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# Studies on Mesoionic Compounds. III.[1] Synthesis of $\psi$-3-Aryl-5-imino-3,5-dihydro-1-oxa-2,3,4-triazole Hydrochlorides and Their Derivatives

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Several hitherto unknown mesoionic compounds, $\psi$-3-aryl-5-imino-3,5-dihydro-1-oxa-2,3,4-triazole hydrochlorides (III) were synthesized starting from monoarylhydrazines (IV) *via* cyanohydrazines (V) and nitrosocyanohydrazines (VI). The mesoionic compounds (III) were converted into their N-acyl derivatives (VIII) by treatment with various acylating agents. The free base (VII) was isolated in crystalline from the 3-phenyl homolog of III by treatment with aqueous bicarbonate; although the corresponding sydnonimine hydrochloride has been known to result in the ring opening under similar conditions.

Recently, Kier, *et al.*[3] synthesized a number of 3-substituted $\psi$-5-keto-3,5-dihydro-1-oxa-2,3,4-triazoles (I) and disclosed that some of the compounds were hypotensive in the animal tests. A similar observation was made by us[4] with sydnonimine hydrochlorides (II) having secondary amines as substituents at the 3-position. In the hope of finding further improved hypotensive agents, we have attempted to synthesize new mesoionic compounds (III), which are structurally isosteric to sydnonimine hydrochlorides and are the imino derivatives of I.

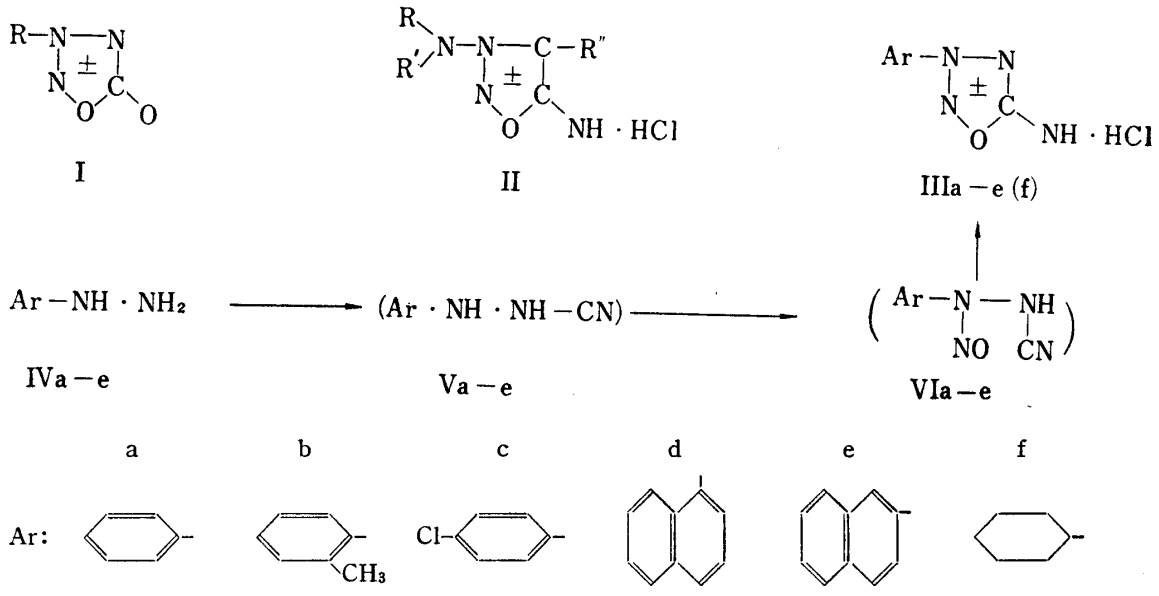



Chart 1

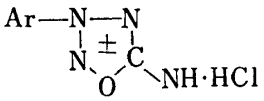
To date there has been reported only one compound, $\psi$-3-cyclohexyl-5-imino-3,5-dihydro-1-oxa-2,3,4-triazole hydrochloride (IIIf),[5] in the $\psi$-oxatriazole imine system. This mesoionic

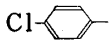
1) Part II: K. Masuda, T. Kamiya, Y. Imashiro, and T. Kaneko, *Chem. Pharm. Bull.* (Tokyo), **19**, 72 (1971).
2) Location: *Juso-Nishinocho, Higahiyodogawa-ku, Osaka.*
3) L.B. Kier, A. Al-Shamma, D. Campbell, P. Patil, and A. Tye, *Nature*, **210**, 742 (1966); L.B. Kier, A. Al-Shamma, R. Hahn, and A. Tye, *J. Pharm. Sci.*, **55**, 1467 (1966).
4) K. Kikuchi, M. Hirata, A. Nagaoka, and Y. Aramaki, *Japan. J. Pharmacol.*, **20**, 23 (1970).
5) W.G. Finnegan and R.A. Henry, *J. Org. Chem.*, **30**, 567 (1965).

compound was synthesized by ring closure of 1-cyclohexyl-2-guanyl-1-nitrosohydrazine, which was prepared from cyclohexanone in three steps.

In the present study $\phi$-5-imino-3,5-dihydrooxatriazole hydrochlorides (IIIa—e) were synthesized by a different route, which we designed on the basis of the usual method for the synthesis of sydnonimines.[6] The intermediary cyanohydrazines (V) and nitrosohydrazines (VI) corresponding to $\alpha$-aminonitriles and nitroso-$\alpha$-aminonitriles in the synthesis of sydnonimines were obtained by the reaction of monoarylhydrazines (IV) with bromocyanogen followed by nitrosation of the resulting V. It was unsuccessful to isolate these intermediates owing to their extreme instability except for the cyanohydrazine Ve, which was isolated in a crystalline form and identified by the infrared (IR) spectrum (3300, 2200 $cm^{-1}$). The last step for the synthesis of III from VI was carried out by treatment of the solution containing VI with alcoholic hydrochloric acid; the yields, physicochemical properties and elementary analyses of IIIa—e are summarized in Table I.

Table I. $\phi$-3-Aryl-5-imino-3,5-dihydro-1-oxa-2,3,4-triazole Hydrochloride



| | Ar | Yield[a] (%) | mp (°C) | IR ($cm^{-1}$) | Formula | Analysis (%) Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| IIIa |  | 60.5 | 191—192 (decomp.) | 1690 | $C_7H_7ON_4Cl$ | 42.33 | 3.55 | 28.21 | 42.32 | 3.44 | 28.24 |
| IIIb |  | 55 | 166—168 (decomp.) | 1700 | $C_8H_7ON_4Cl \cdot 1/2H_2O$ | 43.35 | 4.55 | 25.28 | 43.72 | 4.45 | 25.59 |
| IIIc |  | 61 | 196 (decomp.) | 1700 | $C_7H_6ON_4Cl_2$ | 36.07 | 2.60 | 24.04 | 36.11 | 2.73 | 23.78 |
| IIId |  | 59 | 175—180[b] (decomp.) | 1740 | $C_{11}H_9ON_4Cl \cdot 1/2H_2O$ | 51.27 | 3.91 | 21.74 | 51.07 | 3.34 | 21.24 |
| IIIe |  | 61 | 180—181 (decomp.) | 1700 | $C_{11}H_9ON_4Cl \cdot H_2O$ | 49.54 | 4.16 | 21.01 | 49.61 | 4.22 | 20.88 |

a) overall yield of IV → V → VI → III
b) When temperature was raised in a slow rate IIId turned to a brownish mass at about 170° and did not show a discrete melting point.

In the IR spectra, all the four compounds (IIIa—e) showed intense absorption bands near 1700 $cm^{-1}$, which were consistent with the reported value (1694 $cm^{-1}$) of the 3-cyclohexyl derivative (IIIf).[5]

Neutralization of $\phi$-5-imino-3-phenyl-3,5-dihydro-1-oxa-2,3,4-triazole hydrochloride (IIIa) with aqueous bicarbonate in the cold yielded a crystalline yellow base. The structure VII was assigned to this base because, i) the IR spectrum revealed intense absorptions at 1720 and 1670 $cm^{-1}$ while no absorption of a nitrile, ii) the ultraviolet (UV) absorption was more intense than that of phenylhydrazine, and iii) the Liebermann's nitroso reaction was negative. Moreover, the free base was readily converted to the benzoyl and nitroso compounds (VIIIa, IX).[7] This undoubtedly is a rare instance of isolation of a free base of an imino-type mesoionic compound[8] which has been believed difficult to isolate.[6]

6) F.H.C. Stewart, *Chem. Rev.*, **64**, 129 (1964); M. Ohta and H. Kato, *Nippon Kagaku Zasshi*, **86**, 661 (1965).
7) A similar benzoylation or nitrosation procedure with an open-chain N-morpholino-N-nitrosoaminoacetonitrile led to neither benzoyl- nor nitroso-3-morpholinosydnonimine.
8) J.H. Bryden, R.A. Henry, W.G. Finnegan, R.H. Boschan, W.S. McEwan, and R.W. Van Dolah, *J. Am. Chem. Soc.*, **75**, 4863 (1953).

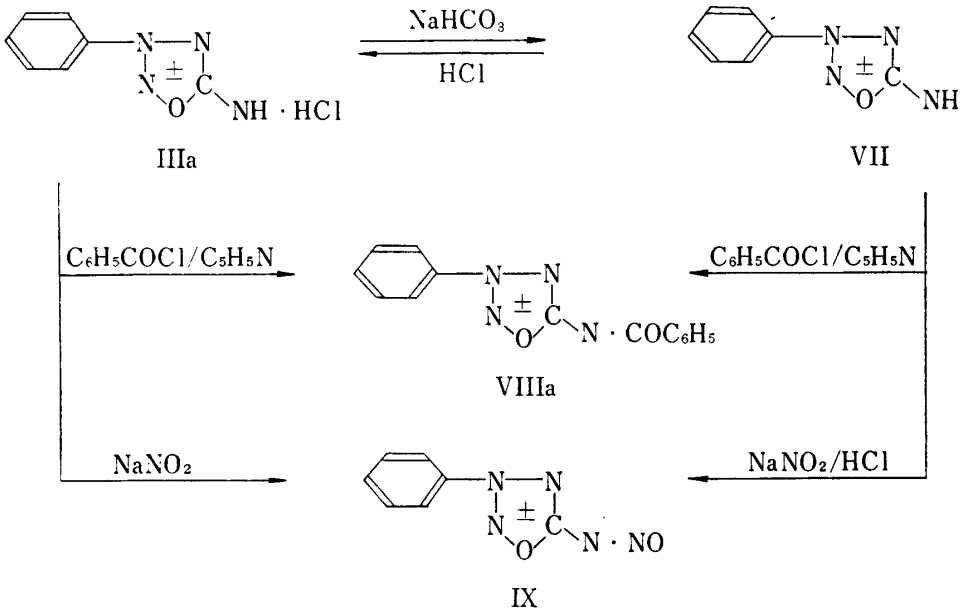



Chart 2

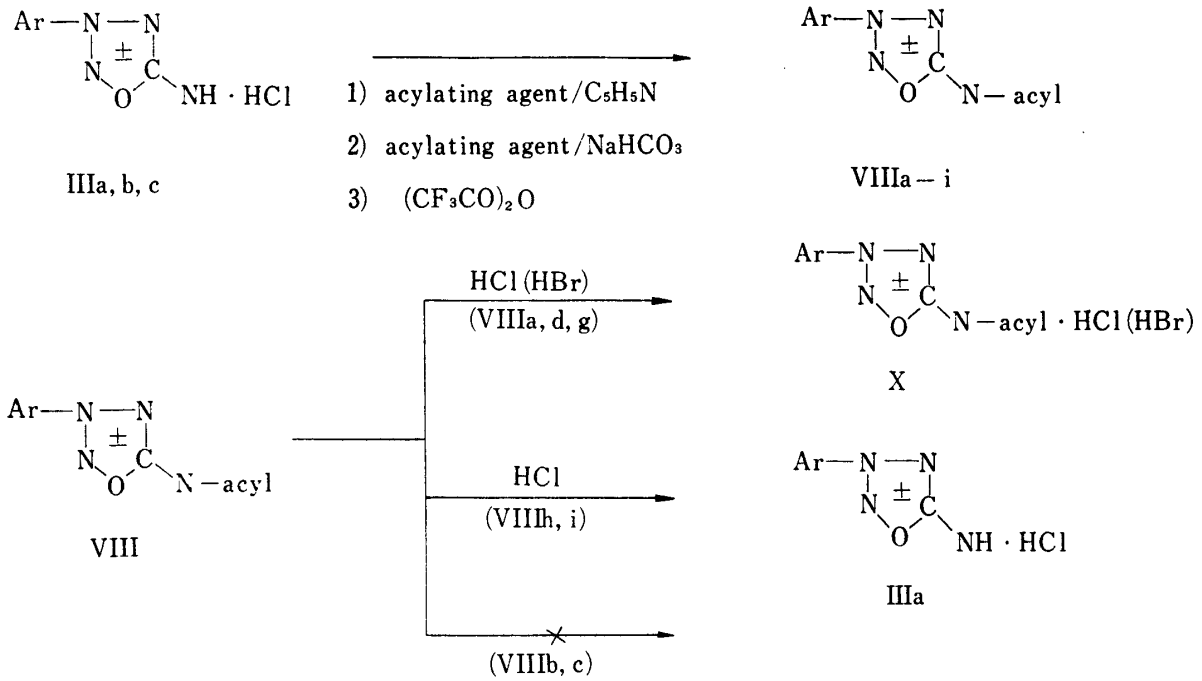
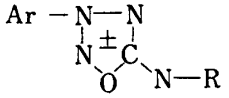
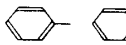
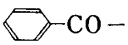
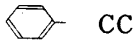
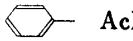
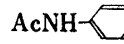
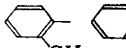
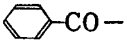
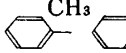
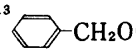
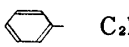
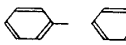
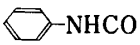
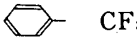
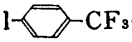



Chart 3

When mesoionic salts (III) were treated with various acylating agents under the conditions where the N-acylsydnonimines were produced from sydnonimine hydrochlorides, the N-acyl derivatives (VIII) were obtained as shown in Chart 3 and Table II. These N-acyl derivatives (VIII) showed reactivities somewhat similar to those of N-acylsydnonimines against acids. Thus, the benzoyl and N-phenylcarbamoyl derivatives (VIIIa, d, g) afforded the salts (X) and the trifluoroacetyl derivatives (VIIIh, i) were deacylated to IIIa, while the trichloroacetyl and N-acetylsulfanyl derivatives (VIIIb,c) remained intact. It should be mentioned, however, that the salts of N-acyl derivatives, unlike N-acylsydnonimine salts, were not stable.

Table II. N-Acyl-$\phi$-3-aryl-5-imino-3,5-dihydro-1-oxa-2,3,4-triazole



| | Ar | R | Yield (%) | mp (°C) | IR[a] ($cm^{-1}$) |
|---|---|---|---|---|---|
| VIIIa |  |  | 97 | 165—167 | 1647 |
| VIIIb |  | $CCl_3CO-$ | 97 | 169—171 | 1640 |
| VIIIc |  | AcNH-  $-SO_2-$ | 82 | 237 | 1706<br>1680 |
| VIIId |  |  | 91 | 145—147 | 1660 |
| VIIIe |  |  | 67 | 151—152 | 1680 |
| VIIIf |  | $C_2H_5OCO-$ | 80.5 | 115—117 | 1690 |
| VIIIg |  |  | 92 | 162—165 (decomp.) | 1666 |
| VIIIh |  | $CF_3CO-$ | 84.5 | 137—138 | 1685 |
| VIIIi | Cl-  | $CF_3CO-$ | 30 | 155—157 | 1690 |

| | Formula | Analysis (%) Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|
| VIIIa | $C_{14}H_{10}O_2N_4$ | 63.15 | 3.79 | 21.04 | 63.08 | 3.71 | 21.15 |
| VIIIb | $C_9H_5O_2N_4Cl_3$ | 35.15 | 1.64 | 18.22 | 34.92 | 1.55 | 18.17 |
| VIIIc | $C_{15}H_{13}O_4N_5S$ | 50.13 | 3.65 | 19.49 | 50.29 | 3.70 | 19.41 |
| VIIId | $C_{15}H_{12}O_2N_4$ | 64.28 | 4.32 | 19.99 | 64.47 | 4.50 | 20.22 |
| VIIIe | $C_{15}H_{12}O_3N_4$ | 60.80 | 4.08 | 18.91 | 60.74 | 4.22 | 19.14 |
| VIIIf | $C_{10}H_{10}O_3N_4$ | 51.28 | 4.30 | 23.92 | 51.32 | 4.47 | 23.97 |
| VIIIg | $C_{14}H_{11}O_2N_5$ | 59.78 | 3.94 | 24.90 | 60.12 | 3.94 | 25.00 |
| VIIIh | $C_9H_5O_2N_4F_3$ | — | — | 21.70 | — | — | 21.96 |
| VIIIi | $C_9H_4O_2N_4F_3Cl$ | — | — | 19.15 | — | — | 19.36 |

Table III. IR Absorption of Reaction Product of N-Acyl-$\phi$-3-aryl-5-imino-3,5-dihydro-1-oxa-2,3,4-triazole (VIII) with Acid

| Starting material | Reagent | IR ($cm^{-1}$) |
|---|---|---|
| VIIIa | HCl–MeOH | 1730 |
| VIIIa | HBr–AcOH | 1734 |
| VIIIb | HCl–MeOH | 1640 |
| VIIIc | HCl–MeOH | 1706, 1680 |
| VIIId | HCl–MeOH | 1720 |
| VIIIg | HCl–MeOH | 1740 |
| VIIIh | HCl–MeOH | 1690 |
| VIIIi | HCl–MeOH | 1700 |

## Experimental[9]

**General Preparation of $\phi$-3-Aryl-5-imino-3,5-dihydro-1-oxa-2,3,4-triazole Hydrochloride (III) (see Table I)**——A solution of 5.3 g of BrCN in 30 ml of dry ether was added to a stirred solution of 0.1 mole of

9) Melting points are uncorrected. Unless otherwise specified, infrared spectra were measured in Nujol mull with a Hitachi EPS-2 spectrometer, and ultraviolet spectra were measured in methanol.

monoarylhydrazine (IV) dissolved in a dry solvent (ether, tetrahydrofuran or a mixture of them) at −5—0°. After being stirred for 1 hr in the cold the solution was filtered to remove the crystals of IV·HBr, which were washed with dry ether. The combined filtrate and washing was chilled to −20——40° and to this was introduced dry gaseous nitrous acid over a period of 3 hr. An excess of methanolic hydrochloric acid was added to the reaction mixture and the solution was allowed to stand for 4 hr at 5°. A crystalline product was obtained by filtration and recrystallized from EtOH or EtOH–ether to give III.

**φ-5-Imino-3-phenyl-3,5-dihydro-1-oxa-2,3,4-triazole (VII), Free Base of IIIa**——To a solution of 1 g of IIIa in 20 ml of $H_2O$ was added 1 g of $NaHCO_3$ under stirring at 0°. The reaction mixture was saturated with NaCl and extracted three times with a total of 300 ml of ether. The combined ether extract was dried over $MgSO_4$ and evaporated under reduced pressure to yield 0.7 g (87%) of VII as yellow prisms, mp 80—83° (decomp.), IR: 1720, 1670 $cm^{-1}$. This showed negative Liebermann's nitroso reaction. *Anal.* Calcd. for $C_7H_6ON_4$: C, 51.85; H, 3.73; N, 34.55. Found: C, 52.22; H, 3.79; N, 34.56.

Treatment of VII with methanolic hydrochloric acid yielded IIIa; similarly, acylation of VII with benzoylchloride in dry pyridine gave N-benzoyl-φ-5-imino-3-phenyl-3,5-dihydro-1-oxa-2,3,4-triazole (VIIIa) in a high yield. The product thus obtained was identical with an authentic sample obtained by the acylation of IIIa.

Treatment of VII with dry gaseous nitrous acid in MeOH at 5° yielded reddish purple crystals of IX, mp 76—78°. The same crystals were obtained by the reaction of IIIa with $NaNO_2$ according to the procedure of Ohta, *et al.*[10]

**General Preparation of N-Acyl-φ-3-aryl-5-imino-3,5-dihydro-1-oxa-2,3,4-triazole (VIII) (see Table II)**——1) To a stirred suspension of 5 mmole of III in 5 ml of dry pyridine was added dropwise 5.5 mmole of an acylchloride at 5°. After the addition, the mixture was kept stirring for additional 2 hr at 5°, and the mixture was diluted with cold water. The crystals separated were filtered, washed with water and recrystallized from EtOH to yield VIII.

2) To a stirred solution of 5 mmole of III in 10 ml of water were added 5.5 mmole of an acylating agent and 0.5 g of $NaHCO_3$ through different dropping funnels in small portions, while the temperature of the reaction mixture being kept at 5°. The mixture was stirred for additional 1 hr at 10° and the crystals separated were worked up as described above to yield VIII.

3) Finally powdered crystals (5 mmole) of III were dissolved in an excess of trifluoroacetic anhydride. After being kept standing at room temperature for 2 hr, the excess anhydride was evaporated under reduced pressure. The crystalline residue was recrystallized from EtOH to yield VIII.

**Reaction of N-Acyl-φ-3-aryl-5-imino-3,5-dihydro-1-oxa-2,3,4-triazole (VIII) with Acids**——To a cooled solution of VIII in MeOH was added a slightly excess amount of HCl–MeOH or 25% HBr–AcOH. The solution was evaporated to dryness under reduced pressure to give a crystalline residue, which showed the IR spectrum as shown in Table III.

**Acknowledgement** The authors express their deep gratitude to Dr. S. Tatsuoka for kind encouragement. Thanks are also due to Dr. K. Morita and Mr. Y. Imashiro for their discussions throughout this work.

10) H. Kato, M. Hashimoto, and M. Ohta, *Nippon Kagaku Zasshi*, **78**, 707 (1957).