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Synthesis & Reactions of 4,6,7,8-Tetrahydro-5(1*H*)-cinnolinones†‡

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Phenacyldimedone, acetonyldimedone and analogues of general structure **1** undergo reaction with hydrazine, alkylhydrazine and phenyl- and 4-nitrophenyl-hydrazines to form 4,6,7,8-tetrahydro-5(1*H*)-cinnolinones (**2**) while **1b** and 2,4-dinitrophenylhydrazine afford the perhydroindole **4b**. Tetrahydrocinnolinones **2a**, **2e** and **2f** yield the partially aromatised oximes **7a-c**, while the keto acid **13** gives the decarboxylated oxime **14** or the acylnitrone **15**. 1-Aminoalkyl- and 1-alkylcinnolinones (**2b-d** and **2g**) form the same oxime **7a** with concomitant loss of the 1-substituent presumably through a quaternary salt of the type **9**. 1,3-Diphenylcinnolinone **2b** is transformed under identical conditions to the quaternary salt **10a** in addition to two other products **11** and **12**. The oximes **7a-c**, **14** and the nitrone **15** on treatment with PPA do not yield the ring enlarged Beckmann products, but undergo Semmler-Wolff aromatisation to afford 5-aminocinnolines (**19a-d** and **20**). Compound **19a** is also formed from **7a** with conc. sulphuric acid or pyridine-phosphorous oxychloride and from 7,8-dihydro-5(1*H*)-cinnolinone (**16**) by a Schmidt reaction. Structures **19a-d** have been established by deaminating **19c** to known 3-phenylcinnoline and by the formation of pyrazolocinnoline **22** from the diazotisation of **19b**. While a number of interesting products are obtained from the oxime **7a** with a variety of acidic reagents, only phosphorous pentachloride transforms it to the expected pyridazinoazepinone **30**. The study has led to a number of unexpected reactions which have been rationalised.

Phenacyldimedone and analogues of the general structure **1** have not only great utility in the synthesis of heterocycles but also undergo unexpected reactions[1]. Reactions of **1a** with primary amines like anilines afford 1-arylperhydroindoles exhibiting antiimplantation activity[2], while with 1-aminopiperidine and N,N-disubstituted hydrazines, 3-aminoperhydroindoles[3,4] are produced. Hydrazine and some monosubstituted hydrazines afford 4,6,7,8-tetrahydro-5(1*H*)-cinnolinones of the type **2**, some of which have CNS depressant activity[5]. In a preliminary communication[6], we have commented on the unexpected formation of the oxime **7a** from **2a** and its unusual conversion into the aminocinnoline **19a** under Beckmann transformation conditions. Subsequently, we extended our study on the formation of cinnolines from **2** to nitrophenylhydrazines and investigated in some depth the origin of oximes **7** from **2** and their fate under a variety of acidic conditions. The results are presented in this paper.

Formation of 4,6,7,8-*tetrahydro*-5(1*H*)-*cinnolinones*

In an earlier paper[5], we have published several examples wherein R – R_3 were extensively varied, with R_3 being mostly H or aminoalkyl group. We have not studied the reaction of **1a** and **1b** with phenyl, 4-nitrophenyl- and 2,4-dinitrophenyl-hydrazines. The reaction of phenylhydrazine with **1a** gave rise to the cinnolinone **2b**. In the PMR spectrum of this product, the protons at C-6 and C-8 appeared as singlets at δ 2.21 and 2.31 respectively. On the other hand, in the PMR spectrum of the cinnolinone **2i**, obtained from **1d** and phenylhydrazine, the pairs of protons at C-6 (δ 2.19, 2.41) and C-8 (δ 1.99, 2.52) became nonequivalent because of the substituent at C-4. Since the phenyl group at C-1 can be expected to have a greater shielding effect on the protons at C-8 than on the ones at C-6, the proposed assignment is more realistic than a transposed one. The reaction of **1b** with 4-nitrophenylhydrazine gave rise to two products with m.p.s 108-10° and 295-98°. The former, $C_{17}H_{19}N_3O_3$, was clearly the expected cinnolinone **2j** which showed a two-proton singlet for C-4 methylene protons at δ 3.00 in its PMR spectrum. The latter product, $C_{34}H_{38}N_6O_6$ ($M^{+\cdot} - 1$ at *m/z* 625) appeared to consist of two monomeric units, one being the cinnolinone **2j**; but instead of a two-proton singlet for C_4-H_2 at δ 3.00, two singlets were observed at 5.13 and 5.42, integrating for only one proton. Further, the indole unit **4a** also seemed to be present as evident from a high-field multiplet for two protons at C-2‴ and C-6‴ at δ 6.38 (see below), a singlet for one proton at C-3, and two broad singlets at 10.02 and 10.04 together integrating for one proton (NH). Considering that the CH_2 group at position-4 in **2j** will be activated for addition of a C=O group, we wish to formulate the dimeric product tentatively as a diastereoisomeric mixture of **3**, arising by reaction of **4a** with **2j**.

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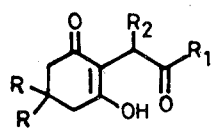
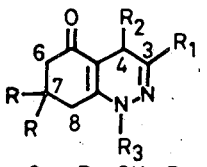
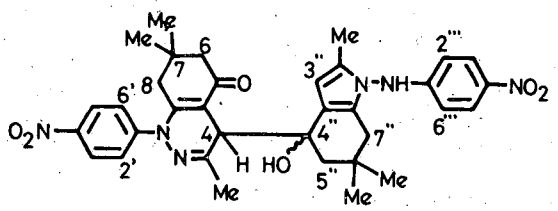


1 a R = CH_3 ; R_1 = Ph , R_2 = H
b R = R_1 = CH_3 ; R_2 = H
c R = R_2 = H ; R_1 = Ph
d R = R_2 = CH_3 ; R_1 = Ph



2 a R = CH_3; R_1 = Ph ; R_2 = R_3 = H
b R = CH_3 ; R_1 = Ph ; R_2 = H ; R_3 = $(CH_2)_2NMe_2$
c R = CH_3 ; R_1 = Ph ; R_2 = H ; R_3 = $(CH_2)_2NEt_2$
d R = CH_3 , R_1 = Ph , R_2 = H , R_3 = $(CH_2)_3NMe_2$
e R = R_1 = CH_3 ; R_2 = R_3 = H
f R = R_2 = R_3 = H ; R_1 = Ph
g R = R_3 = CH_3 ; R_1 = Ph ; R_2 = H
h R = CH_3 , R_1 = R_3 = Ph , R_2 = H
i R = R_2 = CH_3 ; R_1 = R_3 = Ph
j R = R_1 = CH_3 ; R_2 = H ; R_3 = 4-$NO_2C_6H_4$
k R = R_1 = CH_3 ; R_2 = CH_2CO_2H ; R_3 = H
l R = R_1 = CH_3 ; R_2 = CH_2CO_2Et ; R_3 = H



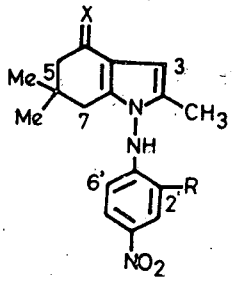
3

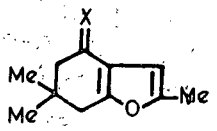
Unfortunately the high-field signals in the PMR spectrum of **3** were not amenable to incisive analysis. 2,4-Dinitrophenylhydrazine and **1b** again gave rise to two products with m.ps 210-12° and 270-72°. The former, $C_{17}H_{18}N_4O_5$, was not a cinnoline and was recognized readily to be the indole **4b**, the PMR spectrum of which exhibited a singlet for C_3-H at δ 6.40, a singlet for NH at 10.12 and a doublet for C-6′ proton at 6.33. An interesting observation in the spectrum was the splitting of protons at C-7 into an *AB* quartet, apparently due to differential shielding by the dinitrophenyl group held orthogonally (perhaps in a rigid ring by hydrogen bonding of the 2′-NO_2 group with the NH proton). The higher melting product from this reaction was identified as the 2,4-dinitrophenylhydrazone (**4c**) and **4b**. An alternative structure for **4c** would have been **5b** which was prepared unambiguously by acid-induced cyclization of **1b** to furan **5a** followed by reaction with 2,4-dinitrophenylhydrazine. In the event, **4c** was found to be different from **5b**. In contrast to **1b**, 2-phenacylcyclohexanone (**6a**) reacted with 2,4-dinitrophenylhydrazine to give only the bis-hydrazone **6b**.

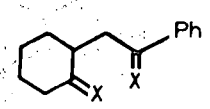
Oximation studies on 4,6,7,8-*tetrahydro*-5(1*H*)-*cinnolinones*

Reaction of the cinnolinone **2a** with two moles of hydroxylamine hydrochloride in pyridine at 100° for several hours gave in about 95% yield, the oxime **7a** ($M^{+\cdot}$ at *m/z* 267) rather than the expected one (M 269). The aromatisation of the dihydropyridazine ring was inferred from the disappearance of the two-proton singlet around δ 3.0 ($C_4 - H_2$) in **2a** and the appearance of a singlet at 8.28 due to $C_4 - H$ in **7a**; singlets due to protons at C-6 and C-8 also experienced a downfield shift. The cinnolinones **2e** and **2f** gave rise to similar aromatised oximes **7b** and **7c** respectively in high yields. Reaction of **2a** with methoxylamine also led to the formation of the aromatised methoxime. Treatment of **7a** with toluenesulphonyl chloride in pyridine merely led to O-sulphonation and not to the expected Beckmann transformation product. Hydrolysis of **7a** with dil. sulphuric acid gave the ketone **16** in a low yield. This ketone was obtained in a better yield by treatment of **2a** with either methane- or *p*-toluene-sulphonyl chloride in pyridine. Exposure of **2a** to hot pyridine also led to the formation of **16** but in only 10% yield, rest of the starting material being recovered. Hence, a spontaneous aerial oxidation of **2a** to **16** could be ruled out as a sole prior step to the formation of **7a**, leaving hydroxylamine responsible for much of the aromatisation reaction. In occasional runs of **7a**, the PMR as well as mass spectra of the crude product showed the presence of **16**. Thus, oxidation of **2a** to **16** by hydroxylamine followed by further reaction with excess hydroxylamine may be a major route for the formation of **7a**.

Another interesting observation in the oximation studies was the transformation of 1-methyl(**2g**)- and 1-aminoalkyl(**2b-2d**)-cinnolinones into the same oxime **7a** in moderate yields by reaction with excess hydroxylamine hydrochloride in pyridine. It was readily ascertained that the 1-methyl derivative (**2g**) was totally resistant to aerial oxidation in hot pyridine. Hence, in these cases it was likely that 1-alkylquaternary salts of **7a** were formed which suffered



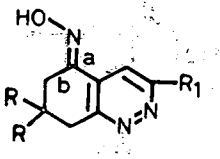


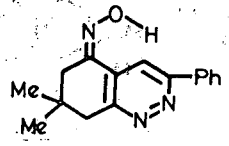


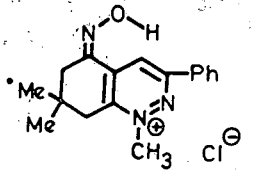
4 a R = H ; X = O
b R = NO_2 ; X = O
c R = NO_2 ; X = 2,4-di$NO_2C_6H_3NHN$

5 a X = O
b X = 2,4-di$NO_2C_6H_3NHN$

6 a X = O
b X = 2,4-di$NO_2C_6H_3NHN$







7 a R = CH_3, R_1 = Ph
b R = R_1 = CH_3
c R = H, R_1 = Ph

8

9

dealkylation. This was demonstrated by carrying out the reaction of **2g** with an equimolar quantity of hydroxylamine hydrochloride in pyridine. The product mixture contained not only oxime **7a** and ketone **16**, but also the quaternary chloride **9** (PMR: N_1-CH_3 at δ 4.63 and C_4-H at 8.93; $M^{+\cdot}$ at *m/z* 281 for betaine). That the oxidation process was at least partly radical-induced, became evident during the oximation of the 1,3-diphenylcinnolinone (**2h**) with excess hydroxylamine hydrochloride. The product mixture contained besides the 1-phenylquaternary salt **10a**, small quantities of 1,3,4-triphenylcinnolinone oxime (**11**) and 1-unsubstituted 4-hydroxycinnolinone (**12**). Structures of these products are based on elemental analyses and mass and PMR spectral data, especially PMR (**11**: signals for protons of three phenyl groups, singlet for C_4-H at δ 5.55; **12**: signals for protons of one phenyl group, singlet for C_4-H at δ 6.91).

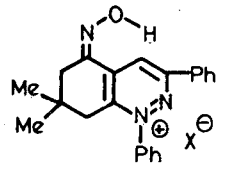
Lastly, we studied the oximation of cinnolinone resulting from the triketo acid **13**. This on reaction with excess hydrazine hydrate in ethanol suffered decarboxylation and gave the cinnolinone **2k** as an oil which without purification was treated with hydroxylamine to afford the oxime **14**. On the other hand, **2k** could be esterified with ethanol to give the cinnolinone **21** which afforded the tricyclic system **15** with hydrazine. The structure of **15** is based on elemental analysis and mass spectrum. In the mass spectrum, there was a prominent (M − 16) peak as would be expected by the presence of a nitrone group. The PMR spectrum of **15** could be run only in trifluoroacetic acid and indicated that in this solvent it existed completely in the enolic form (**15b**) (singlet for =CH at δ 7.40; no signal for CH_2).

Intramolecular oxidation-reduction of ketocinnoline **2a** *to hydroxycinnoline* **18**

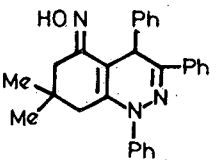
Treatment of **2a** in dioxane with dil. HCl under reflux transformed it into the isomeric alcohol **18** (yield 60%) which was also obtained from **16** by reduction with sodium borohydride. The formation of **18** from **2a** can be visualised to have occurred through the species **17** by a prototropic shift. The structure of **18** (IR: no C=O, but OH band) was specially supported by PMR data (singlet for C_4-H at δ 8.15, multiplet for C_5-H at 4.85 and nonequivalence of the two hydrogen atoms at C-6).

Behaviour of oxime **7a-c** *and* **14** *and pyridocinnolinone* **15** *towards PPA*

An attempted Beckmann rearrangement of **7a** with hot PPA resulted in the unexpected formation of **19a** in 70% yield by a Semmler-Wolff rearrangement[6]. The same transformation was brought about by hot conc. sulphuric acid or phosphorous oxychloride-pyridine in 85 and 40% yields respectively. Similar PPA-induced rearrangements occurred with **7b**, **7c** and **14** to afford induced **19b-d** in 95, 50 and 65% yields respectively. The product obtained by the action of PPA on **15** was not the expected lactam **21**, but it was the hydrolysis product **20** although the mass spectrum showed the



10 a X = Cl
b X = I



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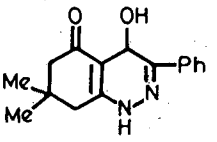

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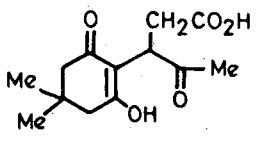

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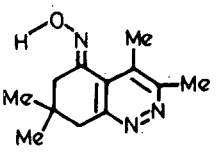

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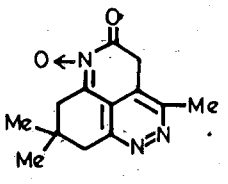
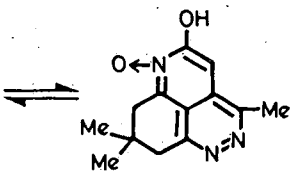
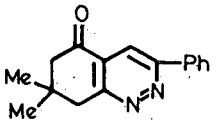


15a



15b



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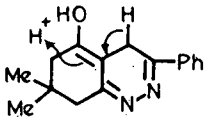

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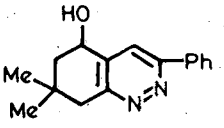

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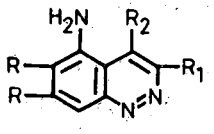
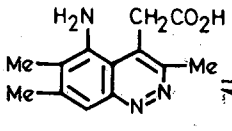
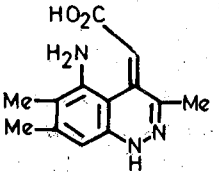


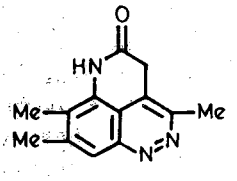
19a R = Me ; R_1 = Ph ; R_2 = H
b R = R_1 = Me , R_2 = H
c R = R_2 = H ; R_1 = Ph
d R = R_1 = R_2 = Me



20a



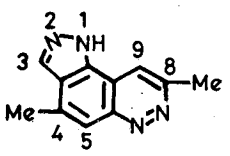
20b



21

molecular ion peak at *m/z* 227 corresponding to the cyclodehydration product **21**. Compound **20** was soluble in aq. sodium hydroxide and besides giving correct elemental analysis it exhibited typical bathochromic shifts in acidic medium compared to neutral solvent[6]. The PMR spectrum in DMSO-d_6 displayed two singlets at δ 5.45 and 6.40. We wish to propose tentatively that **20** exists as a mixture of the tautomers **20a** and **20b** and ascribe the two signals respectively to the vinylic proton in the former and the CH_2 protons in the latter. The amine **19b** was routinely transformed into chloracetyl (**25a**) and pyrrolidinoacetyl (**25b**) derivatives and **19a** into dicloracetyl **26** derivative for biological screening.

The structures of **19c-d** rested firmly on elemental analysis and UV, IR, mass and PMR spectral data, the last one being of the greatest diagnostic significance. Thus, in the PMR spectrum of **19**, the singlets due to protons at C-6 and C-8 observed for **7a** at δ 2.67 and 3.05, disappeared to give rise to a singlet in the aromatic region at 7.60, while the two methyl groups appeared as downfield singlets at 2.33 and 2.47 from their original position at 1.07 in **7a**. Compound **19b** and even more so **19d** are the interesting examples of 5-aminocinnolines sprinkled liberally with methyl groups. Diazotisation-deamination of **19c** afforded 3-phenylcinnoline identical with a known sample. The marked upfield shift of C_4-proton in the latter



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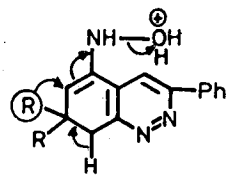

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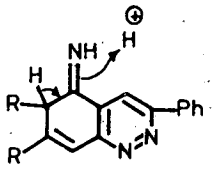

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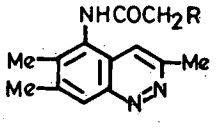
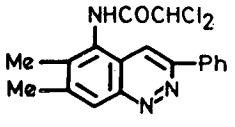


25a R = Cl

b R = Pyrrolidino



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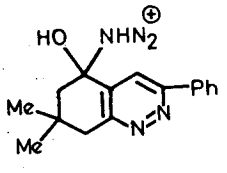
compared to the same proton in **19c** would be explicable on the basis of deshielding influence of the amino group at position-5 in **19c**. A similar reaction performed on **19b** did not lead to deamination. Instead pyrozole **22** was formed indicating that one of the methyl groups which had migrated in the rearrangement of **7b** had wandered to position-6 rather than 8 resulting in the formation of **19b** and not its 7,8-dimethyl isomer. Pyrazole formation in this reaction was unexpected but not entirely unprecedented, since the diazotisation of 3-aminolepidine has been reported to yield a pyrozoloquinoline[8].

From a comparison of the chemical shifts for C_4-H proton in ketone **16** (δ 8.22) and oxime **7a** (δ 8.28), we have concluded that the latter has *E*- rather than *Z*-configuration (**8**). In a few other oxime the N − OH bond is tilted towards the pyridazine ring as in **9** (probably) (C_4-H δ 8.93), **10a** (C_4-H δ 9.20) and **36** (certainly) (C_4-H, δ 9.33). A Beckmann rearrangement of **7a** would required bond-a attached to the electron-poor pyridazine ring to migrate. We have proposed[6] that this is probably a more energy-demanding process than the Semmler-Wolff aromatisation for which many mechanisms differing only in details have been proposed[9,10]. We feel that oxime **7a** may exist in equilibrium with species **23** (protonated form), wherein the loss of a water molecule would trigger loss of a proton from position-8 followed by migration of methyl group to C-6. Imine **24** thus arising would tautomerise to the aminocinnoline **19a**. Oximes of heterocyclic ketones such as 5-keto-5,6,7,8-tetrahydroquinoline have been shown recently to undergo facile Semmler-Wolff rearrangement[11–17]. Parallels to the transformation **15**→**21** have also been reported very recently in quinoline series[18–20].



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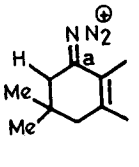

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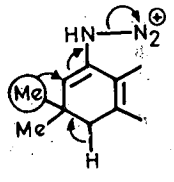

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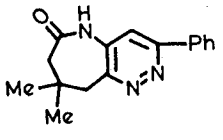

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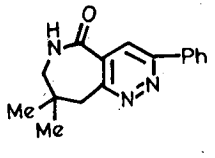


31

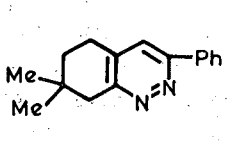
Attempted Schmidt reaction on ketone **16**

Ketone **16** was inert towards sodium azide and trifluoroacetic acid—anhydride mixture, but in the presence of conc. sulphuric acid conversion to **19a** occurred in 75% yield. The reaction can be envisaged to proceed through the standard intermediate species **27** and **28** (configuration of $=NH_2^{(+)}$ assumed to be the one shown). The reluctance again of the electron-deficient bond-a in **28** to migrate nudges the molecule to tautomerise to **29** which by the loss of nitrogen goes over to species **24** and thence inevitably to amine **19a**. At the time of our preliminary disclosure[6], this was the only recorded abnormal Schmidt rearrangement, the recalcitrancy being traceable to the attachment of the ketone to the electron-deficient pyridazine ring. Latter, some 5-oxo-5,6,7,8-tetrahydroquinolines were also reported to be transformed partly into 5-aminoquinolines and partly into pyridoazepines under the Schmidt reaction conditions[12].

Behaviour of oxime **7a** *towards other acidic reagents*

The transformation of **7a** into **19a** by PPA, conc. sulphuric acid or phosphorous oxychloride-pyridine has been already recorded as also its hydrolysis to ketone **16** with hot dil. sulphuric acid. Several other reagents were tried. Phosphorous pentachloride was uniquely able to bring about the much-sought-after rearrangement to the azepinone, although in unspectacular yield (11.5%). The *E*-configuration of the oxime **7a** should dictate the formation of **30** rather than **31**. The former was indeed the structure of the product, since the singlet due to C_4-H had moved upfield to δ 7.67 compared to its position in **7a** (δ 8.28).

Further the NH signal at δ 10.0 was only a singlet. Reaction of **7a** with formic acid gave a cumbersome mixture of four products which was separated into its components by fractional crystallization and chromatography. Two were known compounds, viz. **2a** formed by reductive hydrolysis and **16** by oxime cleavage. The third product was the dihydrodesoximino derivative **32** and the fourth, the product of reductive formylation, **33**. Structures **32** and **33** were firmly supported by mass and PMR spectral data. The PMR analysis of the total crude product revealed the composition of the mixture as: **2a** (10%), **16** (10%), **32** (50%) and **33** (30%). Finally the oxime **7a** was treated with hot 6 *N* hydrochloric acid in dioxane. The PMR analysis of the total crude product showed it to be a mixture of **7a** (10%), **16** (30%) and a new compound found to be the chloroketone **35** (60%) which on crystallization from ether followed by ethanol gave fairly pure **35a** in about 25% yield. The chloroketone **35a** was characterized by elemental analysis and mass (M^+ at *m/z* 286, 288) and PMR (C_6-H as singlet at δ 4.40) and nonequivalence of C_8-protons. The formation of **35a** can be visualized to have occurred by the addition of chloride ion to species **23** to afford **34** and subsequent hydrolysis. We considered an alternative possibility of hydroxylamine and hydrochloric acid reacting together to generate chlorine which can halogenate **16** to produce **35a**. The hydrolysis of **7a** with 6 *N* hydrochloric acid was accordingly carried out in the presence of excess hydroxylamine hydrochloride and the product chromatographed over silica gel. Chloroketone **35a** was again obtained, but only in about 13% yield. A more polar product from the column analyzed for the molecular formula $C_{32}H_{31}N_5O_4$, although the mass spectrum did not show the molecular ion due to extensive decomposition. The PMR spectrum showed signals for four different tertiary methyl groups, a singlet due to CH $-$O, two different signals for the proton on the pyridazine ring, one of them being very low field (δ 9.33) and an oximino proton. These data could be best accommodated by the structural representation **36a** with unresolved ambiguity about the nature of R and R_1 and also regarding the stereochemistry of the carbon atoms involved in the ether linkage. The third and most polar product was tentatively considered to be **36b**, although the mass spectrum did not show the molecular ion to confirm the molecular formula. Products **36a** and **36b** probably arise by partial or complete oximation of the diketone corresponding to **36a**. The origin of this diketone can be traced to **35a** yielding the hydroxyketone **35b** which is further oxidised to a diketone and the two involving themselves in an intermolecular hemiketal formation. The oximino group in **36a** is deliberately oriented as shown, because of the occurrence of the signal for the concerned proton at C-4′ at a very low field (δ 9.33), compared to the other C_4-H (δ 8.42). Treatment of **7a** with acetic acid saturated with hydrogen chloride gas also gave chloroketone **35a** in 15% yield, the rest of the oxime being recovered. The formation of α-



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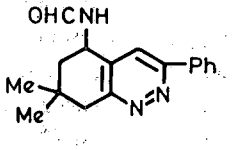

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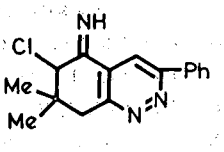

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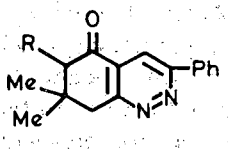
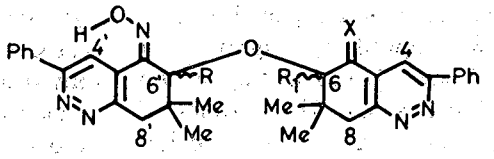


35 a R = Cl

b R = OH



36 a X = O, R = H, R_1 = OH or vice versa

b X = NOH, R = H, R_1 = OH

chlorotetralone from tetralone oxime using Beckmann's mixture has been reported[21].

Experimental Procedure

Formation of 4,6,7,8-*tetrahydro*-5-(1*H*)-*cinnolinones* (**2**)

Ketone **1a** (3.9 g), phenyl hydrazine (1.7 g) and ethanol (20 ml) were heated under reflux for 20 hr. The solution was evaporated and the residue triturated with hexane to give a solid which was crystallised from methylene chloride-hexane to afford **2h** (2.9 g), m.p. 131-33°; PMR ($CDCl_3$): δ 1.03 (*s*, 6H, 2 × CH_3), 2.21 (*s*, 2H, C_6-H_2), 2.31 (*s*, 2H, C_8-H_2), 3.52 (*s*, 2H, C_4-H_2), 7.22-7.56 (*m*, 8H, Ar-*H*), 6.96-7.16 (*m*, 2H, Ar-*H*).

Ketone **1d** (0.7 g) and phenylhydrazine (0.35 g) were warmed in ethanol (3 ml). The solution was left at 28° for 24 hr and made acidic with 3*N* hydrochloric acid. The solid product was crystallised from ether-hexane to give **2i** (0.8 g), m.p. 156-60° (Found: C, 80.0; H, 7.2; N, 8.3. $C_{23}H_{24}N_2O$ requires C, 80.2; H, 7.0; N, 8.1%); M^+ at *m/z* 344; PMR ($CDCl_3$): δ 0.96 (*s*, 3H, CH_3), 1.08 (*s*, 3H, CH_3), 1.12 (*d*, *J* = 7 Hz, 3H, C_4-CH_3), 1.99 (*d*, *J* = 17 Hz, C_8-H), 2.19 (*d*, *J* = 16 Hz, C_6-H), 2.41 (*d*, *J* = 16 Hz, C − H), 2.52 (*d*, *J* = 17 Hz, C_8-H), 4.44 (*q*, *J* = 7 Hz, 1H, C_4-H), 7.22-7.56 (*m*, 8H, Ar-*H*), 7.78-8.04 (*m*, 2H, Ar-*H*).

Ketone **1b** (2.00 g) and 4-nitrophenylhydrazine (1.5 g) were heated under reflux for 20 hr and cooled. The precipitate was filtered off and the filtrate concentrated to remove a further crop. The final mother liquor deposited crystals which were recrystallized from ethanol to give **2j** (1 g), m.p. 108-10° (Found: C, 65.3; H, 6.3; N, 13.1. $C_{17}H_{19}N_3O_3$ requires C, 65.2; H, 6.1; N, 13.4%); M^+ at *m/z* 313; PMR ($CDCl_3$): δ 1.03 (*s*, 6H, 2 × CH_3), 2.08 (*s*, 3H, C_3-CH_3), 2.30 (*s*, 4H, C_6-H_2 and C_8-H_2), 3.00 (*s*, 2H, C_4-H_2), 7.47 (*m*, 2H, C_2-H and C_6-H), 8.27 (*m*, 2H, $C_{3'}-H$ and $C_{5'}-H$).

The ethanol-insoluble precipitate was **3** (1 g), m.p. 295-98° (Found: C, 64.7; H, 6.3; N, 13.8. $C_{34}H_{38}N_6O_6$ requires C, 65.2; H, 6.1; N, 13.4%); $(M^+ - 1)$ at *m/z* 625; PMR (DMSO-$CDCl_3$): δ 5.1, 5.4 (2*s*, together 1H, C_4-H), 6.38 (*m*, $C_{2'''}-H$ and $C_{6'''}-H$), 6.43 (*s*, 1H, $C_{3'''}-H$), 7.50-7.77 (*m*, 2H, Ar-*H*), 7.95-8.35 (*m*, 4H, Ar-*H*), 10.02, 10.04 (2*s*, together 1H, NH).

Ketone **1b** (1 g) in ethanol (10 ml) was added to a warm solution of 2,4-dinitrophenylhydrazine (1 g) in ethanol (50 ml) containing conc. hydrochloric acid (2 ml). After 16 hr at 28°, the red crystalline precipitate was filtered and washed with ethanol, yield 0.7 g. Recrystallisation from methylene chloride-methanol gave **4c** (0.5g), m.p. 270-72° (d) (Found: C, 50.9; H, 4.1; N, 20.2. $C_{23}H_{22}N_8O_8$ requires C, 51.3; H, 4.1; N, 20.8%); M^+ at *m/z* 538. The ethanol mother liquor from the above reaction slowly deposited a light orange solid which recrystallized from methylene chloride-ether to give **4b**; yield 0.7 g, m.p. 210-12° (Found: C, 57.3; H, 5.4; N, 15.7. $C_{17}H_{18}N_4O_5$ requires C, 57.0; H, 5.1; N, 15.6%); M^+ at *m/z* 358; PMR ($CDCl_3$): δ 1.07, 1.11 (2*s*, each 3H, 2 × CH_3), 2.12 (*s*, 3H, C_2-CH_3), 2.29 (*d*, *J* = 16 Hz, 1H, C_7-H), 2.36 (*s*, 2H, C_5-H_2), 2.64 (*d*, *J* = 16 Hz, 1H, C_7-H), 6.33 (*d*, *J* = 9 Hz, C_6-H), 6.40 (*s*, 1H, C_3-H), 8.32 (*d* × *d*, *J* = 9, 3 Hz, C_5-H), 9.15 (*d*, *J* = 3 Hz, $C_{3'}-H$), 10.12 (*s*, 1H, NH). Treatment of ketone **4b** with 2,4-dinitrophenylhydrazine gave **4c**, m.p. and m.m.p. 270-72°.

This compound was different from the isomeric dinitrophenylhydrazone (**5b**) of furan **5a** which was made as follows: Ketone **1b** (1 g), ethanol (10ml) and conc. sulphuric acid (3drops) were heated under reflux for 22 hr. The solution was evaporated and the residue chromatographed over silica gel (50 g) using methylene chloride-hexane (3 : 1) as eluant. Furan **5a** was obtained in the first two fractions as a gum which slowly solidified, yield 0.8 g, m.p. 67-69°, M^+ at *m/z* 178; PMR ($CDCl_3$): δ 1.10 (*s*, 6H, 2 × CH_3), 2.10 (*s*, 3H, C_2-CH_3), 2.13 (*s*, 2H, C_5-H_2), 2.65 (*s*, 2H, C_7-H_2), 6.20 (*s*, 1H, C_3-H); gave a dinitrophenylhydrazone (**5b**) m.p. 212-14°; m.m.p. with **4b** was depressed (Found: C, 56.9; H, 5.3; N, 15.3. $C_{17}H_{18}N_4O_5$ requires C, 57.0; H, 5.1; N, 15.6%).

2-Phenacylcyclohexanone **6a** (1 g) in ethanol (10 ml) was added to a warm solution of 2,4-dinitrophenylhydrazine (0.95 g) in ethanol (150 ml) and conc. hydrochloric acid (2 ml). After 72 hr at 28°, the red precipitate was filtered and recrystallized from methylene chloride-ether to give the bis-2,4-dinitrophenylhydrazone (**6b**) as orange crystals, yield 0.1 g, m.p. 250-53° (Found: C, 54.7; H, 4.3; N, 19.5. $C_{26}H_{24}N_8O_8$ requires C, 54.2; H, 4.2; N, 19.4%).

Oximation studies on 4,6,7,8-*tetrahydro*-5(1*H*)-*cinnolinones*

Cinnolinone **2a** (7.0 g) and hydroxylamine hydrochloride (3.8 g) were heated in pyridine (30 ml) on a water-bath for 16 hr. The resultant solution was diluted with water and the solid filtered and recrystallized from ethanol to give the oxime **7a** (6.9 g), m.p. 261-62° (Found: C, 71.7; H, 6.8; N, 15.4. $C_{16}H_{17}N_3O$ requires C, 71.9; H, 6.4; N, 15.7%); M^+ at *m/z* 267; PMR (DMSO-d_6 + $CDCl_3$): δ 1.07 (*s*, 6H, 2 × CH_3), 2.67 (*s*, 2H, C_6-H_2), 3.05 (*s*, 2H, C_8-H_2), 7.35-7.70 (*m*, 3H, Ar-*H*), 7.90-8.20 (*m*, 2H, Ar-*H*), 8.28 (*s*, 1H, C_4-H), 11.92 (*s*, 1H, NOH). The same oxime was obtained in 15-50% yield when the cinnolines **2b-2d** were treated with hydroxylamine in a similar way. The product was isolated by extraction of the diluted

pyridine solution with ether, evaporation and crystallization of the residue from ethanol.

When **7a** was treated with *p*-toluenesulphonyl chloride in pyridine at 28° for 16 hr, it formed the O-tosyl derivative, m.p. 158-59° (Found: C, 65.5; H, 6.0; N, 10.1. $C_{23}H_{23}N_3O_3$ requires C, 65.5; H, 5.5; N, 10.0%); PMR ($CDCl_3$): δ 1.05 (*s*, 6H, 2 × CH_3), 2.45 (*s*, 3H, Ar-CH_3), 2.73 (*s*, 2H, C_6-H_2), 3.10 (*s*, 2H, C_8-H_2), 7.35-8.15 (*m*, 9H, Ar-*H*), 8.15 (*s*, 1H, C_4-H).

Ketone **2a** (0.5 g), methoxylamine.HCl (0.35 g) and pyridine were heated at 100° overnight. The solution was poured into water and the product filtered and crystallized from ethanol to give the methoxime (0.4 g), m.p. 140-44° (Found: C, 72.4; H, 7.0; N, 14.9. $C_{17}H_{19}N_3O$ requires C, 72.6; H, 6.8; N, 14.9%); PMR ($CDCl_3$): δ 1.03 (*s*, 6H, 2 × CH_3), 2.55 (*s*, 2H, C_5-H_2), 3.02 (*s*, 2H, C_7-H_2), 4.03 (*s*, 3H, OCH_3), 7.30-7.65 (*m*, 3H, Ar-*H*), 7.95-8.20 (*m*, 2H, Ar-*H*), 8.25 (*s*, 1H, C_4-H).

Ketone **2e** (16.0 g) and hydroxylamine hydrochloride (12.0 g) when heated in pyridine (50 ml) at 100° for 16 hr gave the oxime **7b** (16 g), m.p. 260-61° (from methanol) (Found: C, 64.5; H, 7.6; N, 20.6. $C_{11}H_{15}N_3O$ requires C, 64.4; H, 7.4; N, 20.5%); PMR (DMSO-d_6 + $CDCl_3$): δ 1.00 (*s*, 6H, 2 × CH_3), 2.57 (*s*, 2H, C_4-H_2), 2.61 (*s*, 3H, C_3-CH_3), 2.94 (*s*, 2H, C_8-H_2), 7.72 (*s*, 1H, C_4-H), 11.85 (*s*, 1H, NOH).

Similarly **1c** gave the oxime **7c**, m.p. 280-82° (from methanol) (Found: C, 70.1; H, 5.6; N, 17.6;. $C_{14}H_{13}N_3O$ requires C, 70.3; H, 5.5; N, 17.6%); PMR (DMSO): δ 7.35-7.70 (*m*, 3H, Ar-*H*), 7.85-8.20 (*m*, 2H, Ar-*H*), 8.25 (*s*, 1H, C_4-H), 11.97 (*s*, 1H, NOH).

Ketoacid **13**[22] (2.55 g) was mixed with hydrazine hydrate (1 g) when an exothermic reaction took place. The mixture was diluted with ethanol (20ml), brought to reflux on a water-bath and set aside for ½ hr. The solution was concentrated to a small volume and treated with alcoholic HCl, when excess hydrazine separated out as hydrochloride, m.p. 207° (d). It was filtered off and the filtrate diluted with ether to give the oxocinnoline hydrochloride (**2k**, HCl) as a yellow oil (2 g). This salt was heated with hydroxylamine hydrochloride (1 g) and pyridine (10 ml) for 6 hr on a steam-bath. After removal of pyridine *in vacuo*, ice was added to give the oxime **14** (0.5 g), m.p. 243-45° (d) (from benzene-ethanol) (Found: C, 66.1; H, 8.0; N, 19.0. $C_{12}H_{17}N_3O$ requires C, 65.7; H, 7.8; N, 19.2%); PMR ($CDCl_3$ + DMSO-d_6): δ 1.03 (*s*, 6H, 2 × CH_3), 2.57 (*s*, 3H, C_3-CH_3), 2.70 (*s*, 3H, C_4-CH_3), 2.70 (*s*, 2H, C_6-H_2), 2.93 (*s*, 2H, C_8-H_2), 10.85 (*s*, 1H, NOH).

Keto acid **13** (2.55 g) was treated with hydrazine hydrate (1 g) and left in ethanol (5 ml) at 28° for 16 hr. More ethanol (50 ml) and sulphuric acid (2 ml) were added and the solution again was left at 28° for 48 hr. The separated hydrazine sulphate was filtered off and the filtrate evaporated. The residue was treated with sodium bicarbonate and extracted with ether to give **2l** as an oil (2 g). It was heated with hydroxylamine hydrochloride (1.5 g) in pyridine (5 ml) at 100° for 16 hr to give 4,5,7,8-tetrahydro- 3,8,8-trimethyl 5-oxo-9*H*-pyrido[4,3,2-*de*]cinnoline-6-oxide (**15**) (0.75 g) (from ethanol); m.p. 285° (d) (Found: C, 64.0; H, 6.2; N, 17.1. $C_{13}H_{15}N_3O_2$ requires C, 63.7; H, 6.2; N, 17.1%); $M^{+\cdot}$ at *m/z* 245; PMR (CF_3CO_2H): δ 1.40 (*s*, 6H, 2 × CH_3), 2.90 (*s*, 3H, C_3-CH_3), 3.35 (*s*, 2H, C_6-H_2), 3.53 (*s*, 2H, C_8-H_2), 7.40 (*s*, 1H, =CH).

Oximation of 4,6,7,8-*tetrahydro*-1,7,7-*trimethyl*-3-*phenyl*-5(1*H*)-*cinnolinone*

Ketone **2g** (2.7 g), hydroxylamine hydrochloride (0.75 g) and pyridine (25ml) were heated under reflux for 22 hr. The solvent was evaporated and the residual blackish gum washed with water. The aqueous washing was extracted with ether and the water layer evaporated to dryness. The residue was crystallised from ethanol-ether to give **9** (0.5 g), m.p. 239-40° (Found: C, 57.4; 57.4; H, 6.7; 6.6; N, 11.3; Cl, 13.3, 13.0. $C_{17}H_{20}ClN_3O.2H_2O$ requires C, 57.6; H, 6.8; N, 11.9; Cl, 10.0%); $M^{+\cdot}$ at *m/z* 281 (for betaine); PMR (DMSO-d_6): δ 1.10 (*s*, 6H, 2 × CH_3), 2.53 (*s*, 2H, C_6-H_2), 2.67 (*s*, 2H, C_8-H_2), 4.63 (*s*, 3H, $N-CH_3$), 7.45-7.80 (*m*, 3H, Ar-*H*), 7.85-8.35 (*m*, 2H, Ar-*H*), 8.93 (*s*, 1H, C_4-H), 12.70 (*s*, 1H, NOH). The water-insoluble gum was triturated with ethanol to give the oxime **7a** (0.6 g), m.p. and m.m.p. 250°. Ketone **16** was present in the mother liquor as revealed by TLC and mass spectrometry. When the reaction between the ketone **2g** (0.8 g) and hydroxylamine hydrochloride (0.7 g) in pyridine (5 ml) was carried out on a steam-bath for 16 hr and the reaction mixture worked-up (evaporation and trituration with water), a gum was obtained which became crystalline with ether to afford the oxime **7a** (0.5 g), m.p. 253° (d).

Oximation of 4,6,7,8-*tetrahydro*-7,7-*dimethyl*-1,3-*diphenyl*-5(1*H*)-*cinnolinone*

A mixture of ketone **2h** (2.8 g), hydroxylamine hydrochloride (2 g) and pyridine (15 ml) was heated at 90° for 18 hr and the solvent removed. The residual gum was washed with a little water and then extracted with ether. The ether-insoluble residue (0.85 g) was recrystallised from methanol-ether to give **10a**, m.p. 261-63° (Found: C, 69.0; H, 6.3; N, 11.2; Cl, 11.2. $C_{22}H_{22}ClN_3O$ requires C, 69.6; H, 5.8; N, 11.2; Cl, 9.3%); $M^{+\cdot}$ at *m/z* 343 (for betaine); PMR (DMSO-d_6): δ 1.0 (*s*, 6H, 2 × CH_3), 2.71 (*s*, 2H, C_6-H_2), 2.95 (*s*, 2H, C_8-H_2), 7.53-7.73 (*m*, 34, Ar-*H*), 7.81 (*s*, 5H, NC_6H_5), 8.00-8.27 (*m*, 2H, Ar-*H*), 9.30 (*s*, 1H, C_4-H), 12.95, (*s*, 1H, NOH). The chloride could be exchanged with iodide ion to provide the quaternary

iodide **10b**, m.p. 257-59° (from methanol-ether) (Found: C, 56.0; H, 5.0; N, 9.3. $C_{22}H_{22}IN_3O$ requires C, 56.1; H, 4.7; N, 8.9%); $M^{+\cdot}$ at *m/z* 343 (for beatine); PMR (DMSO-d_6): δ 1.00 (*s*, 6H, $2\times CH_3$), 2.72 (*s*, 2H, C_6-H_2), 2.96 (*s*, 2H, C_8-H_2), 7.53-7.76 (*m*, 3H, Ar-*H*), (*s*, 5H, NC_6H_5), 8.00-8.27 (*m*, 2H, Ar-*H*), 9.20 (*s*, 1H, C_4-H), 12.95 (*s*, 1H, NOH).

The ether-soluble part from the oximation was chromatographed over silica gel., elution of the column being done with chloroform. Approximately 25 ml fractions were collected. Fractions 1-4 eluted a yellow band from which **11** (50 mg) was obtained; m.p. 208-10° (from methylene chloride-hexane) (Found: C, 79.2; H, 6.9; N, 9.6. $C_{28}H_{27}N_3O$ requires C, 79.8; H, 6.5; N, 10.0%); $M^{+\cdot}$ at *m/z* 421; PMR (DMSO-d_6): δ 0.84, 0.89 (2*s*, 6H, $2\times CH_3$), 1.63 (*d*, $J=18$ Hz, C_8-H), 2.00 (*d*, $J=18$ Hz, C_8-H), 2.36 (*s*, 2.36 (*s*, 2H, C_6-H_2), 5.55 (*s*, 1H, C_4-H), 7.09-7.56 (*m*, 13H, Ar-*H*), 7.76-7.95 (*m*, 2H, Ar-*H*), 10.65 (*s*, 1H, NOH).

Fractions 5-10 were found by TLC to be a mixture of the above, ketone **16** and alcohol **12**. The last compound was obtained from fraction-12 by evaporation and trituration with ethanol ether; yield 10 mg; m.p. 216-18° (Found: C, 70.8; H, 7.1; N, 10.0. $C_{16}H_{18}N_2O_2$ requires C, 71.1; H, 6.7; N, 10.4%); M^+ at *m/z* 270; PMR (DMSO-d_6): δ 1.03 (*s*, 6H, $2\times CH_3$), 2.16 (*s*, 2H, C_6-H_2), 2.55 (*s*, 2H, C_8-H_2), 6.91 (*s*, 1H, C_4-H), 7.11-7.51 (*m*, 3H, Ar-*H*), 7.53-7.77 (*m*, 2H, Ar-*H*), 10.09 (broad *s*, 1H, OH), 11.11 (broad *s*, 1H, NH).

Fraction 13 gave a gummy solid becoming crystalline with ethanol, m.p. 224°. It was probably the betaine of **10a**; $M^{+\cdot}$ at *m/z* 343; PMR (DMSO-d_6): δ 1.00 (*s*, 6H, $2\times CH_3$), 2.72 (*s*, 2H, C_6-H_2), 2.95 (*s*, 2H, C_8-H_2), 7.27-7.63 (*m*, 3H, Ar-*H*), 7.95-8.30 (*m*, 2H, Ar-*H*), 7.82 (*s*, 5H, $N-C_6H_5$), 9.22 (*s*, 1H, C_4-H).

7,8-Dihydro-7,7-dimethyl-3-phenyl-5-6(H)-cinnolinone (**16**)

(a) Tetrahydroketone **2a** (0.5 g) was heated in pyridine (5 ml) on a water-bath for 16 hr and the solution diluted with water. The precipitate was filtered and recrystallised from methanol to give the starting material (0.4 g). The mother liquor was evaporated and the residue dissolved in ether. The ether solution first deposited crystals of **2a**, and then a yellow solid. The latter was recrystallised from ethanol to give **16** (50 mg), m.p. 121-23° (Found: C, 76.5; H, 6.5; N, 11.3. $C_{16}H_{16}N_2O$ requires C, 76.1; H, 6.4; N, 11.1%); $M^{+\cdot}$ at *m/z* 252; IR (nujol): νC=O at 1690 cm^{-1}; PMR ($CDCl_3$): δ 1.15 (*s*, 6H, $2\times CH_3$), 2.63 (*s*, 2H, C_6-H_2), 3.30 (*s*, 2H, C_8-H_2), 7.35-7.65 (*m*, 3H, Ar-*H*), 8.03-8.25 (*m*, 2H, Ar-*H*), 8.22 (*s*, 1H, C_4-H).

(b) The above ketone was obtained in 30% yield by heating **2a** (1.3 g) with methanesulphonyl chloride (0.6 g) in pyridine (10 ml) on a water-bath for 16 hr. A much better yield (75%) was obtained by conducting the reaction with *p*-toluenesulphonyl chloride. In both cases, the reaction mixture was worked-up by evaporation of pyridine, addition of water and extraction of the product with ether.

(c) Hydrolysis of the oxime **7a** with acid provided another route to **16**. Thus, oxime **7a** (1 g), 10% sulphuric acid (20 ml) and dioxane (10 ml) were heated under reflux for 16 hr. The solvent was removed and the aqueous solution made ammoniacal. The precipitate was filtered and crystallized from ethanol to give the starting material **7a** (0.4 g) m.p. 258-62°. The mother liquor was evaporated and the residue fractionally crystallized from ether to give the oxime **7a** as the less soluble part (0.2 g) and ketone **16** (0.1 g) m.p. 120-22° as the more soluble fraction.

3-Phenyl-5-hydroxy-7,7-dimethyl-5,6,7,8-tetrahydrocinnoline (**18**)

Ketone **16** (3.2 g) in methanol (30 ml) was treated with sodium borohydride (1 g) in portions. After 1 hr, solvent was removed and the residue treated with water. The resultant solid (3 g, m.p. 174-77°) was filtered and crystallised from ethanol-ether to give **18**, m.p. 181-82° (Found: C, 75.4; H, 7.4; N, 11.0. $C_{16}H_{18}N_2O$ requires C, 75.6; H, 7.1; N, 11.0%); $M^{+\cdot}$ at *m/z* 254; IR (nujol): νOH at 3180 cm^{-1}; PMR ($CDCl_3$ + DMSO-d_6): δ 1.0 (*s*, 3H, CH_3); 1.20-2.35 (*m*, 2H, C_6-H_2), 2.95 (*s*, 2H, C_8-H_2), 4.85 (*m*, 1H, C_5-H), 5.40 (*brs*, 1H, OH); 7.25-7.60 (*m*, 3H, Ar-*H*), 7.85-8.20 (*m*, 2H, Ar-*H*), 8.15 (*s*, 1H, C_4-H).

It was also obtained by heating ketone **2a** (0.8 g) in dioxane (10 ml) and 3*N* hydrochloric acid (25 ml) under reflux for 4 hr. The solution was cooled and made alkaline. The gummy precipitate was recrystallised from ether to afford **18** (0.5 g), m.p. 177-80° identical with the above sample.

PPA rearrangement of the oximes **7**

The oxime **7a** (5 g) was heated with polyphosphoric acid (50 g) at 150° for 5 hr. The mixture was treated with ice and made ammoniacal. The product was filtered and recrystallized from ethanol to give the aminocinnoline **19a** (3.3 g), m.p. 209-11° (Found: C, 76.9; H, 6.2; N, 17.1. $C_{16}H_{15}N_3$ requires C, 77.1; H, 6.1; N, 16.9%); $M^{+\cdot}$ at *m/z* 249; IR (nujol): νNH_2 3230, 3330 cm^{-1}; PMR ($CDCl_3$ + DMSO-d_6): δ 2.33 (*s*, 3H, CH_3), 2.47 (*s*, 3H, CH_3), 5.55 (*br s*, 2H, NH_2), 7.35-7.85 (*m*, 3H, Ar-*H*), 8.22-8.60 (*m*, 2H, Ar-*H*), 8.87 (*s*, 1H, C_4-H), 7.60 (*s*, 1H, C_8-H).

Compound **19a** was also obtained in 45% yield when a mixture of $POCl_3$ and pyridine was used instead of PPA and in quantitative yield by heating with 6 parts of conc. sulphuric acid at 120° for 10 min.

The oxime **7b** (18 g) was heated with PPA (180 g) to afford the aminocinnoline **19b** (16.5 g), m.p. 235-36° (Found: C, 70.4; H, 7.0; N, 22.6. $C_{11}H_{13}N_3$ requires C, 70.6; H, 7.0; N, 22.4%) [HCl salt: m.p. 268-71° (from methanol-ether)]; PMR (DMSO-d_6): δ 2.22 (*s*, 3H, CH_3), 2.43 (*s*, 3H, CH_3), 2.83 (*s*, 3H, C_3-CH_3), 4.60 (*br s*, NH_2), 7.50 (*s*, 1H, C_8-H), 8.13 (*s*, 1H, C_4-H).

The oxime **7c** (6 g) when treated with PPA (75 g) gave the aminocinnoline **19c** (2.7 g), m.p. 219-21° (from ethanol) (Found: C, 75.6; H, 5.3; N, 18.6. $C_{14}H_{11}N_3$ requires C, 76.0; H, 5.0; N, 19.0%); PMR (DMSO): δ 7.00 (*q*, 1H, C_6-H), 7.35-7.90 (*m*, 3H, Ar-*H*), 8.50-8.70 (*m*, 2H, Ar-*H*), 8.95 (*s*, 1H, C_4-H).

The oxime **14** likewise gave **19d** in 65% yield (from ethanol-ether), m.p. 206-7° (Found: C, 71.9; H, 7.8; N, 21.0. $C_{12}H_{15}N_3$ requires C, 71.6; H, 7.5; N, 20.9%); PMR ($CDCl_3$ + DMSO-d_6): δ 2.13 (*s*, 3H, C_6-CH_3), 2.39 (*s*, 3H, C_7-CH_3), 2.72 (*s*, 6H, C_3- and C_4-CH_3).

Compound **15** (1.4 g) was heated with PPA (20 g) for 7 hr at 130-140°. The mixture was cooled and treated with ice and excess ammonia. The green coloured product (**20**) was filtered off, yield 1.2 g, m.p. >300°. A sample was crystallized from aq. DMSO, m.p. >300° (Found: C, 64.4; H, 6.7; N, 17.4. $C_{13}H_{15}N_3O_2$ requires C, 63.7; H, 6.2; N, 17.1%); M^+ at *m/z* 227; IR (nujol): νNH_2 and νOH at 3440 and 3300 cm^{-1} respectively; νCO 1670 cm^{-1}; UV (MeOH): λ_{max} at 284 (sh), 294, 320 and 410 nm; UV (1*N* HCl): 274 (sh), 286, 312 (sh), 324 (sh), 336 (sh) and 454 nm; PMR (DMSO-d_6): 2.08, 2.10, 2.26 (3*s*, each 3H, 3 × CH_3), 5.45 (*s*, 2H, CH_2), 6.4 (*s*, 1H, =CH), 10.0 [*br s*, NH_2 (7)], 11.55-11.82 [*br s*, CO_2H (7)].

Chloroacetyl and pyrrolidinoacetyl derivatives of the amine **19b**

The amine **19b** (2.8 g) was dissolved in chloroform (150 ml) and THF (50 ml). The solution was mixed with sodium bicarbonate (2.5 g) in water (25 ml) and treated under stirring with chloroacetyl chloride (1.7 g) in chloroform (5 ml). After 4 hr, the chloroform layer was separated, washed with water, dried and evaporated. The residue was triturated with hexane and crystallized from chloroform-ether to give the chloroacetyl derivative **25a** (2.6 g), m.p. 265° (d) (Found: C, 58.8; H, 5.6; N, 15.8. $C_{13}H_{14}ClN_3O$ requires C, 59.2; H, 5.4; N, 15.9%).

The above chloroacetyl derivatives (2.5 g) was mixed with pyrrolidine (5 ml) when an exothermic reaction occurred. After further heating on a water-bath for 4 hr, the reaction mixture was treated with water and the product extracted with chloroform. Evaporation of the chloroform layer gave **25b** (2.2 g), m.p. 186-88°. (from ethanol-ether) (Found: C, 68.6; H, 7.5; N, 18.5. $C_{17}H_{22}N_4O$ requires C, 68.4; H, 7.4; N, 18.8%).

5-(N-Dichloroacetyl amino-6,7-dimethyl-3-phenyl-cinnoline (**26**)

The amine **19a** (4.2 g) was treated with dichloroacetyl chloride (2.5 g) as described above to give the dichloroacetyl derivative (**26**; 1.5 g), m.p. 224-26° (from acetone-ether) (Found: C, 60.4; H, 4.3; N, 11.9. $C_{18}H_{15}Cl_2N_3O$ requires C, 60.0; H, 4.2; N, 11.7%).

Deamination of 5-amino-3-phenyl-cinnoline (**19c**)

The aminocinnoline **19c** (1.1 g) was dissolved in conc. hydrochloric acid (3 ml) and water (10 ml) and the solution diazotised at 0° by treating with sodium nitrite (0.4 g) in water (3 ml). Hypophosphorous acid (10 ml) was then added at 0° and the mixture stirred for 1 hr at this temperature and at 28° for 16 hr. It was then filtered and the filtrate made ammoniacal. The greenish precipitate was filtered off and recrystallized from methanol to give 3-phenylcinnoline (0.1 g), m.p. 121-23°, undepressed by admixture with a sample obtained by decarboxylation of 3-phenyl-cinnoline-4-carboxylic acid[7] (Found: C, 81.3; H, 5.0; N, 13.6. $C_{14}H_{10}N_2$ requires C, 81.5; H, 4.9; N, 13.6%); PMR ($CDCl_3$): δ 7.20-8.67 (*m*, 9H, Ar-*H*), 8.05 (*s*, 1H, C_4-H).

Diazotisation of 5-amino-3,6,7-trimethyl-cinnoline (**19b**)

The aminocinnoline **19b** (1.1 g) was dissolved in boiling methanol (40 ml) containing benzene (10 ml). To the hot solution was added conc. sulphuric acid (1.2 g) followed by solid sodium nitrite (0.7 g) in small protions. The mixture was then heated under reflux for 4hr and cooled. The precipitated salts were filtered off. The filtrate was concentrated and diluted with water. The clear solution was made ammoniacal when the pyrazolocinnoline **22** separated out. It was filtered and recrystallised from DMF: yield; 0.8 g, m.p. >300° (Found: C, 66.7; H, 5.2; N, 28.4. $C_{11}H_{10}N_4$ requires C, 66.7; H, 5.1; N, 28.3%); M^+ at *m/z* 198; PMR (CF_3CO_2H): δ 3.0 (*s*, 3H, C_4-CH_3), 3.27 (*s*, 3H, C_8-CH_3), 7.97 (*s*, 1H, C_5-H), 9.58 (*s*, 1H, C_3- and C_9-H).

Schmidt reaction on ketone **16**

To a solution of the ketone **16** (1.2 g) in conc. sulphuric acid (5 ml) was added sodium azide (1 g) in small portions with cooling. After 2 hr, ice and excess ammonia were added. The precipitate was filtered and crystallized from ethanol to afford the aminocinnoline **19a** (0.9 g), m.p. and m.m.p. with an authentic sample, 206-8°.

Acid-catalyzed reactions of the oxime **7a**

(a) With phosphorous pentachloride

The oxime **7a** (1.3 g) was dissolved in THF (30 ml)

and chloroform (50 ml) and left with phosphorous pentachloride (2.1 g) at 0° for 4 hr and then at 28° for 16 hr. The solvents were removed *in vacuo* and the residue was treated with ice and ammonia and extracted with ether. The ether layer was evaporated to give a residue (1.5 g) from which again by extraction with ether and concentration, the pyridazino-azepinone **30** (0.15 g) was obtained. It was crystallised from ethanol; m.p. 230-31° (Found: C, 72.0; H, 6.7; N, 15.9. $C_{16}H_{17}N_3O$ requires C, 71.9; H, 6.4; N, 15.7%); $M^{+\cdot}$ at *m/z* 267; PMR ($CDCl_3$): δ 1.27 (*s*, 6H, 2 × CH_3), 2.30 (*s*, 2H, C_6-H_2), 3.13 (*s*, 2H, C_8-H_2), 7.25-7.55 (*m*, 3H, Ar-*H*), 7.67 (*s*, 1H, C_4-H); 7.85-8.25 (*m*, 2H, Ar-*H*), 10.0 (*s*, 1H, NH).

(*b*) *With formic acid*

The oxime **7a** (2 g) and 80% formic acid (40 ml) were heated under reflux for 6 hr. Removal of excess acid followed by addition of ice and ammonia gave a gummy product which became crystalline with ether. It was filtered and recrystallized from ethanol to give **2a** (0.5 g), m.p. and m.m.p. 239°; $M^{+\cdot}$ at *m/z* 254. The etheral filtrate was evaporated and the residue left in ethanol to give yellow crystals of the ketone **16** (0.1 g), m.p. and m.m.p. with an authentic sample, 118-20°. The mother liquor was evaporated and the residue left in ether-hexane to give a crop which on re-crystallization from hexane afforded **32** (0.1 g), m.p. 98-100° (Found: C, 80.1; H, 7.5; N, 11.8. $C_{16}H_{18}N_2$ requires C, 80.6; H, 7.6; N, 11.8%); $M^{+\cdot}$ at *m/z* 238; PMR ($CDCl_3$): δ 1.0 (*s*, 6H, 2 × CH_3), 1.58 (*t*, J = 7 Hz, 2H, C_6-H_2), 2.82 (*t*, J = 7 Hz, 2H, C_5-H_2), 2.97 (*s*, 2H, C_8-H_2), 7.25-7.60 (*m*, 3H, Ar-*H*), 7.45 (*s*, 1H, C_4-H), 7.90-8.20 (*m*, 2H, Ar-*H*).

The mother liquor from the above crystallisation was evaporated and the residue chromatographed over silica gel (15 g) using benzene-chloroform (1:3) as eluant. Fractions of about 25 ml were collected. The first two fractions gave the ketone **16**. Fractions 3 and 4 gave a mixture of **16** and **32**. Fractions 7 and 8 on evaporation gave the formamide **33** (0.15 g) which was crystallised from benzene, m.p. 176-78° (Found: C, 73.0; H, 7.10. $C_{17}H_{19}N_3O$ requires C, 72.6; H, 6.8%); $M^{+\cdot}$ at *m/z* 281; PMR ($CDCl_3$): δ 0.93 (*s*, 3H, CH_3), 1.08 (*s*, 3H, CH_3), 1.20-2.15 (*m*, 2H, C_6-H_2), 2.17 (*br s*, 2H, C_8-H_2), 5.30 (*m*, 1H, C_5-H), 7.25-7.55 (*m*, 4H, NH and Ar-*H*), 7.62 (*s*, 1H, C_4-H), 7.65-8.00 (*m*, 2H, Ar-*H*), 8.33 (*s*, 1H, CHO).

(*c*) *With 6N hydrochloric acid*

The oxime **7a** (1 g), 6*N* hydrochloric acid (20 ml) and dioxane (10 ml) were heated together under reflux for 7 hr. Dioxane was removed *in vacuo* and ammonia added to the residual solution. Extraction with chloroform and evaporation of solvent gave a gum which became crystalline with ether, yield 0.6 g, m.p. 155-65°; recrystallisation from ethanol gave slightly impure **34** (0.25 g), m.p. 167-69°. The reaction was then carried out with 4 times the quantity of reactants, extra hydroxylamine hydrochloride (3 g) being added. The total crude product (4 g), m.p. 110-40° was chromatographed over silica (60 g). Fractions of about 50 ml were collected. Initial elution was done with chloroform.

Seven fractions were combined and evaporated to give **34** (0.5 g), m.p. 170-72° (from ethanol) (Found: C, 67.3; H, 5.5; N, 10.0; Cl, 12.4. $C_{16}H_{15}ClN_2O$ requires C, 67.0; H, 5.3; N, 9.8; Cl, 12.4%); $M^{+\cdot}$ at *m/z* 286, 288; IR (nujol): νCO at 1720 cm^{-1}; PMR ($CDCl_3$): δ 1.22, 1.25 (2*s*, 6H, 2 × CH_3), 3.25 (*d*, J = 18 Hz, 1H, C_8-H), 3.63 (*d*, J = 18 Hz, 1H, C_8-H), 4.40 (*s*, 1H, C_6-H), 7.40-7.70 (*m*, 3H, Ar-*H*), 8.00-8.30 (*m*, 2H, Ar-*H*), 8.27 (*s*, 1H, C_4-H). Elution with chloroform—1% methanol (3 × 50 ml) gave a material (2 g) from which **36a** (0.75 g), m.p. 223° (d), was obtained by crystallisation from ethanol (Found: C, 69.8; H, 5.7; N, 13.4. $C_{32}H_{31}N_5O_4$ requires C, 69.9; H, 5.7; N, 12.8%); IR (nujol): νCO at 1720 cm^{-1}; PMR ($CDCl_3$ + DMSO-d_6): δ 1.12, 1.20, 1.30, 1.37 (4*s*, 3H each, 4 × CH_3), 3.08 (*br s*, 1H, OH), 3.38 (slightly *br s*, 4H, 2 × CH_3), 5.22 (*s*, 1H, CH − O), 7.25-7.80 (*m*, 2H, Ar-*H*), 7.85-8.30 (*m*, 2H, Ar-*H*), 8.42 (*s*, 1H, C_4'−H), 9.33 (*s*, 1H, C−H), 12.87 (*s*, 1H, NOH). Elution with chloroform—2% methanol (3 × 50 ml) gave a material (0.4 g) which on crystallisation from chloroform-methanol gave **36b** (~0.1 g), m.p. 218-20° (Found: C, 68.0; 68.0; 68.2; H, 6.7, 6.7, 6.7; N, 15.8; 15.6. $C_{32}H_{32}N_6O_4$ requires C, 68.1; H, 5.7; N, 14.9%).

The same chloroketone (**34**) was obtained in 15% yield when oxime **7a** (1.5 g) was heated under reflux for 4 hr with acetic acid saturated with HCl gas. The chloroketone was obtained in the more soluble fraction by fractional crystallization from methanol.

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