Tetronic Acids and Derivatives; Part VI[1]. A Convenient Synthesis of New 4-Oxo-2-phenyl-2*H*-4,6-dihydrofuro[3,4-*d*]triazole and 4-Oxo-4,6-dihydrofuro[3,4-*c*]furazan Systems

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Continued interest in tetronic acids chemistry led us to consider the synthetic usefulness of (5*H*)-furan-2-ones, bearing two azomethine groups at the 3 and 4 positions, i.e. **4-7**, for the elaboration of fused furo[3,4-*d*]triazoles **8** and furo[3,4-*c*]furazans **9** bearing a lactone ring suitable for further transformations to the almost unknown 4-(1-hydroxyalkyl)-2*H*-*vic*-triazoles **10** and 3-(1-hydroxyalkyl)-furazans **11**.

Although the preparation of compounds **4a**, **5a**, **7a** ($R^1=R^2=H$) had been described in early 1900's[2,3], the first example of a cyclodehydration reaction was only recently reported with the conversion of the dehydroascorbic acid to compound **5** ($R^1=H$, $R^2=CHOH-CH_2OH$) and its subsequent cyclisation to corresponding fused triazole **8**[4].

Generalization of the above procedure to 3-unsubstituted tetronic acids **1a-c** by sequential coupling with benzenediazonium sulfate to **2a-c**[2], oximation with hydroxylamine hydrochloride and sodium acetate[2], and cyclodehydration of intermediates **5a-c** in acetic anhydride afforded 2-oxo-2-phenyl-2*H*-2,6-dihydrofuro[3,4-*d*]triazoles **8a-c** in 40–50% overall yield.

This three-step elaboration of compounds **8** was simplified by considering the isomeric 3-hydroxyimino-2-oxo-4-phenylhydrazonotetrahydrofurans **6a-c** as possible starting materials. 3-Unsubstituted tetronic acids **1** give a purple coloration on treatment with sodium nitrite as a result of the formation of the sodium salt of 3-hydroxyimino-2,4-dioxotetrahydrofurans **3**. Acidification gives the easily oxidisable free oxime[3] corresponding to **3**, which was characterised spectrally[6] and converted to the phenylhydrazones **6**. However, we have found that the tedious isolation of the

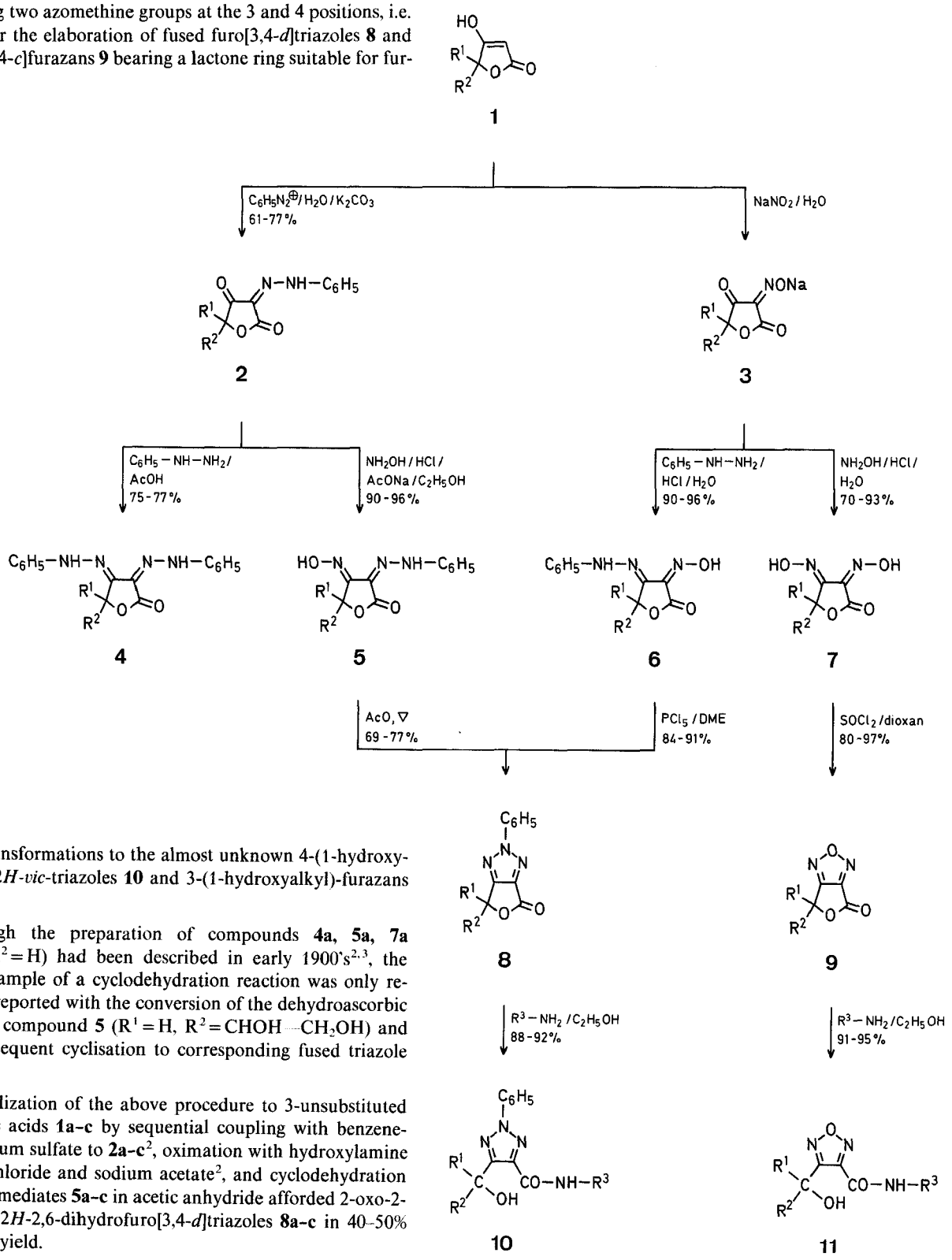

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Table 1. 4-Oxo-2-phenyl-2*H*-2,6-dihydrofuro[3,4-*d*]triazoles **8** and 4-Oxo-4,6-dihydro[3,4-*c*]furans **9**

Product	R^1	R^2	Yield[a] [%]	m.p. (solvent)	Molecular formula[b]	I.R. ($CHCl_3$) ν [cm^{-1}]	^{1}H-N.M.R. (acetone-d_6) δ [ppm]
8a	H	H	84 (69)	170° (ethanol)	$C_{10}H_7N_3O_2$ (201.2)	1800, 1605	5.6 (s, 2H); 7.7 (m, 3H); 8.3 (m, 2H)
8b	H	CH_3	88 (75)	139° (ethanol)	$C_{11}H_9N_3O_2$ (215.2)	1800, 1605	1.78 (d, 3H, J=7 Hz); 6.11 (q, 1H, J=7 Hz); 7.83 (m, 3H); 8.33 (m, 2H)
8c	CH_3	CH_3	91 (77)	117° (ethanol)	$C_{12}H_{11}N_3O_2$ (229.3)	1790, 1600	1.82 (s, 6H); 7.7 (m, 3H); 8.33 (m, 2H)
9a	H	H	80	68° (ethanol)	$C_4H_2N_2O_3$ (126.1)	1805, 1600	5.7 (s, 2H)
9b	H	CH_3	90	53° (ethanol)	$C_5H_4N_2O_3$ (140.1)	1805, 1600	1.97 (d, 3H, J=7 Hz); 6.0 (q, 1H, J=7 Hz)
9c	CH_3	CH_3	97	68° (ethanol)	$C_6H_6N_2O_3$ (154.1)	1805, 1600	1.98 (s, 6H)

[a] Cyclodehydration step; data in parentheses refer to Method A.
[b] The microanalyses are in satisfactory agreement with the calculated values (C ±0.20, H ±0.08, N ±0.30).

Table 2. 5-Carboxamido-4-(1-hydroxyalkyl)-2-phenyl-2*H*-*vic*-triazoles **10** and 4-Carboxamido-3-(1-hydroxyalkyl)-1,2,5-oxadiazoles **11**

Product	R^1	R^2	R^3	Yield [%]	m.p. (solvent)	Molecular formula[a] or Lit. m.p.	I.R. ($CHCl_3$) ν [cm^{-1}]	^{1}H-N.M.R. (acetone-d_6) δ [ppm]
10a	H	H	H	87	146° (ethanol)	146°[4]	3515; 3405; 3350 (br); 1680; 1590	4.95 (s, 2H); 4.98 (m, 1H); 7.6 (m, 2H); 7.7 (m, 3H); 8.33 (m, 2H)
10b	H	H	$CH_2C_6H_5$	91	161° (ethanol)	$C_{17}H_{16}N_4O_2$ (308.3)	3410 (w); 3300 (w); 1665; 1600 (w); 1565	4.6 (3 lines, 2H); 4.90 (3 lines, 2H); 5.5 (m, 1H); 7.5 (s, 5H); 7.75 (m, 3H); 8.33 (m, 2H); 9.33 (m, 1H)
10c	CH_3	CH_3	CH_3	92	126° (50% aq. ethanol)	$C_{13}H_{16}N_4O_2$ (260.3)	3460 (s); 3340 (br); 1665; 1600 (w); 1570	1.66 (s, 6H); 2.9 (s, 1H); 3.1 (d, 3H; J=4 Hz); 6.91 (s, 1H); 7.75 (m, 3H); 8.33 (m, 2H)
11a	H	H	H	91	126° (ethanol)	$C_4H_3N_3O_3$ (157.1)	3520; 3400; 1720; 1605	4.8 (s, 1H); 4.93 (s, 2H); 8.5 (m, 2H)
11c	CH_3	CH_3	H	93	118° (ethanol)	$C_6H_9N_2O_3$ (171.2)	3500; 3395; 1710; 1600	1.85 (s, 6H); 5.80 (m, 1H); NH_2 not observed.

[a] The microanalyses are in satisfactory agreement with the calculated values (C ±0.18, H ±0.12, N ±0.27).

unstable oxime can be circumvented by directly adding the purple solution of sodium nitrite and tetronic acid to phenylhydrazine hydrochloride in aqueous solution; compounds **6** were then isolated in fair yield by a simple filtration.

The final cyclodehydration can be realised in a variety of acidic conditions, including hot acetic anhydride, polyphosphoric acid, or thionyl chloride, but an excessive darkening generally occurred and a material consuming charcoaling step was often required. A cleaner reaction was finally performed with phosphorus pentachloride in dimethoxyethane at room temperature to expected compounds **8** (75–87% overall yield), identical in all respects with the materials isolated as described above.

Although the elaboration of the 2-phenyl-2*H*-triazole ring by the oxidative aniline-elimination from osazones in carbohydrates is a well-documented procedure[7], generalization to tetronic acids osazones **4**, readily available from the compounds **2** and phenylhydrazine[2], completely failed under a variety of conditions[8]. By a related procedure, addition of the purple solution of the sodium salt **3** to an aqueous solution of hydroxylamine hydrochloride afforded, after filtration, pure 3,4-bis[hydroxyimino]-2-oxo-tetrahydrofurans **7**, which were readily converted to 4-oxo-4,6-dihydrofuro[3,4-*c*]furazans **9** by treatment with thionyl chloride in dioxan.

The synthetic potentiality of the lactone ring of compounds **8** and **9** in the elaboration of highly functionalised 1,2,3-triazoles and 1,2,5-oxadiazoles was illustrated by the almost quantitative cleavage with ammonia or amines to give 5-carboxamido-4-(1-hydroxyalkyl)-2-phenyl-2*H*-*vic*-triazoles **10** and 4-carboxamido-3-(1-hydroxyalkyl)-1,2,5-oxadiazoles **11**[9].

The spectral properties of compounds **4**–**7** are now being investigated.

All intermediates, collected in crystalline form, were recrystallised once from an appropriate solvent and used without additional purification in the following steps. M.p.'s were in agreement with available literature data.

4-Oxo-2-phenyl-2*H*-2,6-dihydrofuro[3,4-*d*]triazoles 8; General Procedure:

Method A: A mixture of 3-phenylhydrazonotetronic acid **2**[10] (20 mmol), hydroxylamine hydrochloride (5.6 g, 80 mmol), and sodium acetate (5.6 g, 69 mmol) in absolute ethanol (200 ml) is heated

on a steam bath for 3 h. The resultant solution is then concentrated in vacuo, and water (100 ml) is added. The solid that separates is collected, washed with water (3 × 25 ml), dried, and recrystallised once from ethanol to give yellow needles of *4-hydroxyimino-2-oxo-3-phenylhydrazinotetrahydrofurans* **5**; yield (m.p.): **5a** 90% (236°; Lit. [2] m.p. 236°); **5b** 92% (184°); **5c** 96% (221°).

These oxime-hydrazones **5** (10 mmol) and acetic anhydride (10 ml) are heated on a steam bath for 35 minutes. The yellow solution is then cooled and poured into crushed ice (100 g); the yellow solid that separates is collected, washed with 5% aqueous sodium hydrogen carbonate solution (3 × 10 ml), then with water (2 × 10 ml), dried, and recrystallised once from ethanol to give almost colorless needles of the title compounds **8** (Table 1).

Method B: Sodium nitrite (3.45 g, 50 mmol) is added portionwise to a stirred solution of tetronic acid **1** (50 mmol) in water (30 ml). The purple solution is stirred for 15 min at room temperature and then added dropwise to a vigorously stirred solution of phenylhydrazine hydrochloride (8.67 g, 60 mmol) in water (100 ml) at 0°. The purple coloration gradually fades and orange needles of *3-hydroxyimino-2-oxo-4-phenylhydrazonotetrahydrofurans* **6** precipitate within 1–2 h at 0–5°. The solid is then collected and dried. Recrystallisation from ethanol affords yellow needles of almost pure material; yield (m.p.): **6a** 90% (190°); **6b** 91% (136°); **6c** 96% (131°).

To a cooled solution (0°) of these compounds **6** (10 mmol) in dry dimethoxyethane (25 ml), phosphorus pentachloride (2.5 g, 12 mmol) is added portionwise. The reddish solution is then stirred in a stoppered flask for 2 h at room temperature and poured into ice/water (100 ml). The tan solid that separates is collected and purified as described in Method A (Table 1).

4-Oxo-4,6-dihydrofuro[3,4-*c*]furazans 9; General Procedure:
A purple solution of sodium salt of 3-hydroxyiminotetronic acid (10 mmol), prepared as above, is dropwise added (within 30 min) to a vigorously stirred solution of hydroxylamine hydrochloride (1.37 g, 20 mmol) in water (20 ml). The purple coloration gradually fades within 1–2 h at room temperature and almost pure *3,4-bis[hydroxyimino]-2-oxotetrahydrofurans* **7** precipitate as white needles. Yield (m.p.): **7a** 70% (188–189°, Lit. [3] m.p. 181–183°); **7b** 83% (183–184°); **7c** 93% (208°).

To a stirred solution of these dioximes **7** (10 mmol) in dioxan (10 ml), thionyl chloride (1 ml, 14 mmol) is dropwise added. The resultant yellow solution is stirred overnight in a stoppered flask and then concentrated in vacuo. The resultant crystalline material is recrystallised once from ethanol to give the pure title compounds. Analytically pure samples are prepared by vacuum sublimation at 40–50°/1 torr (Table 1).

5-Carboxamido-4-(1-hydroxyalkyl)-2-phenyl-2*H*-*vic*-triazoles 10:
To a stirred solution of compound **8** (5 mmol) in absolute ethanol (10 ml), amine [7.5 mmol; neat benzylamine or commercial aqueous solution of methylamine (33%) or 10 normal solution] is added. The mixture is briefly heated on a steam bath and allowed to stand overnight at room temperature. Concentration in vacuo affords the crystalline title compounds which are recrystallised once from an appropriate solvent (Table 2).

4-Carboxamido-3-(1-hydroxyalkyl)-1,2,5-oxadiazoles 11:
To a stirred solution of compounds **9** (5 mmol) in absolute ethanol (10 ml), 10 normal aqueous ammonia solution (0.75 ml) is added dropwise at 0°. The solution is allowed to warm to room temperature for 1 h and then concentrated in vacuo. The clear residual oil readily crystallizes upon cooling in ice and occasional scratching and is then recrystallised from ethanol (Table 2).

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[1] Part V, S. Gelin, P. Pollet, *J. Heterocycl. Chem.* **16**, 505 (1979).
[2] L. Wolff, *Justus Liebigs Ann. Chem.* **312**, 155 (1900).
[3] L. Wolff, *Justus Liebigs Ann. Chem.* **291**, 244 (1896).
[4] M. El Sekily et al., *Carbohydr. Res.* **59**, 141 (1977).
[5] For a recent preparation see P. Pollet, S. Gelin, *Tetrahedron* **34**, 1453 (1978).
[6] P. Pollet, *Thesis*, Lyon, 1979.
[7] C. D. Hudson, *J. Org. Chem.* **9**, 470 (1944).
W. T. Haskins, R. M. Hann, C. D. Hudson, *J. Am. Chem. Soc.* **69**, 3032 (1947).
[8] See for related examples: S. H. El Ashry et al., *J. Chem. Soc.* **1968**, 2251.
[9] Although no data are actually available for our compounds **11**, handling should be done with special care since related 4-carboxamido-3-methylfurazans have been reported to be acute poisons; see A. Fundaro, *Bull. Soc. Ital. Biol. Sper.* **50**, 1654 (1974); *C. A.* **83**, 90 988 (1975).
[10] Prepared by the procedure of L. Pons, H. Veldstra, *Recl. Trav. Chim. Pays-Bas* **74**, 1217 (1955).

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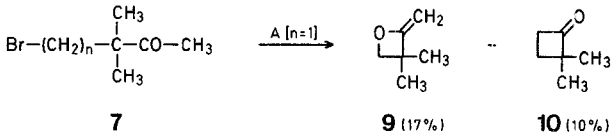
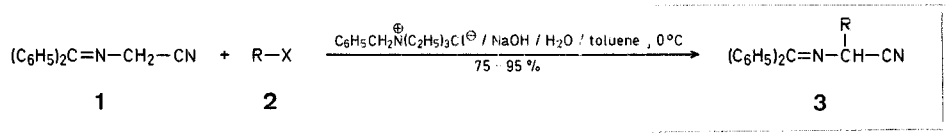
Abstract 5528, *Synthesis* **1979** (7), 554;
The formula scheme for the conversion **7**→**9**+**10** should be as follows:



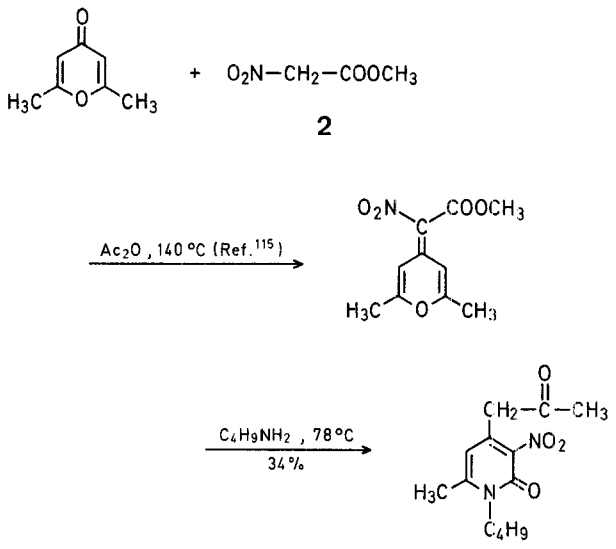
7 **9** (17%) **10** (10%)

Abstract 5556, *Synthesis* **1979** (8), 629;
The formula scheme for the conversion **1**+**2**→**3** shou d be as follows:



1 **2** **3**

M. T. Shipchandler, *Synthesis* **1979** (9), 666–686;
The second reaction in Scheme **P** (p. 682) should be as follows:



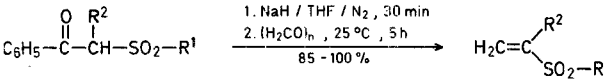
2

G. Sosnovsky, J. A. Krogh, S. G. Umhoefer, *Synthesis* **1979** (9), 722–724;
The heading for the third column of the Table (p. 723) should be as follows:

Solvent[c]
(Reaction
time[d] [h])

C. Venturello, R. D'Aloisio, *Synthesis* **1979** (10), 790–793;
The last two lines of the third paragraph of the right hand column on page 791 should read as follows:
drazines and of the not easily accessible 3-acetyl-5-methylisoxazole[4].

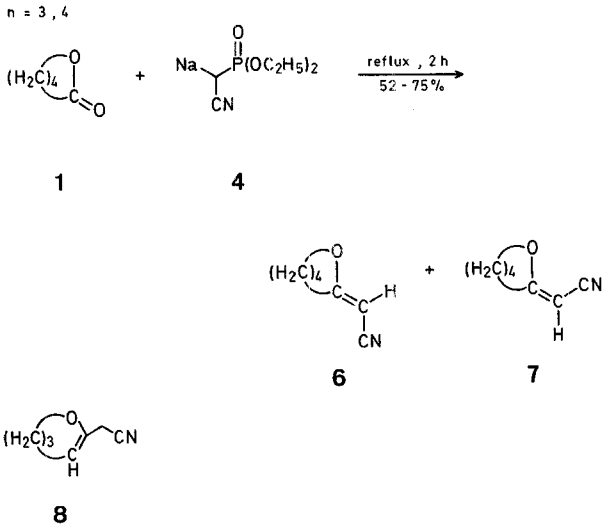
Abstract 5616, *Synthesis* **1979** (10), 840;
The formula scheme for the conversion **1**→**2** should be as follows:



1 **2**

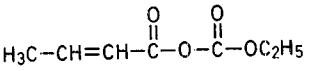
Abstract 5627, *Synthesis* **1979** (11), 917;
The title should be as follows:
[1,4]-Addition of 1,3-Dithianes to 2-Cycloalkenones.

Abstract 5637, *Synthesis* **1979** (11), 920;
The lower part of the formula scheme should be as follows:



1 **4** **6** **7** **8**

C. Goasdoue, R. Couffignal, *Synthesis* **1979** (12), 954–955;
The structure of compound **5** (p. 955) should be as follows:



5

P. Pollet, S. Gelin, *Synthesis* **1979** (12), 977–979;
The correct names for compounds **8** and **9** are 4-oxo-2-phenyl-2,6-dihydro-4*H*-furo[3,4-*d*]-1,2,3-triazoles and 4-oxo-4*H*,6*H*-furo[3,4-*c*][1,2,5]oxadiazoles, respectively.