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SYNTHESES USING ISOXAZOLES—V[1]

THE REARRANGEMENT OF PHENYLHYDRAZONES OF 4,5,6,7-TETRAHYDRO-4-OXO-ISOXAZOLO[2,3-a]-PYRIDINIUM BROMIDES

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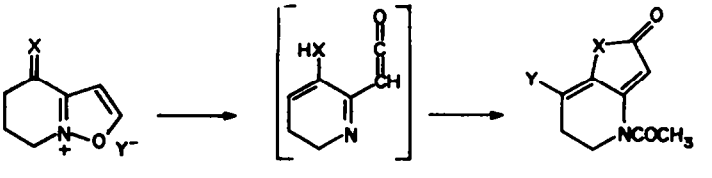
Abstract—Rearrangement of the phenylhydrazone (6) and the 2,4-dinitrophenylhydrazone (7) from 4,5,6,7-tetrahydro-4-oxo-isoxazolo[2,3-a]pyridinium bromide (1), by boiling acetic anhydride, gave the 1-(N-anilino)pyrrolo[3,2-b]pyridinones, (9, 12 and 13), and the pyrazolo[4,3-b]pyridine-3-carboxaldehyde (8) or its diacetate (11).

We have reported[2,3] that rearrangement of the oxoisoxazolo[2,3-a]pyridinium salts (1), by boiling acetic anhydride, gave the furo[3,2-b]pyridinone (2), while the similar rearrangement of the oximes (3) gave the pyrrolo[3,2-b]pyridinones (4).[4] The postulated intermediate in both cases was a keten (5) which could cyclise under nucleophilic attack from the enol or hydroxyenamino group (XH) giving respectively a furanone or a pyrrolone. We reasoned that, in similar circumstances, a hydrazone of ketone (1) with two potentially nucleophilic centres could provide two series of cyclisation products, with pyrrolone or pyridazinone rings; we have rearranged the phenylhydrazone (6) and the dinitrophenylhydrazone (7) of ketone (1), and two types of product are indeed formed.

The phenyl hydrazones (6 and 7) were obtained in excellent yield from the ketone (1) and the appropriate hydrazine in ethanol or in acetic acid. The phenylhydrazone (6) was heated with acetic anhydride just to the boiling point, the solution decanted and the procedure repeated on the undissolved solid till none remained (Procedure A); prolonged boiling (Procedure B) gave different products which are described below. Evaporation of the solution (Procedure A) gave a black solid; column chromatography of this gave two major products, isomers, of molecular formula $C_{15}H_{15}N_3O_2$. The first of these to be eluted, a solid, m.p. 133° had λ_{max} at 223, 275 and 323 nm ($\log_{10}\epsilon$ 3.31, 2.79, 2.82) and ν_{max} at 1675 cm^{-1} (broad). These absorptions were quite different from those of the pyrrolopyridinones (4). The ^1H NMR spectrum showed peaks at δ2.0 (2H, m), 2.1 (3H, s, CH_3CO) 2.75 (2H, t, CH_2 C=N), 3.1 (2H, t, CH_2CO), 7.1–7.5 (5H, m, C_6H_5), and 9.8 p.p.m. (1H, s). The mass spectrum showed a molecular ion at 269 mu, and a loss of 42 (CH_2CO), with a strong peak at 77 (C_6H_5) and at 43 (CH_3CO). Taken together this spectral data is best accommodated by the formula 8, as the reduced 4 - acetyl - 3 - formyl - 2 - phenylpyrazolo[4,3-b]pyridine. The presence of the formyl group, indicated by the ^1H absorption at δ9.8 and the ν_{max} at 1675 cm^{-1} was confirmed by the ^{13}C NMR spectrum (off resonance decoupled) which showed the signal at 180.3 ppm in the CO region as a doublet. The second isomer, obtained in yields up to 58%, was also solid, m.p. 214–215°, and had λ_{max} 272 and 344 ($\log_{10}\epsilon$ 4.11, 3.51), ν_{max} at 3420, 1700 and 1615 cm^{-1}. The UV spectrum was reminiscent of the pyrrolopyridinone obtained by deacetylation of compound 4; the ^1H NMR spectrum showed peaks at δ 2.1 (3H, s, CH_3CO), 2.4 (2H, m, CH_2C=C), 3.3 (2H, m, CH_2N), 4.8 (1H, d, J = 1 Hz), 5.3 (1H, br s, NH), 5.5 (1H, d of tr, J = 1 and 5 Hz) and 7.1–7.5 ppm (5H, m, C_6H_5). On addition of D_2O, the broad singlet at δ5.5 disappeared, and the signal at δ3.3 sharpened to a triplet, confirming its position next to the NH (vinylogous amide, slowly exchanging). This observation also clears up the ambiguity of the position of the single acetyl group which must be on the aniline residue, and not on N4; the compound is hence the pyrrolopyridinone (9).

If the solution obtained by procedure A was boiled (10–15 min), different products were obtained. Separation by preparative layer chromatography of the crude material gave three major bands; the band of highest R_F was an oil, shown by its molecular formula, $C_{12}H_{14}N_2O_3$, and its very simple ^1H NMR to be tri-(N-acetyl) phenyl-



1: X = O, Y = Cl, Br
3: X = NOH, Y = Cl, Br
6: X = NNHC$_6$H$_5$, Y = Br
7: X = NNHC$_6$H$_3$(NO$_2$)$_2$-2,4, Y = Br

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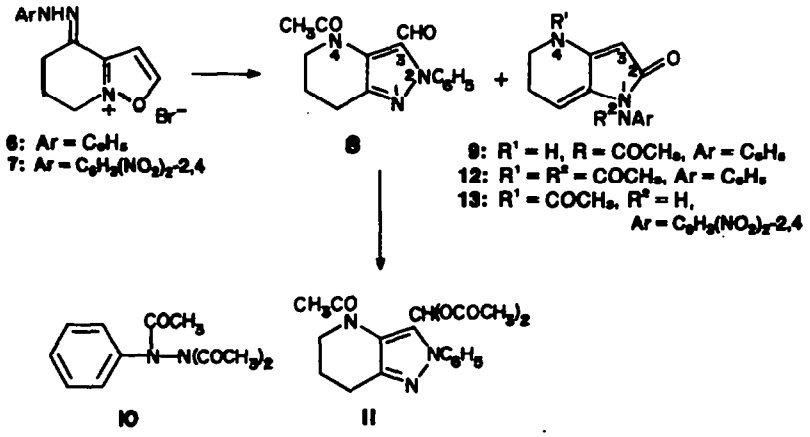
2: X = O, Y = H
4: X = NH, Y = Cl, Br



6: Ar = C_6H_5
7: Ar = $C_6H_3(NO_2)_2$-2,4

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9: R' = H, R = $COCH_3$, Ar = C_6H_5
12: R' = R^2 = $COCH_3$, Ar = C_6H_5
13: R' = $COCH_3$, R^2 = H, Ar = $C_6H_3(NO_2)_2$-2,4

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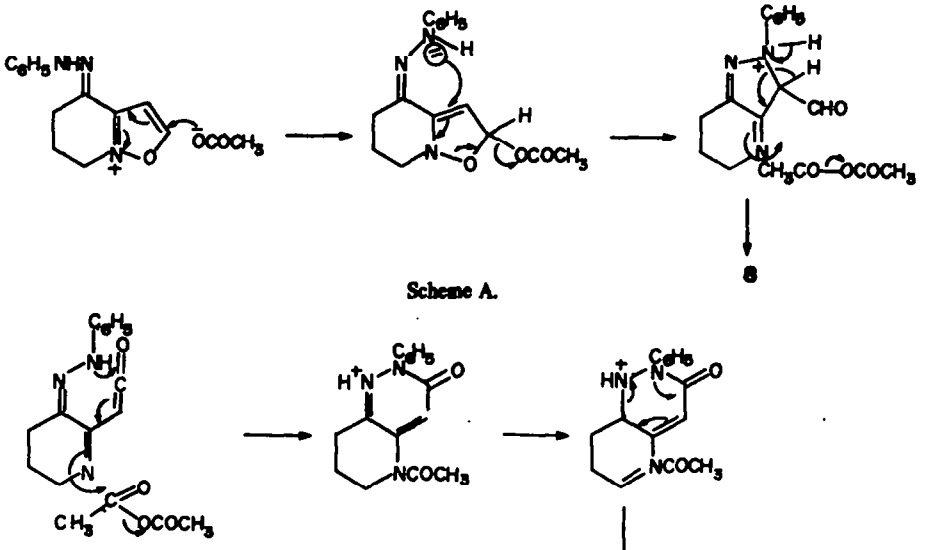
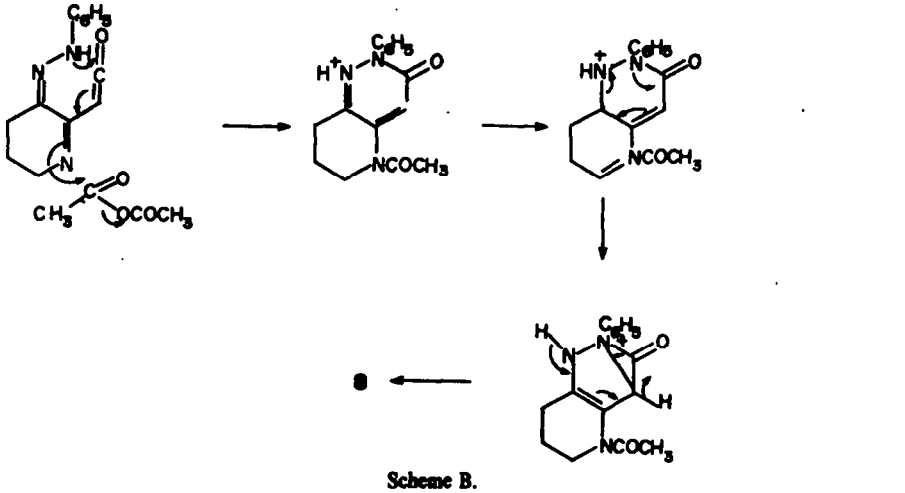
hydrazine (10). The compound with intermediate R_f value (14% yield) m.p. 152–154°, had a molecular formula $C_{19}H_{21}N_3O_5$. The UV absorption was simple, ν_{max} 265 nm ($\log_{10}\epsilon$ 3.76) and there were strong absorptions in the IR spectrum at 1760, 1660, 1400 and 1240 cm^{-1}. The ^1H NMR spectrum showed peaks at δ1.85 (6 H, s, CH_3CO), 2.0 (2 H, m), 2.2 (3 H, s, CH_3CO), 2.8 (2 H, t), 3.7 (2 H, t, CH_2N), 7.1–7.7 (5 H, C_6H_5) and 7.9 (1 H, s). The mass spectrum showed a molecular ion at 371 mu and a major loss of 144 to give a peak at 269 mu ($CH_3CO + CH_3CO_2$) and then 42 to give the base peak at 227 mu; there were also peaks at 77 ($C_6H_5^+$) and at 43 ($CH_3\dot{C}O$) mu. The similarity of the aliphatic section of this compound to that of compound 8 was apparent from the ^1H NMR; the CH signal (^1H NMR at 7.7) was no longer carbonylic, being found at 83.9 ppm in the ^{13}C NMR spectrum. The simplest formula which fits the spectral data is that of the diacetate (11) from the aldehyde (8). The fluorescent band of lowest R_f from procedure B gave an oil in yields of up to 50%, for which consistent analyses could not be obtained, probably because of its considerable sensitivity to hydrolytic conditions. The molecular ion at 311 amu and the ^1H NMR spectrum which showed peaks at δ2.1 (3 H, s, CH_3CO), 2.3 (3 H, s, CH_3CO), 2.6 (2 H, m), 3.8 (2 H, t, CH_2N) 5.75 (1 H, d of tr, J = 1 and 5 Hz), 6.25 (1 H, d, J = 1 Hz), and 7.4 (5 H, m, C_6H_5), leave little doubt that this is the diacetyl derivative (12). Hydrolysis was very rapid with ethanolic sodium hydroxide, and gave the monoacetyl pyrrolopyridinone (9). A notable feature of the pyrrolopyridinones is the cross ring coupling from H3 to H7 of approximately 1 Hz.

We hoped to influence the cyclisation of the intermediate keten, and hence the ratio of pyrrolone to pyridazinone, by varying the basic strength of the NH in the



Scheme A.



Scheme B.

hydrazone. Attempts to prepare simple hydrazones or N,N-dimethylhydrazones were unsuccessful; it is probably that the greater basic strength of the aliphatic hydrazines causes ring opening reactions such as those we have described elsewhere.[1,2] The 2,4-dinitrophenylhydrazone (7), by procedure A, gave many products; intensive chromatography gave only one fully characterised product, shown by its spectral data to be the acetylpyrrolopyridinone (13). The molecular formula was $C_{15}H_{13}N_5O_6$. λ_{max} 216, 269 and 332 nm ($\log_{10}\epsilon$ 4.20, 4.23, 3.14) and ν_{max} 1715 cm^{-1}. The ^1H NMR spectrum in DMSO-d_6 showed peaks at δ1.85 (3 H, CH_3CO), 2.0 (2 H, m) 3.85 (2 H, t, CH_2N), 5.75 (1 H, d of tr, J = 1 and 5 Hz), 6.15 (1 H, d, J = 1 Hz, H3), 6.9 (1 H, d), 8.25 (1 H, d of d), 8.85 (1 H, d), and 11.4 ppm (1 H, brs, exch. D_2O). The position of the N-acetyl group is established by chemical shift of the NH (in compounds of type 9 the NH shift is 5–6 ppm) and by the absence of any NH to CH_2 coupling, removable by deuterium exchange.

There are two routes by which the pyrazolopyridines might be formed from salt 6 by hot acetic anhydride. In the first, Scheme A, acetate addition to the isoxazolium salt gives an intermediate (14) which can cyclise as shown with loss of acetate and subsequent acetylation of the piperideine nitrogen. In the other route, Scheme B, the previously postulated keten intermediate (15) cyclises with the N^{α} of the phenylhydrazone to give a pyridopyridazinone (16). Such compounds are known[5] to undergo ring contraction under acid conditions; although aldehydes have not been reported, carboxylic acids have, and the mechanism shown would account for the formation of a pyrazolopyridine aldehyde.

EXPERIMENTAL

M.ps were determined on a Kofler heated stage and are uncorrected. Column chromatography was on Woelm alumina, activity 4, and preparative layer chromatography on 40 × 20 cm plates of Merck Silicagel PF_{254}.

4,5,6,7 - Tetrahydro - 4 - oxoisoxazolo[2,3-a]pyridinium Bromide Phenylhydrazone (6). Prepared as previously described.[1]

2,4-Dinitrophenylhydrazone of compound (1). Solns of 1 (0.5 g) and of 2,4-dinitrophenylhydrazine (0.45 g) each in glacial AcOH (10 ml) were mixed and boiled (1 hr) then cooled. The ppt was recrystallised from MeOH to give the *dinitrophenylhydrazone bromide* (7), m.p. >300° (0.9 g, 98%). (Found: C, 37.5; H, 3.3; N, 16.4. $C_{13}H_{12}BrN_5O_6$ requires: C, 38.0; H, 3.25; N, 16.65%). δ_{max} (EtOH) 209, 238 and 253 nm ($\log_{10}\epsilon$ 3.25, 3.14, 3.28). δ (CF_3CO_2H) 2.9 (2 H, m), 3.3 (2 H, t), 7.6 (1 H, d, J 2 Hz, H3), 8.3 (1 H, d), 8.7 (1 H, q), 8.95 (1 H, d, J 2 Hz, H2) and 9.25 ppm (1 H, d).

Reaction of phenylhydrazone bromide (6) *with acetic anhydride*

Procedure A. The salt 6 (4 g) was heated with Ac_2O just to the b.p., then the mixture was cooled and filtered. The process was repeated with unreacted salt, until all was dissolved. The combined acetic anhydride solutions were evaporated *in vacuo* and the black oily residue extracted with chloroform. The chloroform soln was evaporated on to alumina (10 g), and the coated alumina added to the top of an alumina column (150 g). Elution with benzene gave a mixture of products, uncharacterised. Further elution with chloroform/benzene (3:7) gave a solid, recrystallised from absolute ethanol, m.p. 133°, identified as *4,5,6,7 - tetrahydro - 4 - acetyl - 2 - phenylpyrazolo[4,3-b]pyridine - 3 - carboxaldehyde* (8) (0.42 g, 14.5%). (Found: C, 66.6; H, 5.6; N, 15.3. $C_{15}H_{15}N_3O_2$ requires: C, 66.9; H, 5.6; N, 15.6%). Spectral data given in Discussion. Further elution with chloroform/benzene (1:1) gave a solid, recrystallised from MeOH as yellow needles, m.p. 214–215°, identified as *5,6 - dihydro - 1 - (N-acetanilidinyl) - 4 H - pyrrolo - [3,2-b]pyridin - 2 - one* 9 (1.7 g, 58%). (Found: C, 67.1; H, 5.65; N, 15.25. $C_{15}H_{15}N_3O_2$ requires: C, 66.9; H, 5.6; N, 15.6%). Spectral data given in discussion.

Procedure B. As in Procedure A, but when all the salt 6 had dissolved boiling was continued for 10–15 min, the soln darkening considerably. Evaporation of Ac_2O gave a black solid, extracted with chloroform. Chloroform soluble material was separated by plc (eluted with EtOH) giving three fluorescent bands, described in decreasing R_f values; *Band* 1. When extracted this gave a yellow oil *N,N,N'-tri-acetylphenylhydrazine.* (Found: C, 61.05; H, 6.15; N, 11.75. $C_{12}H_{14}N_2O_3$ requires: C, 61.35; H, 6.0; N, 11.95%). λ_{max} (95% EtOH) 230 ($\log_{10}\epsilon$ 3.80). *Band* 2: This gave solid, as crystals from absolute ethanol, m.p. 153–154°, identified as the *pyrazolo[4,3-b]pyridine - 3 - carboxaldehyde diacetate*, 11 (0.39 g, 14.4%). (Found: C, 61.4; H, 5.7; N, 11.45. $C_{16}H_{21}N_3O_5$ requires: C, 61.45; H, 5.65; N, 11.3%). Spectral data given in Discussion. *Band* 3 gave an oil, which could not be crystallised, and gave irregular analyses. The spectral data, given in the Discussion, showed it to be almost pure diacetyl compound (12). A sample (100 mg) in EtOH (10 ml) was treated with 2 N NaOH (2 ml) with an immediate colour change (yellow to orange). The EtOH was removed *in vacuo*, and the residue extracted with chloroform, the chloroform solution dried ($MgSO_4$) and the chloroform evaporated. The yellow oily residue was purified by plc (EtOAc). Recrystallisation (from MeOH) of the solid extracted from the major band gave yellow needles, m.p. 214°, identical (mixed m.p.) with those of 9 prepared by procedure A (70 mg, 80%).

Reaction of 2,4-dinitrophenylhydrazone bromide (7) *with hot acetic anhydride*

By procedure A described above, the residue from the Ac_2O being purified by plc (EtOAc/toluene, 3:1). Only one product was characterised, *5,6 - dihydro - 4 - acetyl - 1 - (N - (2,4 - dinitro)anilinyl) - 5 H - pyrrolo[3,2-b]pyridin - 2 - one* (13), crystals from acetonitrile, m.p. 221°, (0.2 g, 11.6%). (Found: C, 50.45; H, 3.95; N, 19.2. $C_{15}H_{13}N_5O_6$ requires: C, 50.15; H, 3.9; N, 19.5%). Spectral data is given in Discussion.

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