

SYNTHESIS OF PYRIDAZINES via FURAN VINAMIDINIUM SALTS

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Reaction of 5-(N,N-dimethylamino)-2-furfurylidene-N,N-dimethyliminium bromide (*I*) with hydrazine affords 3-hydrazone-2,3,4,5-tetrahydro-6-methylenehydrazonopyridazine (*III*). 5-(N,N-Dialkylamino)-2-arylazofuran salts *II* react with the same reagent to give 3,6-disubstituted pyridazines *V*. The structure of the synthesized compounds was identified by ¹H NMR and mass spectra.

Thanks to the biological activity of many pyridazine derivatives¹ the pyridazine chemistry has been well investigated²⁻⁵. Among many methods leading to pyridazines²⁻⁵ those starting from furan derivatives are usually advantageous. The unsaturated 1,4-dicarbonyl building blocks are obtained from 2,5-dialkoxy-2,5-dihydrofurans prepared in turn by addition of bromine and alcohol to the corresponding furans. Subsequent reaction with hydrazine leads then to pyridazine derivatives⁶⁻¹⁴. The same principle is used in methods starting from 2(3*H*)-furanones¹⁵⁻²¹ or 3(2*H*)-furanones²²⁻²⁵. In the present paper we describe the preparation of pyridazine derivatives from furan vinamidinium salts^{26,27} *I* or *II* (ref.²⁸).

In general, the odd carbon atoms in vinamidinium salts²⁹ are relatively electron-deficient being thus susceptible to an attack by nucleophilic reagents. This fact has been utilized in the reactions with hydrazine. Treatment of compound *I* with hydrazine hydrate in ethanol afforded 3-hydrazone-2,3,4,5-tetrahydro-6-methylenehydrazonopyridazine (*III*). In all probability, the reaction of the compound *I* starts by an attack by hydrazine at the position 5 of the furan ring, followed by addition to the enamine system³⁰. Subsequent ring opening and ring closure afford then the corresponding tetrahydropyridazine derivative. Under the same reaction conditions, the parent 5-(N,N-dimethylamino)-2-furancarbaldehyde reacts with hydrazine to give the azine derivative *IV* whereas the ring transformation product *III* has not been observed.

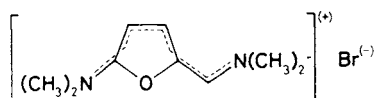
Pyridazine derivatives were successfully prepared from the "aza"-analogues of the vinamidinium salt *I*, 5-(N,N-dialkylamino)-2-arylazofuran salts *II*. The compounds *II* react with hydrazine hydrate under formation of the corresponding 3-arylazo-6-

-(*N,N*-dialkylamino)pyridazines *V* in very good yields (Table I). The prepared derivatives were identified by elemental analysis, UV, ¹H NMR and mass spectra.

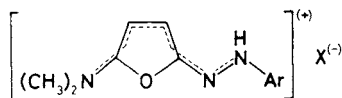
TABLE I
6-(*N,N*-Dialkylamino)-3-arylazopyridazines *V*

Compound	Formula ^a (mol. w.)	M.p., °C (yield, %)	Calculated/found ^b			λ_{\max} (log ϵ)
			% C	% H	% N	
<i>Va</i>	C ₁₂ H ₁₃ N ₅ (227.3)	174–176 (78)	63.42	5.76	30.81	373
			62.97	5.78	30.67	(3.09)
<i>Vb</i>	C ₁₂ H ₁₂ N ₆ O ₂ (272.3)	182–183 (89)	52.93	4.44	30.86	344
			53.06	4.46	31.12	(3.14)
<i>Vc</i>	C ₁₂ H ₁₂ N ₆ O ₂ (272.3)	233–235 (86)	52.93	4.44	30.86	384
			52.84	4.61	30.63	(2.98)
<i>Vd</i>	C ₁₂ H ₁₂ N ₆ O ₂ (272.3)	305–308 (88)	52.93	4.44	30.86	413
			52.43	4.37	30.48	(3.02)
<i>Ve</i>	C ₁₃ H ₁₅ N ₅ (241.3)	212–213 (52)	64.71	6.27	29.02	372
			64.42	6.19	28.85	(3.16)
<i>Vf</i>	C ₁₃ H ₁₅ N ₅ O (257.3)	170–172 (51)	60.69	5.88	27.22	370
			60.23	6.07	26.98	(3.09)
<i>Vg</i>	C ₁₄ H ₁₆ N ₆ O (284.3)	313–315 (71)	59.14	5.67	29.56	388
			58.81	5.53	29.58	(3.13)
<i>Vh</i>	C ₁₂ H ₁₂ BrN ₅ (306.2)	192–193 (52)	47.08	3.95	22.87	384
			46.85	4.04	22.79	(3.15)
<i>Vi</i>	C ₁₃ H ₁₄ N ₆ O ₂ (286.3)	220–222 (76)	54.54	4.93	29.35	344
			54.43	5.19	29.72	(3.20)
<i>Vj</i>	C ₁₄ H ₁₄ N ₆ O ₃ (314.3)	oil (52)	53.50	4.49	26.74	397
			53.12	4.63	26.68	(2.65)
<i>Vk</i>	C ₁₄ H ₁₄ N ₆ O ₃ (314.3)	200–202 (62)	53.50	4.49	26.74	400
			53.61	4.56	26.87	(2.94)
<i>Vl</i>	C ₁₄ H ₁₄ N ₆ O ₃ (314.3)	256–259 (92)	53.50	4.49	26.74	405
			53.40	4.43	26.79	(3.34)
<i>Vm</i>	C ₁₄ H ₁₄ gBrN ₅ O (348.2)	190–191 (80)	48.29	4.05	20.11	374!
			47.95	3.92	20.04	(3.10)

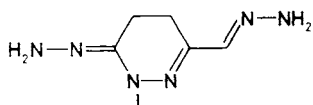
^a In all cases molecular peak was found by mass spectrometry; ^b *Vh*: calculated 26.10% Br, found 26.22% Br, *Vm*: calculated 22.95% Br, found 23.05% Br.



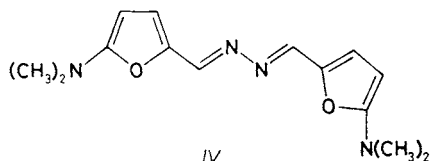
I



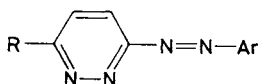
II







III



IV



- Va*, R = (CH₃)₂N; Ar = C₆H₅
Vb, R = (CH₃)₂N; Ar = 2-NO₂-C₆H₄
Vc, R = (CH₃)₂N; Ar = 3-NO₂-C₆H₄
Vd, R = (CH₃)₂N; Ar = 4-NO₂-C₆H₄
Ve, R = (CH₃)₂N; Ar = 4-CH₃-C₆H₄
Vf, R = (CH₃)₂N; Ar = 4-CH₃O-C₆H₄
Vg, R = (CH₃)₂N; Ar = 4-CH₃CONH-C₆H₄

- Vh*, R = (CH₃)₂N; Ar = 3-Br-C₆H₄
Vi, R = (CH₃)₂N; Ar = 3-NO₂-4-CH₃-C₆H₃
Vj, R = ; Ar = 2-NO₂-C₆H₄
Vk, R = ; Ar = 3-NO₂-C₆H₄
Vi, R = ; Ar = 4-NO₂-C₆H₄
Vm, R = ; Ar = 3-Br-C₆H₄

Thus, the reaction of furan vinamidinium salts with hydrazine represents a new, very simple and elegant approach to 3,6-disubstituted pyridazines.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Ultraviolet spectra were measured on a Specord UV-VIS (Zeiss, Jena) spectrophotometer in 5 mm cells in acetone solutions, concentration $1 \cdot 10^{-3}$ – $1 \cdot 10^{-4}$ mol l⁻¹ (ϵ in m² mol⁻¹). ¹H NMR spectra were taken in hexadeuteriodimethyl sulfoxide on a Tesla BS 487 C (80 MHz) spectrometer (CW mode), internal standard tetramethylsilane. Mass spectra were obtained with an MS 902 S (AEI Manchester) spectrometer, direct inlet, electron energy 70 eV, electron current 100 μ A, ionization chamber temperature according to the sample volatility.

5-(N,N-Dimethylamino)-2-furalazine (IV)

Hydrazine hydrate (2 ml) in ethanol (5 ml) was added at 10–15°C to a stirred solution of 5-(N,N-dimethylamino)-2-furancarbaldehyde (0.33 g; 2 mmol) in ethanol (10 ml). After stirring at room temperature for 2 h, the mixture was taken down in vacuo and the dry residue was partitioned between ice-cold water (50 ml) and ether. The ethereal layer was washed with water, dried and the solvent was evaporated under diminished pressure. The obtained oily product IV crystallized on standing, m.p. 142–144°C; yield 0.35 g (65%). For C₁₄H₁₈N₄O₂ (274.3) cal-

culated: 61.29% C, 6.61% H, 20.42% N; found: 60.99% C, 6.55% H, 20.50% N. ^1H NMR spectrum ($\text{C}^2\text{H}_3\text{COC}^2\text{H}_3$): 7.97 s, 1 H (CH); 6.81 d, 11 H (H-3, $J = 4$); 5.22 d, 1 H (H-4); 2.92 s, 6 H (CH_3).

3-Hydrazono-2,3,4,5-tetrahydro-6-methylenehydrazonopyridazine (III)

A solution of hydrazine hydrate (2 ml) in ethanol (5 ml) was added in one portion to a stirred suspension of *I* (0.79 g; 3 mmol) in ethanol (10 ml). The reaction mixture turned yellow and became homogeneous. After 3–4 h of stirring a solid separated which was filtered and washed with ethanol. Crystallization from methanol afforded 0.43 g (93%) of *III*, m.p. 193–195°C. For $\text{C}_5\text{H}_{10}\text{N}_6$ (154.1) calculated: 38.95% C, 6.54% H, 54.50% N; found: 39.28% C, 6.72% H, 54.64% N. ^1H NMR spectrum ($\text{C}^2\text{H}_3\text{COC}^2\text{H}_3$): 7.26 s, 1 H (CH); 6.80 s, 4 H (NH_2); 2.50 to 2.02 m, 4 H (H-3,3, H-4,4). UV spectrum (methanol, λ_{max} (nm) (log ϵ): 322 (3.47). Mass spectrum: $\text{M}^{+\cdot}$ 154.

3-Arylazo-6-(N,N-dialkylamino)pyridazines *V*

Hydrazine hydrate (2 ml) in ethanol (5 ml) was added at room temperature to a stirred suspension of *II* (3 mmol) in ethanol (10 ml). After stirring for 3–4 h at room temperature the mixture was concentrated under diminished pressure and treated with ice-cold water (50 ml). The separated solid was filtered, washed with water and crystallized from methanol. Characteristic data for compounds *V* are given in Table I.

^1H NMR spectra of 3-arylazo-6-(N,N-dialkylamino)pyridazines *V*:

Va: 3.22 s, 6 H (CH_3); 7.16 d, 1 H (H-5, $J = 10$); 7.75 d, 1 H (H-4); 7.93–7.48 m, 5 H (H arom.).

Vb: 3.46 s, 6 H (CH_3); 7.11 d, 1 H (H-5, $J = 10$); 7.48 d, 1 H (H-4); 8.28–6.87 m, 4 H (H arom.).

Vc: 3.21 s, 6 H (CH_3); 7.14 d, 1 H (H-5, $J = 10$); 7.78 d, 1 H (H-4); 8.37–7.92 m, 3 H (H arom.); 8.52 s, 1 H (H arom.).

Vd: 3.25 s, 6 H (CH_3); 6.82 d, 1 H (H-5, $J = 10$); 7.98 d, 1 H (H-4); 8.07 d, 2 H (H arom., $J = 9$); 8.40 d, 2 H (H arom.).

Ve: 2.37 s, 3 H (CH_3); 3.21 s, 6 H (CH_3); 7.12 d, 1 H (H-5, $J = 10$); 7.31 d, 2 H (H arom., $J = 8$); 7.70 d, 1 H (H-4); 7.77 d, 2 H (H arom.).

Vf: 3.30 s, 3 H (OCH_3); 3.30 s, 6 H (CH_3); 7.10 d, 1 H (H-5, $J = 10$); 7.25 d, 2 H (H arom., $J = 9$); 7.72 d, 2 H (H arom.); 7.87 d, 1 H (H-4).

Vg: 2.07 s, 3 H (CH_3); 3.20 s, 6 H (CH_3); 7.15 d, 1 H (H-5, $J = 10$); 7.31 d, 2 H (H arom., $J = 9$); 7.75 d, 1 H (H-4); 7.87 d, 2 H (H arom.); 10.07 s, 1 H (NH).

Vh: 3.21 s, 6 H (CH_3); 7.15 d, 1 H (H-5, $J = 10$); 7.72 d, 1 H (H-4); 7.50–7.85 m, 3 H (H arom.); 7.97 s, 1 H (H arom.).

Vi: 3.18 s, 6 H (CH_3); 7.26 d, 1 H (H-5, $J = 10$); 7.37 d, 1 H (H arom., $J = 9$); 7.50 s, 1 H (H arom.); 7.79 d, 1 H (H-4); 7.87 d, 1 H (H arom.); 2.34 s, 3 H (CH_3).

Vj: 3.47 m, 8 H ($\text{O}-\text{CH}_2-\text{CH}_2-\text{N}$); 7.18 d, 1 H (H-5, $J = 10$); 6.87–7.87 m, 4 H (H arom.); 8.06 d, 1 H (H-4).

Vk: 3.30 m, 8 H ($\text{O}-\text{CH}_2-\text{CH}_2-\text{N}$); 7.42 d, 1 H (H-5, $J = 10$); 7.87 d, 1 H (H-4); 8.47 to 8.87 m, 3 H (H arom.); 8.58 s, 1 H (H arom.).

VI: 3.15 m, 8 H ($\text{O}-\text{CH}_2-\text{CH}_2-\text{N}$); 7.35 d, 1 H (H-5, $J = 10$); 7.81 d, 1 H (H-4); 8.05 d, 2 H (H arom., $J = 9$); 8.40 d, 2 H (H arom.).

ν_{m} : 3.73 m, 8 H (O—CH₂—CH₂—N); 7.35 d, 1 H (H-5, $J = 10$); 7.77 d, 1 H (H-4); 7.52 to 7.87 m, 3 H (H arom.); 7.98 s, 1 H (H arom.).

REFERENCES

1. Kleman A., Engel J.: *Pharmazeutische Wirkstoffe: Synthesen, Patente, Anwendungen*. Thieme Verlag, Stuttgart 1978.
2. Tišler M., Stanovnik B.: *Adv. Heterocycl. Chem.* 9, 211 (1968).
3. Tišler M., Stanovnik B.: *Adv. Heterocycl. Chem.* 24, 363 (1979).
4. Jacobs T. L. in the book: *Heterocyclic Compounds* (R. C. Elderfield, Ed.), Vol. 6, p. 101. Wiley, New York 1957.
5. Tišler M., Stanovnik B. in the book: *Comprehensive Heterocyclic Chemistry* (A. R. Katritzky and C. H. W. Rees, Eds), Vol. 3, p. 1. Pergamon Press, Oxford 1984.
6. Clauson-Kaas N., Limberg F.: *Acta Chem. Scand.* 1, 619 (1947).
7. Clauson-Kaas N., Si-Oh Li, Elming N.: *Acta Chem. Scand.* 4, 1233 (1950).
8. Elming N.: *Acta Chem. Scand.* 6, 512 (1952).
9. Fastorp J., Raleigh D., Schniepp L. E.: *J. Am. Chem. Soc.* 72, 869 (1956).
10. Letsinger R., Lasco R.: *J. Org. Chem.* 21, 764 (1956).
11. Levisalles J.: *Bull. Soc. Chim. Fr.* 1957, 997.
12. Levisalles J.: *Bull. Soc. Chim. Fr.* 1957, 1004.
13. Levisalles J.: *Bull. Soc. Chim. Fr.* 1957, 1009.
14. Robba M.: *Ann. Chim. Paris* 5, 351 (1960).
15. Rao Y. S.: *Chem. Rev.* 1964, 353.
16. Rao Y. S.: *Chem. Rev.* 1976, 625.
17. Boyd G. V., Heatherington K.: *J. Chem. Soc., Perkin Trans 1*, 1973, 2532.
18. Elkasaby M. A., Elkady M., Nour E. A. N.: *Indian J. Chem., B* 15, 436 (1977).
19. El-Hashash M. A., Abdalla M., Essawy A., El-Gendy A. M.: *Pak. J. Sci. Ind. Res.* 1980, 254.
20. Abdalla M., Soliman E. A., Hamad A. A., Osman M. W.: *Rev. Roum. Chim.* 25, 1549 (1980).
21. Tauřík J., Conquelet J. D., Conquelet J. M., Carpy A.: *J. Heterocycl. Chem.* 21, 305 (1984).
22. Gelin S., Galliard A.: *C. R. Acad. Sci. Paris* 275, 897 (1972).
23. Gelin R., Gelin S.: *J. Heterocycl. Chem.* 14, 75 (1977).
24. Gelin S., Chabannet M.: *Synthesis* 1978, 448.
25. Jägersten S.: *Ark. Kemi* 1969, 261.
26. Gracza T., Arnold Z., Kováč J.: *Collect. Czech. Chem. Commun.* 49, 1600 (1984).
27. Kováč J., Gracza T., Arnold Z.: *Heterocycles* 21, 448 (1984).
28. Gracza T., Arnold Z., Kováč J.: *Collect. Czech. Chem. Commun.* 53, 1053 (1988).
29. Lloyd D., McNab H.: *Angew. Chem.* 88, 496 (1976).
30. Haynes L. W. in the book: *Enamines: Synthesis, Structure and Reactions* (A. G. Cook, Ed.), p. 59. Marcel Dekker. New York 1969.

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