# SYNTHESIS AND CYCLIZATION OF SOME N-OXIDES OF 2-PYRIDYLHYDRAZONES OF MESOXALIC ACID DERIVATIVES*

Jan SLOUKA and Vojtěch BEKÁREK

*Department of Analytical and Organic Chemistry, Palacký University, 771 46 Olomouc*

Received July 10th, 1987

*Dedicated to Prof. J. Hadáček on the occasion of his 80th birthday.*

Coupling of diazotized 2-aminopyridine-1-oxide with ethyl cyanoacetylcarbamate, cyanoacetamide, malononitrile, and 2-benzimidazolylacetonitrile in an acid medium afforded N-oxides of the corresponding 2-pyridylhydrazones *Ia*—*Id*, which also exist in the N-hydroxyazine tautomeric forms *IIa*—*IId* as confirmed by IR spectroscopy. Hydrazone *Ia* was thermally cyclized to give 2-(pyridine-1-oxide-2-yl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (*IIIa*) which was converted into the corresponding thioamide *IIIb*, acid *IIIc*, and amidoxime *IIId*.

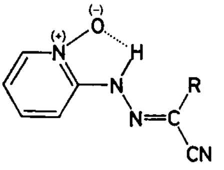
Heterocyclic amines represent starting material for the preparation of heterocyclic azo compounds or hydrazones, provided, of course, that their diazotization gives sufficiently stable diazonium salts. For example, in the pyridine series the coupling proceeds smoothly with pyridine-3-diazonium salts whereas the isomeric 2- and 4--diazonium salts are too unstable to be of any use. This, however, does not apply to their N-oxides which are stable and couple with reactive aromatic components[1–4]. The stability of pyridin-1-oxide-2-diazonium salts is also enhanced by the ring-chain tautomerism leading to formation of 1,2,3,5-oxatriazolo[4,5-*a*]pyridinium salts[1,2]. Whereas coupling reactions of these pyridine-1-oxide-2-diazonium salts with aromatic amines and phenols are known[1–3], no data on reaction with compounds containing a reactive methylene group were available. In the present communication we turned therefore our attention to reactions of this type.

We have found, however, that under usual reaction conditions, i.e. in an acetate buffer, no coupling of pyridine-1-oxide-2-diazonium chloride with cyanoacetic acid derivatives takes place. Apparently, under these conditions the diazonium salt is completely converted into the little reactive 1,2,3,5-oxatriazolo[4,5-*a*]pyridinium acetate or even to 7-acetoxy-7,8-dihydro-1,2,3,5-oxatriazolo[4,5-*a*]pyridine before it can react with the active methylene group.

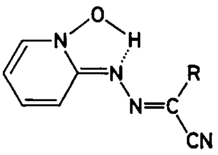
---

* Part XXI in the series Cyclization Reactions of Hydrazones; Part XX: Acta Univ. Palacki. Olomuc., Fac. Rerum Nat. *88*, 231 (1987).

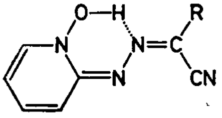
Unlike most of the known coupling reactions, the coupling of pyridine-1-oxide-2-diazonium chloride with reactive methylene groups proceeds in a strongly acidic medium. Diazotization of 2-aminopyridine-1-oxide in hydrochloric acid followed by coupling of the formed diazonium salt with ethyl cyanoacetylcarbamate, cyanoacetamide, malononitrile or 2-benzimidazolylacetonitrile in an aqueous solution in the absence of any base afforded in good yields N-oxides of the corresponding hydrazones *Ia*–*Id* which may, of course, also exist in the tautomeric 1-hydroxy-1,2-dihydropyridine-2-ylidenehydrazone forms *II-E* or *II-Z*. In the geometric isomers



*I*

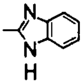


*II-E*



*II-Z*

In formulae *I* and *II*: *a*, R = $CONHCOOC_2H_5$ *b*, R = $CONH_2$
*c*, R = CN *d*, R =



*II-E* we may assume the presence of a five-membered chelate ring while a six-membered chelated ring should exist in the case of *II–Z* isomers. However, the total number of the possible isomers is greater because (save the dinitrile *Ic* (or *IIc*)) any of the isomers *I*, *II-E* or *II-Z* can exist in two further geometric isomers at the double bond in the aliphatic part of the molecule. Thus, compound *Ic* can exist in three, other hydrazones in six, isomers. These considerations are in accord with the IR spectroscopic studies of the mentioned compounds.

Infrared spectra of the dinitrile *Ic* exhibited three nitrile stretching vibration bands at 2 233, 2 219, and 2 210 $cm^{-1}$ indicating the presence of three isomers. Three bands were also observed in the C=N vibration region (1 528, 1 513, and 1 530 $cm^{-1}$). The strongest band in the spectrum, at 1 315 $cm^{-1}$ (in KBr), corresponds to stretching vibration of the N-oxide group[5-7]. In dichloromethane, this band is shifted to higher wavenumbers (1 333 $cm^{-1}$), the shift being probably related with disappearance of the intermolecular association (originally present in the solid *Ic*) with the N-oxide oxygen atom as electron donor. Two bands appear at 846 and 835 $cm^{-1}$ in the region of in-plane vibration of the N-oxide group[8], δ(N—O). These data are compatible with the structure *Ic*. The presence of isomers *II* is indicated (besides the bands in the CN region) by a band at 3 408 $cm^{-1}$ (in dichloromethane), probably due to the N—OH group. Upon replacement of $^{14}N$ by $^{15}N$ in the hydrazone group the C=N bands at 1 528, 1 513, and 1 503 $cm^{-1}$ were converted into a broad band at 1 495 $cm^{-1}$ and a shoulder at 1 510 $cm^{-1}$, and the bands at 1 435 and 1 270 $cm^{-1}$ were shifted. Also in the spectrum of compound *Ib* two nitrile stretching vibration bands at 2 230 and 2 207 $cm^{-1}$ (the latter 5 times weaker) show the presence of at least two isomers. The same conclusion can be drawn from the existence of two nitrile bands in the spectrum of hydrazone *Ia* (in KBr as well as dichloromethane). The strongest bands are those of the carbamate C=O group at 1 785 $cm^{-1}$ and of the carbamate N—H group at 3 347 $cm^{-1}$. The low wavenumber of the hydrazone N—H band (3 175 $cm^{-1}$ in dichloromethane) indicates that the hydrogen atom of this group is bonded by intramolecular hydrogen bond to the amide carbonyl oxygen atom, similarly as in all previously prepared ethyl arylhydrazonocyanoacetylcarbamates[9,10]. This result speaks thus in favour of the Z-isomer of *Ia*.

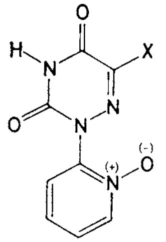
In all the hydrazones the isomers interconvert easily as indicated by intensity changes of the characteristic IR bands on standing, heating or crystallization of the substances.

All the hydrazones *I* (or their tautomers *II*) are weak acids that dissolve not only in alkali metal hydroxides and carbonates but also in hydrogen carbonates to give salts from which the original acids *I* (or *II*) can be recovered by acidification. However, longer treatment with alkali metal carbonates or hydroxides results in cleavage of the molecule.

Thanks to the formation of mesomeric anion with highest electron density at the N-oxide oxygen atom, the hydrazone *Ia* is completely resistant to alkaline cyclization to the corresponding 6-azauracil derivative, a reaction proceeding very smoothly with other ethyl arylhydrazonocyanoacetylcarbamates[11,12]. Neither proceeds smoothly the thermal cyclization, performed at the melting point temperature or in refluxing high-boiling solvent: the cyclization to 2-(pyridine-1-oxide-2-yl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (*IIIa*) can take place only with the Z-isomer of *Ia* and thus the presence of other isomers lowers the observed yield of the cyclization. On the other hand, the low yield of the thermal cyclization shows that, under the conditions used, there is no conversion of the other isomers into the Z-isomer which would cyclize.

The properties of compound *IIIa* resemble those of analogous 1-aryl-6-azauracil-5-carbonitriles. This concerns the acidity or reactivity of the nitrile group, as well as the stretching vibration band of this group at 2 245 $cm^{-1}$. However, the strongest

IR bands are those of carbonyl (1 720 cm$^{-1}$) and N-oxide (1 243 cm$^{-1}$). In an attempt to prepare 1-(α-pyridyl)-6-azauracil-5-carbonitrile, isomeric with the previously prepared β-pyridyl derivative[12], we tried to remove reductively the oxygen atom from the pyridine ring. However, this N-oxide proved to be very stable: on reflux of *IIIa* with a stannous salt or triphenylphosphine in ethanol the starting compound was recovered; the same result was obtained with an alkali metal hypophosphite in the presence of palladium[13]. Similarly, no reduction was observed on treatment with hydrogen sulfide which added to the nitrile group to form the corresponding thioamide *IIIb*. Acid hydrolysis of the nitrile *IIIa* afforded acid *IIIc*, reaction with hydroxylamine led to amidoxime *IIId*.



*IIIa*, X = CN

*IIIb*, X = $CSNH_2$

*IIIc*, X = COOH

*IIId*, X = $C(=NOH)NH_2$

## EXPERIMENTAL

Melting points were determined on a Boetius block and are uncorrected. IR spectra were taken on an IR-75 spectrometer (Zeiss, Jena) both in KBr and dichloromethane. Electronic spectra were measured on a Unicam SP 1800 spectrophotometer.

### Ethyl Pyridine-1-oxide-2-ylhydrazonocyanoacetylcarbamate (*Ia*)

A solution of 2-aminopyridine-1-oxide[14] (2·25 g; 20·4 mmol) in a mixture of water (20 ml) and 37% hydrochloric acid (13 ml) was cooled in an ice bath and diazotized with a solution of sodium nitrite (1·38 g; 20·0 mmol) in ice-cold water (10 ml). After standing in the ice bath for 30 min, the mixture was added in one portion to a stirred solution prepared by dissolution of ethyl cyanoacetylcarbamate in hot water (900 ml) and cooling to 0—3°C. The mixture was set aside at 0—5°C for 48 h with intermittent stirring. The separated yellow crystals were collected, washed with water and dried on air at room temperature; yield 4·52 g (76%) of the monohydrate, m.p. 176—178°C (decomposed and resolidified). For $C_{11}H_{13}N_5O_5$ (295·2) calculated: 44·74% C, 4·44% H, 23·72% N; found: 44·84% C, 4·27% H, 23·54% N. Crystallization from ethanol afforded the anhydrous compound of the same m.p. For $C_{11}H_{11}N_5O_4$ (277·2) calculated: 47·65% C, 4·00% H, 25·26% N; found: 47·60% C, 3·95% H, 25·28% N. IR spectrum (KBr, cm$^{-1}$): 3 347 (ν(N—H)), 3 190 (ν(N—H)), 2 222 (ν(CN)), 2 207 (ν(CN)), 1 785 (carbamate ν(C=O)), 1 700 (ν(C=O)), 1 539 (ν(C=N)), 1 515, 1 295 (ν(N—O)), 1 274 (ν(N—N)), 845 (δ(N—O)), 761, 581. (Dichloromethane, $cm^{-1}$): 3 400, 3 175. UV spectrum ($5 . 10^{-5}$ mol $l^{-1}$ in water) $\lambda_{max}$, nm (log ε): 224 (4·16), 406 (4·34).

Compound *Ia*, containing $^{15}N$ in the hydrazone group, was prepared using $Na^{15}NO_2$. The following bands in the IR spectrum of this derivative were shifted (in parentheses wavenumbers, $cm^{-1}$, for the $^{15}N$-derivative): 1 539 (1 524), 1 515 (1 498), 1 274 (1 270), 845 (844), 771 (769), 581 (579).

### Pyridine-1-oxide-2-ylhydrazonocyanoacetamide (*Ib*)

A solution of the diazonium salt prepared as described above was added in one portion to a stirred solution of cyanoacetamide (6·40 g; 76·1 mmol) in ice-cold water (70 ml). The mixture was set aside at 0—5°C for 72 h with intermittent stirring, the separated compound was collected on filter, washed with water and air-dried at room temperature; yield 4·10 g (92%) of the monohydrate of *Ib*, m.p. 203—205°C (decomp.). The anhydrous product was obtained on drying at 60°C. For $C_8H_7N_5O_2$ (205·2) calculated: 46·83% C, 3·44% H, 34·12% N; found: 46·68% C, 3·50% H, 33·97% N. IR spectrum (KBr, $cm^{-1}$): 3 535, 3 426, 3 335, 3 136, 2 230, 2 207, 1 691, 1 656, 1 601, 1 556, 1 513, 1 451, 1 394, 1 262, 1 211, 842, 773. UV spectrum ($5 . 10^{-5}$ mol $l^{-1}$ in water) $\lambda_{max}$, nm (log ε): 228 (4·14), 264 (4·02), 348 (4·13).

### Pyridine-1-oxide-2-ylhydrazonomalononitrile (*Ic*)

A solution of the diazonium salt prepared above was added to a solution of malononitrile (6·00 g; 90·9 mmol) in ice-cold water (40 ml). After 24 h the crystalline compound was collected on filter, washed with water and dried; yield 3·62 g (97%), m.p. 153—157°C (decomp.; water). For $C_8H_5N_5O$ (187·2) calculated: 51·34% C, 2·69 H, 37·42% N; found: 51·21% C, 2·67% H, 37·40% N. UV spectrum ($5 . 10^{-5}$ mol $l^{-1}$ in ethanol) $\lambda_{max}$, nm (log ε): 227 (3·96), 251 (3·85), 285 (3·79), 407 (4·39). IR spectrum (KBr, $cm^{-1}$): 2 233, 2 219, 2 210 (ν(CN)), 1 618, 1 580, 1 516, 1 505, 1 435, 1 360, 1 315 (ν(N—O)), 1 270, 846 (δ(N—O)), 768. (Dichloromethane, $cm^{-1}$): 3 408 (ν(O—H)), 3 155 (ν(N—H)), 1 333 (ν(N—O)), 845 (δ(N—O)).

### 2-(Pyridine-1-oxide-2-ylhydrazono)-2-(benzimidazol-2-yl)acetonitrile (*Id*)

A solution of the diazonium salt prepared as described above was added to a stirred solution prepared by dissolving 2-benzimidazolylacetonitrile (3·60 g; 22·9 mmol) in hot water (2 000 ml) and cooling to 0—5°C. After standing at 0—5°C for 48 h with intermittent stirring, the mixture was filtered, the crystalline product washed with water and dried at 100°C; yield 5·50 g (99%). The product was crystallized from aqueous ethanol, m.p. 239—241°C (decomp.). For $C_{14}H_{10}.N_6O$ (278·3) calculated: 60·42% C, 3·62% H, 30·20% N; found: 60·23% C, 3·78% H, 30·09% N. IR spectrum (KBr, $cm^{-1}$): 2 227, 1 615, 1 578, 1 548, 1 514, 1 507, 1 405, 1 320, 1 280, 1 243, 1 198, 1 193, 833, 760, 744, 703. UV spectrum ($5 . 10^{-5}$ mol $l^{-1}$ in ethanol) $\lambda_{max}$, nm (log ε): 259 (4·09), 277 (4·02) 383 (4·39).

### 2-(Pyridine-1-oxide-2-yl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (*IIIa*)

A mixture of anhydrous finely powdered *Ia* (1·39 g; 5·01 mmol) and decalin (15 ml) was heated to 130°C for 10 min and then refluxed for 20 min. After cooling, the crystalline product was collected on filter, washed with hexane and dried to give 825 mg (71%) of the crude product. Two crystallizations from water (with charcoal) afforded 375 mg (32%) of almost colourless crystals, m.p. 273—275°C (decomp.). For $C_9H_5N_5O_3$ (231·2) calculated: 46·76% C, 2·18% H, 30·30% N; found: 46·80% C, 2·17% H, 30·42% N. IR spectrum (KBr, $cm^{-1}$): 3 120 (ν(N—H)), 2 245 (ν(CN)), 1 720 (ν(C=O)), 1 243 (ν(N—O)), 850 (δ(N—O)), 771 (γ(C—H)). UV spectrum ($5 . 10^{-5}$ mol $l^{-1}$ in water), $\lambda_{max}$, nm (log ε): 261 (4·20).

### 2-(Pyridine-1-oxide-2-yl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbothioamide (*IIIb*)

A mixture of *IIIa* (120 mg; 0·52 mmol), water (8 ml), and 25% aqueous ammonia (0·6 ml) was saturated with hydrogen sulfide, allowed to stand in a stoppered flask at room temperature for 25 h and evaporated in vacuo. The residue was dissolved in a mixture of water (6 ml) and 25% aqueous ammonia (0·3 ml). After addition of a small amount of charcoal the solution was filtered and the filtrate acidified to pH 1. Next day the crystals were collected, washed with water and dried at 100°C; yield 110 mg (80%), m.p. 226—228°C (decomp.) (water). For $C_9H_7$.$N_5O_3S$ (265·2) calculated: 40·76% C, 2·66% H, 26·41% N; found: 40·65% C, 2·72% H, 26·67% N.

### 2-(Pyridine-1-oxide-2-yl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylic Acid (*IIIc*)

A mixture of *IIIa* (120 mg; 0·52 mmol), 37% hydrochloric acid (6 ml), and water (3 ml) was refluxed for 3 h and then evaporated in vacuo. The residue was mixed with a small amount of ice-cold water, the crystals were collected, washed with a small amount of ice-cold water and dried at 100°C; yield 105 mg (81%). Crystallization from water afforded material melting at 205—207°C (decomposed on rapid heating). For $C_9H_6N_4O_5$ (250·2) calculated: 43·21% C, 2·42% H, 22·40% N; found: 43·24% C, 2·61% H, 22·19% N.

### Amidoxime of 2-(Pyridine-1-oxide-2-yl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylic Acid (*IIId*)

Hydroxylamine hydrochloride (70 mg) was added to a solution of *IIIa* (120 mg; 0·52 mmol) and 25% aqueous ammonia (1·0 ml) in water (10 ml). After standing for 10 days in a stoppered flask at room temperature, the mixture was evaporated in vacuo and the residue was mixed with water (1 ml) and several drops of acetic acid. Next day, the crystals were collected, washed with a small amount of water and dried at 100°C, yield 123 mg (90%), m.p. 238—240°C (decomp.). For $C_9H_8N_6O_4$ (264·2) calculated: 40·91% C, 3·05% H, 31·81% N; found: 40·69% C, 3·13% H, 31·65% N.

## REFERENCES

1. Katritzky A. R.: J. Chem. Soc. (London) *1957*, 191.
2. Becker H. G. O., Bottcher H., Haufe H.: J. Prakt. Chem. *312*, 433 (1970).
3. Lewis Ch. E., Paul A. P., Tsang S. M., Leavitt J. J.: U.S. 3,051 697; Chem. Abstr. *59*, 5291 (1963).
4. Ochiai E.: J. Org. Chem. *18*, 534 (1953).
5. Costa G., Blasina P., Sartori G.: Phys. Chem. *4*, 24 (1955).
6. Noel R. H., Wolf R., Gallias F.: C. R. Acad. Sci. *242*, 1873 (1956).
7. Wiley R. H., Slaymaker S. C.: J. Am. Chem. Soc. *79*, 2233 (1957).
8. Shindo H.: Pharm. Bull. (Tokyo), *6*, 117 (1958).
9. Bekárek V., Slouka J.: Collect. Czech. Chem. Commun. *35*, 2936 (1970).
10. Bekárek V., Slouka J.: Collect. Czech. Chem. Commun. *39*, 566 (1974).

11. Slouka J., Peč P.: Monatsh. Chem. *96*, 1874 (1965).
12. Slouka J.: Montsh. Chem. *97*, 448 (1966).
13. Boyer S. K., Bach J., McKenna J., Jagdmann E. jr: J. Org. Chem. *50*, 3408 (1985).
14. Delarge J., Thomas L.: Farmaco, Ed. Sci. *21*, 846 (1966).

Translated by M. Tichý.