DRUG RESEARCH : THE SCOPE FOR NOVEL CHEMISTRY

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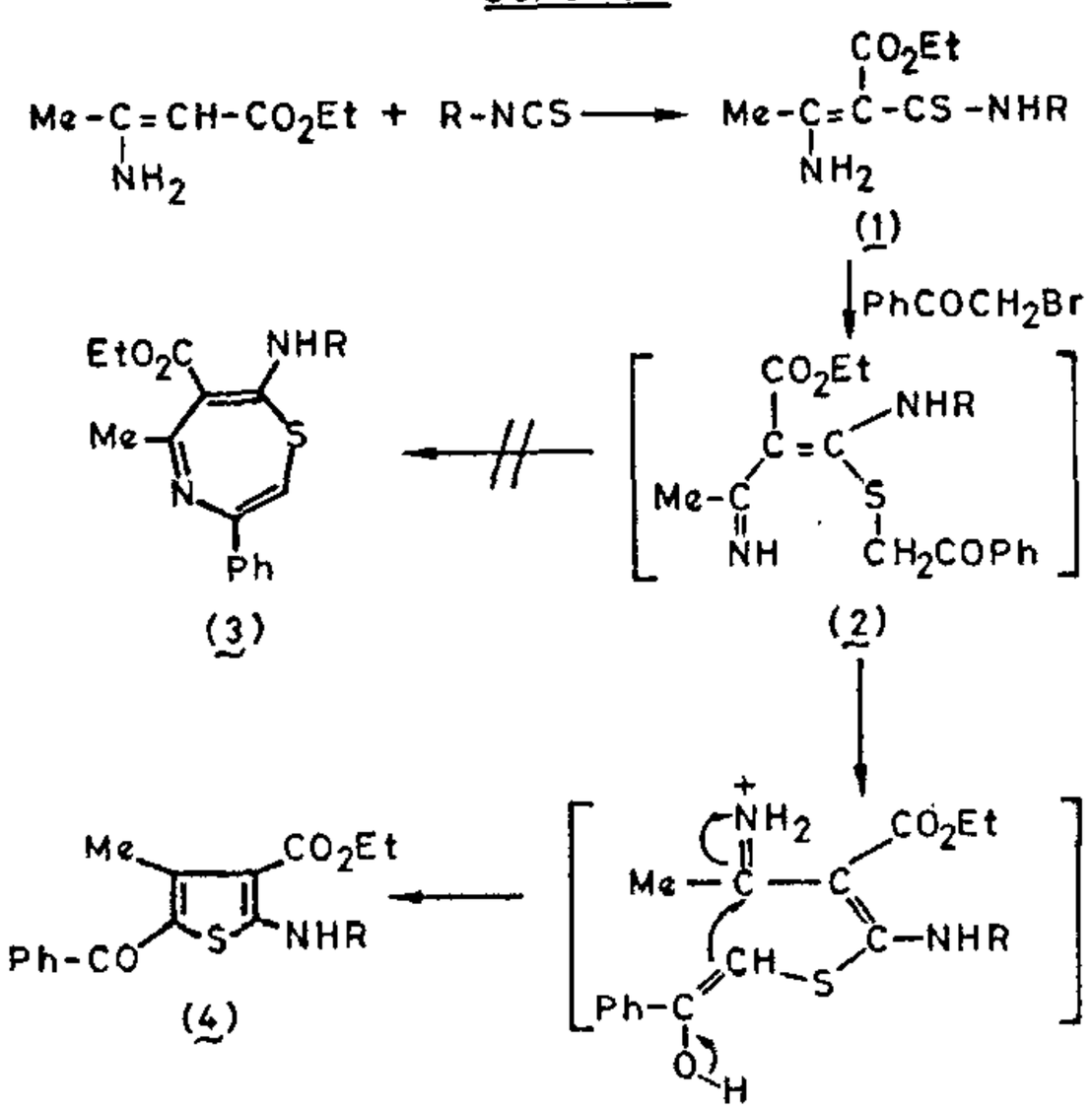
IT is a popular misconception that drug research involves only routine chemistry and often trivial molecular manipulations. While it is true that changing the substitution pattern in an active substrate structure is an essential part of optimizing the activity, it is also a fact that drug research is not incompatible with exciting new chemistry. This article gives a few examples from our own research to prove this point.

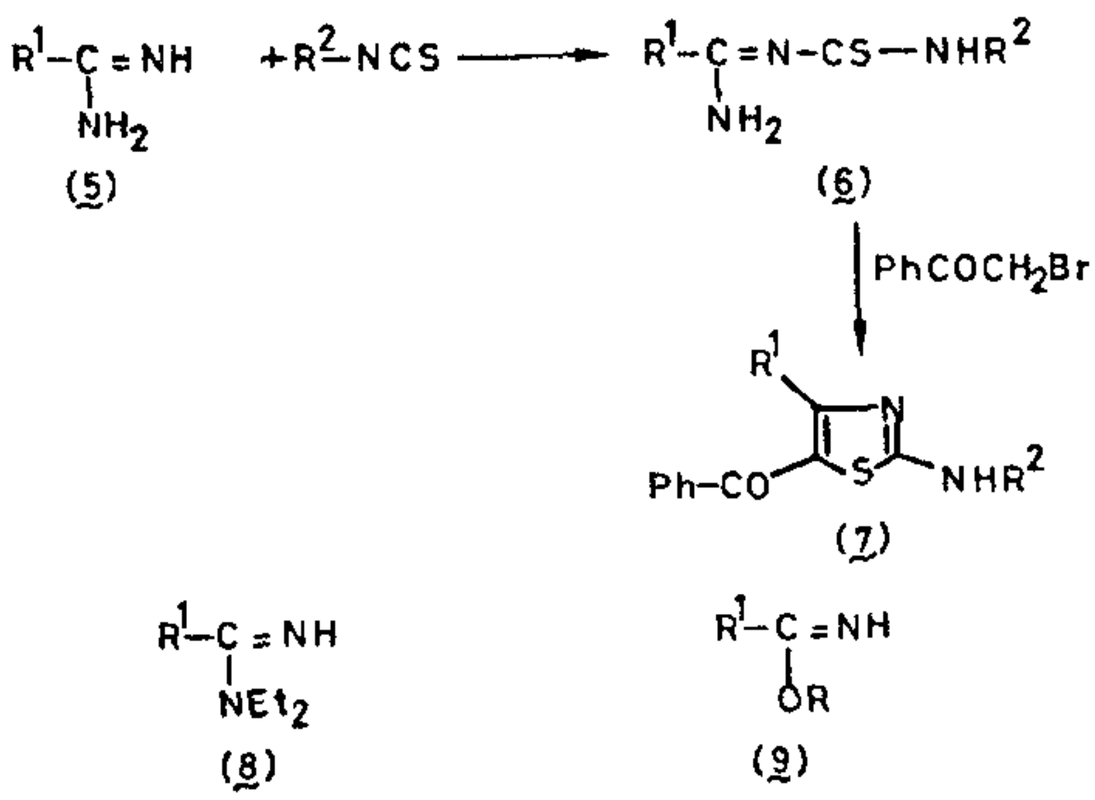
A few years back[1], we allowed the adducts (1) of β-aminocrotonic ester and isothiocyanates to react with phenacyl bromide. At that time we were curious to know whether this would lead to the thiazepine (3). Instead, we found to our surprise that the product was the thiophene (4). Obviously the methylene group next to the sulphur in the intermediate S-alkylated derivative (2) is sufficiently active to displace ammonia from the protonated imine (Scheme 1). The substituents on the thiophene ring thus formed, can be varied over a wide range. The ethyl ester at position 3 could be changed to a *t*-butyl ester, a ketone, or even a nitro group[2–4]; phenacyl bromide could be replaced by α-chloroacetoacetic ester[5] or bromonitromethane[6] leading to a carboxylic ester or a nitro group at position 5. RNCS could be an aliphatic, aromatic or an acyl isothiocyanate.

A more interesting extrapolation of this reaction consisted in the replacement of the C=C of the enamine by C=N, *i.e.*, in the use of amidines as starting materials. As before, addition to an isothiocyanate followed by condensation with an α-halo ketone led to thiazoles (7) (Scheme 2)[7].

Scheme 1



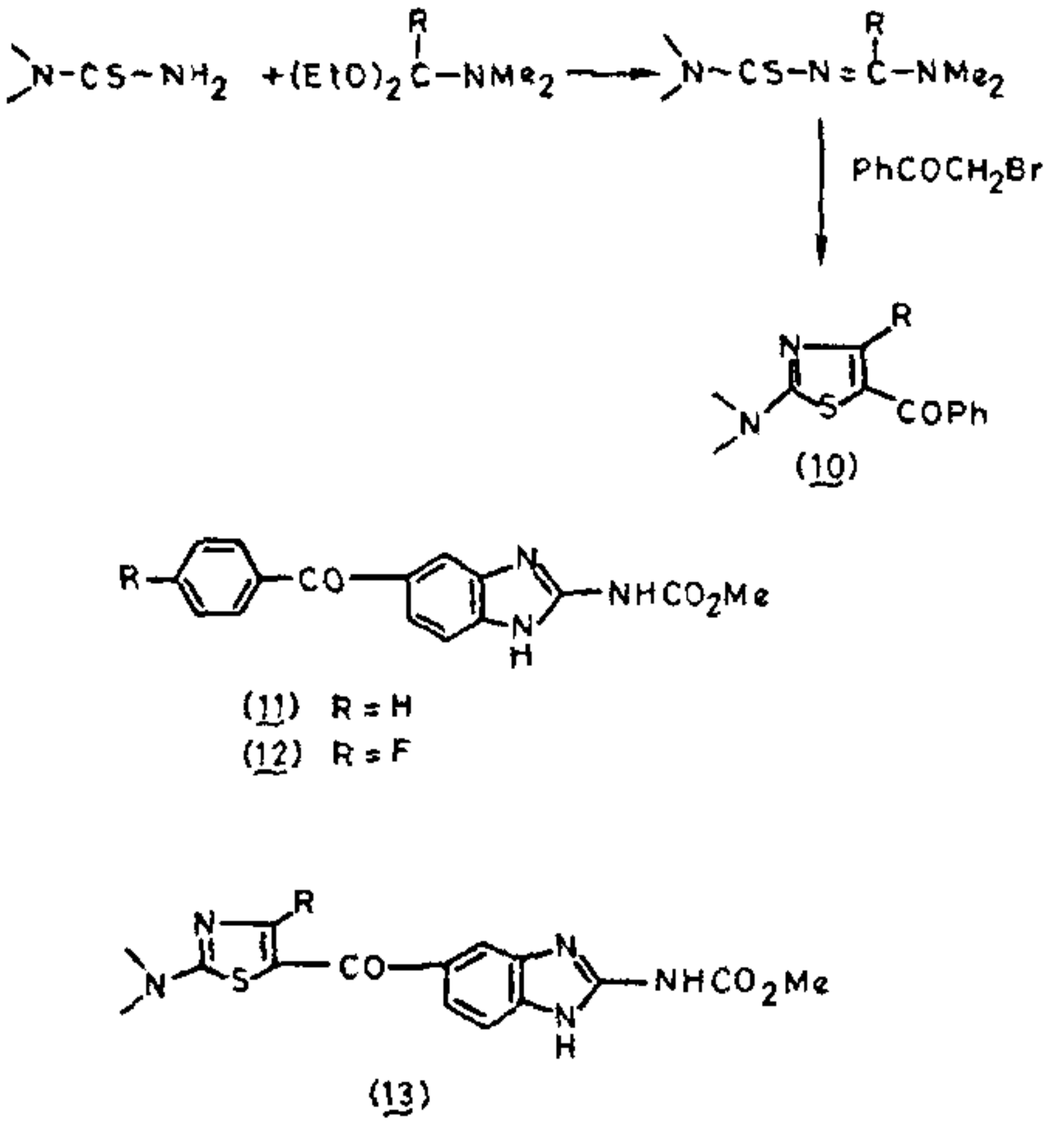
Scheme 2



Several lines of investigation emerged at this stage. We first considered variation in the leaving group at the cyclization step. This became necessary since unsubstituted amidines such as (5) are difficult to handle as free bases. We discovered soon that N, N-disubstituted amidines (8) were ideal for this purpose[8]. The iminoether (9) could also be used as a starting material, but the yields were lower, undoubtedly due to the fact that protonated amines are better leaving groups than alcohols[9].

The next problem was to extend this route for the synthesis of 2-dialkylamino-5-acylthiazoles (10). Obviously the amidine – isothiocyanate adducts (6) are not suited for this purpose. Of the several possibilities we investigated, the route shown in Scheme 3

Scheme 3



was the most satisfactory. This involves condensation of an N, N-dialkylthiourea with an amideacetal and subsequent reaction with phenacyl bromide. The stage was now set for a practical application of all these synthetic studies.

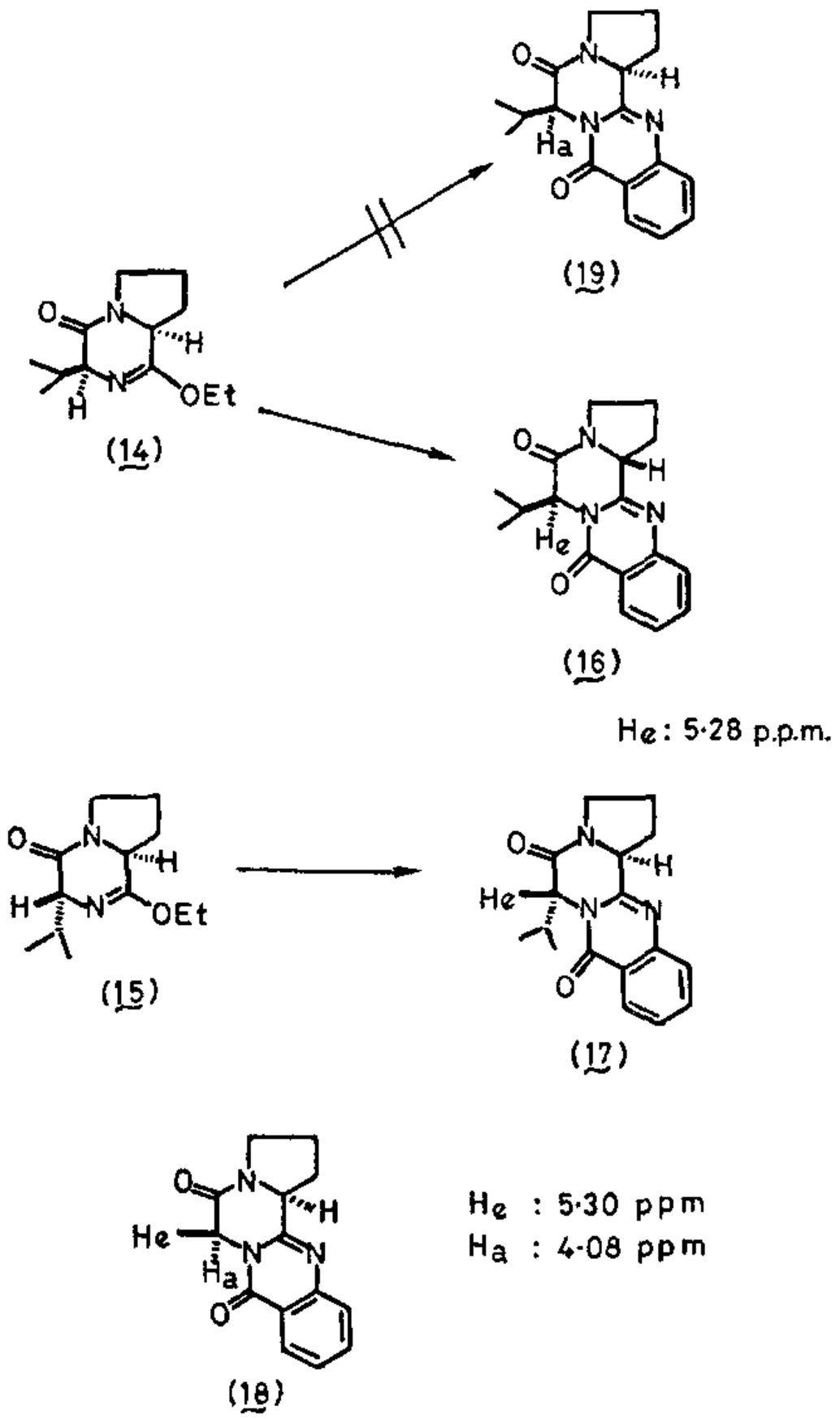
Intestinal helminthic infections are among the most prevalent diseases of man. One of the most commonly prescribed drugs for such parasitic infections is mebendazole (11)[10]. A related compound, flubendazole (12), is also reported to have a wide spectrum of activity against parasites[11]. It was obvious to us that our new thiazole synthesis was capable of leading to thiazoloyl benzimidazoles (13); the use of an appropriately substituted phenacyl bromide, followed by standard synthetic manipulations would convert the benzene ring in (7) or (10) into a benzimidazole. This has indeed been acheived, and has provided us with some promising new antiparasitic compounds[12].

We have so far traced the development of one aspect of our work—from the discovery of a new reaction and exploration of its scope to its application for the construction of useful anthelmintic compounds. It is also possible that chemical insight might be gained as an off-shoot of drug research. One such example is given below.

Quinazolones are known to display a wide variety of pharmacological effects ascribable to their action on the central nervous system. We decided to investigate the effect of fusing the quinazolone ring to a cyclodipeptide unit. As a part of this effort, the two diastereomeric cyclodipeptide monoiminoethers (14) and (15) were prepared from the corresponding diketopiperazines, cyclo (L-Val-L-Pro) and cyclo (D-Val-L-Pro) respectively. The iminoethers were then reacted with anthranilic acid to produce the fused quinazolones. To our surprise, it turned out that the products were enantiomers, instead of being diastereomers. They had $[\alpha]_D$ values of +178·5° and −178° respectively. This incidental observation led us to explore the subtler aspects of stereochemistry and conformation of the molecules, originally synthesised for evaluation as drugs.

It was obvious that in the reaction of either (14) or (15) with anthranilic acid, epimerization at one, and only one, centre must have occurred; and it was easy to deduce that this epimerization involved a proline centre[13]. By comparison of the chemical shift of the proton associated with the valine unit in the enantiomeric pair of products (16) and (17) with those of the "equatorial" and "axial" H atoms of the model compound (18) (derived from glycine, L-proline and anthranilic acid), it was proved that this H atom in (16) and (17) lies in the plane of the rings and the isopropyl group sticks out of the plane of the molecule (Scheme 4). It was therefore clear that the proline-epimerization had occurred

Scheme 4



in the transformation of the iminoether (14) with a *cis*-orientation of the two hydrogens to the quinazolone (16) with a *trans*-orientation. In contrast, the iminoether (15) retains the *trans*-configuration in going to the product (17). We can offer a rationalization for this behaviour. The situation with the isopropyl group in the "equatorial" position, [as in (19)] is sterically very unfavourable; the only reasonable way in which ring C can change its conformation to permit the isopropyl group to occupy the "axial" position would be by epimerization at the proline centre.

We have pursued this line of argument further by snipping off ring D, thereby permitting flexibility to ring C. In the unsubstituted derivative (20) (derived from glycine, sarcosine and anthranilic acid), the H_a and H_e occur as a singlet at around 4.6 ppm (time-averaged mean between the values for the "equatorial" and "axial" hydrogen chemical shifts), indicating conformational mobility. However, with the introduction of a methyl substituent in (21) (derived from L-alanine, sarcosine and anthranilic acid), the chemical shift of the alanine proton freezes at 5.39 ppm proving that the molecule prefers that conformation (22) in which the alanine hydrogen lies in the plane of the ring, with the methyl group above the plane. This situation remains unchanged even up to 150°, indicating the extent to which the quinazolone carbonyl-equatorial methyl interaction is disfavoured[14].

The above conclusions, deduced from NMR data, have been fully confirmed recently in Bangalore by X-ray crystallography[15].

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ANNOUNCEMENT

XTH INDIAN COLLOQUIUM ON MICROPALEN-TOLOGY AND STRATIGRAPHY

The above colloquium will be held during December 21–23, 1982 at the Department of Geology and Palaeontology, Maharashtra Association for the Cultivation of Science, Pune.

Further details can be had from Dr. R. M. Badve, Geology Department, Maharashtra Association for the Cultivation of Science Research Institute, Pune-411 004.

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The above institution has decided to publish a journal early in July this year. Research articles from all the disciplines of mental health and neuro sciences are invited for publication in the journal, subject to the following conditions:—

1. Articles, should conform to the international standards in presentation. The material presented should be the outcome of original research.
2. Articles may be submitted in duplicate, typed in double line space and leaving sufficient margin on either side.
3. Articles may be presented in the following form: Abstract, Summary, Materials and methods, Results and discussion, Conclusion and References.

Gerneral: In the assessment of papers submitted to the Journal, great importance is attached to conciseness and clarity. Authors should check the accuracy of all references in their manuscript and ensure that dates and spellings correspond in the text and reference list.

For details please contact: G. N. Narayana Reddy, Director, National Institute of Mental Health and Neuro Sciences, Bangalore-560 027.