RECENT DEVELOPMENTS IN THE FISCHER INDOLE SYNTHESIS

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THE Fischer indole synthesis would be completing hundred years of its discovery during this year (1983); but it is a reaction of continuous interest even today. This is obviously due to its versatility and wide applicability in obtaining indoles and indole derivatives, as exemplified by the syntheses of a number of biologically important natural and synthetic products like reserpine, strychnine, yohimbine, ellipticine, indomethacin etc. There have been excellent articles and monographs reviewing all aspects of the Fischer indole synthesis,[1-3] and there are articles dealing with particular aspects of the reaction like mechanism of the reaction, displacement of methoxyl group and rearrangement of arylhydrazones[4-7]. The object of this review is to give an account of significant articles that have appeared after these monographs. An attempt is made to review articles dealing with the mechanism of the reaction, regioselectivity and rearrangements during the reaction.

A. SYNTHESIS OF INDOLE AND FURTHER EVIDENCE FOR THE SECOND AND THIRD STAGE OF THE MECHANISM

The Fischer indole synthesis consists of heating phenylhydrazones of enolisable carbonyl compounds in the presence of catalysts such as zinc chloride, ethanolic hydrogen chloride, sulphuric acid, acetic acid, polyphosphoric acid, boron triflouride etherate etc., to produce indoles. Although the Fischer indole synthesis is the most versatile method for the synthesis of indoles direct synthesis of indole itself from acetaldehyde phenylhydrazone was a complete failure till recently. Failure of the formation of indole during this reaction was attributed mainly to the fact that indole formed, invaraibly reacted with the starting material acetaldehyde phenylhydrazone. Thus in all previous attempts probably it was not the nonformation, but failure in the isolation of indole itself, that led to this exception to the Fischer indole synthesis. Nakasaki and Yamamoto[8] have now overcome this difficulty by using a flow method with a stream of carrier gas to remove indole from contact with the reaction mixture immediately after its formation. Thus by passing acetaldehyde phenylhydrazone in a stream of nitrogen through porous beads, coated with zinc chloride packed in a cumbustion tube and heating to 290-300° indole was obtained along with aniline and acetonitrile. This is the first report of direct synthesis of indole from acetaldehyde phenylhydrazone by means of zinc

chloride, the catalyst originally introuduced by Fischer[9,10]. However, an earlier Japanese patent[11] and Russian papers by Suvorov *et al.*[12] also describe the preparation of indole from acetaldehyde phenylhydrazone using γ-alumina.

Recently carbon 13 NMR spectroscopy has been used for the first time to investigate the mechanism of this reaction[13]. Imine intermediate corresponding to the stage of the reaction after the benzidine type of the rearrangement and before closure of the five membered heterocyclic ring has been characterised by following, *in situ*, the reaction of N_2-*p*-chlorobenzoyl-N_2-*p*-methylephenylhydrazene (1) (numbers in brackets denote the fig number in the chart) and levulinic acid, leading to indomethacin (6). Mixture of (1) in acetic acid, levulinic acid and hydrochloric acid was taken in a well stoppered NMR tube and the reaction was carried out at 50° for a period of one hr. Carbon 13 observations were made at approximately 20° with various reaction periods. Following the time evolution of ^{13}C-spectra, the disappearance of the hydrazone as well as the growth of the product
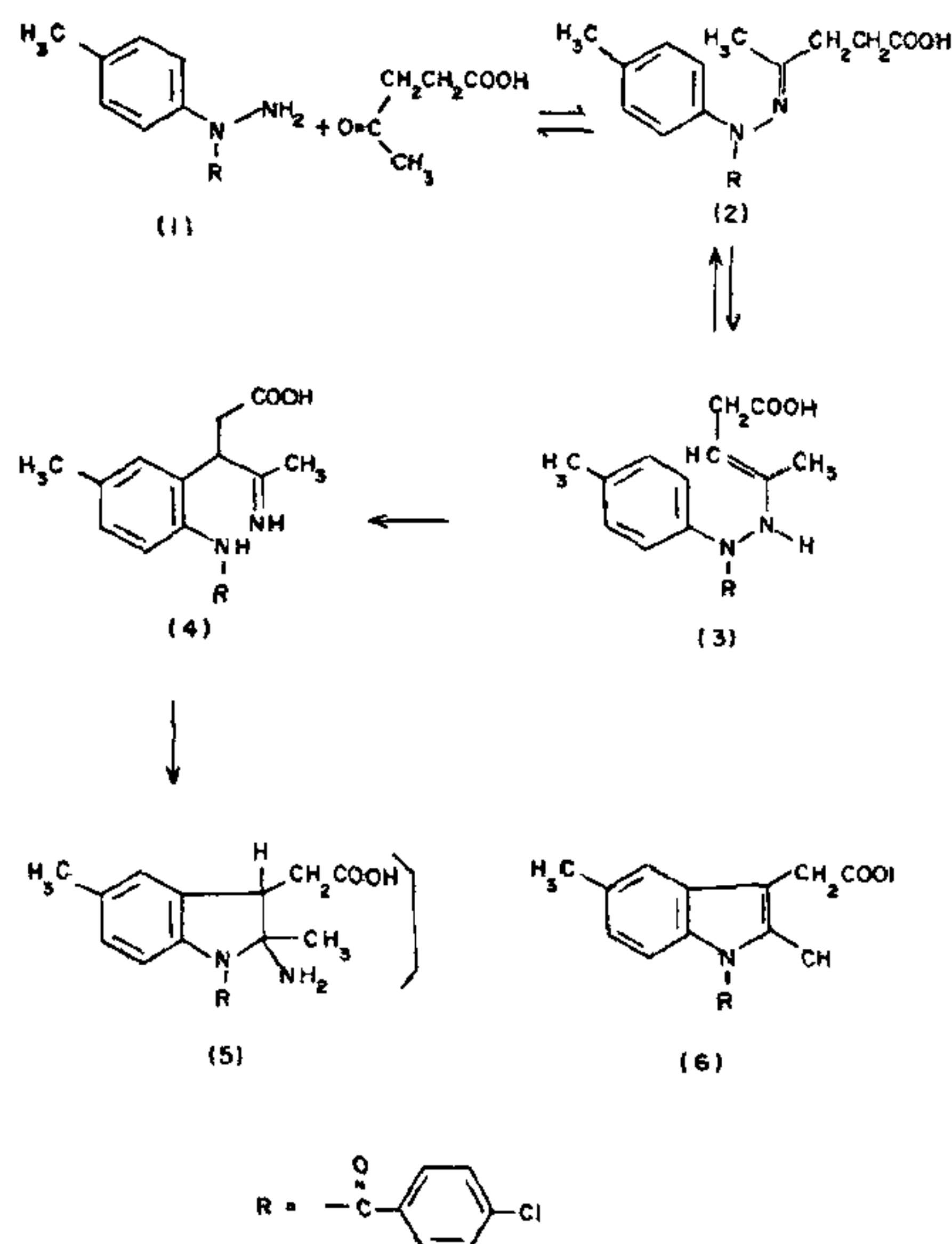

Scheme I

indomethacin could be very easily visualised. Strong signals in the zero time run were taken as reference signals for (2) (scheme 1). ^{13}C-spectrum obtained for a reaction time (15 min), when the concentration of the intermediate had peaked, exhibitted clear features of the intermediate. Despite the interference from (6), (1) and (2), several signals for the intermediate could be well resolved. Of the three possible intermediates (3), (4) and (5) the following observations in the spectrum allowed only (4) as the correct structure for the intermediate. The observations made were (i) the presence of a methine carbon at 45 ppm along with a substituted one at 198 ppm., (ii) presence of eight fully substituted sp[2] carbon atoms. The structure of the intermediate has also been confirmed by following the natural abundance of ^{15}N-NMR.

Forrest and Chen[14] have isolated a 2-aminoindoline derivative which can eliminate the amine and thus truly perform the suggested last step of the Fischer indole synthesis. Thus 1-acetyl-2-*o*-toulidinoindoline was obtained by intramolecular condensation of β-(*o*-acetotoluidino)-2-aminostyrene, catalysed by molecular seive in refluxing benzene. Indoline underwent elimination of 2-amino function (*o*-toluidine) to form N-acetylindole, with extreme ease. This is a reaction which is equivalent to the last step of the Fischer indole synthesis.
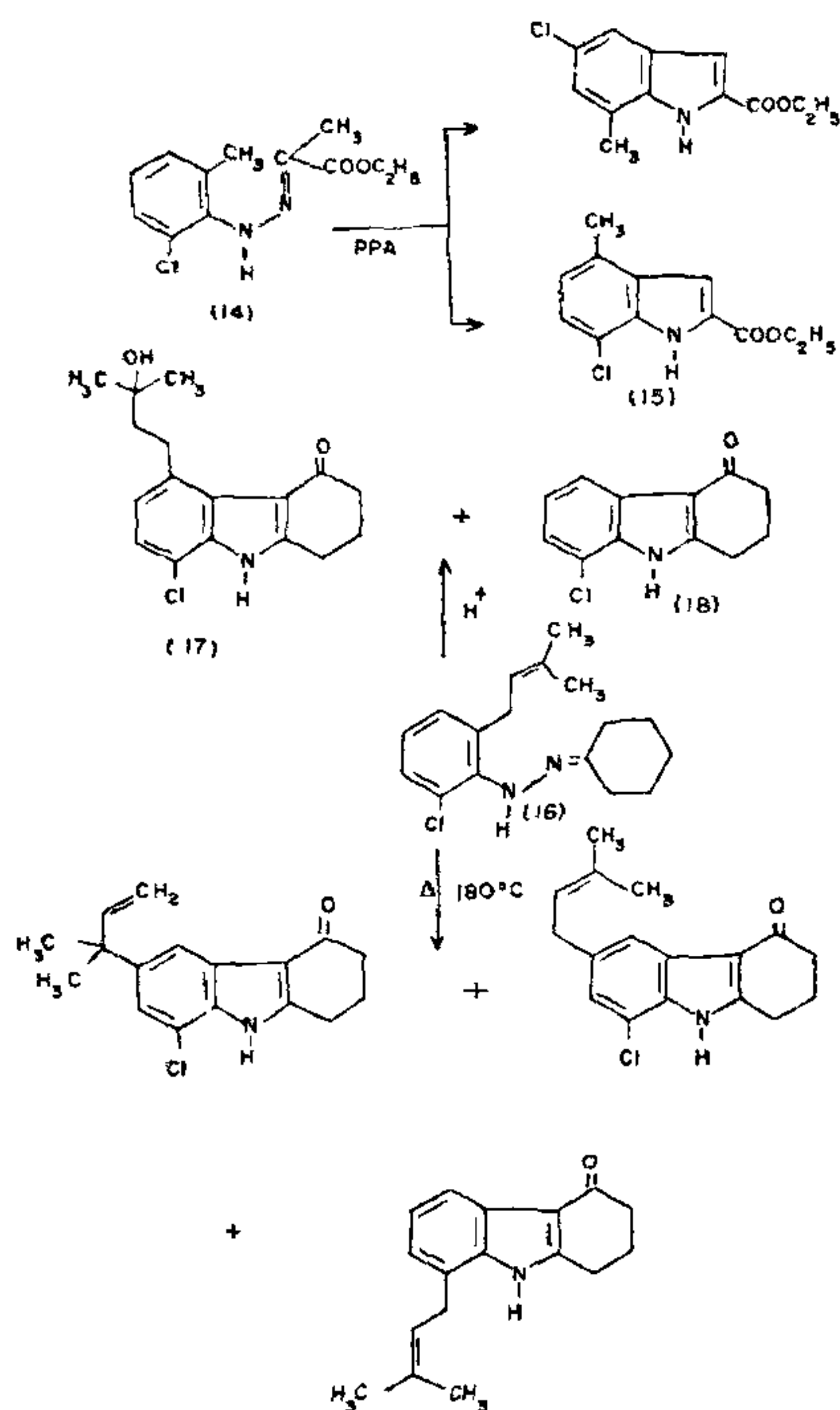
B. REGIOSELECTIVITY:

Recently Russian workers[15-17] have reported interesting findings during the Fischer indolisation of unsymmetrically substituted N,N-diarylhydrazones. They subjected cyclohexanone N-phenyl-N-*p*-tolylhydrazone (7a) to the Fischer indolisation and obtained 1, 2, 3, 4 - tetrahydro - 6 - methyl - 9 - phenylcarbazole (8a) (Scheme 2). Similar cyclisation of cyclohexanone diarlhydrazone (9a) gave carbazole (10a). From the above experiments it is concluded that the direction of the indolisation depends upon the substituents in the aryl moiety; the directive influence of the substituent being MeO>Me and Me>H. The preferential indolisation was also observed when cyclohexanone moiety was replaced by 4-thiapyranone and N-methyl-4-piperidone as in the case of diarylhydrazones (7b,c) and (9b,c). However, when one of the phenyl groups of diarlhydrazones carried a chloro, methoxy or carbethoxy substituent, the above preferential cyclisation does not seem to occur; instead mixtures of products are obtained in such cases. Cyclisation of diarylhydrazones (11) gave carbazoles (12) and (13). From these experiments it has been concluded that ring closure during the Fischer indolisation occurred *via* a [3,3] sigmatropic rearrangement and not by electrophilic attack on the benzene rings.

a X = CH₂
b X = S
c X = NCH₃

(7) (8)
(9) (10)

(11)

iso propyl alcohol, + H⁺

(12) Scheme 2 (13)
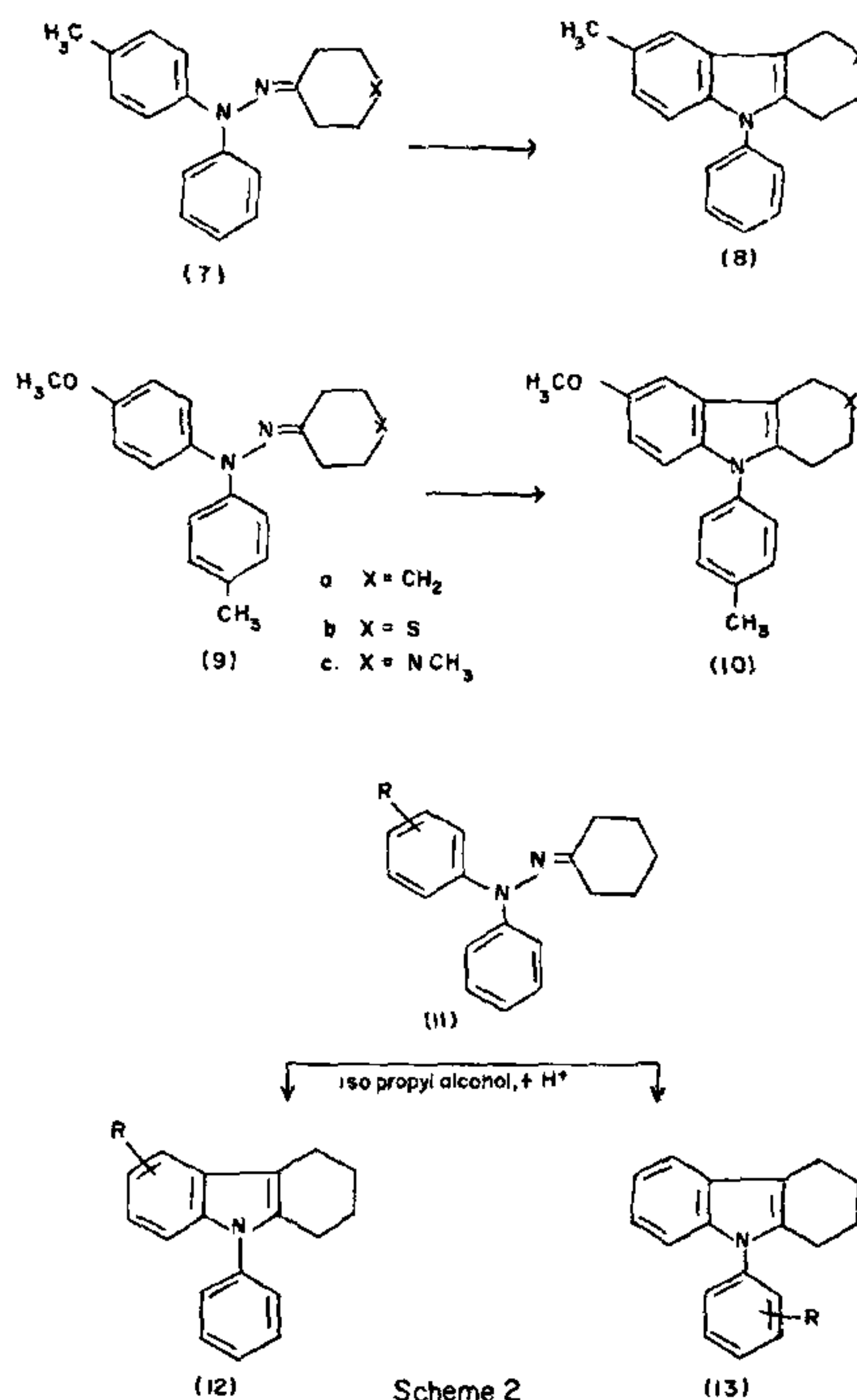
C. MIGRATION:

Holla and Ambekar[18] have investigated the indolisation of unsymmetrically *o*-disubstituted arylhydrazones with a view to studying the preferential group migration. They subjected ethyl pyruvate-2-chloro-6-methylphenylhydrazone (14) to polyphosphoric acid catalysed cyclisation and obtained ethyl 4-methyl-7-chloroindole-2-carboxylate (15) as the only indolic product in 10% yield. (Scheme-3) Earlier Baldwin and Tzodikov[19] have also observed this kind of preferential migration during the sulphuric acid catalysed indolisation of phenylhydrazone (16). They obtained 4-oxocarbazole (17) in 2% yield, along with 8-chloro-1,2,3,4-tetrahydro-4-oxocarbazole (18). The formation of (17) presumably results from hydration followed by 1,2,-shift of the resulting alkyl group. Thermal indolisation of this hydrazone (16) gave various rearranged and elimination products as shown in Scheme-3; interestingly enough no product arising of halogen migration was observed. Thus these results indicate that 1,2-migration of methyl group is prefered to 1,3-halogen migration during the indolisation of unsymmetrically *o*-disubstituted arylhydrazones.
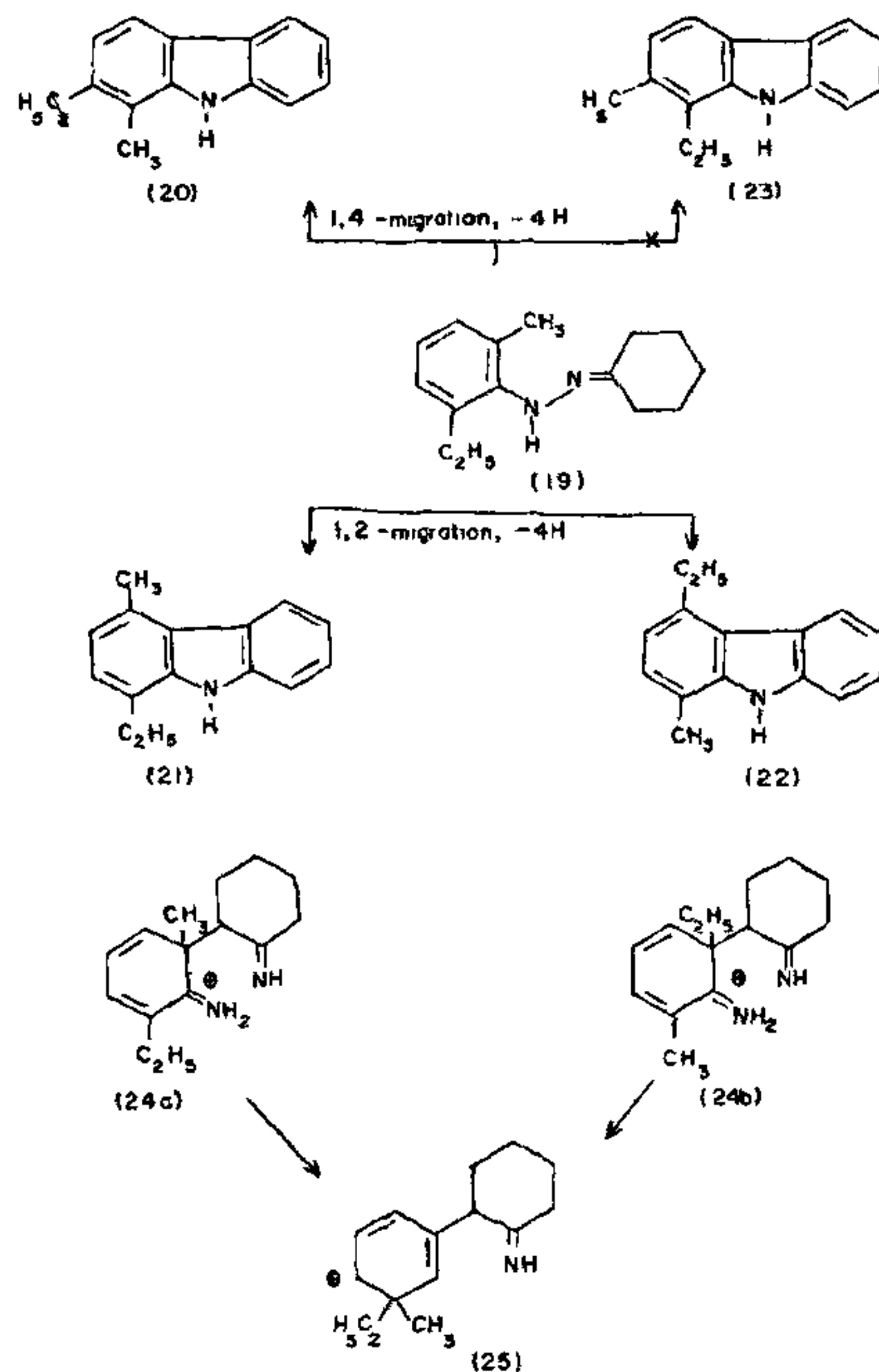
Scheme 3

Fischer indolisation actually proceeds by a formal 1,5-alkyl shift followed by a 1,2-shift. They carried out the indolisation of cyclohexanone 2-ethyl-6-methylphenylhydrazone (19) in acetic acid. Dehydrogenation of indolised products gave a mixture of 2-ethyl-1-methylcarbazole (20), 1-ethyl-4-methylcarbazole (21),4-ethyl-1-methylcarbazole (22) -1-ethylcarbazole and -1-methylcarbazole.No trace of 1-ethyl-2-methylcarbazole (23) resulting from a 1,4-methyl migration could be detected even by g.l.c., technique (Scheme-4). The carbazoles (21) and (22)

Scheme 4

1,3-Migration of methyl group during the Fischer indolisation has also been observed by Fusco and Sannicolo[20]. They have proved by deuterium labelling studies that 1,3-migration of methyl group occurs by two consecutive 1,2-shifts and not by direct 1,3-shift.

1,4-Methyl migration, formerly believed to occur only in mesitylhydrazone of cyclohexanone[21] is now observed in mesitylhydrazone of acyclic ketone also[22]. However, the exact mechanism of 1,4-methyl migration during this reaction is yet to be understood. Carlin and Moores[21] preferred to explain this by a diret transannular 1,4-migration mechanism, rejecting the alternative explanation ivolving three series of 1,2-methyl shift. Dewar[23] subsequently favoured 1,2-migration mechanism on theoretical grounds. But recently Fusco and Sannicolo[24] have provided experimental evidence against 1,2-migration mechanism. Their experimental results can only be explained by a mechanism involving a direct transannular 1,4-migration.

Very recently Miller and Matjeka[25] have shown that the apparent 1,4-methyl migration during the

are formed obviously by the 1,2-migration of methyl group and ethyl group in the intermediate carbonium ions (24a) and (24b) respectively. Formation of 2-ethyl-1-methylcarbazole (20) could be explained by a direct transannular 1,4-shift of ethyl group in (24b). Elimination of ethyl group and methyl group from the ions (24a) and (24b) accounts for the formation of 1-ethylcarbazole and 1-methylcarbazole respectively. However this mechanism fails to explain why a methyl 1,4-migration in (24a) does not occur.

Further, product analysis of the reaction indicates that (20), (22) and 1-methylcarbazole together account

for more than 60% yield. These are the products obtainable from the migration or the elimination of ethyl group in carbonium ion (24b). Similarly, (21) and 1-ethylcarbazole together account for less than 30% yield. These are the products obtainable from the carbonium ion (24a). This means that , (24b) is formed in preference to (24a). This further leads to the conclusion that, attack takes place during cyclisation preferentially at a carbon atom carrying bulkier substituent. This is in fact a situation which is not favourable for Fischer indole cyclisation

In order to account for the nonformation of (23) and the apparent cyclisation of (19) at the carbon atom bearing bulkier substituent, Miller and Matjeka assumed that intermediates (24a) and (24b) rearrange to form intermediate carbonium ion (25). In this carbonium ion, ethyl group migrates in preference to methyl group, which is in analogy with the acid catalysed rerrangement of 4-methyl-4-ethylcyclohexadienone, in which ethyl group migrates 55 times as rapidly as methyl group[26.] Rearrangements of (24 a,b) to form (25) represent overall 1,5-alkyl shifts. At present, it is impossible to distinguish between the direct 1,5-shifts of the migrating groups and a sequence of 1,2-shifts. They have also proposed that steric factors play a major role in determining whether migrating groups undergo 1,2-shifts or 1,4-shifts during the Fischer indole cyclisation.

D. MISCELLANEOUS REACTIONS

Ishii *et al.* have observed that in addition to nucleophiles like chloride ion or ethyl alcohol present in the reaction medium, other nucleophiles also get incorporated into indole ring during Fischer indole cyclisation[27]. These nucleophiles may be derived from enolisable dicarbonyl compounds or indoles. The products obtained by such incorporation reactions are 6-substituted indoles. Ishii and coworkers[28] classify these reactions as ortho-C_6-abnormal Fischer reactions. Reactions leading to 5-substituted indoles are classified as ortho-C_5-abnormal Fischer reactions[29].

A new transformation during the Fischer indole synthesis has been reported recently by Holla and Ambekar[30]. When the sulphuric acid catalysed cyclisation of ethyl α-(p-chlorophenylhydrazono)furan-2-propionate (26a) was carried out in an attempt to prepare ethyl 5-chloro-3-(2'-furyl)indole-2-carboxylate (27a), an unusual product was obtained in 40% yield while the desired indole (27a) was obtained in only 10% yield. The unusual product was later identified as 3-[5'-(N-p-chlorophenyl-3'-ethoxycarbonyl)pyrazolyl]-2-propen-1-ol (30a). This transformation into pyrazolyl allyl alcohols was

found to be a general reaction of phenylhydrazones (26); and presumably occurs by rearrangement of a spiro intermediate (29) which is formed by the protonation of the furan ring before or after the tautomerisation of phenylhydrazone (26) into enehydrazine (28) as shown in the Scheme-5.
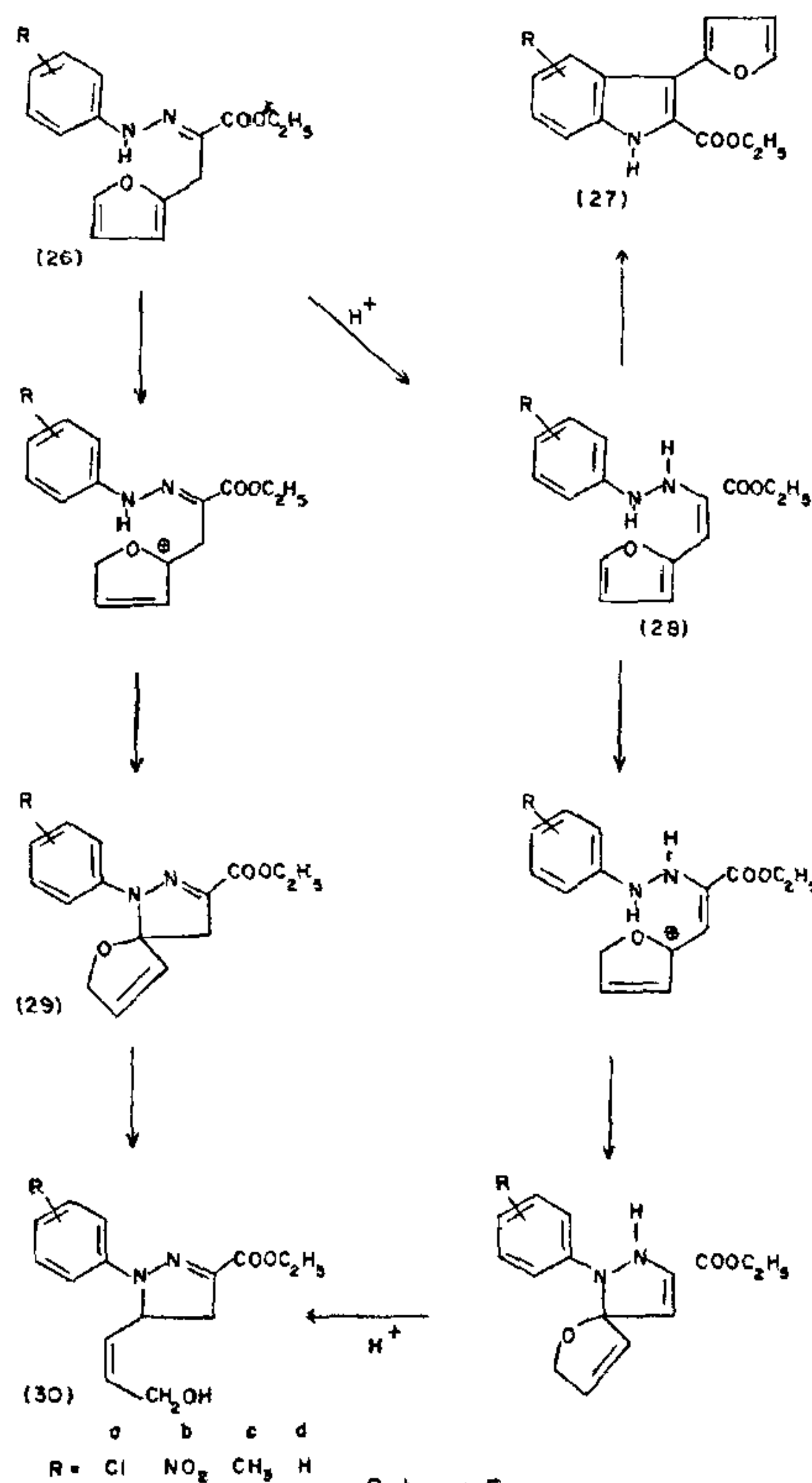
Scheme 5

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