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Recent developments in the chemistry of perhydroindoles and perhydrocinnolines†

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Abstract. Recent synthetic routes to the tetrahydro, hexahydro and octahydro derivatives of indoles are reviewed. An interesting one is the formation of 3-amino-4-oxo-4,5,6,7-tetrahydroindoles in the reaction of 2-phenacyl cyclohexane-1,3-diones with 1,1-disubstituted hydrazines. Antifertility, CNS depressant and antiinflammatory activities have been encountered for perhydroindoles besides other biological activities. Hexahydrocinnolines are obtained from the reaction of 2-phenacyl (acetonyl) cyclohexanones and cyclohexane-1,3-diones with hydrazines, while octahydrocinnolines are formed from cyclohexanone-2-acetic acids and hydrazines in two steps. 5-oxo-5,6,7,8-hexahydrocinnolines and their oximes undergo anomalous and interesting aromatisation reactions. Some hexahydrocinnolines are CNS depressants while octahydrocinnolines are analgesics. More importantly, they are precursors for interesting azamorphinans.

Keywords. Perhydroindoles; perhydrocinnolines; antifertility; CNS depressants; analgesics; azamorphinans; aromatization; antiinflammatory activities.

1. Introduction

There is a growing volume of literature pertaining to heterocycles fused to a cyclohexane ring, much of this from the point of view of biological activity. An outstanding example is perhaps molindone, a 4-keto-4,5,6,7-tetrahydroindole (1) which is a neuroleptic and, in low doses, an anxiolytic (Rubin *et al* 1967). A variety of other biological activities have been also obtained for perhydroindoles (Nagarajan 1981; Nagarajan and Arya 1982). The isolation of mesembrine (2) from *Sceletium namaquense* (Jeffs 1981) and the incorporation of the octahydroindole ring system in the erythrina alkaloids (Dyke and Quessy 1981), hasubanan alkaloids (Inubushi and Ibuka 1977) and in the amaryllidaceae alkaloids (Fuganti 1975) have generated voluminous chemistry. Perhydroindazoles (3) have antiviral properties (Blatter and Lucas 1972), while reduced benzimidazoles (4) are reported to be antiinflammatory (Halpern 1969) (chart 1). Much interesting synthetic chemistry has emanated from the area of perhydroindoles as evidenced by the work of Weiss *et al* (1969) and of perhydrocinnolines (Kametani 1980). For several years, we had been engaged in exploring the potential of perhydroindoles and perhydrocinnolines as candidate drugs for diverse indications and were rewarded both in terms of biological activities as well as novel chemistry. In this article, we propose to summarise our work briefly, while simultaneously noting highlights of other contemporary contributions in this field.

2. Perhydroindoles

2.1 *Synthesis of* 4,5,6,7-*tetrahydroindoles*

2.1a *Knorr synthesis of pyrroles*: Extension of the Knorr synthesis of pyrroles from 1,4-diketones to the diones (6) affords easy access to compounds of type (8). Alkylation

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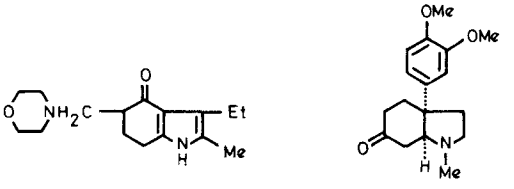
of enamine (5) with α-haloketones provides the starting materials, which are condensed with primary amines. An interesting extension is to N,N-disubstituted hydrazines, *e.g.* N-aminopiperidine which is condensed with (7) to lead to the formation of the novel tetrahydroindole (9). The synthesis is applicable for 2,3-trimethylene (10) and 2,3-pentamethylene pyrroles (11) as well (Nagarajan *et al* 1984; Bell *et al* 1970) (chart 2).

2.1b *From cyclohexanone enamines and α-bromoacetaldehyde*: (Zav'yalov and Skoblik 1976) (chart 3).

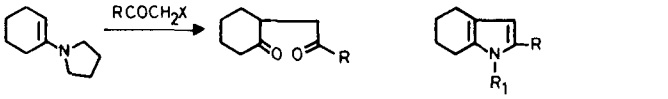
2.1c *From cyclohexanone enamine and oximes of α-haloketones*: (Nakanishi *et al* 1981) (chart 4).

2.1d *From cyclohexanone oxime and vinyl chloride*: (Trofimov *et al* 1981). A variation of this procedure uses ethylene (Trofimov *et al* 1978) (chart 5).

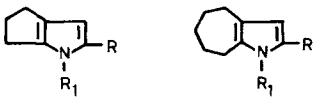


(1) (2) (3) (4)

(Chart 1)

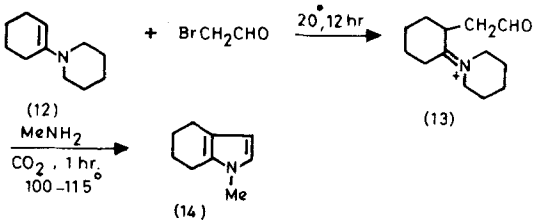


(5) (6) R = Alkyl, Aryl (8) R = R1 = alkyl, aryl etc.
(7) R = Ph (9) R = Ph, R1 = piperidino



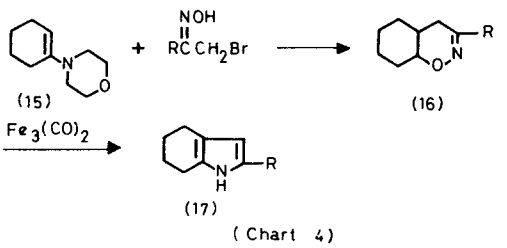
(10) (11)

(Chart 2)

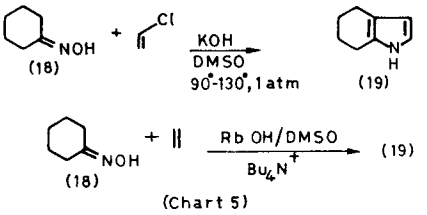


(12) (13) (14)

(Chart 3)



(Chart 4)



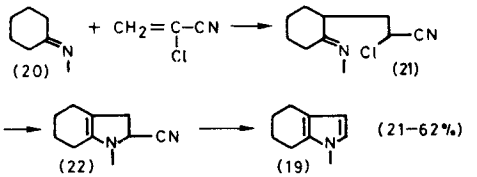
(Chart 5)

2.1e *From cyclohexanoneimines and α-chloroacrylonitrile*: (Olessen *et al* 1978) (chart 6).

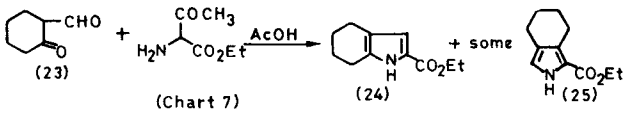
2.1f *From 2-formylcyclohexanone and ethyl α-aminoacetoacetate*: (Zav'yalov and Skoblik 1977). Regioselectivity in this condensation reaction has been discussed (chart 7).

2.1g *From cyclohexane-1,2-dione*: (Trost and Keinen 1980) (chart 8).

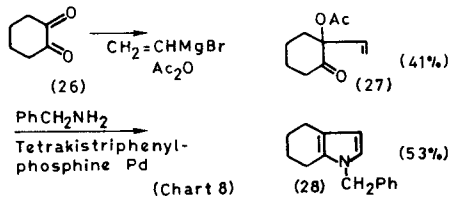
2.1h *From 4-oxo-4,5,6,7-tetrahydroindoles*: (Remers and Weiss 1972; Takagi *et al*



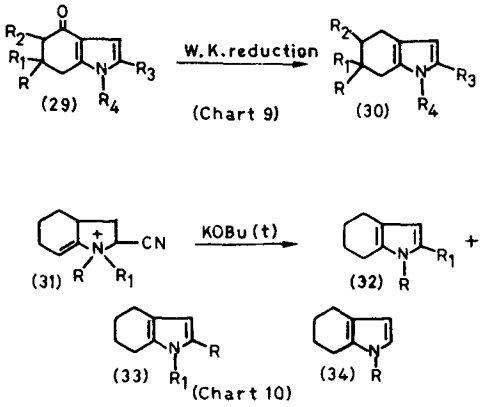
(Chart 6)



(Chart 7)



(Chart 8)



1973; Nagarajan *et al* 1984; Kost *et al* 1966) (chart 9). 4-oxo-4,5,6,7-tetrahydroindoles can be deoxygenated using Wolff-Kischner reaction or catalytic hydrogenation.

2.1i *From a hexahydroindole by Stevens rearrangement*: (Madsen and Lawesson 1976) (chart 10).

From a preparative point of view, route 2.1a may be considered to be most convenient and suitable and expected to provide a wide variety of 4,5,6,7-tetrahydroindoles.

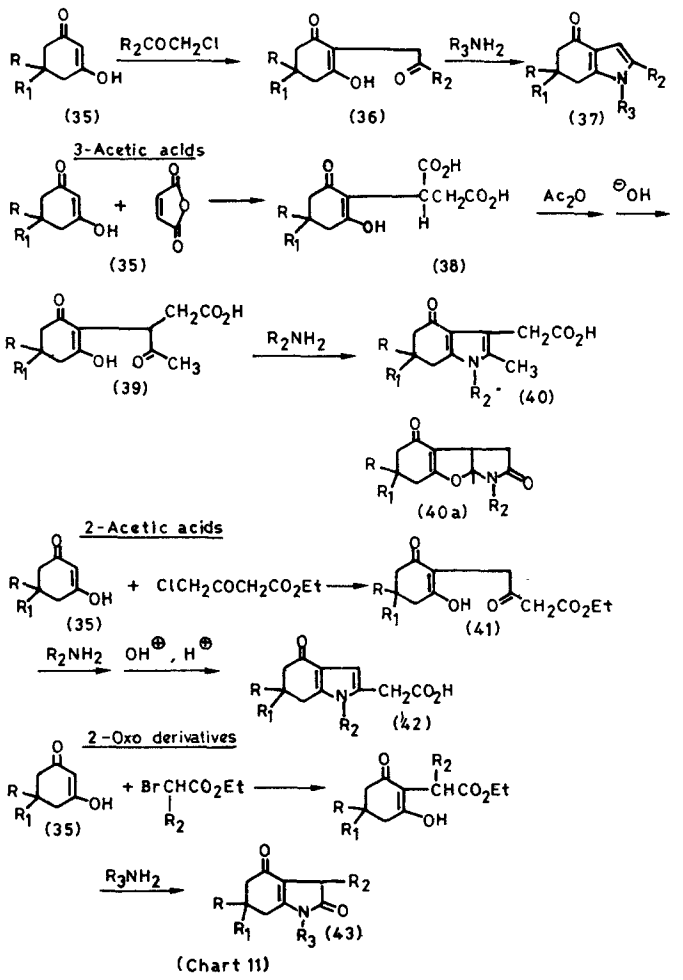
2.2 4-*oxo*-4,5,6,7-*tetrahydroindoles*

2.2a '*Knorr synthesis*': This procedure (Stetter and Siehnhold 1955; Stetter and Lanterbach 1962) is versatile and has been used by several groups of workers including our group (Nagarajan *et al* 1984; Remers and Weiss 1965; Ramadas *et al* 1978; Schoen and Finizio 1971) (chart 11). Yields are generally high.

The route has been extended to provide oxotetrahydroindoles (40) and (42) carrying acetic acid side chain at position 3 or 2 (Nagarajan 1981) and to 4-oxo-4,5,6,7-tetrahydrooxindoles (43) (Nagarajan and Shenoy unpublished) (chart 11). Along with (40), occasionally tricyclic products (40a) were isolated. The synthesis of acid (3a) from dimedone and maleic acid is reported (Schaeffer and Vince 1962).

2.2b *An unusual reaction of 2-phenacyl-dimedone formation of 2-aryl-3-amino-4-oxo-4,5,6,7-tetrahydroindoles*: In contrast to the reaction of 2-phenacyl cyclohexanone with 2-aminopiperidine to form 1-piperidino derivative (a), 2-phenacyl dimedone (44) behaves anomalously towards this reagent to form the 3-piperidinoindole (45) in good yield. The reaction is general for other 1,1-substituted hydrazines and 2-phenacyl dimedones carrying substituents on the 2-phenyl group, products analogous to (45) being formed in moderate to good yields (Nagarajan and Shah 1972). 2-Acetonyl dimedone however does not undergo this reaction. 2-Phenacylcyclohexane-1,3-dione and N-aminopiperidine form both types of products. The anomalous reaction is visualised to proceed as shown in chart 12.

In consonance with the proposed mechanism, 2-phenacyldimedone and N,N-dimethyl hydrazine undergo reaction in the presence of excess morpholine to afford the 3-morpholino derivative (51) as the major and the 3-dimethylamino compound (52) as



(Chart 11)

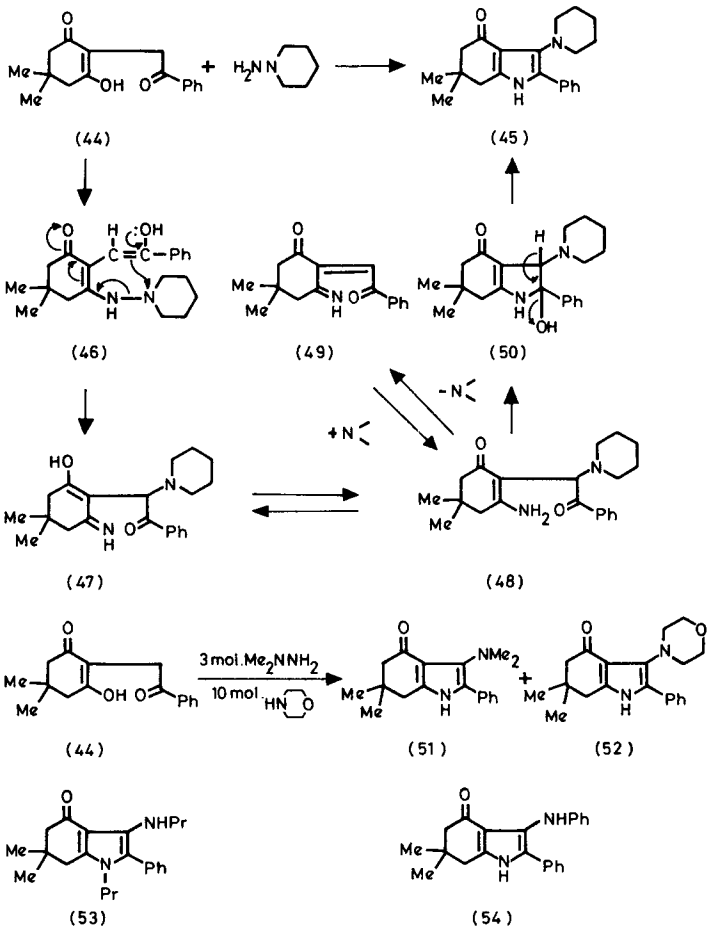
the minor products (chart 12). Further, use of excess *n*-propylamine or aniline instead of morpholine in this reaction gave products (53) and (54) respectively incorporating these amines (chart 12).

Blocking of position 3 for aromatisation could be expected to afford further interesting variation. The reaction of propiophenone derivative (55) with N-aminopiperidine did in fact take a slightly different turn, forming (56) and (57) by a sequence of rational reactions (Nagarajan and Shah unpublished) (chart 13).

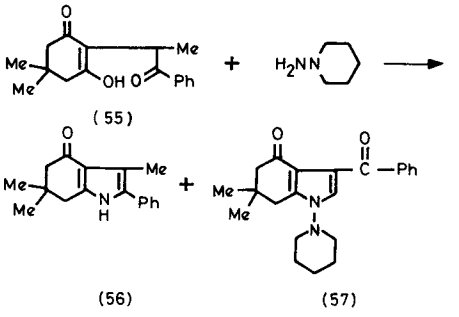
The proof of the structure of the anomalous products rested both upon a degradation sequence as well as on synthesis (chart 14).

2.2c *From* 2-*propargylcyclohexane*-1,3-*diones*: (Schulte *et al* 1963; Schoen and Pachter 1968) (chart 15).

2.2d *From cyclohexane*-1,3-*diones and isonitrosoketones*: (Hauptmann *et al* 1966) (chart 16). R_2 and R_3 can be varied quite extensively in this route.



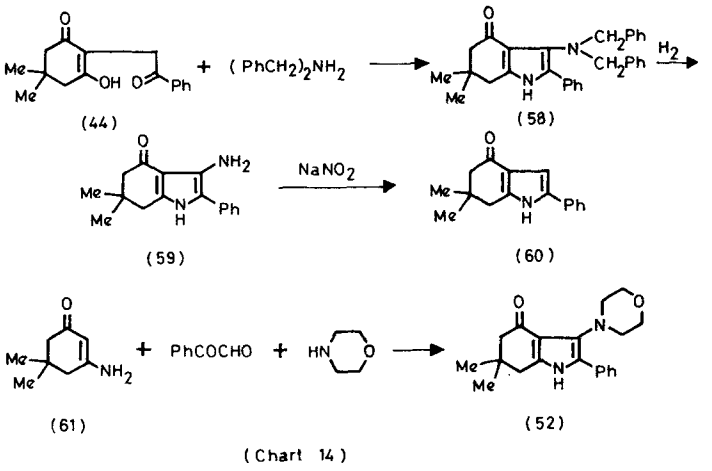
(Chart 12)



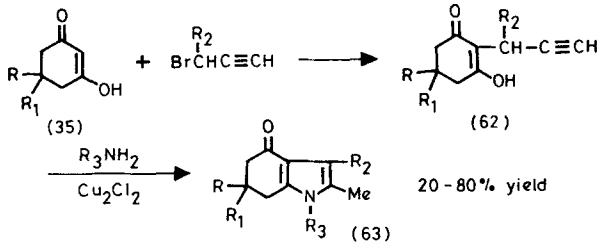
(Chart 13)

2.2e *From cyclohexane-1,3-diones and aminoacetals*: (Bobbit *et al* 1978) (chart 17). Compounds (65) have been converted to β-carbolines.

2.2f *From cyclohexane-1,3-dione enamine and ethyl α-bromoacetate*: (Murata *et al* 1973) (chart 18).



(Chart 14)



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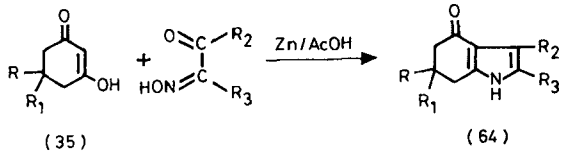
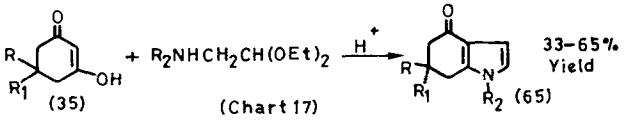
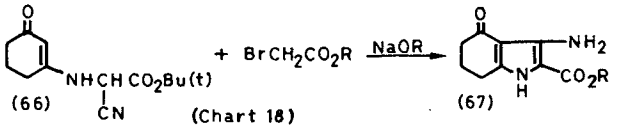


(Chart 16)



(Chart 17)



(Chart 18)

2.2g *From 4-oxo-4,5,6,7-tetrahydrobenzofuran carboxylic acid derivatives*: (Stetter and Lauterbach 1962; Nagarajan and Shenoy unpublished) (chart 19).

2.3 *5-Oxo-4,5,6,7-tetrahydroindoles*

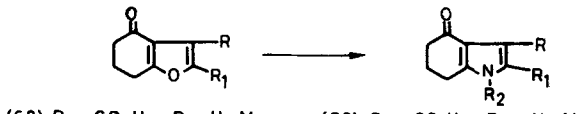
Birch reduction of 5-methoxyindole serves as a route for this group of compounds (Teuber and Schmitt 1969; Remers *et al* 1967) (chart 20). In the presence of ruthenium catalyst, (72) is reduced to an octahydroindole (chart 20).

2.4 *Some reactions of 4,5,6,7-tetrahydroindoles*

2.4a *Dehydrogenation*: 4,5,6,7-Tetrahydroindoles are dehydrogenated catalytically into aromatic indoles (Bell *et al* 1970) while the oxo-derivatives are transformed to 4-hydroxyindoles (Remers and Weiss 1965).

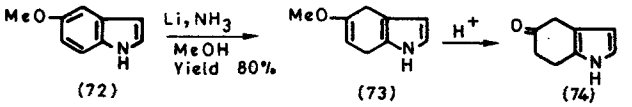
2.4b *Mannich reaction*: 4,5,6,7-Tetrahydroindole (75), formaldehyde and morpholine afford readily under acid catalysis, the base (76), while the 4-oxo derivative (77) undergoes aminomethylation reluctantly at both positions 3 and 5 (Nagarajan *et al* 1984) (chart 21). When position 3 is blocked and especially with no alkyl groups at position 6, aminomethylation occurs with great facility at position 5 (Schoen and Pachter 1968).

2.4c *Ring expansion of 4-oxo-4,5,6,7-tetrahydroindoles* 13: Beckmann rearrangement of oxime (80) takes place regiospecifically to afford pyrroloazepine (81) (Nagarajan *et al*



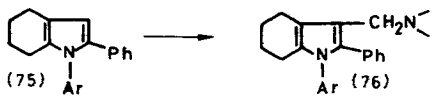
(68) R = CO_2H; R_1 = H, Me (70) R = CO_2H; R_1 = H, Me
(69) R = Me; R_1 = CO_2H (71) R = Me; R_1 = CO_2H

(Chart 19)

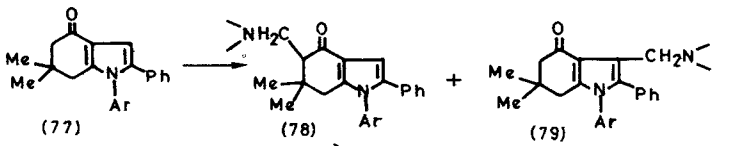


(72) (73) (74)

(Chart 20)



(75) (76)



(77) (78) (79)

Ar = 4-fluorophenyl; N = morpholino

(Chart 21)

1984) (chart 22). The formation of both isomeric pyrroloazepines from analogous oximes has been reported earlier (Stoll and Troxler 1968).

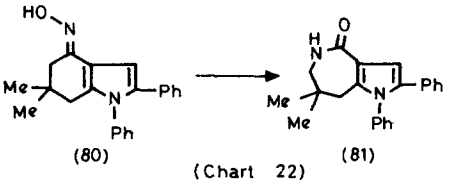
2.4d *Villsmeier-Haack and Wittig reactions*: Products of these reactions of 4-oxo-4,5,6,7-tetrahydroindoles and subsequent utilization for the construction of heterocycles have been extensively reviewed (Weiss *et al* 1969).

2.4e *Ring annelation of 4-oxo-4,5,6,7-tetrahydroindoles*: Reaction of the ketocarboxylate (82) with hydrazines gives rise to the tricyclic system (83) (Nagarajan and Shah unpublished; Remers *et al* 1971) (chart 23). With *o*-aminobenzophenones and (84) a tetracyclic system (85) results (Takagi *et al* 1973) (chart 23).

2.5 *Hexahydroindoles*

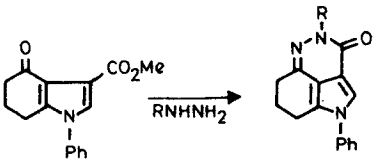
2.5a *2,3,4,5,6,7-Hexahydro-4-Oxoindoles*: 2-Allyldimedone (86) heated with *p*-fluoraniline affords (87) in modest yield (Nagarajan *et al* 1984) (chart 24).

2.5b *3a,4,5,6,7,7a-Hexahydro-3H-indoles*: Reduction of the unsaturated oxime (88) with zinc and acetic acid leads interestingly to the formation of hexahydroindoles (89) and (90) (Wagner-Jauregg and Roth 1960) (chart 25). Dry distillation of trans-2-

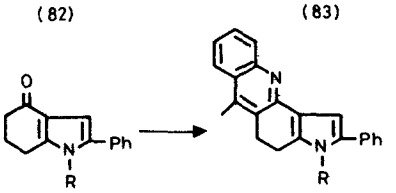


(80) (81)

(Chart 22)

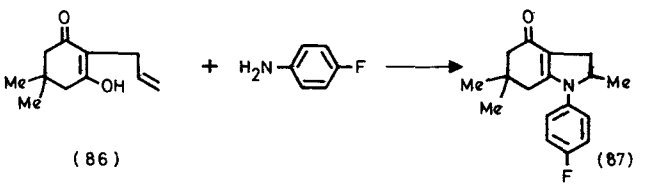


(82) (83)



(84) (85)

(Chart 23)



(86) (87)

(Chart 24)

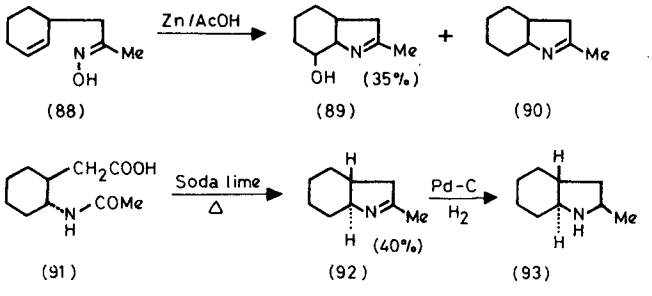
acetamido-1-cyclohexane acetic acid (91) gives rise to the trans-derivative (92) which was further reduced to the octahydroindole (93) (Murakoshi *et al* 1964) (chart 25).

2.5c *3a,4,5,6,7,7a-Hexahydro-1H-indoles*: Palladium-catalyzed intramolecular amination of the olefin (94) provides the hexahydroindole (95) in 48% yield (Hegedus and Mckearin 1982) (chart 26).

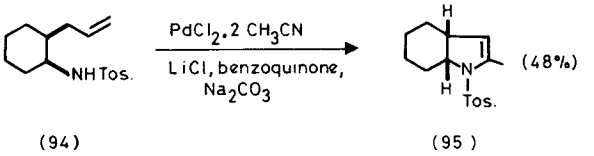
2.5d *2,3,4,5,6,7-Hexahydroindoles*: These seem to exist in the enamine form rather than as the imine with the double bond at 1,7a position. However, the imine form is encountered in the nitrone (100) and the 7,7-disubstituted derivative (104).

2.5d(i) *From cyclohexanone and ethanolamine*: (Yusupov *et al* 1979) (chart 27).

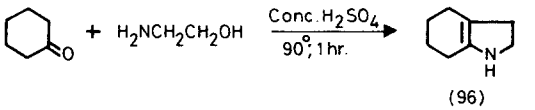
2.5d(ii) *From 2-(nitroethyl)cyclohexanones*: (Moorjani *et al* 1979; Feuer *et al* 1968) (chart 28). The use of zinc and ammonium chloride for the reduction provides a nitrone which undergoes addition of Grignard reagents to give octahydroindoles (Lunt 1963).



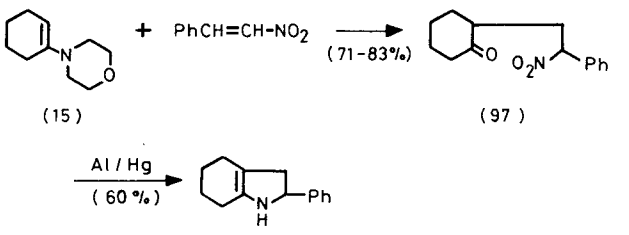
(Chart 25)



(Chart 26)



(Chart 27)



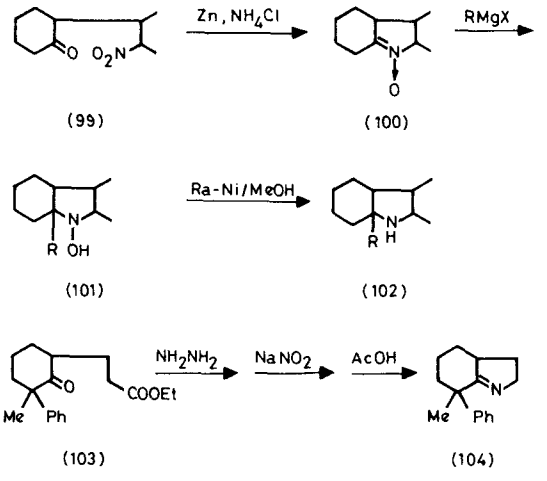
(Chart 28)

2.5d(iii) *From cyclohexanone-2-propionic acid*: (Kost *et al* 1964) (chart 29).

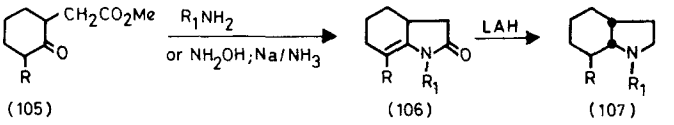
2.5e 2,3,3*a*,4,5,6-*Hexahydroindoles*: Under certain conditions the intramolecular condensation of an amino group with cyclohexanone leads to products with the double bond at 3a, 7 position.

2.5e(i) *From 7-substituted cyclohexanone-2-acetic acid*: (Bertho and Schmidt 1964; Kost and Rudakova 1965) (chart 30). In the Russian work (106) R = Ph upon hydrogenation with platinum in acetic acid gives the *trans* oxindole. Compounds (106) where R is a β-phenylethyl group have been cyclised to the erythrina skeleton (Mondon *et al* 1959). Fujisawa *et al* (1965a) (chart 31).

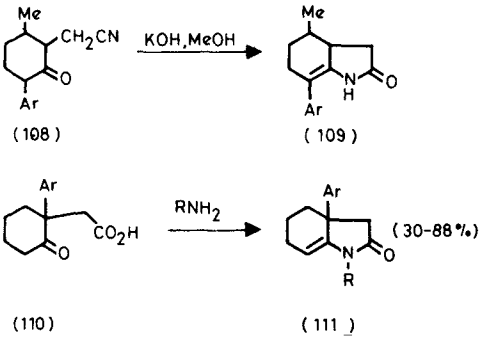
2.5e(ii) *From 2-arylcyclohexanone-2-acetic acids*: (Langlois *et al* 1971) (chart 31). (111) has been reduced further and cyclised to give the crinane ring system.



(Chart 29)



(Chart 30)



(Chart 31)

2.5f *From hydrogenation of indoline*: (Butula and Kuhn 1968) (chart 32).

2.6 2,3,3*a*,4,5,6,7,7*a*-1*H*-*Octahydroindoles*

Voluminous chemistry relating to this system as a component of alkaloids has been adequately reviewed (Jeffs 1981; Dyke and Quessy 1981; Fuganti 1975). Hence only very few routes will be mentioned briefly.

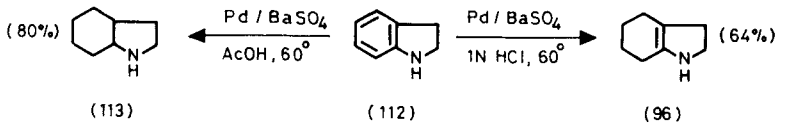
2.6a *Catalytic hydrogenation of indoles, and dihydro, tetrahydro and hexahydroindoles*: Reaction of 2-methylindole with *n*-propanol in toluene in the presence of Raney nickel and aluminium *n*-propoxide leads to the *n*-propyl compound as well as the octahydro derivative as a minor basic product (Botta *et al* 1979). 1-Methyl-7-methoxyindole upon reduction using platinum catalyst in acetic acid leads to *cis*-octahydro-1-methylindole along with the 7(e) methoxy derivative (Mokotoff 1973). For other reductions, see Toth (1967), Toth and Gerces (1971), Cohen and Heath-Brown (1965) and Trofimov *et al* (1978a).

2.6b *Addition of aryllithiums to hexahydroindole*: (Godefroi 1962) (chart 33).

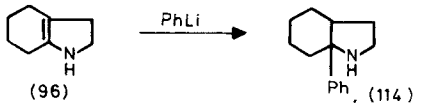
2.6c *From cyclohexanone-2-acetic acid*: (Valodine *et al* 1965) (chart 34). With N-methylformamide, both *cis* and *trans* 1-methyloctahydroindoles were obtained.

2.6d *From N-chloramines*: The intramolecular cyclisation of suitable N-chloramines under acidic solvolytic conditions is regioselective for enol ether and dioxalanes and affords octahydroindole (Furstoss *et al* 1976).

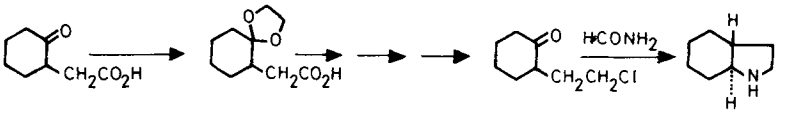
2.6e *From aziridine and diethyl malonate*: (Kojima and Tomioka 1976) (chart 35).



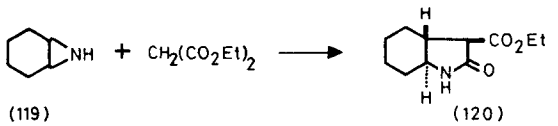
(Chart 32)



(Chart 33)



(Chart 34)



(Chart 35)

2.6f *From an annealed cyclohexanone*: (Jeffs and Molina 1973) (chart 36). The paper is especially interesting for its discussion of conformational features.

2.6g *Synthesis of mesembrine-like compounds*: (Taguchi *et al* 1970; see also Jeffs 1981) (chart 37). (127) was further reduced to the alcohols and subjected to the Pictet-Spengler reaction to form dihydrocrinine models.

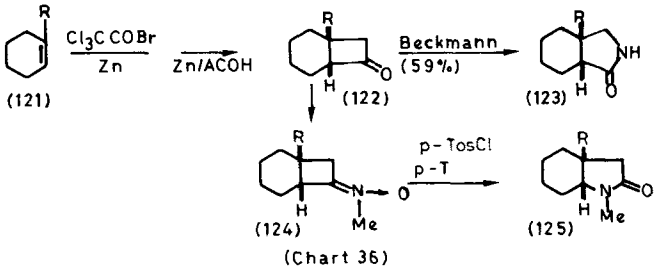
2.7 *Biological activity of perhydroindoles*

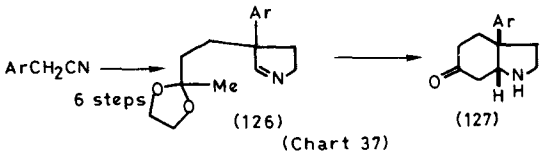
2.7a *Antifertility activity*: The following derivatives showed marked antiimplantation activity in the rat (Nagarajan *et al* 1984), (130) being the most potent (chart 38).

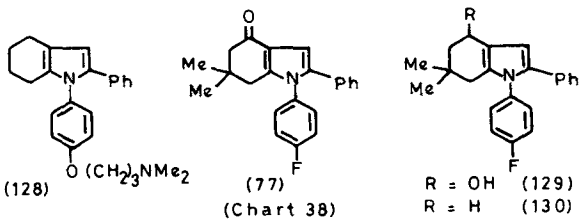
2.7b *Hypoglycemic activity*: Oxotetrahydroindole-3-acetic acids (131) and (132) exhibited activity in both the normal and streptozotocin diabetic rat (Nagarajan 1981· Talwalker 1981) which was not mediated by inhibition of gluconeogenesis. Related 2-acetic acids or 2- or 3-carboxylic acids were inactive.

2.7c *Antiinflammatory-analgesic activity*: 4-Oxo-4,5,6,7-tetrahydroindoles (133) and (134) had antiinflammatory activity in the carragenin rat paw oedema test and were also analgesic. They had no prostaglandin synthetase inhibitory activity *in vitro*, and were inactive in the chronic adjuvant arthritis model in the rabbit (Nagarajan and Shenoy unpublished results).

2.7d *Other activities*: The neuroleptic activity of molindone has been mentioned already (Rubin et al 1967). Derivatives of octahydroindoles have been reported to be







curare-like (Luellmann *et al* 1967), ganglion-blockers (Nerurkar 1968), ataractics (Boehringer and Soehne 1962), spasmolytics (Enenkel *et al* 1963) and useful as intermediates for antitussives (Fujisawa *et al* 1965) and as fungicides and herbicides (Himmele and Pommer 1980; Foerester *et al* 1979; Sturm and Vogel 1974).

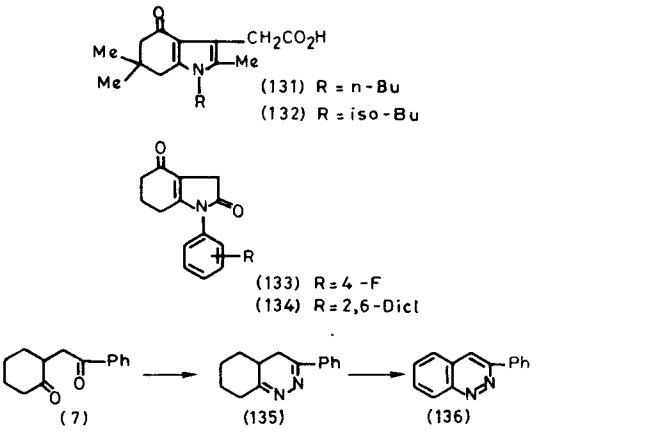
3. Perhydrocinnolines

3.1 *Hexahydrocinnolines*

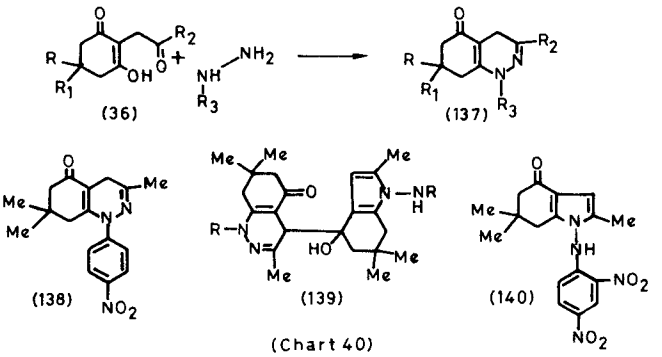
Condensation of 2-phenacylcyclohexanone (7) with hydrazine affords (135), which has been aromatised to (136) (Baumgarten 1958) (chart 39).

3.2 5-*Oxo*-1,4,5,6,7,8-*hexahydrocinnolines*

These became available by the interaction of 2-acetonyl or 2-phenacyl cyclohexane-1,3-diones with hydrazines or monosubstituted hydrazines (chart 40). The reaction is versatile and has been extensively studied (Nagarajan *et al* 1976; Nagarajan *et al* unpublished). Condensation of 2-acetonyl dimedone with *p*-nitrophenylhydrazine



(Chart 39)



(Chart 40)

afforded (138) and (139) while with 2,4-dinitrophenylhydrazine, indole (140) results presumably because of the low nucleophilicity of the aniline nitrogen.

3.3 *Octahydrocinnolines*

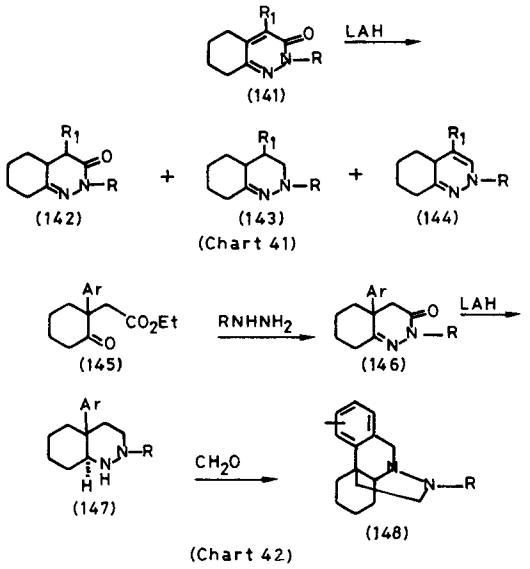
LAH reduction of the condensed pyridazinone leads to a complex mixture of products (Daunis *et al* 1972) (chart 41).

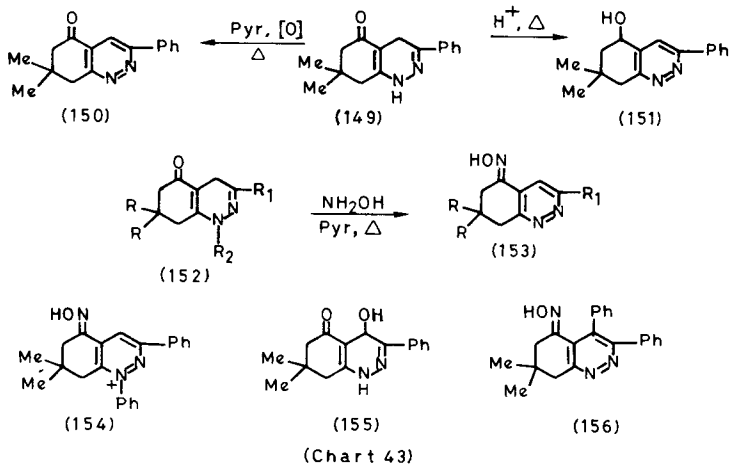
3.4 *Decahydrocinnolines*

A series of publications have appeared from Japan on the synthesis of this class of compounds as analgesics and as intermediates for 9-azamorphinans (Kametani 1980 and references cited therein). These compounds have been covered by patents also (Grelan 1981) (chart 42).

3.5 *An unusual sequence of reactions of* 5-*oxo*-1,4,5,6,7,8-*hexahydrocinnolines*

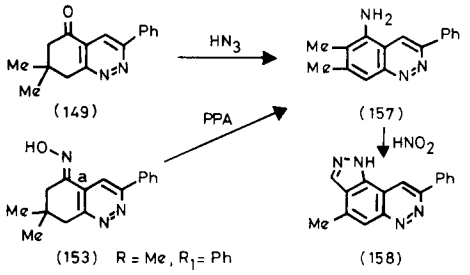
3.5a *Oximination*: We shall describe in this section, published (Nagarajan and Shah 1973) and unpublished (Nagarajan *et al*, unpublished) work on interesting transformations of (149). Prolonged exposure of a hot solution of (149) in pyridine to air, or better to *p*-toluenesulphonyl chloride, led to the formation of the aromatic product (150), while with acid, an internal oxidation-reduction took place to form (151). The oxime (153) (R = Me; R_1 = Ph) of (150) was obtained directly in near quantitative yield by reaction of (149) with excess hydroxylamine in pyridine. 1-Substituted derivatives (152) also afforded the aromatised oximes (153) in low yield. The reaction presumably occurs by hydroxylamine functioning as an oxidising agent, since quaternary salts of the type (154) could be isolated from (152) (R = Me; R_1 = R_2 = Ph). The reaction may be mediated by radicals as evidenced by the isolation of products such as (155) and (156) from the same reaction (chart 43).



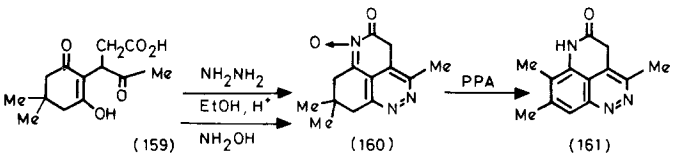


(Chart 43)

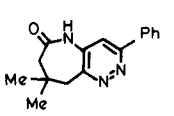
3.5b *Attempted Beckmann transformation of oximes* (153) *and Schmidt reaction on ketone* (150): Treatment of the ketone (150) with sodium azide and sulphuric acid gave in high yield 5-aminocinnoline (157) which also resulted from oxime (153) (R = Me; R_1 = Ph) by rearrangement in the presence of PPA, sulphuric acid or $POCl_3$-pyridine. The aromatisation reaction, involving the Semmler-Wolff rearrangement, was general for similar oximes. The position of the methyl group was easily ascertained by the fortuitous formation of the pyrazole (158) during an attempted deamination of (157) after diazotisation. The configuration of oxime (153) as shown and the reluctance of the bond *a* attached to the electron deficient pyridazine ring are considered to be the factors favouring Semmler-Wolff rearrangement (chart 44). Semmler-Wolff rearrangement was observed in the following special case as well (chart 45) (Nagarajan unpublished). While many acidic conditions transformed oximes (153) to 5-aminocinnolines, only PCl_5 brought about the desired Beckmann transformation to (162) but in 10% yield and conc. HCl gave rise to a mixture of products from which the α-chloroketone (163) was isolated (chart 46) (Nagarajan and Shah unpublished). The formation of 2-



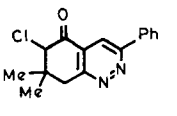
(Chart 44)



(Chart 45)

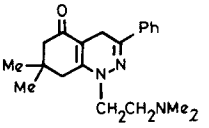


(162)

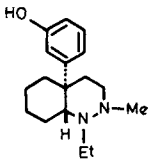


(163)

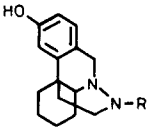
(Chart 46)



(164)



(165)



(166)

(Chart 47)

chlorotetralone by the action of Beckmann's mixture on α-tetralone oxime is known (Conley and Ghosh 1971). Reaction of the oxime with formic acid led to hydrolysis, reductive formylation and reductive deoximation.

3.6 *Biological activities of perhydrocinnolines*

A number of 1-aminoalkyl-5-oxo-1,4,5,6,7,8-hexahydrocinnolines, *e.g.* (164) are potent, but toxic CNS depressants (Nagarajan *et al* 1976). Decahydrocinnolines, *e.g.* (165) have analgesic activity (Kametani *et al* 1973) while the derived 9-azamorphinans (166) are even more potent (Kametani *et al* 1970) (chart 47).

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