Tetrahedron. Vol. 24, pp. 5059 to 5065. Pergamon Press 1968. Printed in Great Britain

REACTION OF PYRYLIUM SALTS WITH NUCLEOPHILES—VII[1]

CONVERSION OF 2,4,6-TRIPHENYLPYRYLIUM INTO ISOXAZOLE OR PYRAZOLE DERIVATIVES BY HYDROXYLAMINE OR PHENYLHYDRAZINE

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(*Received in the UK* 4 *January* 1968; *accepted for publication* 4 *March* 1968)

Abstract—The reaction of 2,4,6-triphenylpyrylium (II) with hydroxylamine affords the monoxime (IVB, Y = O) of the pseudobase. It isomerizes readily into the 3,5-diphenyl-5-phenacyl-2-isoxazoline (VB, Y = O). Mineral acids split IVB or VB (Y = O) into acetophenone and 1,3-diphenylisoxazole (VII, Y = O). Similarly, the reaction products of II with phenylhydrazine ("α-" and "β-pyranolhydrazides") afford on treatment with hot mineral acids 1,3,5-triphenylpyrazole and acetophenone. The structures previously proposed for these "pyranolhydrazides" must be changed into IVB and VB (Y = NPh). The structure of the reaction product of II with hydrazine is different and will be discussed in a later report.

Reaction of 2,4,6-*triphenylpyrylium with hydroxylamine*

Two independent reports described the preparation of pyridine-N-oxides from alkyl-substituted pyrylium salts and hydroxylamine.[3,4] The attempt to obtain by this method 2,4,6-triphenylpyridine-N-oxide (I, Y = O) (which had been prepared in low yield by oxidation of triphenylpyridine with perbenzoic acid[5]) gave products differing from those expected.

Treatment of a suspension of 2,4,6-triphenylpyrylium perchlorate (II) in aqueous ethanol with hydroxylamine (III, Y = O) afforded a colourless compound (IV), m.p. 125°, which was very easily convertible into an isomeric compound (V), m.p. 124°* on recrystallization or simply by standing in solution at room temperature. Compound IV could, however, be isolated pure by a simple technique employed previously,[6] namely dissolution in cold ether and fractional evaporation of the solvent in vacuum. In solid state IV can be conserved indefinitely, being thus more stable than the primary reaction product of 2,4,6-triphenylpyrylium with ammonia.[6]

Compound IV presents in KBr pellet strong IR bands at 1222, 1675 and 3360 cm^{-1}. In ethanol it has an absorption band at 244 nm ($\varepsilon = 31,000$) with a shoulder at ca. 270 nm; in cyclohexane the band has a pronounced vibrational structure with peaks at 233 s, 238 s, 243, 249, 254, 260 and 267 s nm.† In deuterochloroform, besides NMR peaks due to the 15 phenyl protons, it presents singlet peaks at τ 3·20 (one proton) and 5·91 (two protons). All these spectra in solution pass gradually into the spectra of compound V.

Compound V presents in KBr pellet strong IR bands at 915, 1362 and 1694 cm^{-1}

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* The m.p. of the mixture IV + V presents depression.

† A shoulder is denoted by s.

and no band above 3100 cm^{-1}. In ethanol it presents a band at 251 nm (ε = 22,500) with a shoulder at 276 nm, which does not reveal any hyperfine structure in cyclohexane. The NMR spectrum in $CDCl_3$ consists, besides the multiplet due to the 15 phenyl protons, in a singlet peak at τ 6·32 (two protons) and an AB quadruplet (two protons) at 210·2, 227·0, 239·4 and 256·8 c/s (at 60 Mc) leading[7] to τ values of 5·91 and 6·32, and to a coupling constant J_{AB} = 17·5 c/s. Spin decoupling confirms these values.

On treatment with 70% perchloric acid, compounds IV or V give a red solution. If this solution is heated at 100–150° an exothermal reaction takes place. These compounds are split into acetophenone VI (identified as its 2,4-dinitrophenylhydrazone) and 3,5-diphenylisoxazole (VII, Y = O). The latter product was identified by comparison (mixed m.p. and infrared spectra[8]) with the authentic compound obtained from dibenzoylmethane and hydroxylamine.[9]

The course of these reactions may be understood by admitting that the primary product is an open-chain monoxime of 2,4,6-triphenylpyrylium pseudobase with formula IVB (Y = O). This formula accounts for the conjugated carbonyl (phenyl alkenyl ketone) and hydroxyl stretching infrared bands, for the presence of a vinylic proton (τ 3·20) and a methylene group (τ 5·91, in good agreement with values 5·72–5·82 τ for methylene groups in pyrylium pseudobases[10]), as well as for the vibrational structure of the UV absorption band due to the rigid chalcone chromophore.

An intramolecular addition of the nucleophilic YH group to the activated carbon–carbon double bond in IVB converts IVB into the isoxazoline derivative VB (Y = O). Similar ring closures leading to pyrazolines were recently reported.[11,12] This intramolecular addition takes precedence in this case over the dehydration which prevails in the alkyl-substituted derivatives leading to pyridine-N-oxides (I, Y = O). An alternative seven-membered dehydration product VIII would be expected to be less stable because with 8 π-electrons it cannot be aromatic. Formula VB accounts for the observed C=O stretching frequency (phenyl alkyl ketone), for the UV and NMR spectra (ketonic methylene singlet at τ 6·32, and the AB system for the isoxazolinic methylene protons, with the geminal coupling constant 17·5 c/s deshielded differently by the vicinal phenyl and phenacyl groups), and for the acid splitting leading to an aromatic 5-membered heterocyclic system.

A compound analogous to IVA, but lacking the possibility of tautomerization to IVB or of cyclization to V is the addition product of the cyanide anion to the 2,4,6-triphenylpyrylium cation.[13] In its NMR spectrum (in deuterochloroform) the two vinylic protons appear at τ 1·63 and 2·69 with a long-range coupling constant of 1·4 c/s (spin decoupling helps in picking out the latter proton doublet from the phenyl multiplet). These low values of the chemical shift characterize the 1,3,5-triphenyl-2,4-pentadien-1-one system IVA; an α-pyranic formula analogous to X would afford higher τ values (τ = 5·11 in an α-pyran lacking phenyl groups, and 3·97 in its *cis*-dienonic valence tautomer[14]).

Reaction of 2,4,6-*triphenylpyrylium with phenylhydrazine*

The reaction of 2,4,6-triphenylpyrylium perchlorate (II) with phenylhydrazine (III, Y = NPh) was first described by Schneider[15] who reported that the crystalline primary product ("α-pyranolhydrazide") underwent an isomerization into a "β-

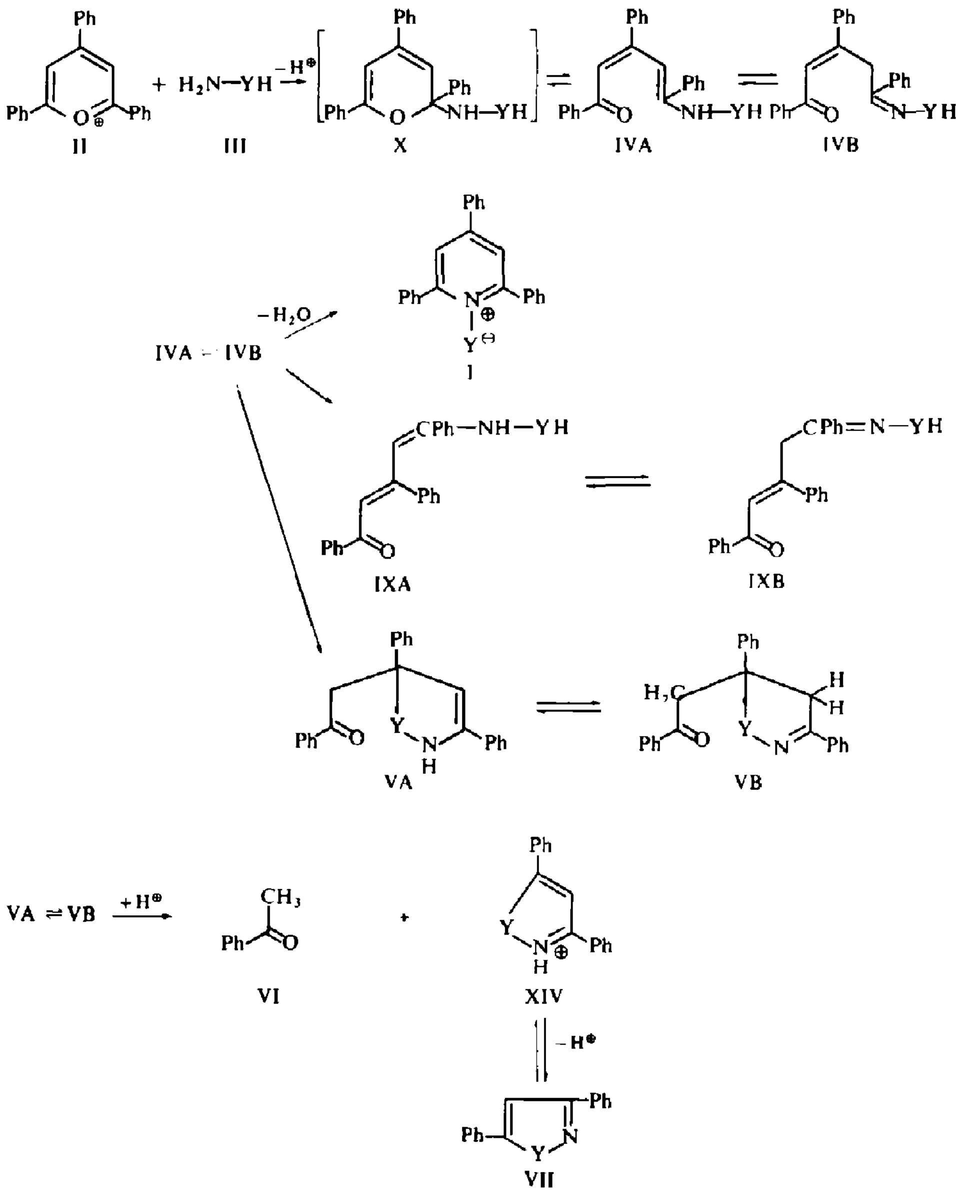

CHART 1. Reaction of 2,4,6-triphenylpyrylium (II) with the nucleophile III leading to compounds I, IV–VII, IX, X and XIV.

pyranolhydrazide" on refluxation in ethanol. The structures of the isomeric products were discussed by two groups of authors.[13,16] On the basis of UV and IR spectral evidence it was argued that a *cis–trans* isomerism was probably involved,[13] i.e. that the primary "α-pyranolhydrazide" had the *cis* structure IVB, Y = NPh, whereas the isomerization product ("β-pyranolhydrazide") was probably the *trans*-isomer IXB, Y = NPh. In fact, only the former isomer was able to undergo dehydration in hot acetic acid yielding the pyridinium derivative I (Y = NPh). In more recent years, several examples of *cis–trans* isomerizations in adducts of pyrylium salts with nucleophiles have been definitely established.[10, 17–19] However, the marked differences between the NMR spectra of the two "pyranolhydrazides" require a revision of the previous structure assignment.[13] The "α-pyranolhydrazide" presents in $CDCl_3$ singlet peaks at τ 1·55 (broad, one NH proton), 3·33 (one vinyl proton) and 5·85 (two protons). The "β-pyranolhydrazide" has a more complicated NMR spectrum: an AB quartet at 203, 221, 244 and 262 c/s with coupling constant 18·0 c/s and chemical shifts 5·83 and 6·43 τ (one proton each) and a doublet of intensity corresponding to two protons at τ 5·98 with a small and unaccounted splitting of 1·9 c/s. Both "pyranolhydrazides" present, in addition, peaks due to the four phenyl groups; the "β-pyranolhydrazide" has a strong upfield peak in this range, at 3·02 τ, probably due[20] to the N-Ph group.

The similarity of the NMR spectra when Y = O or NPh makes it plausible that the "pyranolhydrazides" have formulas IVB (α) and VB (β). This is supported by the IR absorption spectra[13] which show that the "α-pyranolhydrazide" has a C=O stretching frequency at 1677 cm^{-1} and a strong NH stretching band at 3300 cm^{-1} (KBr pellet) while the "β-pyranolhydrazide" has a CO stretching band at 1700 cm^{-1}. Other structures which could be considered, such as XI–XIII, do not agree with the experimental data.

On treatment with 70% perchloric acid, the "α-pyranolhydrazide" afforded a red solution which darkened on heating. On dilution with water, a tar containing the perchlorate of 1,3,5-triphenylpyrazole (XIV, Y = NPh) separated in moderate yield. The second reaction product was acetophenone (VI). The same two products were obtained in high yield from the "β-pyranolhydrazide" and perchloric acid: no colour developed on mixing these reagents; short heating at 100–120° gave acetophenone and the same perchlorate with no side-products. Alkalinization of the perchlorate afforded 1,3,5-triphenylpyrazole (VII, Y = NPh). The products were identified by mixed m.p. and IR spectra with authentic acetophenone 2,4-dinitrophenylhydrazone and with 1,3,5-triphenylpyrazole or its perchlorate (prepared from dibenzoylmethane and phenylhydrazine[9, 21]).

Reaction of 2,4,6-*triphenylpyrylium with hydrazine*

How cautiously one must refrain from generalizations is apparent from the study of the reaction between 2,4,6-triphenylpyrylium (II) and hydrazine hydrate (III, Y = NH). On mixing these reagents in ethanol, a pale yellow compound m.p. 192° crystallized. It did not present any C=O, saturated C—H, or N—H bands in the IR spectrum. In the range 1200–1700 cm^{-1} it has the following bands (intensities are indicated in brackets): 1613 (s), 1583 (m), 1545 (m), 1487 (vs), 1452 (s), 1358 (vs), 1333 (s), 1316 (s) and 1241 (ms) cm^{-1}. The NMR spectrum presents along with the multiplet due to the three Ph groups, three one-proton peaks at τ: (1) 3·37, distorted triplet; (2), 5·66, doublet of doublets; and (3), 7·41, doublet of doublets. Coupling constants checked by decoupling experiments are: $J_{1,2} = 2{\cdot}5$; $J_{1,3} = 1{\cdot}5$; $J_{2,3} = 12{\cdot}3$ c/s. These data agree with structure XV (and also with the less probable structures XVI and XVII) better than with other possibilities (VIII or XVIII), but a definite assignment is postponed for a later paper. This compound does not afford acetophenone and 3,5-diphenylpyrazole on treatment with acids.

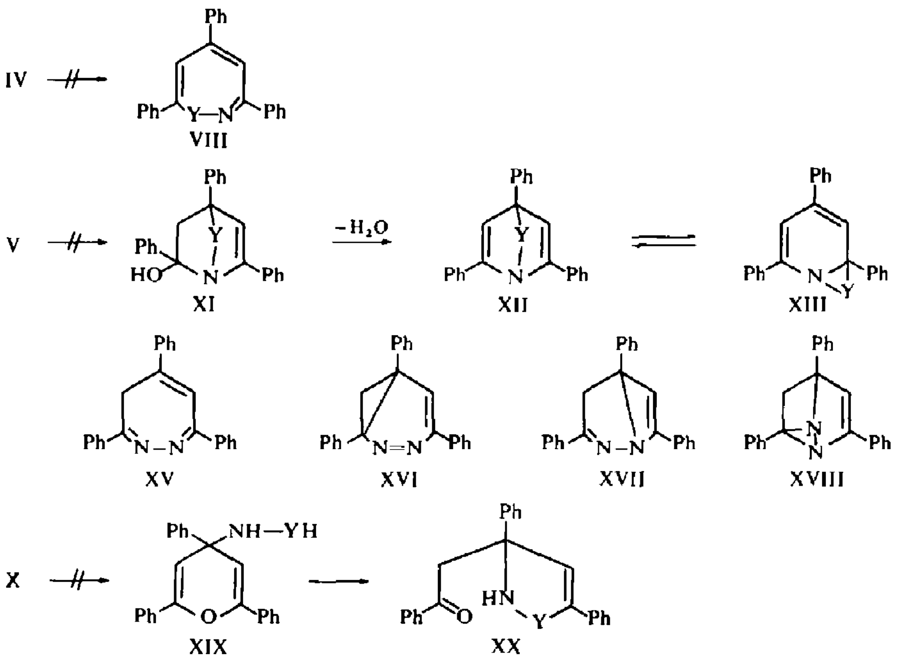

CHART 2 Uncertain or disproved structures VIII, XI–XIII, XV–XX.

DISCUSSION OF THE RESULTS

It is interesting to compare the formation of aza-aromatic 5-membered heterocyclic compounds from pyrylium salts and hydroxylamine or phenylhydrazine with the formation of naphthalenes from pyrylium salts (e.g. 2,4,6-triphenylpyrylium) and benzylmagnesium chloride.[22] Both reactions consist in the addition of the nucleophile to the pyrylium cation leading to a labile primary product which isomerizes easily into a more stable compound. Treatment with strong acids causes both these products to split off a molecule of methylene ketone (e.g. acetophenone) leaving an aromatic ring system. This can be formed also directly from the corresponding nucleophilic reagent (NH_2OH,[9] $PhNHNH_2$,[21] or $PhCH_2MgCl$[23,24]) and a 1,3-diketone (e.g. dibenzoylmethane). It is noteworthy that pyrylium salts are readily formed from methylene ketones and 1,3-diketones[25–27] in the presence of strong acids; the reactions compared here proceed as if this pyrylium ring closure were reversible.

When the nucleophile is the benzyl anion, there is no possibility of cyclization to a 5-membered product analogous to V,* so that only three structures analogous to IV, X and XIX (open-chain dienone, its valence-tautomer[14] α-pyranic derivative, and γ-pyranic derivative, respectively) can be involved. Pyranic structures seem to be more stable when the sp^3-hybridized ring C atom is bonded to exocyclic C or H atoms, than when it is bonded to N or O atoms. When the nucleophile has structure III, Y = O (or NPh), a γ-pyranic derivative XIX is not formed (the α-pyran X is a transient valence-isomer of IV): the ring-opening and reclosure of XIX would lead

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* Dehydration to a biphenyl derivative analogous to I is, however, possible.[22,28]

to an isoxazoline derivative XX isomeric with V. Such a formula XX cannot accomodate a methylene group in the ring and is therefore ruled out by the NMR spectrum (it could be formed also by direct reaction of the bidentate nucleophile H_2N—YH at the Y extremity).

In conclusion, the reaction of 2,4,6-triphenylpyrylium salts (II) with hydroxylamine or phenylhydrazine (III) converts these salts into the monoxime or monophenylhydrazone of the pseudobase (IVB); intramolecular cyclization causes isomerization of these compounds into 3,5-diphenyl-5-phenacyl-2-isoxazoline (VB, Y = O) and 1,3,5-triphenyl-5-phenacyl-2-pyrazoline (VB, Y = NPh). Hot mineral acids split these compounds (IVB or VB) into acetophenone and 3,5-diphenylisoxazole or 1,3,5-triphenylpyrazole. Thus pyrylium salts are able to be converted into 5-membered aza-heterocyclic compounds. Until now the oxidation of alkyl-substituted pyrylium salts by hydrogen peroxide affording 2-acyl-3,5-dialkylfurans[29] was the only known reaction converting pyrylium salts into 5-membered heterocyclic compounds. That 4-pyrones react with hydroxylamine and hydrazine leading under ring contraction to isoxazoles and pyrazoles is known since a long time.[30–34] Recently, similar ring contractions were observed in the reaction of pyrimidines with hydrazine.[35,36]

EXPERIMENTAL

Reaction of 2,4,6-*triphenylpyrylium perchlorate with hydroxylamine.* Finely ground II,[37] (20·4 g, 50 mmoles) suspended in 500 ml EtOH was treated at 15° with a cold soln of 14 g hydroxylammonium chloride and 8 g NaOH in 60 ml water. On mixing, the suspension dissolved and shortly afterwards colourless crystals appeared. Cautious dilution with water completed the crystallization. After standing in ice-water for 30 min the ppt was filtered off, and dried in vacuum. The crystals were dissolved in ether, filtered from traces of unreacted perchlorate, and the solvent was removed in vacuum without heating, affording colourless crystals of the *monoxime* IVB (Y = O), m.p. 125°. (Found: C, 81·1; H, 6·7; N, 4·4. $C_{23}H_{19}NO_2$ requires: C, 80·9; H, 5·6; N, 4·1%).

On refluxation in acetic acid or on recrystallization from hot EtOH, the above compound afforded 3,5-*diphenyl*-5-*phenacyl*-2-*isoxazoline* (VB, Y = O), m.p. 124°. (Found: C, 82·3; H, 6·3; N, 4·3. $C_{23}H_{19}NO_2$ requires: C, 80·9; H, 5·6; N, 4·1%).

Formation of 3,5-*diphenylisoxazole.* On heating the above compounds IVB or VB (Y = O), in excess 70%-perchloric acid at 100° for 15 min or at 150° for 1 min, the initially red soln darkened. On dilution with water and ether and on scratching, a solid compound crystallized. After filtration and washing with water and ether, it had m.p. 138°. It was recrystallized from EtOH and identified as VII (Y = O) by comparison with the authentic compound prepared[9] from dibenzoylmethane and hydroxylamine.

The ethereal washings were separated, evaporated, and treated with Brady's reagent, affording acetophenone 2,4-dinitrophenylhydrazone, identified by comparison with authentic product.

Formation of 1,3,5-*triphenylpyrazole.* The reaction of 2,4,6-triphenylpyrylium perchlorate with phenylhydrazine was described previously.[13,15,16] The primary product, "α-pyranolhydrazide" is the monophenylhydrazone IVB, Y = NPh. The isomerized product, "β-pyranolhydrazide", is VB (Y = NPh). The former affords a red coloration on treatment with 70%-perchloric acid in the cold. The latter gives no coloration and no reaction with cold perchloric acid. On heating the latter compound in excess 70% perchloric acid at 100–110° for 10 min, diluting with cold water, filtering off and washing the ppt with water and ether, the perchlorate of XIV (Y = NPh) was obtained smoothly in ca. 80% yield, m.p. 245° from acetic acid. (Found: C, 63·64; H, 4·29; N, 7·16. $C_{21}H_{17}ClN_2O_4$ requires: C, 63·56; H, 4·32; N, 7·06%). The product was identified by comparison with authentic compound (prepared from dibenzoylmethane and phenylhydrazine,[21] and converted into the perchlorate with perchloric acid in EtOH).

The ethereal washings afforded on evaporation of the solvent acetophenone, identified as 2,4-dinitrophenylhydrazone, in ca. 75% yield.

Alkalinization of the perchlorate in aqueous EtOH gave VIII (Y = NPh), m.p. 138°, identified (IR spectrum, mixed m.p.) with the authentic compound.

Apparatus. IR spectra were recorded with a Zeiss–Jena UR-10 apparatus, UV spectra with an Optica-Milan CF-4 apparatus, and NMR spectra with Varian HR-100 and A-60A machines.

Acknowledgement –The assistance of Mrs. Maria Roman and Mrs. Cornelia Popescu for the elementary analyses, Mrs. Elena Romas for recording infrared spectra, Mrs. Maria Paraschiv for recording ultraviolet absorption spectra, and Mrs. Alice Trestianu, Dr Gordon J. T. Tiddy, Dr. W. Silhan and Mr. Filip Chiraleu for the nuclear magnetic resonance spectra is gratefully acknowledged.

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