Pyridazines. XLV [1]. On the Mechanism of an Unusual 1,2-Diazine → 1,2-Diazole Ring Contraction

Gottfried Heinisch*, Thierry Huber and Christina Langer [2]

Institute of Pharmaceutical Chemistry, University of Vienna,
Währinger Strasse 10, A-1090 Vienna, Austria

Walter Gössler and Gert Kollenz

Institute of Organic Chemistry, Karl-Franzens University Graz,
Heinrichstrasse 28, A-8010 Graz, Austria

Received January 24, 1989

Starting with succinic acid-2,3-^{13}C, phenyl(4-pyridazinyl)methanol-4,5-^{13}C was prepared in order to gain insight into the mechanism of an unusual pyridazine into pyrazole rearrangement reported previously. According to the ^{13}C-nmr spectrum of labeled 1-phenyl-2(4-pyrazolyl)ethanone obtained upon *p*-toluenesulfonic acid mediated ring contraction, the methylene and the pyrazole C-4 carbon atoms of the reaction product originate from the pyridazine carbon atoms 4 and 5 of the educt. Thus, a mechanism for this ring-transformation is proposed involving well stabilized carbocations as intermediates.

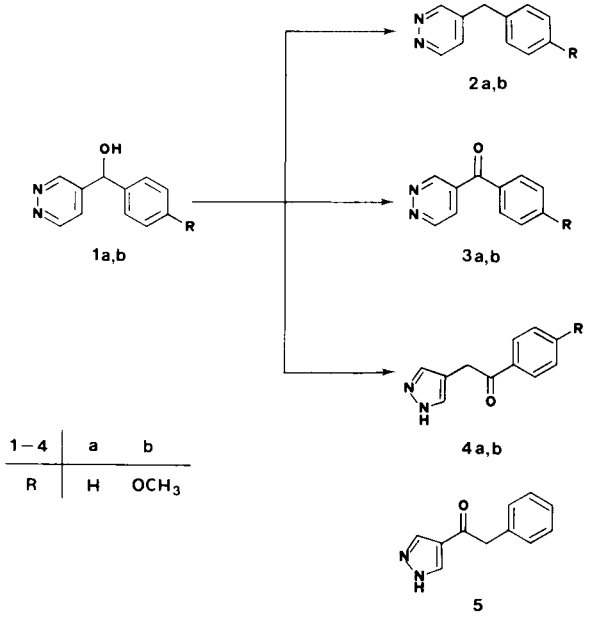
J. Heterocyclic Chem., **26**, 1009 (1989).

Previously, it has been reported [3] that treatment of aryl(4-pyridazinyl)methanols **1a, 1b** with *p*-toluenesulfonic acid in 2-dimethylaminoethanol solution does not result in the expected [4] formation of ethers, but instead affords a mixture of products **2, 3** formed by a dismutation reaction [5] along with a C-4 substituted pyrazole derivative **4**. The assignment of the 1-aryl-2-(4-pyrazolyl)ethanone structure for the surprising ring contraction products **4** has been based on a degradation experiment (affording 4-pyrazolecarboxylic acid) together with spectroscopic data suggesting the oxo function to be in conjugation with the (substituted) phenyl moiety [3]. Recently, the synthesis of the pyrazole derivative **5** by an unambiguous route has been achieved [6] and compound **5** turned out not to be identical with the product obtained from **1a**. Thus, there cannot be any doubt about the structure previously proposed for compounds **4a,b**.

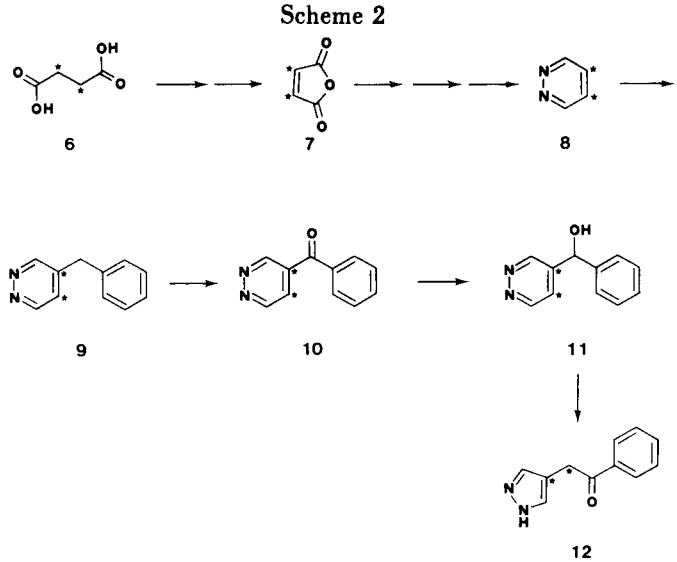
Here we report on the synthesis of ^{13}C-labeled phenyl(4-pyridazinyl)methanol **11** and on its conversion into the corresponding pyrazole derivative. This investigation was undertaken in order to elucidate the fate of carbon atoms 4 and 5 of the pyridazine ring thus to gain some insight into the mechanism which accounts for this 1,2-diazine → 1,2-diazole transformation.

In the reaction sequence applied for the preparation of pyridazine-4,5-^{13}C **8**, succinic acid-2,3-^{13}C **6** (labeling degree approx. 16%) was employed as the starting material. Transformation of **6** into maleic anhydride-2,3-^{13}C **7** *via* fumaric acid-2,3-^{13}C was achieved following a procedure utilized by Nystrom *et al.* [7] for the synthesis of [2,3-^{14}C] **7**. Reaction of **7** with hydrazine sulfate [8] followed by phos-

Scheme 1



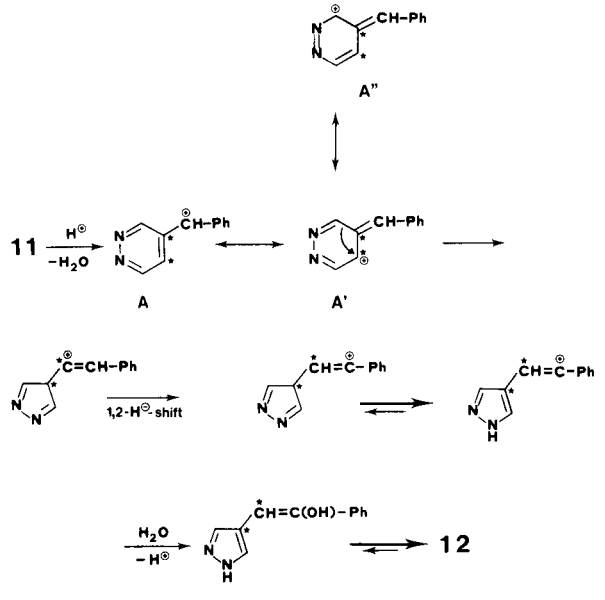
Scheme 2



phorus oxychloride mediated chlorination according to ref [9] afforded 3,6-dichloropyridazine-4,5-^{13}C. Pyridazine-4,5-^{13}C **8** then was obtained in 85% yield by reductive dehalogenation [9] under atmospheric pressure in the presence of a large excess of ammonia. Phenyl(4-pyridazinyl)methanol-4,5-^{13}C (**11**) finally was prepared as displayed in Scheme 2 according to ref [10] by homolytic benzylation of **8** followed by selenium dioxide oxidation and reduction of the diazabenzophenone **10** thus obtained. The overall yield of **11** (related to **8**) could be raised from 21% [10] up to 30% by using crude products **9** and **10** in this reaction sequence.

In the ^{13}C-H-decoupled ^{13}C-nmr spectrum of 1-phenyl-2-(4-pyrazolyl)ethanone **12**, obtained from **11** upon *p*-toluenesulfonic acid mediated ring contraction [3], the signals δ = 34 ppm and δ = 112 ppm, respectively, appear as doublets (^2Jcc = 50.5 Hz) indicating a vicinal position of the labeled carbon atoms in the ring contracted molecule **12**. According to ref [3] these signals are assigned to the methylene carbon atom and the pyrazole C-4 atom. These experimental findings in principle are in agreement with several alternative routes concerning this unusual pyridazine → pyrazole rearrangement, which have been discussed previously [3,11]. The obviously most reasonable reaction pathway is outlined in Scheme 3.

Scheme 3



Considering a marked double bond character of the C-4, C-5 bond in the pyridazine system [12], stabilisation of a carbo cation **A**, formed *via* initial protonation of the OH-function in the alcohol **11**, might be well anticipated [13]. From the resonance structure **A'** with an exocyclic C=C bond, the ring contraction process is understandable since a quite similar behaviour has been observed with alicyclic cations [14]; ring contraction occuring *via* resonance structure **A"** has to be ruled out since this would lead to a C-3 substituted pyrazole derivative. A 1,2-hydride shift in the vinylium ion obtained from **A'** then would afford a more stable one, in which the positive charge is adjacent to the phenyl group [15]. Tautomerisation of the 4*H*-pyrazolenine moiety (4π-system) into the aromatic pyrazole ring (6π-system) [16] followed by addition of water finally gives the enolic form of **12**.

The previously reported [3] experimental finding that phenylpyridylmethanols, when treated with *p*-toluenesulfonic acid in 2-dimethylaminoethanol solution at 150°, do not afford analogous ring transformation products is not a contradictory one to the reaction mechanism proposed, since there is a significant difference in the pK values of pyridine and pyridazine (p$K_{pyridine}$ = 5.2, p$K_{pyridazine}$ = 2.3) [17], which makes protonation of the oxygen in the case of pyridine derived diarylmethanols as the initial attack more unlikely.

In view of the mechanism for the transformation of **11** into **12** discussed above, our observation that the isomeric phenyl(3-pyridazinyl)methanol [18] does not undergo an analogous ring contraction reaction is not surprising: if the alcoholic side chain is attached to C-3 of the 1,2-diazine ring, stabilisation of the carbocation (initially formed by dehydratation) by mesomeric contribution of the pyridazine system certainly is less favoured.

Further investigations also with regard to the simultaneously occuring thermally initiated dismutation reaction of aryl(4-pyridazinyl)methanols are envisaged.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. The glc analyses were carried out with a Hewlett Packard 5890A/5970B-MSD, using a 12m HP1-FS-WCOT column. The ^{13}C-nmr spectrum was obtained on a Varian XL-200 instrument; chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. For analytical tlc, DC-Alufolien, Kieselgel 60 F_{254} (Merck) were used. Column chromatography was performed on Kieselgel 60 (70-230 mesh, Merck), medium pressure liquid chromatography (mplc) in Lobar^R glass columns filled with 250 g of LiChroprep^R Si 60 (Merck).

Fumaric acid-2,3-^{13}C.

Preparation was accomplished following the procedure given in ref [7], starting with 885 mg (7.50 mmoles) of succinic acid-2,3-^{13}C (**6**) (labeling degree approximately 16%). After recrystallisation from water using 50 mg of charcoal, 700 mg (80%) of fumaric acid-2,3-^{13}C, mp 266-268° (ref [7]: 86%, mp 268°) was obtained.

Maleic Anhydride-2,3-^{13}C (**7**).

A mixture of 1.50 g (12.93 mmoles) of fumaric acid-2,3-^{13}C (labeling degree approximately 8%) and 14 g (98.59 mmoles) of

phosphorus pentoxide was heated to 155-160° for 3.5 hours in a Kugelrohr apparatus at 1 mbar. The liberated maleic anhydride-2,3-^{13}C (1.21 g (96%), mp 50-52°) was collected by cooling the recipient with dry ice (ref [7], 96%, mp 54°).

1,2-Dihydro-3,6-pyridazinedione-4,5-^{13}C.

Compound **7** (1.21 g, 12.38 mmoles) was reacted with 1.61 g (12.38 mmoles) of hydrazine sulfate following the procedure given in ref [8] to yield 1.05 g (76%) of 1,2-dihydro-3,6-pyridazinedione-4,5-^{13}C, mp 290-295° (ref [8], 78%, mp 306-307°).

3,6-Dichloropyridazine-4,5-^{13}C.

1,2-Dihydro-3,6-pyridazinedione-4,5-^{13}C (1.05 g, 9.41 mmoles) was refluxed in 87 ml of phosphorus oxychloride for 5 hours. After removal of excess reagent *in vacuo*, the cooled residue was poured onto ice and ammonium hydroxide (32%) was added until the suspension was slightly alkaline to litmus. The mixture was extracted with dichloromethane, the combined extracts were dried over anhydrous sodium sulfate and the solvent was evaporated *in vacuo*. The residue was passed through a short silica gel column using ethyl acetate as the eluent to yield 1.22 g (86%) of 3,6-dichloropyridazine-4,5-^{13}C, mp 68° (ref [9], 81%, mp 68-69°).

Pyridazine-4,5-^{13}C (**8**).

A solution of 1.22 g (8.09 mmoles) of 3,6-dichloropyridazine-4,5-^{13}C in 8.1 ml of ammonium hydroxide (32%) and 8.6 ml of ethanol containing 80 mg of palladium-charcoal (10%) was hydrogenated at atmospheres pressure until there was no starting material detectable by tlc (ethyl acetate). After removal of the catalyst, the solution was extracted with dichloromethane and the combined organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* followed by passing the residue obtained through a silica gel column [ethyl acetate:methanol (3:1)] afforded 550 mg (85%) (ref [9], 61%) of pure **8** (glc analysis).

4-Benzylpyridazine-4,5-^{13}C (**9**).

A mixture of 350 mg (2.06 mmoles) of silver nitrate, 4.67 g (34.34 mmoles) of phenylacetic acid, 550 mg (6.88 mmoles) of **8** and 6.9 ml of 2*N* sulfuric acid was heated to 60-70° under stirring and a solution of 4.71 g (20.64 mmoles) of ammonium peroxodisulfate in 20 ml of water was added within 20 minutes. After stirring and heating to 70-90° for 30 minutes, the mixture was allowed to cool and was then extracted with 40 ml of dichloromethane. The organic layer was separated and extracted with 2*N* sulfuric acid. The combined aqueous layers were cooled, made alkaline with 50% aqueous sodium hydroxide and extracted exhaustively with dichloromethane. After drying the combined organic layers over anhydrous sodium sulfate, the solvent was removed *in vacuo* and 818 mg of crude **9** was obtained, which was used in the next reaction step without further purification.

4-Benzoylpyridazine-4,5-^{13}C (**10**).

A solution of 818 mg of crude **9** in 23 ml of glacial acetic acid was added dropwise to a stirred suspension of 2.55 g (23.00 mmoles) of selenium dioxide in 23 ml of glacial acetic acid. After heating to 100° for 1 hour, the mixture was filtered, the ice-cooled filtrate was made alkaline by addition of 50% aqueous sodium hydroxide and was then extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and 711 mg of crude **10** was obtained.

Phenyl-4-pyridazinylmethanol-4,5-^{13}C (**11**).

To a solution of 711 mg of crude **10** in 21 ml of methanol, 167 mg (4.18 mmoles) of sodium borohydride was added within 15 minutes. The mixture was stirred at room temperature for 1 hour, then acidified with 2*N* sulfuric acid and methanol was removed *in vacuo*. The ice-cooled solution was made alkaline with 50% aqueous sodium hydroxide and was then extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a brown oil, which was purified by column chromatography (ethyl acetate), and 384 mg of pure (glc analysis) **12** (30% related to **8**) was obtained (ref [10], 21%).

1-Phenyl-2-(4-pyrazolyl-4-^{13}C)ethanone-2-^{13}C (**12**).

Compound **11** (384 mg, 2.06 mmoles), 197 mg (2.21 mmoles) of 2-dimethylaminoethanol and 496 mg (2.47 mmoles) of *p*-toluenesulfonic acid monohydrate were heated in a Kugelrohr apparatus at 150° *in vacuo* (10^{-2} mbar) for 2.5 hours. The resulting mixture was dissolved in dichloromethane and the solution was passed through a short silica gel column using ethyl acetate as the eluent. The solvent was removed *in vacuo* and the residue was subjected to mplc [ethyl acetate:dichloromethane (2:1)] to yield fraction A: 71 mg (19%) of **10**, fraction B: 92 mg (24%) of **12**, fraction C: 39 mg (11%) of **9** (ref [3], 11% of **10**, 29% of **12**, 8% of **9**).

Compound **12**.

This compound had mp 150-152° (ref [3], 153-155°); ^{13}C-nmr (deuteriodimethyl sulfoxide): δ 34 (d, J = 50.5 Hz, CH_2), 112 (d, J = 50.5 Hz, pyrazole C-4), 128 (phenyl C-2,3,4,5,6), 133 (pyrazole C-3,5), 136 (phenyl C-1), 197 (C=O).

Acknowledgement.

The authors wish to express their gratitude to the "Fonds zur Föderung der Wissenschaftlichen Forschung" for supporting this investigation (project P6260C). We are grateful to Prof. Dr. H. Sterk (University of Graz) for recording the ^{13}C-nmr spectrum.

REFERENCES AND NOTES

[1] Pyridazines **XLIV**: M. Grabenwöger, N. Haider and G. Heinisch, *Ann. Chem.*, submitted.

[2] Part of Diploma Thesis of C. L., University of Vienna, 1989.

[3] G. Heinisch and R. Waglechner, *J. Heterocyclic Chem.*, **21**, 1727 (1984).

[4] H. Herstel, G. van Hell, D. Mulder and W. T. Nauta, *Arzneim.-Forsch.*, **18**, 827 (1968).

[5] G. Heinisch, E. Luszczak and M. Pailer, *Monatsh. Chem.*, **105**, 763 (1974).

[6] G. Heinisch, W. Holzer and T. Huber, *Arch. Pharm. (Weinheim)*, **320**, 1267 (1987).

[7] R. F. Nystrom, Y. H. Loo and J. C. Leak, *J. Am. Chem. Soc.*, **74**, 3434 (1952).

[8] J. Patterson, L. Braun, N. Haidar, J. Huang and W. Smith, *J. Labeled Compd. Radiopharm.*, **24**, 442 (1978).

[9] R. H. Mizzoni and P. E. Spoerri, *J. Am. Chem. Soc.*, **73**, 1873 (1951).

[10] G. Heinisch, A. Jentzsch and M. Pailer, *Monatsh. Chem.*, **105**, 648 (1974).

[11] R. Waglechner, Dissertation, University of Vienna, 1984.

[12a] R. N. Castle, "Pyridazines", John Wiley and Sons Inc., New York, 1973, p 2; [b] G. Heinisch and R. Waglechner, *Monatsh. Chem.*, **115**, 1171 (1984).

[13] J. March, "Advanced Organic Chemistry", 2nd Ed, McGraw-Hill Inc., Tokyo, 1977, p 151.

[14] G. A. Olah, "Carbokationen und Elektrophile Reaktionen", Verlag Chemie GmbH, Weinheim, 1974, p 128.

[15a] M. Hanack, *Angew. Chem., Int. Ed. Engl.*, **17**, 333 (1978); [b] G. Hammer, T. Bäßler and M. Hanack, *Chem. Ber.*, **107**, 1676 (1974).

[16] M. P. Sammes and A. R. Katritzky, "Advances in Heterocyclic Chemistry", Vol **34**, Academic Press, New York, London, 1983, p 53.

[17] A. Albert, "Chemie der Heterocyclen", Verlag Chemie GmbH, Weinheim, 1962, p 332.

[18] I. Garland, L. Hatton, W. Leeds and E. Parnell, German Offen. 2557956 (1976); *Chem. Abstr.*, **85**, 177470 (1976).