

tion of these masses and length scales in (6) yield unacceptably high neutrino masses, m_ν , as much as ~ 400 eV in the worst cases. The resolution of this paradox has been sought in terms of other forms of unseen matter like back-holes. However, it is interesting and gratifying to note that all these missing mass on different scales can be accommodated within the frame-work of neutrinos of an unique mass dominating the clustering in the universe. The essential elements of this explanation are: a) neutrinos condense only on the scale of the clusters b) the galaxies and other systems merely perturb the phase-space distribution of the neutrinos c) the perturbed phase-space distribution, derived self-consistently, exhibit many fascinating features like non-dispersive propagation of density perturbations and generate the requisite gravitational binding even on small scales. The mathematical theory based on collisionless Boltzmann equation appropriate to neutrinos with only weak interactions will be presented elsewhere.

1. Weinberg, S. in *Gravitation and Cosmology*, (Wiley) 1972.
2. Gerstein, S. S. and Zeldovich, Ya. B., *JETP Lett.*, 1966, **4**, 120.
3. Cowsik, R. and McClelland, J., *Phys Rev. Lett.*, 1972, **29**, 669.
4. Szalay, A. S. and Marx, G., *Astron. Astrophys.*, 1976, **49**, 437.
5. Bernstein, J. and Feinberg, G., *Phys. Lett.*, 1981, **101B**, 39.
6. Lee, B. and Weinberg, S., *Phys. Rev. Lett.*, 1977, **39**, 165.
7. Yang, J., Schramm, D. N., Steigman, G. and Rood, R. T., *Appl. J.*, 1974, **227**, 697.
8. Turner, M., in *Neutrino Mass Mini Conference*, Univ. of Wisconsin (eds.) V. Bayer, D. Cline.
9. Cowsik, R., *Phys. Rev. Lett.*, 1977, **39**, 784.
10. Cowsik, R., *Phys. Rev.*, 1979, **D19**, 2219.
11. Falk, S. W. and Schramm, D. N., *Phys Lett.*, 1978, **79B**, 511.
12. deRuhula, A. and Glashow, S. L., *Phys Rev. Lett.*, 1980, **45**, 942.
13. Kimble, R., Bowyer S. and Jacobsen, P., *App. J. Lett.*, 1981, **242**, 119.
14. Henry, R. C. in *Recontre de Moriond*, (editions Frontieres, ed. Audouze et al. 1981).
15. Shipman, H. L. and Cowsik, R., *Appl. J. Lett.*, 1981, **247**, 111.
16. Cowsik, R. and McClelland, J., *Appl. J.*, 1973, **180**, 7.
17. Tremaine, S. and Gunn, J. E., *Phys. Rev. Lett.*, 1979, **42**, 407.
18. Aaronson, M., *Appl. J. Lett.*, 1983, **266**, 11.
19. Faber, S. M. and Lin, D. N. C., *Appl. J. Lett.*, 1983, **256**, 17.
20. Lin, D. N. C. and Faber S. M., *Appl. J. Lett.*, 1983, **266**, 21.

Aspects of Steroid Synthesis

G. S. R. Subba Rao

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India.

ONE of the main strategies in the synthesis of natural products is the construction, functionalisation and fragmentation of ring systems to obtain the desired target molecule. Diels-Alder reaction has been widely employed for the construction of ring systems and this reaction involves the addition of a conjugated diene to a dienophile. There are certain limitations to this reaction since a β , β -di substituted dienophile does not participate in additions even with a reactive diene. Further preparation of conjugated dienes present difficulties in view of their ready polymerisation. Cyclohexadienes both conjugated and unconjugated, in particular, the l-methoxy derivatives are readily available by the metal-ammonia reduction of aromatic ethers and these have been successfully used in cycloaddition reactions to obtain adducts which are transformed into the desired products. We have extensively used them for a synthesis of a variety of natural products and I would like to describe some of these syntheses in this lecture.

l-Methoxycyclohexa-1,4-diene, obtained by the metal-ammonia, alcohol reduction of anisole contains a reactive vinyl ether double bond, and an isolated double bond in its structure and one or other or both these features explain its reactivity towards electrophilic reagents and dienophiles. Selective oxidation of the enol-ether bond affords a substrate having a double bond with Z-configuration. This method has been used for stereoscopic generation of Z-olefins. An extension of this process is the oxidative cleavage of l-methoxy-5-methylcyclohexadiene to give a synthon which was coupled with β -ionone resulting in the synthesis of retinoic acid derivatives.

l-Methoxycyclohexa-1,3-diene, which is readily obtained by the base catalysed conjugation of the corresponding 1,4-diene is very reactive as a diene in Diels-Alder and Alder-Rickert reactions. The adducts formed are usually regiospecific and undergo cleavage with the fission of one or two carbon-carbon bonds depending on the nature. Later work showed that the unconjugated dienes can be directly employed for the Diels-Alder reaction indicating that the conjugation proceeds through a charge transfer phenomenon. The use of catalysts like dichloromaleic anhydride, tris-

triphenylphosphine rhodium chloride accelerates the conjugation process and hence the cycloaddition. Thus addition of methyl vinyl ketone to 1-methoxycyclohexa-1,3-diene results in an adduct which on acid hydrolysis affords a ketoenone. This undergoes a base catalysed intramolecular Michael reaction yielding a *cis*-dione. Reaction of dimethyl acetylene dicarboxylate with 1-methoxycyclohexa-1,3-, or 1,4-diene yields an adduct which spontaneously undergoes rapid aromatisation giving 3-methoxyphthalic acid. Addition of alkyl or aryl acetylenic esters with these dienes have been investigated to produce 6-alkyl or 6-aryl salicylic esters. This reaction has been exploited for the synthesis of a number of naturally occurring orsellinic acid derivatives which are derivatives of lichens. Based on this principle, the synthesis of macrolides, lasiodiplodin, Curvularin and Zearalenone has been achieved.

The mesomeric anions, obtained from the methoxycyclohexadienes with bases, can be regiospecifically alkylated or arylated. The resulting compounds, on acid hydrolysis, afford 2-substituted cyclohex-2-en-1-ones which are otherwise difficult to obtain. This principle has been exploited in the total synthesis of a sex pheromone, *Z*-heneicos-11-en-6-one. The intermediate alkylated diene undergoes cycloaddition with alkylacetylenic esters resulting in an alkylated salicylic ester. Thus alkylation of 1,5-dimethoxycyclohexa-1,4-diene with *n*-butyl bromide followed by cycloaddition with methyl 1-octynoate afforded an adduct which readily aromatised to give methyl 3-butyl-2,4-dimethoxy-6-pentyl benzoate. This compound on dimethylation followed by decarboxylation afforded a stenphol, a natural polyketide of fungal origin. This method allows us to prepare a number of compounds which are intermediates in polyketide biosynthesis.

Reaction of 1-methoxy-4-methyl cyclohexa-1,4-diene with acrolein afforded an adduct which was reacted with 3-methoxyphenylpropyl magnesium bromide to yield an alcohol. This was oxidised to the ketone which on acid hydrolysis afforded an unsaturated ketone. This, on treatment with base afforded *cis*-diketone which was cyclised to the tetracyclic ketone having *C/D-cis* geometry. The tetracyclic ketone has been successfully converted into equilenin and oestrone thus completing our own total synthesis of aromatic steroids. This process will be extremely useful in that several unnatural *D*-homo steroids can be readily made with a *cis-C/D* ring junction and find their way as drugs.

Finally the adducts obtained from 5-methoxy-1-methyl-4,7-dihydrohydrindane and chloroacrylonitrile afforded a tricyclic ketone on hydrolysis. This has been converted into a spirocompound by the oxidative cleavage of the double bond, which has been trans-

formed into acorone, thus leading to a stereospecific total synthesis of spiro-[4,5]-decanes. Acid catalysed rearrangement of the alcohol obtained from the above ketone leads to the formation of two compounds (i) an unsaturated ketone and (ii) a saturated ketone. These compounds are precursors for the total synthesis of Zizaene and Cedrene—two different types of complex sesquiterpenes biogenetically derived from the same precursor.

In this lecture, I have tried to summarise the strategies of syntheses of natural products using dihydrobenzenes. Most of the work presented here is unpublished. I am only a spokesman of the work carried out by my able and illustrious colleagues during the last five years at the Indian Institute of Science and I thank all of them for their performance.

Energy Conservation—An Organic Chemist's Attempts

N. S. Narasimhan

Department of Chemistry, University of Poona,
Pune 411 007, India.

SYNTHESIS of drugs is one of the important industrial activities of a country. Development of new and more efficient synthetic methods for drugs are therefore most desirable.

Several drugs incorporate benzene-fused heterocyclic ring systems. The usual methods of synthesis of such ring systems are acid catalysed. The reactions involved proceed, in the aromatic ring, at positions which have more electrophilic reactivity. If one wants the reactions to occur at the less reactive positions, the more reactive positions have to be blocked and after the reaction at the desired position is effected, the block has to be removed. Due to such restrictions several benzene-fused heterocyclic compounds either cannot be synthesised or can be synthesised only through lengthy routes by these acid catalysed methods.

In contrast to the above, heteroatom directed aromatic lithiation reactions, where a lithium atom is introduced in an aromatic ring, in the presence of a substituent carrying an atom with unshared electron pair, due to the unique mechanism operative, proceed at positions not favoured in acid catalysed reactions. Through the organolithium compounds, which have greater reactivity towards electrophiles at positions carrying the lithium atom, reaction can be promoted at positions which are otherwise less reactive.

Using aromatic lithiation reactions new synthesis of several heterocyclic ring systems have been developed by the author. These include synthesis of phthalides, naphthofurans, furocoumarins, benzocoumarins, iso-