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INTRODUCTION

RESEARCH ON ALKALOIDS, IN RETROSPECT AND IN PROSPECT

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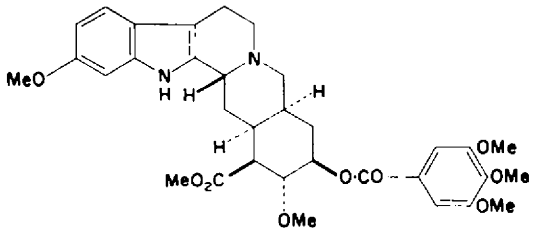
In considering an introduction to this Symposium on New Developments in Alkaloid Chemistry, it is right that one's mind's eye should be cast back to look at the contribution which research on alkaloids has made to the development and vigour of organic chemistry. With pure alkaloids available almost from the start of our science, and with several of them having useful medicinal properties, it is not surprising that they attracted the interest of many great chemists of those times. Indeed, during the classical period of organic chemistry, outstanding contributions to the chemistry of these plant bases were made by Pictet, Perkin, Robinson, Pschorr, Wieland, Willstätter, Karrer, Windaus, Schöpf, Späth and Leuchs. These men were followed, or joined, by many eminent chemists in the 1925–1945 period. The influence which their efforts has had upon organic chemistry as a whole is immense. Perkin's attempts to synthesize quinine which accidentally gave rise to the synthetic dye industry; Willstätter's work on the tropane alkaloids which led to many valuable discoveries including cyclo-octatetraene; Pschorr's phenanthrene synthesis as a direct result of structural work on morphine; the development of important ideas concerning biosynthesis which grew alongside, and in many cases as a result of, increasing knowledge of the structure of alkaloids. The list could be extended but it will suffice to mention the wealth of knowledge concerning properties and reactions which these studies added to the harvest from other fields. Some decline in research effort on the alkaloids occurred during the ten years or so before the middle nineteen forties, but this has been followed by a great expansion in interest and activity which at the present time shows no signs of slackening. This has occurred partly because many of the large pharmaceutical companies have joined in the search for new alkaloids and in the study of their structures, no doubt stimulated by the isolation[1] of reserpine (I). But this effort has been matched by an upsurge of interest and enthusiasm in many academic laboratories where chemists have been attracted by the fascinating problems of structure, stereochemistry, and synthesis in this field.



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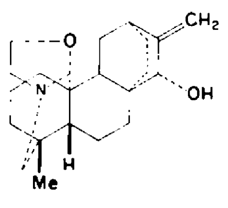

II

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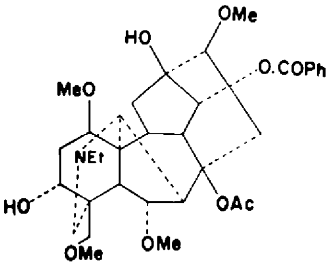
[1] J. M. Mueller, E. Schlittler and H. J. Bein, *Experientia* **8**, 338 (1952).

With all this activity directed towards the alkaloids, it is satisfying to find that this period has been an outstandingly successful one. In giving examples of the progress achieved, it must be stressed that the following pages are intended to be illustrative rather than in any way to give a complete survey. Indeed, if such a survey were attempted, the introduction might well fill several issues.

Several groups of alkaloids of unknown nature were left to us by earlier generations of chemists and these groups represented some of the major unsolved structural problems in the field. Spectacular advances in knowledge of these groups have been made during the past ten years or so. In general, the structures revealed are too complex to have been attacked with any real hope of success with the knowledge, techniques, and equipment of say the nineteen thirties. For example, there has been a complete transformation in our understanding[2] of the diterpene alkaloids isolated from *Aconitum*, *Delphinium*, and *Garrya* species. Two papers in this Symposium deal with the atisine-type alkaloids of which atisine itself has the structure (II). Many fascinating researches[3] have uncovered the structures of those diterpene alkaloids which have rearranged skeletons; aconitine (III) has been a particularly interesting example. In 1956, not a single structure could be given for any of the *Lycopodium* alkaloids but, among others, the structures of annotinine[4] (IV) and lycopodine[5] (V) are now known, and a very satisfying biogenetic pattern is emerging in this group of bases.[6] In the steroidal group of alkaloids, there has been much interest in conessine both structurally[7] and in connexion with the C-18 functionalization of steroids.[8] Also many potentially useful new steroidal alkaloids, including curarizing agents, have been isolated (see p. 126). Rearranged steroidal skeletons have been found in the *Veratrum* alkaloids which extend in complexity from veratramine[9] (VI) to cevine[10] (VII) and its esters. The work on cevine and its relatives is a striking example of the way a difficult structure



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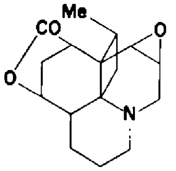

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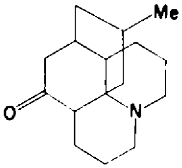

V

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[2] Reviewed by K. Wiesner and Z. Valenta, *Fortschr. Chem. Org. Naturstoffe* **16**, 26 (1958).

[3] K. Wiesner, M. Götz, D. L. Simmons, L. R. Fowler, F. W. Bachelor, R. F. C. Brown and G. Büchi, *Tetrahedron Letters* No. 2, 15 (1959). F. W. Bachelor, R. F. C. Brown and G. Büchi, *Ibid.* No. 10, 1 (1960); K. Wiesner, D. L. Simmons and L. R. Fowler, *Ibid.* No. 18, 1 (1959), and references given therein.

[4] K. Wiesner, Z. Valenta, W. A. Ayer, L. R. Fowler and J. E. Francis, *Tetrahedron* **4**, 87, (1958).

[5] W. A. Harrison and D. B. MacLean, *Chem. & Ind.* 261 (1960) and references given therein.

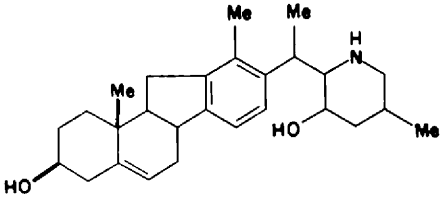
[6] H. Conroy, *Tetrahedron Letters* No. 10, 34 (1960).

[7] H. Favre, R. D. Haworth, J. McKenna, R. G. Powell and G. H. Whitfield, *J. Chem. Soc.* 1115 (1953).

[8] E. J. Corey and W. R. Hertler, *J. Amer. Chem. Soc.* **81**, 5209 (1959); G. Cainelli. M. L. Mihailovic, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **42**, 1124 (1959) and related papers; D. H. R. Barton and J. M. Beaton, *J. Amer. Chem. Soc.* **82**, 2641 (1960).

[9] Ch. Tamm and O. Wintersteiner, *J. Amer. Chem. Soc.* **74**, 3842 (1952).

[10] D. H. R. Barton, O. Jeger, V. Prelog and R. B. Woodward, *Experientia* **10**, 81 (1954); K. J. Morgan and J. A. Barltrop, *Quart. Rev.* **12**, 34 (1958); S. M. Kupchan, W. S. Johnson and S. Rajagopalan, *Tetrahedron* **7**, 47 (1959).



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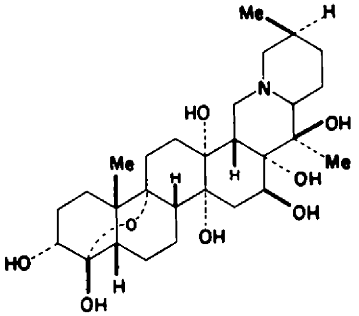
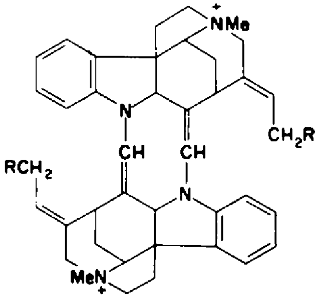


VII

can be elucidated by degradation combined with the extensive use of physical methods and a full application of present knowledge of reaction mechanisms.

Because of their inaccessibility and awkward properties, the quaternary alkaloids of calabash curare have for long appeared in the literature as partial structures showing only fragments of the molecules. Recently, the structures of the key compounds, C-dihydrotoxiferine-I[11] (VIII; R = H) and toxiferine-I[11,12] (VIII; R = OH) have been determined and they are seen to be representatives of a new class of natural products, the dimeric indole alkaloids. With these structures settled, the way has been opened to further structures in this complex group of alkaloids. The Symposium includes an account of the work leading to the structure of the first crystalline calabash curare alkaloid to be isolated, C-curarine-I. Work is proceeding apace on other dimeric indole alkaloids, including geissospermine (see p. 113) in which the two "halves" are linked in a way different from that used in the calabash curare alkaloids.

There is little doubt that the direct X-ray crystallographic method for determination of structure will be used to a steadily increasing extent in natural product work. This is particularly so in the alkaloid field where the necessary heavy atom is so readily introduced. Already this technique has yielded the structures of the rearranged diterpene alkaloids of the lycoctonine type,[13] gelsemine[14] (IX) aspidospermine[15] (X), and



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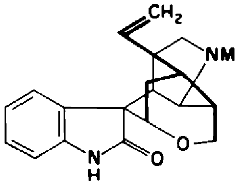

IX

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[11] K. Bernauer, H. Schmid and P. Karrer, *Helv. Chim. Acta* **41**, 1408 (1958); K. Bernauer, F. Berlage, W. von Philipsborn, H. Schmid and P. Karrer, *Ibid.* **41**, 2293 (1958); V. Boekelheide O. Ceder, T. Crabb, Y. Kawazoe and R. N. Knowles, *Tetrahedron Letters* No. 26, 1 (1960).

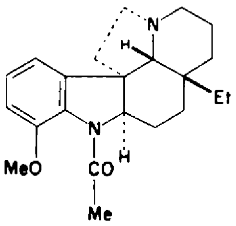
[12] A. R. Battersby and H. F. Hodson, *Proc. Chem. Soc.* 287 (1958). A. R. Battersby and H. F. Hodson, *J. Chem. Soc.* 786 (1960). For reviews see K. Bernauer, *Fortschr. Chem. Org. Naturstoffe* **17**, 184 (1959); A. R. Battersby and H. F. Hodson, *Quart. Rev.* **14**, 77 (1960).

[13] M. Przybylska and L. Marion, *Canad. J. Chem.* **34**, 185 (1956).

[14] F. M. Lovell, R. Pepinsky and A. J. C. Wilson, *Tetrahedron Letters* No. 4, 1 (1959).

[15] J. F. D. Mills and S. C. Nyburg, *J. Chem. Soc.* 1458 (1960).

calycanthine[16] (XI). These bases have all been extensively studied by the degradative approach which, in two of the cases given, yielded virtually simultaneously the same structure as the X-ray method.



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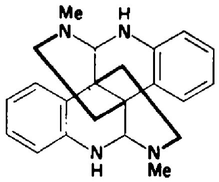
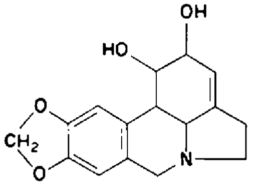


XI

During this same period, new groups of alkaloids have been discovered, and other groups, if not completely new, have been so vastly extended as to have been transformed. This is true of the *Amaryllidaceae* alkaloids[17] where now nearly one hundred are known and the structures of many of them have been worked out. Representative examples are lycorine (XII), haemanthamine (XIII), galanthamine (XIV), and tazettine (XV). As knowledge of this group grew, a close structural relationship between the various members was recognized[18] and explained by a very satisfying and elegant theory[18] based upon phenolic coupling. Moreover, evidence from tracer experiments[19] gives the theory strong support. The number of pure *Rauwolfia* alkaloids has also multiplied to over thirty and in addition to reserpine (I), the structures of ajmaline[20] (XVI) and sarpagine[21] (XVII) are of interest in being tightly caged; closely related



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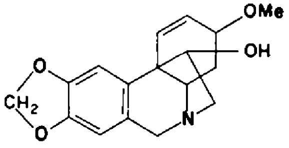

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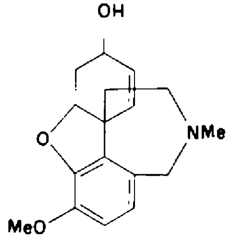

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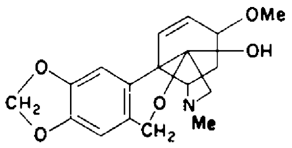

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[16] T. A. Harmor, J. M. Robertson, H. N. Shrivastava and J. V. Silverton, *Proc. Chem. Soc.* 78 (1960).

[17] W. C. Wildman, *The Alkaloids* (Edited by R. H. F. Manske) Vol. VI, p. 290. Academic Press, New York (1960).

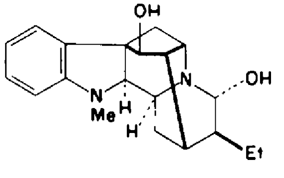
[18] D. H. R. Barton and T. Cohen, *Festschrift Arthur Stoll* p. 117. Birkhauser Verlag, Basel (1957).

[19] A. R. Battersby, R. Binks and W. C. Wildman, *Proc. Chem. Soc.* 410 (1960); see also ref. 38.

[20] R. B. Woodward, *Angew. Chem.* **68**, 13 (1956); Sir R. Robinson, *Ibid.* **69**, 40 (1957) and references given therein; M. F. Bartlett, E. Schlittler, R. Sklar, W. I. Taylor, R. L. S. Amai and E. Wenkert, *J. Amer. Chem. Soc.* **82**, 3792 (1960).

[21] M. F. Bartlett, R. Sklar and W. I. Taylor, *J. Amer. Chem. Soc.* **82**, 3790 (1960) and references given therein.

structures have been found in the calabash curare group.[22] New alkaloidal types have been found in *Tabernathe iboga*[23] and *Voacanga africana*,[24] and the structure of ibogaine[23] (XVIII) shows the unusual seven-membered ring C which characterises this group of bases. Still further new types which lack the "tryptamine"side-chain have been isolated from *Aspidosperma* plants. Examples are uleine[25] (XIX) and ellipticine[26] (XX).



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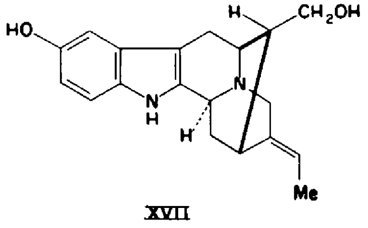

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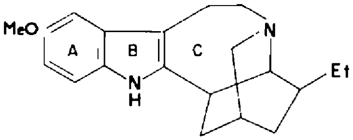

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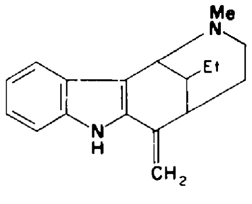

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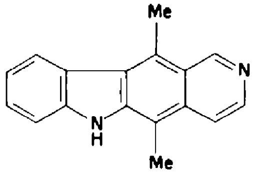

XX

In the isoquinoline series, tremendous progress has been made in the *Erythrina* group[27] leading to many structure elucidations, including erysopine (XXI) and β-erythroidine[28] (XXII). Elsewhere in this series, new structural types are still appearing (see p. 42) and there has been much interest in the stereochemistry and synthesis of isoquinoline alkaloids. Thus the formula (XXIII) is now known to be a complete expression for emetine[29] and this knowledge has been used in a controlled synthesis of

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[22] W. Arnold, W. von Philipsborn, H. Schmid and P. Karrer, *Helv. Chim. Acta* **40**, 705 (1957); A. R. Battersby and D. A. Yeowell, *Proc. Chem. Soc.* 17 (1961).

[23] M. F. Bartlett, D. F. Dickel and W. I. Taylor, *J. Amer. Chem. Soc.* **80**, 126 (1958) and earlier papers.

[24] D. Stauffacher and E. Seeback, *Helv. Chim. Acta* **41**, 169 (1958).

[25] G. Büchi and E. W. Warnhoff, *J. Amer. Chem. Soc.* **81**, 4434 (1959).

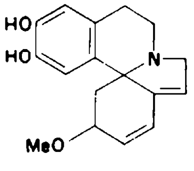
[26] S. Goodwin, A. F. Smith and E. C. Horning, *J. Amer. Chem. Soc.* **81**, 1903 (1959); R. B. Woodward, G. A. Iacobucci and F. A. Hochstein, *Ibid.* **81**, 4434 (1959).

[27] Reviewed by V. Prelog, *Angew. Chem.* **69**, 33 (1957).

[28] Reviewed by V. Boekelheide and V. Prelog, *Progress in Organic Chemistry* (Edited by J. W. Cook) Vol. 3, p. 256. Butterworths, London (1955).

[29] A. R. Battersby, R. Binks and G. C. Davidson, *J. Chem. Soc.* 2704 (1959). A. R. Battersby and S. Garratt, *Ibid.* 3512 (1959; A. R. Battersby, R. Binks and T. P. Edwards, *Ibid.* 3474 (1960); A. Brossi, A. Cohen, J. M. Osbond, Pl. A. Plattner, O. Schnider and J. C. Wickens, *Ibid.* 3630 (1959); E. E. van Tamelen, P. E. Aldrich and J. B. Hester, *J. Amer. Chem. Soc.* **81**, 6214 (1959); Y. Ban, M. Terashima and O. Yonemitsu, *Chem. & Ind.* 568, 569 (1959).

the Ipecacuanha alkaloids.[30] Also, several simple isoquinoline alkaloids, protoberberines (see p. 46), benzylisoquinolines, and benzophenanthridine alkaloids have been synthesized.



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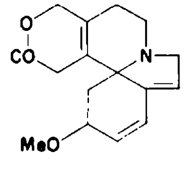

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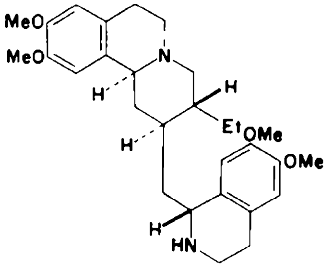

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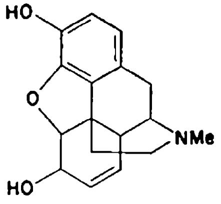

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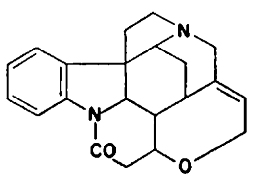

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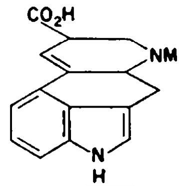


XXVI

At this point, the many brilliant syntheses of complex alkaloids accomplished during the period under review can be collected together. The syntheses of morphine[31] (XXIV), strychnine[32] (XXV), lysergic acid[33] (XXVI), and reserpine[34] (I) amply demonstrate the power of organic synthesis. Around the time these had been completed, Woodward listed[35] a number of objectives for synthesis which included yohimbine[36] (XXVII) and colchicine (XXVIII). Both these difficult objectives have now been reached (see p. 8 and ref. 37) and a synthesis of galanthamine (XIV), patterned on the proposed biosynthetic route, has been achieved.[38]

A major development over the past ten years or so has been the use of radioactive tracers in the study of alkaloid biosynthesis. Much is now known[39] about the biosynthesis of nicotine (XXVIII) the tropane alkaloids, morphine (XXIV) and its relatives, lysergic acid (XXVI), and many simpler structures such as the β-phenylethylamines. Colchicine, as might be expected, is proving to be excitingly unusual.[39] There is much still to be done, but it seems to me that the breakthrough has been made and that progress should now be rapid.

[30] A. R. Battersby and J. C. Turner, *J. Chem. Soc.* 1960, 717; references are given there to other syntheses in this field.

[31] M. Gates and G. Tschudi, *J. Amer. Chem. Soc.* **74**, 1109 (1952); D. Elad and D. Ginsburg, *Ibid.* **76**, 313 (1954).

[32] R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, *J. Amer. Chem. Soc.* **76**, 4749 (1954); R. B. Woodward, *Experientia Suppl.* II (1955).

[33] E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, R. G. Jones and R. B. Woodward, *J. Amer. Chem. Soc.* **76**, 5256 (1954).

[34] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *Tetrahedron* **2**, 1 (1958).

[35] R. B. Woodward, *Perspectives in Organic Chemistry* (Edited by A. R. Todd) p. 155. Interscience, New York (1956).

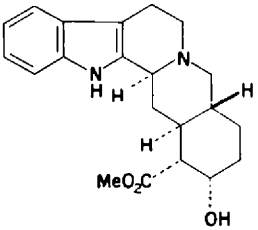
[36] E. E. van Tamelen, M. Shamma, A. W. Burgstahler, J. Wolinsky, R. Tamm and P. E. Aldrich, *J. Amer. Chem. Soc.* **80**, 5006 (1958).

[37] J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel and A. Eschenmoser, *Angew. Chem.* **71**, 637 (1959).

[38] D. H. R. Barton and G. W. Kirby, *Proc. Chem. Soc.* 392 (1960).

[39] Forthcoming review by A. R. Battersby in *Quart. Rev.*

What of the future? There seems to be no sign that all the new structural types of alkaloids have been found. Many new alkaloids will be based upon known skeletons but completely new types are being steadily discovered and my hope and expectation is that this will continue. Thus the prospect seems to be one of increased activity in surveying plants for alkaloids followed by a more rapid determination of the structures of the bases obtained. Without question there will also be a great effort put into the study of alkaloid biosynthesis. Synthesis in the laboratory presents many challenges and lycorine (XII), haemanthamine (XIII), and ajmaline (XVI) all have features which should attract skill and effort. If a still greater challenge is required, then aconitine (III) and cevine (VII) are available.



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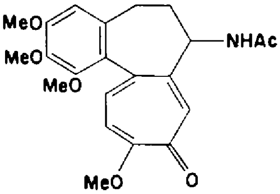
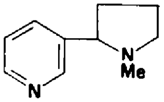


XXVII



XXVIII

I hope that the foregoing paragraphs will have indicated the present flourishing state of alkaloid chemistry and also its bright future. It was these factors which suggested that a Symposium on alkaloids would be timely and welcome. We have been fortunate in securing contributions from many of the outstanding workers in this field and it should be mentioned that an equally strong "team" of different contributors was available. This is indeed a healthy state of affairs. If the present Symposium is judged to add something of value to organic chemistry, then further Symposia might well be arranged in the future so that contributions from other "teams" may be collected together. Comments will be welcomed.