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THE TAUTOMERISM OF HETEROAROMATIC COMPOUNDS WITH FIVE-MEMBERED RINGS—X[1]*

1-PHENYL-1,2,4-TRIAZOLIDINE-3,5-DIONE

A. A. GORDON, A. R. KATRITZKY and F. D. POPP
The School of Chemical Sciences, University of East Anglia, Norwich, England

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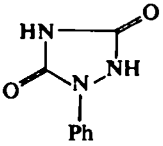
Abstract—1-Phenylurazole is shown by physical measurements to exist predominantly in the dioxo form (I). The structures of its anion and mono-methyl derivatives are also discussed.

1-PHENYLURAZOLE represents one of the most complicated cases of tautomerism yet examined in this series of papers: it could exist in six forms (I–VI), and consequently six dimethyl derivatives should occur. 1-Phenylurazole forms four monomethyl derivatives, and each of these can exist in three tautomeric forms. Little previous work has appeared on this tautomerism: nearly 60 years ago Acree[2] claimed that 1-phenylurazole existed as the monohydroxy-monooxo form (II) on the basis of the formation of the corresponding dimethyl derivative with diazomethane. This criterion is now known to be unsound.[3] Other workers, Ref. 4 have accepted Acree's conclusions. We have now studied 1-phenylurazole and six of its methylated derivatives in an attempt to define their fine structure.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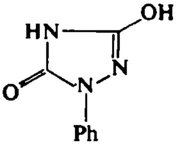
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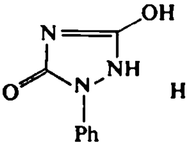
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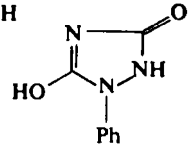
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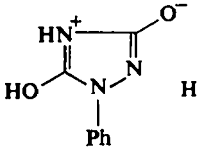
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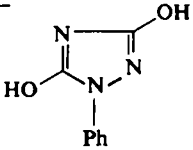
VI

Preparation of compounds. Compounds were prepared by literature methods with modifications as noted in the experimental section. An attempt to prepare 2-methyl-3-methoxy-1-phenyl-1,2,4-triazolin-5-one (or the corresponding 5-methoxy-3-one) by

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* Respectfully dedicated to the memory of Professor H. Stephen, first Executive Editor of Tetrahedron.

[1] Part IX. A. R. Katritzky, F. W. Maine and S. Golding, *Tetrahedron* **21**, 1693 (1965).

[2] S. F. Acree, *Amer. Chem. J.* **38**, 1 (1907).

[3] R. Gompper in *Advances in Heterocyclic Chemistry* (Edited by A. R. Katritzky) Vol. 2; p. 245. Academic Press, New York (1963).

[4] F. Arndt, L. Loewe and A. Tarhan-Akon, *Rev. Fac. Sci. Istanbul* **13A**, 140 (1948).

the reaction of the silver salt of 2-methyl-1-phenyl-1,2,4-triazolidine-3,5-dione gave only the 2,4-dimethyl derivative.

The constitution of the methyl derivatives was assigned by Acree[2,5] on the basis of chemical evidence: the assignments are confirmed by the physical measurements now recorded (e.g. the IR spectra, Table 2).

TABLE 1. UV ABSORPTION MAXIMA

Compound	Anion[a] λ_{max} mμ	Anion[a] $\log_{10}\epsilon$	Neutral[b] λ_{max} mμ	Neutral[b] $\log_{10}\epsilon$	$-H_0$	Cation λ_{max} mμ	Cation $\log_{10}\epsilon$
1-Phenylurazole*	265[c]	3·98	248	4·04	7·9	235	3·97
2-N-Methyl-1-phenyl-1,2,4-triazolidine-3,5-dione	248	3·92	240	3·88	6·7	226†	3·81
3-O-Methyl-1-phenyl-1,2,4-triazolin-5-one	258	3·85	246	3·91	5·6	238	3·79
4-N-Methyl-1-phenyl-1,2,4-triazolidine-3,5-dione	264	4·02	246	4·08	5·6	243	4·00
2,4-N,N′-Dimethyl-1-phenyl-1,2,4-triazolidine-3,5-dione	—		239	3·95	6·7	231	3·84
3,4-O,N-Dimethyl-1-phenyl-1,2,4-triazolin-5-one	—		248	3·99	4·8	238	3·87
3,5-Diethoxy-1,2,4-triazole	—		245[c]	4·00	2·9	228	3·98
3-O-Ethoxy-1-phenyl-1,2,4-triazolidin-5-one	258	3·96	248	3·98	5·6	237	3·93

* di-anion λ_{max}: 278 mμ, $\log_{10}\epsilon$ = 4·02 in 1N NaOH.

† point of inflection

[a] 0·01N NaOH

[b] 1N H_2SO_4

[c] KH_2PO_4 buffer, pH 8

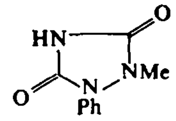
Ultra-violet spectra (Table 1). The UV spectra of the cationic species were all similar, except that the 2-N-monomethyl, and 2,4-N,N′-dimethyl derivatives showed slight hypsochromic shifts. This is probably due to some steric hindrance between the 2-N-methyl group and the phenyl ring. The same pattern of similarities and shifts was found for the neutral species, and also for the mono-anions, so that no conclusion about the tautomeric structure could be drawn. The results are in good agreement with those of previous workers[6] for 1-phenylurazole and its 2-N-methyl derivative, except that the published curve for the (mono) anion of the former was obtained at a pH such that a large quantity of the dianionic form was present.

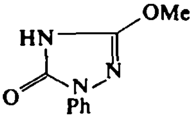
Infrared spectra. IR spectra of all compounds were obtained as nujol mulls;[7] detailed assignment is difficult, but the carbonyl stretching frequencies (Table 2) indicate that oxo-forms, and where possible di-oxo forms, are important for all these compounds. In cells of 5 cm path-length, carbon tetrachloride solutions of the 2-N-methyl and the 3-O-methyl derivatives showed peaks at 3475 and 3460 cm^{-1} (assigned to ν N—H in 4-position), whereas the 4-N-methyl derivative showed a band at 3340 cm^{-1} (assigned to ν N—H in 2-position). These results indicate that these compounds

[5] S. F. Acree, *Ber. Dtsch. Chem. Ges.* **35**, 558 (1902).

[6] J. Bourdais, F. Cugniet, J-C. Prior and P. Chabrier, *Bull. soc. chim. Fr.* 500 (1964).

[7] For details see A. Gordon, M.Sc. Thesis, University of East Anglia, 1965.


VII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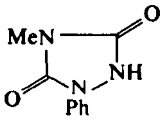

IX

exist in the forms VII–IX respectively. Solubility difficulties prevented the use of NMR spectra.

pK_a *values for proton loss.* The first and second proton losses of 1-phenylurazole, and the proton loss of the monomethyl derivatives, were obtained spectrophotometrically (Table 2). The mono-anion of 1-phenylurazole has the possible tautomeric structures X–XIII: the relative contributions of the first three of these are indicated by the data (it is unlikely that structure XIII occurs to a significant extent). Assuming the structure of the monomethyl derivatives to be VII–IX, the mono-anions of VII and IX can be considered "fixed forms" for the parent mono-anion. This would indicate a ratio of structures X:XI of ca. 100:1, with XII probably somewhat less

TABLE 2. BASICITY MEASUREMENTS AND IR CARBONYL FREQUENCY ASSIGNMENTS

					$\nu C{=}O$ (cm^{-1})	
Compound	pK_a as base[a][b]	Hammett n[b]	Hammett m[c]	pK_a (proton loss)	$^3C{=}O$	$^5C{=}O$
1-Phenylurazole	−4·1	2·5 ± 0·2	1·6 ± 0·2	4·85 ± 0·03[d]	1765	1700
2-N-Methyl-1-phenyl-1,2,4-triazolidine-3,5-dione	−4·7	2·6 ± 0·25	1·6 ± 0·1	6·97 ± 0·01[e]	1785 1755 1745	1710
3-O-Methyl-1-phenyl-1,2,4-triazolin-5-one	−3·4	1·95 ± 0·25	1·2 ± 0·1	6·93 ± 0·01	—	1720
4-N-Methyl-1-phenyl-1,2,4-triazolidine-3,5-dione	−4·2	1·8 ± 0·2	1·2 ± 0·2	4·73 ± 0·02	1760 1730	1690
2,4-N,N′-Dimethyl-1-phenyl-1,2,4-triazolidine-3,5-dione	−4·8	2·9 ± 0·3	1·6 ± 0·2	—	1760	1710
3,4-O,N-Dimethyl-1-phenyl-1,2,4-triazolin-5-one	−3·1	2·0 ± 0·1	1·3 ± 0·1	—	—	1710
3,5-O,O′-Diethoxy-1-phenyl-1,2,4-triazole	−0·55	0·8 ± 0·1	—	—	—	—
3-O-Ethoxy-1-phenyl-1,2,4-triazolin-5-one	−2·9	1·95 ± 0·1	1·2 ± 0·1	6·96 ± 0·02	—	1690

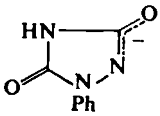
[a] $-H_0$ values given to 0·1 units

[b] calculated using the H_0 acidity function

[c] calculated using the H_A acidity function Ref. 9

[d] pK_a (second proton loss) at 12·20 ± 0·03. Previous determinations by conductivimetric methods: lit.,[3] 4·96; lit.,[6] 4·90; lit.,[6] 5·42 (in 50% MeOHaq).

[e] Previous determination: lit.,[6] 7·48 (in 50% MeOHaq).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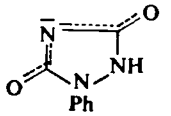
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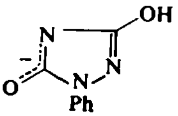
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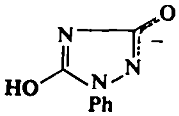
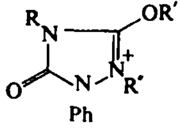

XIII

abundant than XI. The greater stability of X than XI is at first surprising, for on valence bond theory, the negative charge should be more delocalized in XI.

pK_a *values for proton gain* (Table 2). These were determined in sulphuric acid of known concentration by the method of Ref.[8]. Except for 3,5-diethoxy-1,2,4-triazole, none of the compounds are Hammett bases, since the values of n in Table 2 are all considerably greater than unity, nor do they follow the amide acidity function:[9] cf values of m in Table 2.

The parent compound and its 4-N-methyl derivative are of comparable basicity, whereas the 2-N-methyl and the 2,4-N,N′-dimethyl derivatives are weaker by ca. 0·6 pK units, and the 3-O-methyl and 3,4-O,N-dimethyl derivatives are stronger bases by ca. 0·8 pK units than the parent. The simplest explanation is that mesomeric cations of type XIV are formed by all the foregoing compounds, and that substitution of a methyl group in the 4-position has little effect on the basicity of a compound, but that a 2-N-methyl group has a base-weakening effect of ca. 0·6 pK units. It would then follow that the parent compound exists predominantly in the 3,5-dioxo form (I), with the 3-hydroxy-5-oxo form contributing to the extent of some 10% in aqueous media.



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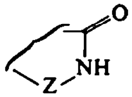

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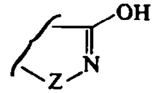

XVI

General discussion. Previous work has indicated that for 3-hydroxy-isoxazoles,[10] 1-substituted-pyrazoles,[11] and -1,2,4- and -1,2,5-oxadiazoles,[12] the 3-hydroxy-form is important. As a generalization, in equilibria of type XV ⇌ XVI, with Zanatom bearing a lone electron pair, the hydroxy-form (XVI) predominates or makes a significant contribution. However, the presence of this structural feature evidently does not invariably lead to a predominance of the hydroxy form. We are now engaged in further work designed to delineate further the occurrence of the hydroxy tautomer in heterocyclic systems.

EXPERIMENTAL

1-Phenylurazole[6] formed needles (from EtOH), m.p. 269° (lit.,[6] 268°).

2-Methyl-1-phenyl-1,2,4-triazolidine-3,5-dione[3] formed needles (from EtOHaq), m.p. 185° (lit.,[3] 185–188°; lit.,[4] 183°; lit.,[6] 180°).

3-Methoxy-1-phenyl-1,2,4-triazolin-5-one. Ethereal diazomethane (ca. 5 g from 20 g nitrosomethylurea in 100 ml ether) was drawn through 1-phenylurazole (6·0 g) on a filter paper in a Buchner funnel into dil acetic acid (20 ml). Ether was evaporated off, and the residue dissolved in EtOH (5 ml) and basified with dil KOH (20 ml). Water (50 ml) was added and the precipitated dimethyl derivatives were separated and a further quantity removed by ether extraction. Acidification with dil H_2SO_4 then gave 3-methoxy derivative (0·65 g, 10%) as white needles (from EtOHaq), m.p. 197° (lit.,[3] 197°).

3-Ethoxy-1-phenyl-1,2,4-triazolin-5-one[3] formed needles (from EtOHaq), m.p. 151° (lit.,[3] 151–152°)

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[8] C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, Naeem Shakir and A. M. White, *Tetrahedron* **21**, 1055 (1965).

[9] K. Yates, J. B. Stevens and A. R. Katritzky, *Canad. J. Chem.* **42**, 1957 (1964).

[10] A. J. Boulton, A. R. Katritzky, A. Majid Hamid and S. Øksne, *Tetrahedron* **20**, 2835 (1964).

[11] A. R. Katritzky and F. W. Maine, *Tetrahedron* **20**, 315 (1964).

[12] A. R. Katritzky, B. Wallis, R. T. C. Brownlee and R. D. Topsom, *Tetrahedron* **21**, 1681 (1965).

4-Methyl-1-phenyl-1,2,4-triazolidine-3,5-dione[3] formed plates (from water), m.p. 220° (lit.,[3] 223–225°, lit.,[4] 223°).

3-Methoxy-4-methyl-1-phenyl-1,2,4-triazolin-5-one[3] formed needles (from EtOHaq), m.p. 95° (lit.,[3] 95°, lit.,[4] 95°).

2,4-*Dimethyl*-1-*phenyl*-1,2,4-*triazolidine*-3,5-*dione*. 2-Methyl-1-phenyl-1,2,4-triazolidine-3,5-dione (0·65 g) was added to ethereal diazomethane (ca. 10 g from 40 g nitrosomethyl urea). Evaporation of the filtered solution gave the dimethyl derivative (0·65 g, 90%) as colourless prisms (from EtOHaq), m.p. 95° (lit.,[3] 95°, lit.,[4] 95°).

3,5-Diethoxy-1-phenyl-1,2,4-triazole[3] formed needles (from EtOHaq), m.p. 51–52° (lit.,[3] 51–53°).

Acknowledgements—This work was carried out during the tenure of an S.R.C. Advance Course Studentship (by A. A. G.) and an Institute of General Medical Science, National Institute of Health, U.S. Public Health Service, Fellowship (F. D. P.).