A STUDY OF THE PREPARATION AND REACTIONS OF THE UNUSUALLY LABILE 5-METHYL[1,2,4]OXADIAZOLO[2,3-c]QUINAZOLIN-2-ONE

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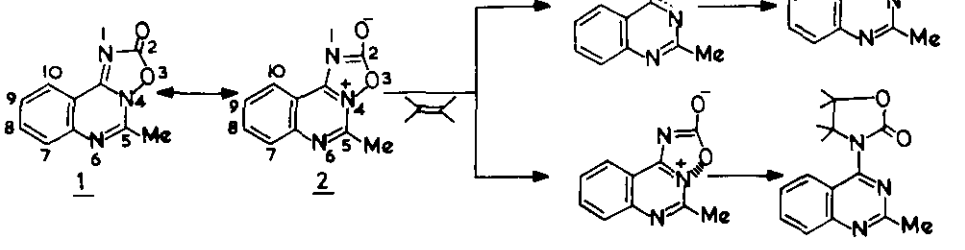
Abstract- A $\pi^2_s + \pi^2_s + \omega^2_s$ cycloaddition of 4-isocyanato-2-methyl quinazoline 3-oxide leads to the title compound, 5-methyl[1,2,4]oxadiazolo[2,3-c]quinazolin-2-one (1). Surprisingly, the weakest bond in 1 is 4-5. Rupture of this bond takes place thermally as well as with $P(OR)_3$ leading to the isomeric, 5-methyl[1,2,4]oxadiazolo[3,4-c]quinazolin-3-one (11). A detailed thermolytic study of 1 has given products arising from scission of the bonds 2-3, 3-4 and 4-5. The 3-4 bond is preferentially broken on photolysis of 1 in MeOH.

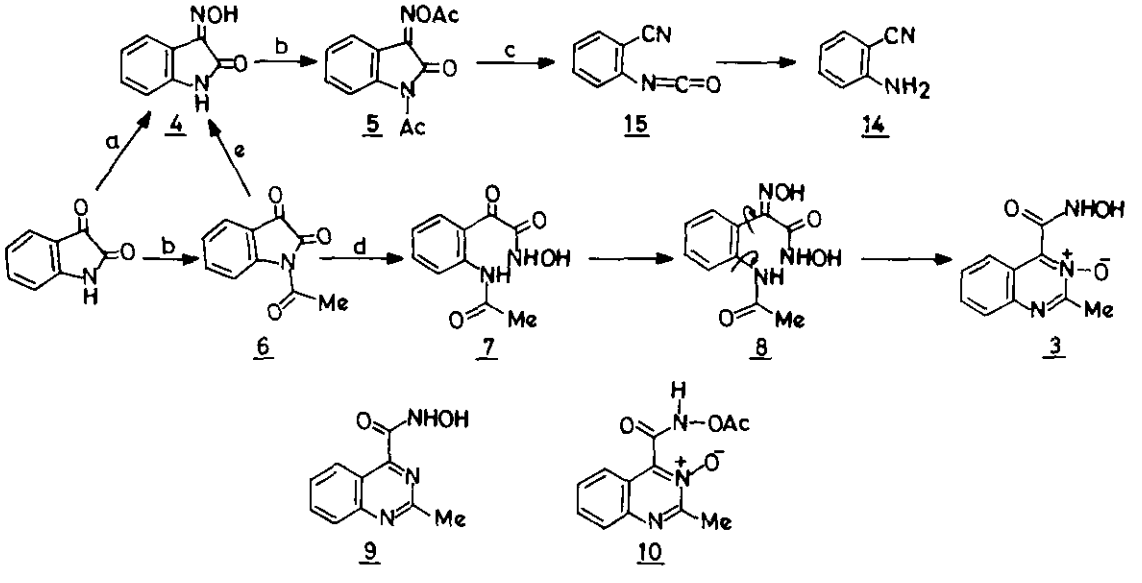
The proven synthetic utility of compounds possessing weak bonds to generate reactive intermediates[1], illustrates a useful concept in organic synthesis, which amounts to the utilization of energy rich molecule to drive unfavorable reactions. 5-Methyl[1,2,4]oxadiazolo[2,3-c]quinazolin-2-one (1), possessing a particularly fragile array of bonds, was considered as an attractive compound that could, in principle, be used to demonstrate either the carboxylate or the carboxamide conjugate base as a 4-component in cycloadditions, a circumstance which, otherwise, is thermodynamically highly unfavourable[2] (Chart 1).

Chart 1



It was anticipated that 1 would receive a significant contribution from the aromatic structure 2 which possesses an unusually fragile 3-4 O-N bond whose rupture would lead to a 1,3-dipole, the presence of which could be demonstrated via cycloaddition to π systems (Chart 1). Although 1 is known[3], details relating to its preparation as well as yields had to be independently developed[2]. Indeed, directions given in the literature, pertaining to reagents and reaction conditions, gave totally different products from those related to 1. Thus, the reaction of N-acetylisatin[4] (6) with hydroxylamine hydrochloride, neutralized either with sodium carbonate or sodium hydroxide, gave none of the reported N-oxide 3, but led to the mono-oxime 4, whose structure was established by transformation to the diacetate 5. It was subsequently discovered that the N-oxide 3, a precursor to the desired 1, can be prepared in 60% yields from 6, under carefully controlled conditions using hydroxylamine hydrochloride, neutralized with sodium acetate. The 6 → 3 change can be rationalized on the basis of intermediates 7 and 8. The structural assignment for the N-oxide 3 is further supported by trimethyl phosphite de-oxygenation to the quinazoline 9 and by acetylation to 10 (Chart 2).

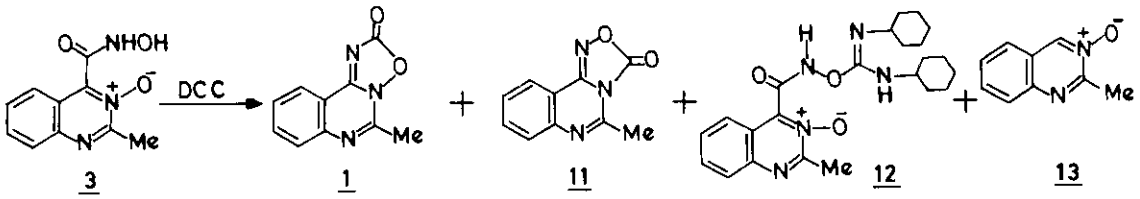
Chart 2



a: NH_2OH b: Ac_2O c: N_3^-, CH_3CN d: $NH_2OH \cdot HCl$, NaOAc e: $NH_2OH \cdot HCl$, Na_2CO_3/NaOH

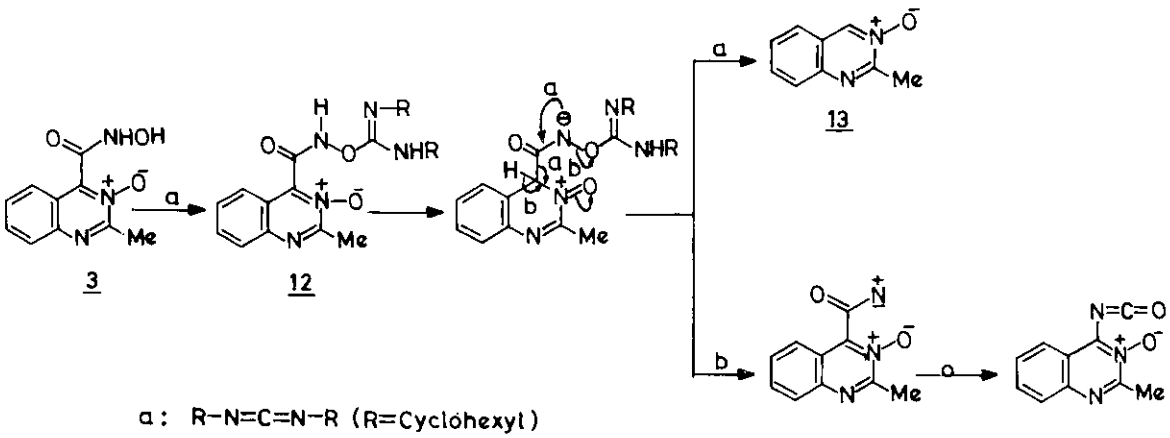
The reaction of the hydroxamic acid N-oxide 3 with an equivalent amount of DCC in refluxing dioxane for 1 h gave, on careful analysis, in addition to 1 (60%), the isomeric 5-methyl[1,2,4]oxadiazolo[3,4-c]quinazolin-3-one (11, 9%), the DCC adduct 12 (6%) and 2-methylquinazoline 3-oxide (13, 15%) (Chart 3).

Chart 3



The formation of compounds 1, 11, 12 and 13 are rationalized in Charts 4 and 5. It is envisaged that the initially formed DCC adduct 12 could fragment by two pathways, leading to either 2-methylquinazoline 3-oxide 13 or to the anticipated acyl nitrene followed by re-arrangement to the isocyanate intermediate (Chart 4).

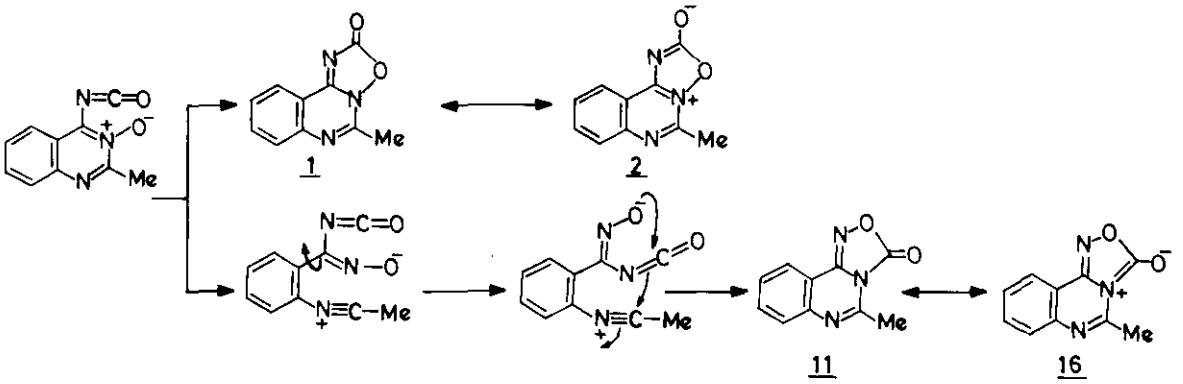
Chart 4



This, in turn, could undergo either cyclization to 1 or, by sequence of 2-3 bond rupture, rotation and cyclization to the isomeric 11 (Chart 5).

Parenthetically, the carbonyl grouping of N-acetylisatin mono-oxime acetate (5), on opening with azide ion, by sequence of events similar to that presented in Charts 2, 4 and 5, could give rise to either 1 or 11. In the event however, the reaction gave, in 53% yields, o-cyanoaniline (14). The formation of 14 could be rationalized on the basis of the intermediate o-cyanophenyl isocyanate (15) that

Chart 5

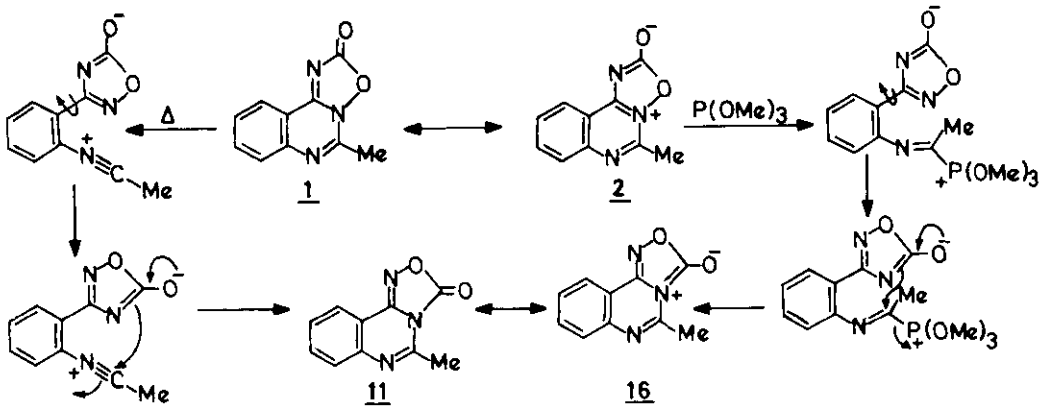


would result by an interesting fragmentation amounting to the loss of elements of acetic anhydride from 5 and initiated by the de-acetylation of the amide function (Chart 2).

The thermal reaction of 1 with a range of π systems, such as, acenaphthylene, diphenylcyclopropenone, diphenylacetylene, cyclohexene, maleic anhydride, quinone and tetraphenylcyclopentadienone (tetracyclone) gave no products from cycloaddition; in each case, the isomeric 11 was isolated in varying yields and in the last two cases, hydroquinone and dihydrotetracyclone were also formed. Thus, equivalent amounts of 1 and tetracyclone when held at 200°C for 10 h gave 20% of dihydrotetracyclone and a 50% yield of 11[2]. The thermal transformation of 1 to 11 could be rationalized on the basis of the rupture of the 4-5 bond followed by rotation and re-cyclization. The 4-5 bond scission can also be brought about by lone pair catalysts as demonstrated by the clean formation of 11 on treatment of 1 with trimethyl phosphite (Chart 6).

The unidirectional nature of the 1 → 11 isomerism deserves comment. The thermal instability of 1 reflects a major contribution of the anticipated structure 2, that could lead to cycloaddition products with π systems. The present work has demonstrated that this process has to compete with the ready scission of the 4-5 bond leading to the isomer 11. Parenthetically, the lack of reactivity of 11 is an indication that in this case the contribution from the structure 16 is marginal. Thus, compound 1 does possess a weak bond, not the expected 4-3 N-O but the 4-5 C-N! Neat thermolysis of 1 at 190°C for 6 h followed by careful and detailed analysis gave, in addition to the expected isomer 11 (11%), 4-amino-2-methylquinazoline (17, 16%)

Chart 6



and compound mp 195°C, the structure 18 of which has been tentatively assigned on the basis of spectral data (yield 8%). It is interesting to observe that compounds 11, 17 and 18 arise by three different mechanistic pathways from 1. Whilst 11 owes its genesis to the 4-5 bond rupture (Chart 6), the formation of compound 17 can be best understood in terms of a homolytic scission of the originally anticipated weak 4-3 N-O bond to give rise to the stabilized 1,3-diradical system 19 (Chart 7). The latter would, as expected, readily lose elements of carbon dioxide giving rise to a nitrene that could pick up hydrogen from the milieu to give 17. We have endeavoured to explain the formation of 18 on the basis of the cycloreversion of 1 to 4-isocyanato-2-methylquinazoline 3-oxide followed by fragmentation and re-combination (Chart 7).

The diradical intermediate 19 also arises on photolysis. Thus, compound 1 on irradiation in MeOH using a Hanovia high pressure source for 6 h gave two crystalline products for which structures 20 and 21 have been assigned on the basis of spectral data (yield: 20:25%, 21:6%). The formation of 20 and 21 is rationalized on the basis of acceptance of elements of MeOH by the nitrene intermediate resulting from the loss of carbon dioxide from 19 leading to 4-amino-3-methoxy-2-methylquinazoline, which on hydrolytic cleavage of either the 3-4 bond (path a) or the 2-3 bond (path b), would give, respectively, 20 and 21 (Chart 8).

Chart 7

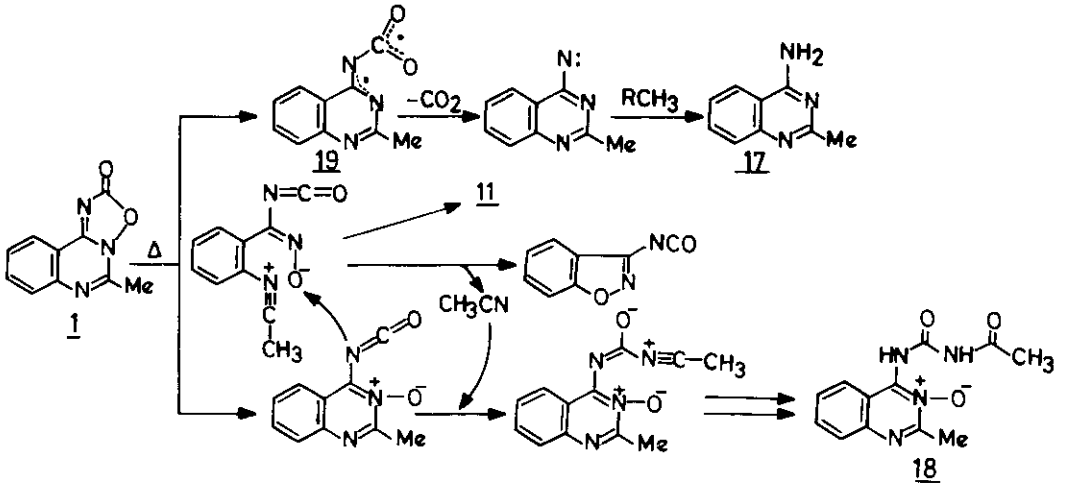
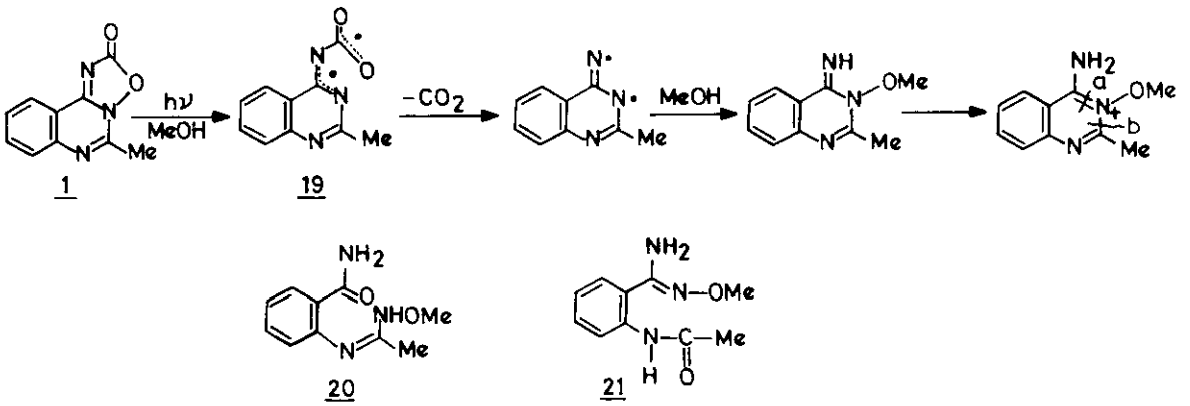


Chart 8



The present work has brought to light diverse subtle facets of reaction mechanisms. Although the title compound undergoes the expected cyclo-reversion and carbondioxide extrusion, endeavours to demonstrate 1 as an unusual partner in cyclo-additions were thwarted by the unexpected fragility of the 4-5 bond and the preference for the homolytic rupture of the 3-4 bond.

ACKNOWLEDGEMENT

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EXPERIMENTAL

Reaction of hydroxylamine hydrochloride with N-acetylisatin: Isolation of isatin monooxime 4

A stirred solution of N-acetylisatin 6 (2g, 0.01 mol) in hot alcohol (50 ml) was admixed with a solution of hydroxylamine - prepared by neutralisation of a solution of $NH_2OH.HCl$ (2g, 0.028 mol) by either sodium carbonate or sodium hydroxide solution in H_2O:EtOH (1:1, 50 ml) - the mixture refluxed for 3 h, concentrated to one-third the volume, left aside in the refrigerator overnight, filtered, washed with dil alcohol and crystallised from hot alcohol to give 1.14g (67%) of 4 as yellow needles, mp 213-214°C; (lit.[5] mp 214°C) IR: ν_{max} (KBr) cm^{-1}: 3240 (NH), 1712 (C=O), 1660 (>C=N-OH); NMR: δ(DMSO) (d_6) (60 MHz) : 9.91 (b, 2H, NH and OH), 7.91 (d, 1H, aromatic), 7.19 (m, 2H, aromatic), 6.85 (m, 1H, aromatic); MS: m/e : 163 (M^+ + 1), 162 (M^+), 145 (M^+ - OH).

Reaction of isatin monooxime 4 with acetic anhydride: Isolation of acetylated product 5

A mixture of 4 (0.2g, 0.0012 mol) and acetic anhydride (5 ml) was refluxed for 3 h, cooled (~20°C), filtered, washed with hexane and recrystallised from benzene to give 0.16 g (53%) of 5, mp185-187°C; Anal.Calcd. for $C_{12}H_{10}N_2O_4$:C, 58.53; H. 4.00, Found: C, 58.79; H, 3.73; MS: m/e: 246 (M^+); IR: ν_{max} (KBr) cm^{-1}: 1800, 1785, 1755; 1715 (C=O); NMR: δ($CDCl_3$) (60 MHz): 8.3-8.0 (m, 2H, aromatic) 7.7-7.3 (m, 2H,aromatic), 2.7 (s, 3H, NOCOC$\underline{H}_3$), 2.43 (s, 3H, N-COC$\underline{H}_3$).

Reaction of N-acetyl isatin 6 with hydroxylamine hydrochloride and sodium acetate: Isolation of the hydroxamic acid 3

Sodium acetate (2g, 0.0245 mol) and hydroxylamine hydrochloride (1g, 0.014 mol) were separately dissolved in minimum amount of water, mixed and added to 6 (1g, 0.0056 mol), ethanol was added gradually and with stirring to the mixture until a clear solution was obtained (~30 ml EtOH), then refluxed for 0.5 h, concentrated to half the volume and left overnight in the refrigerator. The white crystalline 3 was collected, washed with alcohol: water (1:1) and crystallised from hot ethanol. mp 239-240°C (lit.[3] mp 240°C). Yield: 0.66g (57%); Anal.Calcd. for $C_{10}H_9N_3O_3$:C, 54.79; H, 4.11, Found: C, 54.60; H, 4.00; MS: m/e: 219 (M^+), 143 (M^+ - (CONHOH + O)); IR: ν_{max} (KBr) cm^{-1}: 3110 (NHOH), 1655 (C=O), 1308, 1190 (N-O); NMR: δ(DMSO) (d_6) (60 MHz): 7.85-7.6 (m, 4H, aromatic), 6.15 (br, 2H, NH and OH), 2.73 (s, 3H, C$\underline{H}_3$).

Reaction of the hydroxamic acid 3 with trimethyl phosphite: Isolation of 9

A stirred solution of the hydroxamic acid 3 (0.400g, 0.0018 mol) in trimethyl

phosphite (10 ml) was held at 150°C for 8 h, solvents evaporated in vacuo and the residue chromatographed over silica gel. Elution with CH_2Cl_2:MeOH (9:1) gave 0.056g (15%) of 9 as colorless needles, mp 192-197°C; IR: ν_{max} (KBr) cm^{-1}: 3450 (OH), 1710 (C=0); NMR: $\delta(CDCl_3)$ (270 MHz): 8.1 (d, 1H), 7.7 (m, 2H), 7.5 (t, 1H), 2.9 (s, 3H).

Reaction of the hydroxamic acid 3 with acetic anhydride: Isolation of the acetylated product 10

A stirred mixture of the hydroxamic acid 3 (0.5g, 0.0023 mol) and acetic anhydride (5 ml) was held at 100°C for 2 h, poured onto ice-water, filtered, dried and crystallised from ethyl acetate to give 0.187g (31%) of 10, mp 177°C; IR: ν_{max} (KBr) cm^{-1}: 1805, 1740, 1710 (C=0), 1610, 1305, 1190 (N-0); NMR: $\delta(CDCl_3)$ (60 MHz): 7.9-7.5 (m, 4H, aromatic), 2.84 (s, 3H, CH_3), 2.3 (s, 3H, $COCH_3$).

Reaction of the hydroxamic acid 3 with DCC: Isolation of 1, isomer 11, and the quinazoline N-oxides 12 and 13

A mixture of the hydroxamic acid 3 (2g, 0.009 mol) and dicyclohexylcarbodiimide (DCC) (2g, 0.009 mol) in dry dioxane (50 ml) was refluxed for 1 h, and the clear solution left aside overnight. Dicyclohexylurea was filtered off, washed with ethyl acetate, the combined filtrates evaporated in vacuo and the residue on crystallisation from hot ethyl acetate gave 1.10g (60%) of 1 as colorless needles, mp 230-231°C (lit.[3] mp 232-233°C); Anal. Calcd. for $C_{10}H_7N_3O_2$:C, 59.70; H, 3.48; Found: C, 59.72; H, 3.96; MS: m/e : 201 (M^+); IR: ν_{max} (KBr) cm^{-1}: 1810, 1790 (C=0); NMR: δ(DMSO) (d_6) : 8.3-7.5 (m, 4H, aromatic), 2.72 (s, 3H, $-CH_3$).

The filtrate on concentration gave a gummy residue which was chromatographed on a column of silica gel. Elution with ethyl acetate: benzene (15:85) gave 0.16g (9%) of 11 which on crystallisation from methanol yielded prisms, mp 189-190°C (lit.[3] mp 195-197°C) ; Anal. Calcd. for $C_{10}H_7N_3O_2$:C, 59.70; H, 3.48, Found: C, 59.73; H, 3.45; IR: ν_{max} (KBr) cm^{-1}: 1825 (shoulder, C=0), 1785 (C=0), 1635 (C=0); NMR: $\delta(CDCl_3)$ (500 MHz) : 8.08 (d, 1H), 7.77 (t, 1H), 7.7 (d, 1H), 7.55 (t, 1H), (aromatic protons), 2.85 (s, 3H , CH_3).

Further elution with benzene: ethyl acetate (1:1) gave 0.233g (6%) of 12 as yellow crystals mp 200-205°C; IR: ν_{max} (KBr) cm^{-1}: 3320 (NH), 1790 (>C=0), 1630 (>C=0), 1309, 1200 (N-0).

Finally, elution with 100% ethyl acetate followed by preparative tlc of the residue using benzene:ethyl acetate (7:3) as developer gave 0.220g (15%) of 13 as an orange yellow solid, mp 168-169°C; (lit.[6] mp 170.5°C); MS: m/e: 160 (M^+); IR: ν_{max} (KBr)

cm^{-1}: 1660 (w), 1615, 1575, 1195 (N-O), 1310 (N-O); NMR: $\delta(CDCl_3)$ (500 MHz): 8.9 (s, 1H), 7.93 (d, 1H), 7.74 (t, 1H), 7.67 (d, 1H), 7.60 (t, 1H) (aromatic protons), 2.87 (s, 3H, $-CH_3$).

Reaction of N-acetyl isatin-β-oxime-O-acetate 5 with sodium azide: Isolation of o-cyanoaniline (14)

A stirred mixture of 5 (2g, 0.008 mol) and sodium azide (2g, 0.03 mol) and dry acetonitrile (100 ml) was refluxed for 20 h, and filtered. The solvent was evaporated and the residue chromatographed on silica gel. Elution with benzene gave 0.500g (53%) of o-cyano aniline (14), mp 49-50°C (lit.[7] mp 47-49°C). MS: m/e : 118 (M^+); IR: ν_{max} (KBr) cm^{-1} : 3360 ($-NH_2$), 2210 (-CN); NMR: $\delta(CDCl_3)$ (60 MHz): 7.5-6.5 (m, 4H, aromatic), 4.7 (br, 2H, $-NH_2$).

Reaction of 1 with trimethyl phosphite: Isolation of the isomer 11

Under nitrogen and stirring a solution of 1 (0.382g, 0.0019 mol) in dry benzene (10 ml) was admixed with trimethyl phosphite (10 ml) and the mixture refluxed for 12 h. Benzene was evaporated, additional trimethyl phosphite (5 ml) introduced, the mixture held at 150°C for 24 h, concentrated and the residue chromatographed over silica gel. Elution with benzene: ethyl acetate (3:7) gave 0.108g (28%) of the isomer 11, mp 188-190°C.

Thermolysis of 1 : Isolation of 11, 17 and 18

Compound 1 (0.460g, 0.0023 mol) was held at 190°C in a sealed tube for 6 h, cooled, cautiously opened, extracted with ethyl acetate, solvent evaporated and the residue chromatographed on silica gel. Elution with benzene: ethyl acetate (9:1) gave 0.05g (11%) of 11, mp 189-191°C.

Further elution with benzene: ethyl acetate (8:2) gave 0.045g (8%) of 18, mp 195°C; IR: ν_{max} (KBr) cm^{-1}: 3280 (NH), 3240 (NH), 1660 (C=O), 1290 (N-O); MS: m/e: 258 ($M^+ - 2$).

Finally, elution with benzene: ethyl acetate (7:3) gave 0.056g (15%) of 17, mp 225°C (lit.[8] 228-229°C); IR: ν_{max} (KBr) cm^{-1}: 3320 (NH_2), 1655, 1575; MS: m/e : 159 (M^+).

Photolysis of 1 : Isolation of 20 and 21

In five batches, stirred solutions of 1 (0.300g, 0.0015 mol) in methanol (250 ml) were irradiated for 6 h using a 440 watt Hanovia high pressure mercury lamp and a pyrex filter. Solvent was evaporated and the residue crystallised from hot ethyl acetate to give 0.196g (24%) of 20, mp 220°C; IR: ν_{max} (KBr) cm^{-1}: 3320 (NH_2), 1630, 1570

C=0); MS: m/e: 207 (M^+), 163 ($M^+ - CONH_2$), 148 ($M^+ - (CONH_2 + CH_3)$), 133 ($M^+ - (CONH_2 + 2\ CH_3)$).

The filtrate from crystallisation of 20 was evaporated and the residue chromatographed on silica gel. Elution with benzene:ethyl acetate (7:13) gave 0.712g of unchanged 1, mp 225°C.

Further elution with chloroform gave 0.05g (6%) of 21 as a pale yellow crystalline solid, mp 234°C; IR: ν_{max} (KBr) cm^{-1}: 3420 (NH), 3265 (NH_2), 1690, 1670 (C=0), 1630 (C=0); MS: m/e: 207 (M^+), 160 ($M^+ - (CH_3ONH_2)$).

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