PYRAZOLIDINE DERIVATIVES FROM THE CONDENSATION REACTION OF HYDRAZOBENZENE WITH ALIPHATIC ALDEHYDES

Vladimír Hanuš[a], Milan Hrazdira[b]* and Otto Exner[c]

[a] *J. Heyrovský Institute of Physical Chemistry and Electrochemistry, Czechoslovak Academy of Sciences, 121 38 Prague 2,*
[b] *Department of Organic Chemistry, Institute of Chemical Technology, 532 10 Pardubice and*
[c] *Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6*

Received February 26th, 1980

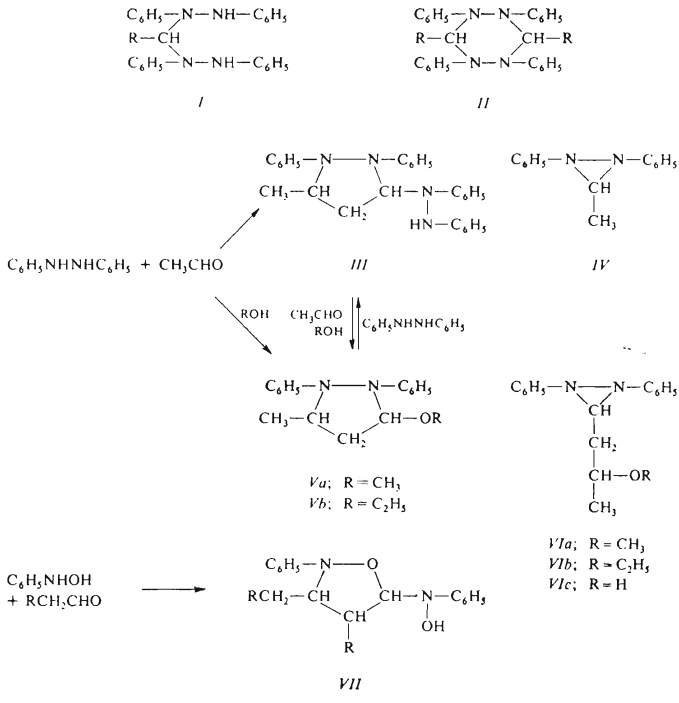
The condensation reaction of hydrazobenzene with ethanal yields products of the pyrazolidine structure, *III* or *V*, according to whether it is carried out in the absence or presence of alcohols, respectively. Propanal reacts similarly to *VIII* while no reaction could be achieved with butanal. The structural evidence is based mainly on the mass and ^{1}H-NMR spectra which disprove the structures *IV* and *VI*, originally suggested by Rassow. The reaction is analogous to the condensation of aliphatic aldehydes with N-phenylhydroxylamine yielding 1,2-oxazolidine derivatives *VII*.

The condensation reaction of aldehydes with hydrazobenzene as a nucleophile was investigated by Rassow and his students seventy years ago[1-4]. Products of three types were described depending on the structure of the aldehyde and conditions. Besides various alkylidenehydrazobenzenes (*I*) and perhydro-1,2,4,5-tetrazines (*II*), unexpected products were obtained from the reaction of ethanal and believed to be diaziridine derivatives[1]. The 1 : 1 product isolated from the reaction without solvent was formulated as *IV*, better characterized products from the methanol or ethanol solutions as *VIa* and *VIb*, respectively. The main reasons for structure assignment were the elemental analyses, ebulliosocpic determination of the molecular weight (in benzene), sensitivity to the acid hydrolysis, and mutual transformations of the compounds. Structures similar to *VI* were assigned also to products obtained from cinnamic aldehyde[4].

The structure *IV* and *VI* appear doubtful within the framework of the general chemistry of diaziridines, they have not even been included into a review on these compounds[5]. The doubts were strenghtened in the course of our first reinvestigation of this problem[6], but only the mass spectra behaviour pointed out to the correct structures *III* and *V*. The formula *III* was further corroborated by the 1,2-oxazoli-

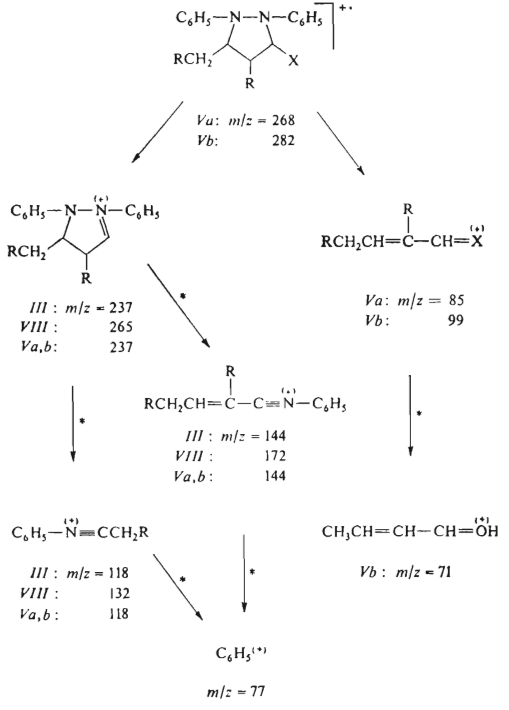
* Present address: Analytical and Physical Laboratory, Monocrystals, 511 19 Turnov.

dine structure *VII* assigned[7,8] to the condensation products of aldehydes with N-phenylhydroxylamine; this finding led us also to reinvestigate similar products from N-alkylhydroxylamines[9]. The analogy of hydrazobenzene and N-phenylhydroxylamine is in fact rather close in these reactions.*



* Quite generally, if the reactivities of oxygen and nitrogen derivatives are to be compared, then very similar pairs of compounds can be derived replacing the oxygen atom by the $-NHC_6H_5$ group[10].

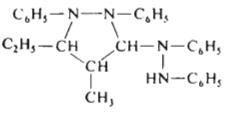
When reproducing Rassow's experiments[1], we paid proper attention to the purity of starting hydrazobenzene (absence of azobenzene) and of the products (control by paper chromatography). Most of the experimental facts have been confirmed, in particular the melting points and elemental analyses. The condensation of hydrazobenzene with ethanal in methanol or in ethanol yielded pure and stable products *Va* and *Vb*, respectively. If the reaction proceeds without a hydroxylic solvent, it is less smooth and the product *III* may be difficult to purify. When working in light petroleum solution, we were not able to isolate the hydroxy derivative, m.p. 116°C,



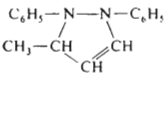
SCHEME 1

which was given[1] the structure *VIc*. The only product, m.p. 151°C, was the same as obtained without solvent. The reaction without solvent is most suitable for preparative work and safely reproducible provided pure starting material is used. Then the only product is *III*, the alternative structure *II* and *IV* could not even be detected as possible contaminations in the crude product. Some experiments carried out with ethanal containing paraldehyde yielded reaction mixtures which were not completely separated; under such conditions *III* need not be the only product. The reaction of hydrazobenzene with propanal afforded also a pyrazolidine derivative (*VIII*), originally formulated[3] as *II* ($R = C_2H_5$).

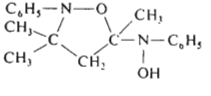
The proof of structures *III*, *V*, and *VIII* is based mainly on mass and ^{1}H-NMR spectra, but as far as only distinguishing of *III* from *II* and *IV* is concerned, even the presence of an N—H vibration frequency in the IR spectrum and the molecular weight would be sufficient. The mass spectra of compounds *III*, *VIII*, and *Va,b* are very similar and reveal a similar structure, incompatible with the formulae *II*, *IV*, or *VI*. The most important differences between individual spectra correspond just to the parts of the molecule in which the respective compounds differ: ions m/z 85 and 99 of the methoxy and ethoxy derivatives (*Va* and *Vb*), homologue increments in the spectrum of *VIII* compared to *III*. Also the fragmentation pattern of the four compounds is rather similar so that it can be represented by a common scheme (Scheme 1). The fragmentation paths were proved by metastable transitions and elemental composition but the origin of the transferred hydrogens has not been checked by deuterium labelling. The molecular ions of *III* and *VIII* were not observed because of an easy loss of diphenylhydrazyl radical producing the ions of the highest $\tilde{m}/\tilde{z}$ 237 and 265, respectively. On the contrary, the molecular ions are the base peaks in the



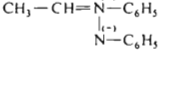
VIII



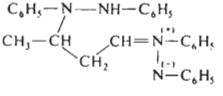
IX



X



XI



XII

spectra of alkoxy derivatives *Va,b*. The relative stabilities of these molecules are just in the reversed order than the stabilities of molecular ions: While *III* and *VIII* are completely stable, *Va* and *Vb* decompose partly in the direct inlet of the mass spectrometer to give the pyrazoline *IX*. The same compound is also present in old samples of *Va,b* and could be isolated from them in submilligram quantities and characterized by its mass spectrum. This spectrum was then used to correct the experimental spectra of *Va,b* for the presence of *IX*; it was substracted in such a ratio to achieve zero abundance of ions m/z 221. The spectra have been already corrected in this way.

An important feature of the ^{1}H-NMR spectra is the signal of the methine proton adjacent to two heteroatoms. It appears as a doublet (δ 4·97 or 5·12) with *Va,b* and as a not fully resolved quadruplet (δ 5·76) with *III*; in either case it reveals the nonequivalency of the two neighouring methylene protons and hence a cyclic structure. In the structure *VIa,b* this signal should appear as a triplet. With the compound *VII* (R = C_2H_5) the corresponding signal was found[7,8] at δ 5·23 or 5·28 as a doublet, J = 5 Hz. Another evidence of the ring closure is given by the signal of the methylene group itself which consists of two multiplets (δ 1·9 and 2·4) in the spectra of *Va,b* and appears as a complex multiplet (δ 2·3) in *III*. With the compound *X* the corresponding signal is represented by two doublets[11] δ 2·12 and 3·09. In the ^{1}H-NMR spectrum of *III* the NH signal (δ 5·19 s) is also important, corresponding to the N—H stretching frequency in the IR spectrum (3344 cm^{-1} in diluted chloroform solution). Otherwise indicate the IR spectra of *III* and *Va,b* the presence of all functional groups present but they cannot decide between the alternative structures. Likewise the remaining physical methods supplied only a subsidiary evidence, if any, of the structures. The electronic spectra (Fig. 1) can be simply interpreted by the presence of the hydrazobenzene system as the single chromophore; the small difference between the spectra of *Va* and hydrazobenzene itself is due to the

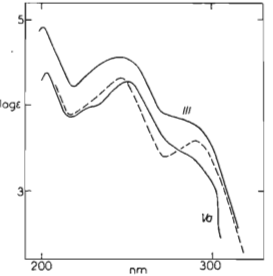


FIG. 1

Ultraviolet Absorption Spectra of Pyrazolidine Derivatives *III* and *Va* (in methanol)

The spectrum of hydrazobenzene (in 95% ethanol, dashed line) according to ref.[12].

restricted mobility of the benzene rings in the former. The absorption coefficient of *III* is twofold since two hydrazobenzene residues are present, one sterically hindered and one not hindered. The dipole moment of *III* is in accord with its structure and can only exclude some strongly polar formulae like nitrone-imines *XI* and *XII*.

The pyrazolidine structures *III* and *V* are also compatible with mutual conversions of these compounds. By the action of ethanal and the respective alcohol[1], *III* is transformed into *Va* or *Vb*; with hydrazobenzene the reverse reaction takes place. The reactions can be explained by an elimination–addition mechanism but they would be difficult to understand in terms of structures *IV* and *VI*. The elimination of an alcohol molecule from *Va,b* was observed even in the evaporation cell of the mass spectrometer as already mentioned. A similar reaction might be responsible for the erroneous molecular weight of *III* determined by ebullioscopy in benzene[1], while cryoscopy gave better but irreproducible results[1]. We found exactly one half of the actual molecular weight by cryoscopy in cyclopentadecanone (m.p. 65°C).* Compound *Va* can be also prepared from 2-butenal in methanol but interestingly enough also from 3-methoxybutanal. The methoxy group of the latter compound does not, however, appear in the product since in ethanol solution only *Vb* is produced. The acid hydrolysis of *III* or *Va* yields ethanal and benzidine and is of no use for structure determination.

The reaction yielding pyrazolidines is certainly not general, it is not even common to all enolizable aldehydes. We were unable to obtain some products from butanal or from 2-ethyl-3-hydroxyhexanal under variable conditions. The unreactivity of 2--methylpropanal and 3-methylbutanal was already reported[3]. Concerning the mechanism of the reaction, it can hardly start by the aldolization of aldehyde since ethanal present in excess remains unchanged. With regard to the reaction of N-phenylhydroxylamine with aldehydes[7–9,11] we suggest the nitron-imine *XI* as a probable intermediate. Some compounds of this type are isolable[13]. The nitron-imine can subsequently dimerize either by a dipolar 1,3-addition as suggested for hydroxylamine analogues[8], or aldolize with the second ethanal molecule and add the second molecule of hydrazobenzene. This latter pathway would suppose the intermediate *XII*; compounds of this type are known in the hydroxylamine series[14] and referred to as the Banfield–Kenyon[15] structure. In terms of this mechanism the formation of *Va* from 2-butenal is easier to understand.

EXPERIMENTAL

Melting points are corrected. The paper chromatography was performed by the descending technique on paper Whatman W4, impregnated with 25% dimethylformamide. The chromatographs were developed with cyclohexane and detected with 1% solution of *p*-dimethylaminobenzaldehyde in ethanol with 1% hydrochloric acid added. The mass spectra were taken on a JEOL JMS D 100 spectrometer using a direct inlet system. Compounds *III* and *VIII* were

* The product from 1,2-bis(4-methylphenyl)hydrazine and ethanal showed similar properties[2] as *III*. The molecular weight determined ebullioscopically in ether revealed, however, a 2 : 2 condensation product and a perhydro-1,2,4,5-tetrazine structure similar to *II* was assigned[2]. A structure like *III* seems more probable even in this case.

evaporated at 120—130°C, *Va,b* at 70—80°C, *IX* at 60°C; the temperature of the ionization chambre was kept at 140°C. The infrared absorption spectra were measured on a Zeiss Jena UR 20 spectrometer, callibration to polystyrene. Wavenumbers are given in cm^{-1}. The ^{1}H-NMR spectra were measured on a JEOL 60 MHz spectrometer with proton stabilization; tetramethylsilane was used as internal standard. Chemical shifts are given in the δ scale. The ultraviolet absorption spectra were measured on a UNICAM SP 800 B spectrometer at a concentration of 10^{-4} mol l^{-1}. The dipole moment was determined in benzene solutions $5 \cdot 10^{-2}$—$5 \cdot 10^{-3}$ mol l^{-1} according to the Halverstadt–Kumler method[16]. The molar refraction was calculated from increments[17]. Hydrazobenzene was purified from the commercial product by reduction with zinc dust and ammonia in order to remove any trace of a yellowish colour, m.p. 127°C (ethanol–cyclohexane 3 : 1).

3-(1′,2′-*Diphenylhydrazino*)-5-*methyl*-1,2-*diphenylpyrazolidine* (III). The condensation of ethanal with hydrazobenzene was carried out according to the literature[1], yield 61% after one crystallization and three digestions with ethanol, m.p. 151°C in agreement with ref.[1], R_F 0·70 (an orange spot). For $C_{28}H_{28}N_4$ (420·5) calculated: 79·96% C, 6·71% H, 13·32% N; found: 79·71% C, 6·66% H, 13·58% N. Molecular weight (cryoscopically in cyclopentadecanone) found 210, 213; calculated M/2 = 210. IR spectrum in KBr disc.: 694 s, 753 s, 958 w, 1163 w, 1262 m, 1379 m, 1456 m (CH_3), 1496 vs, 1599 vs (C_6H_5), 2870 vw, 2939 vw, 2980 w (C—H aliph.), 3025 vw, 3075 vw (C—H arom), 3330 s (N—H); in $CHCl_3$ (saturated solution): 3344 (N—H). ^{1}H-NMR spectrum in $CDCl_3$: 1·36 (d, J = 6 Hz, 3 H, CH_3), 2·3 (m, 2 H, CH_2), 4·25 (m, 1 H, CH-5), 5·19 (s, 1 H, NH), 5·76 (q, 1 H, CH—3), 6·2—7·4 (m, 20 H, C_6H_5). UV spectrum (in methanol); 201 (4·92), 248 (4·58), 284 infl. (3·82). MS [m/z (% base peak)]: 237 (100), 144 (17), 120 (28), 118 (81), 104 (22), 93 (18), 91 (19), 77 (93). Dipole moment (in benzene) $5{\cdot}6 \cdot 10^{-30}$ Cm with a 5% correction for the atomic polarization, $5{\cdot}3 \cdot 10^{-30}$ Cm with a 15% correction.

The same product *III* was also prepared by carrying out the reaction in light petroleum, the compound[1], m.p. 116—117°C was not isolated. Finally, *III* results in the yield of 40% from the reaction of *Va* and hydrazobenzene in equimolar quantities in light petroleum.

Hydrolysis of *III* with 2M hydrochloric acid at room temperature afforded benzidine and ethanal isolated as 2,4-dinitrophenylhydrazone.

3-(1′,2′-*Diphenylhydrazino*)-5-*ethyl*-4-*methyl*-1,2-*diphenylpyrazolidine* (VIII) was prepared from propanal and hydrazobenzene in the same way as the preceding compound, yield 50% m.p. 152°C in agreement with one of the products reported in ref.[3]; the product [3] m.p. 102°C was not isolated. For $C_{30}H_{32}N_4$ (448·6) calculated: 80·32% C, 7·19% H, 12·49% N; found: 80·05% C, 7·24% H, 12·22% N. MS [m/z (% base peak)]: 265 (81), 172 (19), 134 (24, 5) 132 (72), 104 (24), 93 (19), 77 (100).

Butanal or 2-ethyl-3-hydroxyhexanal do not react with hydrazobenzene under similar conditions. No reaction was even achieved with butanal and hydrazobenzene in ethanol at room temperature or at the boiling point, with or without *p*-toluenesulfonic acid.

3-*Methoxy*-5-*methyl*-1,2-*diphenylpyrazolidine* (Va). The reaction of ethanal, hydrazobenzene and methanol was carried out according to the literature[1], yield 60% after crystallization from methanol, m.p. 82°C in agreement with ref.[1], R_F 0·76 (a yellowish brown spot after heating). For $C_{17}H_{20}N_2O$ (268·3) calculated: 76·08% C, 7·51% H, 10·44% N; found: 75·98% C, 7·41% H, 10·07% N. IR spectrum in tetrachloromethane: 691 s, 749 vs, 1114 vs (C—O), 1210 s, (C—N), 1377 m, 1453 m (CH_3), 1492 vs, 1595 vs (C_6H_5), 2825 w, 2875 vw, 2905 w, 2929 m, 2976 m (C—H aliph.), 3015 w, 3036 w, 3066 w (C—H arom.). ^{1}H-NMR spectrum in $CDCl_3$: 1·49 (d, J = 6 Hz, 3 H, CH_3), 1·9 m + 2·4 m (2 H, CH_2), 3·38 (s, 3 H, CH_3O), 4·0 (m, 1 H, CH—5), 4·97 (d, J = 5 Hz, 1 H, CH—3), 6·6—7·4 (m, 10 H, C_6H_5). MS [m/z (% base peak)] 268 (M^+, 100), 237 (29), 210 (21), 209 (24), 195 (14), 118 (70), 104 (23), 93 (35), 85 (23), 77 (71).

UV spectrum in methanol: 204 (4·38), 251 (4·27), 282 infl. (3·46). This compound was also prepared starting from 2-butenal (yield 48%) or from 3-methoxybutanal (yield 57%) under identical conditions as above.

3-*Ethoxy*-5-*methyl*-1,2-*diphenylpyrazolidine* (Vb) was prepared in the same way as *Va* from ethanal and hydrazobenzene in ethanol (yield 61%), or from 3- methoxybutanal (yield 49%); m.p. 68°C in agreement with the literature[1], R_F 0·78 (a yellowish brown spot after heating). For $C_{18}H_{22}N_2O$ (282·4) calculated: 76·56% C, 7·85% H, 9·92% N; found: 76·53% C, 7·66% H, 10·12% N. IR spectrum in tetrachloromethane: 695 s, 755 vs, 1115 vs (C—O), 1209 s (C—N), 1327 s, 1371 s (CH_2), 1380 m, 1455 m (CH_3), 1495 vs, 1598 vs (C_6H_5), 2848 w, 2871 m, 2897 m, 2932 m, 2977 s (C—H aliph.), 3025 m, 3037 m, 3070 m (C—H arom.). ^{1}H-NMR spectrum in $CDCl_3$: 1·10 (t, J = 7 Hz, 3 H, CH_3—CH_2), 1·51 (d, J = 6 Hz, 3 H, CH_3), 1·9 m + 2·4 m (2 H, CH_2—4), 3·65 (q, 2 H, CH_2O), 3·9 (m, 1 H, CH—5), 5·12 (d, J = 5 Hz, 1 H, CH—3), 6·6—7·4 (m, 10 H, C_6H_5). MS [m/z (% base peak)]: 282 (M^+, 100), 237 (36), 210 (27), 209 (29), 195 (15), 118 (70), 104 (21), 99 (40), 93 (60), 77 (87), 71 (26). UV spectrum in methanol: 202 (4·37), 251 (4·26), 283 infl. (3·44).

Thanks are due to Mrs M. Kuthanová, Institute of Chemical Technology, Prague, for dipole moment measurement and to Dr V. Macháček, Institute of Chemical Technology, Pardubice, for ^{1}H-NMR *spectra. The assistance of Mrs P. Marešovská, Institute of Organic Chemistry and Biochemistry, in preparing some compounds is also acknowledged. Elemental analyses were carried out in the Department of Analytical Chemistry, Institute of Chemical Technology, Pardubice.*

REFERENCES

1. Rassow B., Lummerzheim M.: J. Prakt. Chem. [2] *64*, 136 (1901).
2. Rassow B., Rülke K.: J. Prakt. Chem. [2] *65*, 97 (1902).
3. Rassow B., Baumann O.: J. Prakt. Chem. [2] *80*, 511 (1909).
4. Rassow B., Burmeister F.: J. Prakt. Chem. [2] *84*, 249 (1911).
5. Schmitz E.: Angew. Chem. *76*, 197 (1964).
6. Hrazdira M.: *Thesis*. Institute of Chemical Technology, Pardubice 1969.
7. Baker A. D., Baldwin J. E., Kelly D. P., DeBernardis J.: Chem. Commun. *1969*, 344.
8. Kliegel W.: Tetrahedron Lett. *1969*, 2627.
9. Princ B.: *Thesis*. Charles University, Prague 1975; Princ B., Exner O.: This Journal *44*, 2221 (1979).
10. Cornell E. F.: J. Amer. Chem. Soc. *50*, 3311 (1928).
11. Foster R., Iball J., Nash R.: Chem. Commun. *1968*, 1414.
12. Tosi C.: Spectrochim. Acta *22*, 399 (1966).
13. Schmitz E.: Chem. Ber. *91*, 1495 (1958).
14. Brown R. F. C., Clark V. M., Sutherland O. I., Todd A.: J. Chem. Soc. *1959*, 2109.
15. Banfield F. H., Kenyon J.: J. Chem. Soc. *1926*, 1612.
16. Halverstadt I. F., Kumler W. D.: J. Amer. Chem. Soc. *64*, 2988 (1942).
17. Vogel A. I.: J. Chem. Soc. *1948*, 1842.

Translated by the author (O. E.).