperature and then precipitated NaCl was filtered off. 9,10-Phenanthrenequinone (2.5 mmole) was added into the filtrate, and the mixture was stirred for 24 hr at room temperature and then filtered. The precipitates were unchanged 9,10-phenanthrenequinone (20—100 mg). The filtrate was evaporated to dryness under reduced pressure at room temperature and the residue was recrystallized from EtOH. The detailed data were summarized in Table III.

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