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Editorial

Houben-Weyl on Peptides and Peptidomimetics

Abstract: The new five-volume Houben-Weyl treatise on the Synthesis of Peptides and Peptidomimetics is reviewed and recommended. Copyright © 2003 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: Houben-Weyl; peptide synthesis; peptidomimetics

M Goodman (Editor-in-Chief); A Felix, L Moroder and C Toniolo (Editors). *Synthesis of Peptides and Peptidomimetics*, volumes E 22a–e. Georg Thieme Verlag, Stuttgart and New York 2001–2003. Additional and Supplementary Volumes to the 4th edition of *Methoden der organischen Chemie (Houben-Weyl)*, in English. ISBN 3-13-219604-5; 3-13-114424-6; 3-13-125514-5; 3-13-128874-4; and 3-13-136394-0.

Heinrich J Houben, Berlin Theodor Weyl, Leipzig

I have reviewed the first volume of this quintet already, in the *European Peptide Society Newsletter*. My review, which to some extent anticipated the whole thing, has been reproduced in the APS electronic newsletter and quoted elsewhere. It is very flattering to have my thoughts recycled, but it leaves me a bit bereft of new things to prattle on about here. So, with apology, I shall repeat some of what I have already said, diluted with a little meandering.

The launch publicity was coupled to the centenary of Emil Fischer's classic preparation of glycylglycine, which was further celebrated during the 2002 European Peptide Symposium in Sorrento.

Germany laid the foundations of modern organic chemistry (let alone peptide chemistry) during the latter nineteenth and early twentieth centuries. Think of all those classic name reactions with Teutonic tags. It also spawned an exhaustive chemical publishing tradition which endures. The series which was begun by Heinrich J. Houben and Theodor Weyl before any of us were chemically compos, and which is now so widely known by their conjoined names, is part of that legacy. The two volumes of the first edition 1909–1913 became the four volumes of the second (1921–1924) and third (1924–1941) editions; the fourth edition (1974) runs to some seventy core volumes, and nearly a hundred Additional and Supplementary Volumes (the E-series), since 1958. Originally in German of course, it is now published in English.

The publication of the present treatise is itself a major event in the history of peptide chemistry. I must declare a small interest. I was myself a contributor to the first volume, but writing only some 12 pages, amounting to little more than 1% of that volume and considerably less than 0.5% of the complete work. Further, the minor contributors like me were only the private soldiers in this campaign to bring the literature of the subject into digested subjugation and order. As in war, the responsibility and credit for success belongs to the field-marshal and generals — the Editor-in-Chief and Editors who planned the whole thing and guided it through to

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Murray Goodman, Editor-in-Chief, at the APS in Boston, July 2003.

fruition. As a contributor, I can testify that the planning and detailed editing was undertaken with great energy and care: Murray Goodman, Arthur Felix, Luis Moroder, Claudio Toniolo and the team at Georg Thieme all deserve congratulations.

The first Houben-Weyl treatment of peptide synthesis was originally planned, around 1960, to be a component of a single volume of the fourth edition, but as the 1960s passed it became clear that a whole volume was necessary, and when it was finally published under the editorship of Erich Wünsch in 1974, it had swollen to two massive volumes, XV/1 and XV/2. There was a similar expansion while work was in progress on the great work now on my desk, E 22, which was planned to appear as two volumes, then four, and in the end was five, E 22a–e. Whereas the monumental work of 1974 was pretty well exhaustive, the even more monumental work which has now emerged is not, even for publications since 1974. It is comprehensive in its range — over a wider front than before because of the inclusion of peptidomimetic chemistry, which has burgeoned in the meantime — but critical and selective in policy.

Although the Houben-Weyl volumes XV/1 and XV/2 of 1974 will retain their value in many respects as a means of accessing the earlier literature, E 22 is a stand-alone authority on the whole field of peptide and peptidomimetic synthesis.

The standard of the English employed is excellent, and only rarely does a slight awkwardness of

composition or usage slip through to hint that some of the material was conceived and perhaps even drafted in German. But few readers will notice such things.

A feature which may irritate some users, however, is the occasionally intrusive repetition of safety warnings. In a litigious age, the desire of all concerned to protect themselves against accusations of negligent failure to warn is well appreciated. But when it results, for example, in the ritual recitation seven times in the space of three pages (E 22a, pp 429–431) of the hazards of hydrazine, it approaches absurdity. On the other hand, it is not at all absurd that the safety warnings about $BocN_3$ are longer than the experimental description — actually the best advice about $BocN_3$ is 'use something else if you possibly can, and if you must use $BocN_3$, then for goodness sake don't distil it'. Further, the hazards of the stuff are not only explosive. In the years of my innocence, I distilled $BocN_3$ more than once without untoward event — except on one occasion when the instinctive old-fashioned chemist's sniff at the product produced immediate but dramatic pharmacological effects: I fainted — I think it must be a swift short-acting vasodilator. The serious point I want to make is that it is dangerous to give the impression of having included exhaustive safety warnings, because any such attempt is doomed to fail. It fails here, for instance, by not sounding the alarm every time benzene or HF is mentioned, and by describing procedures involving some hazardous reagents (such as oleum, chlorine, ethyl isocyanate, *t*-butyl nitrite, oxalyl chloride) without warnings. The real danger is that novices may fall into the trap of following a prescribed procedure without thinking and assessing hazards for themselves.

My lawyer advises that I should point out here that the paper on which this review is printed is inflammable; further, the ink used may contain toxins, and so eating the *Journal of Peptide Science* is inadvisable.

The editors of E 22 have not slavishly kept to the title they were given. This is a good thing, because quite a bit of useful material on characterization and properties has been included on the one hand, without embracing every last kind of peptidomimetic on the other. It would have been perfectly logical, but somehow absurd, if the synthesis of morphine etc had been included. Morphine is after all the archetypical peptidomimetic — it works by aping enkephalin — but it belongs to another parish. But should it? The demarcation lines have to be drawn somewhere for publication purposes, but intellectually it is not by any means so clear. Classical peptide synthesis involved a very narrow range of chemical reactions, but peptidomimetic chemistry is a much more diverse business, less easily defined. It has opened the doors to the whole gamut of organic chemistry. One wonders indeed whether peptide chemistry should really be hived off as a separate mystery at all. It is convenient, but can lead to a blinkered mindset.

Because the Editors have been hitched to a juggernaut, it is no criticism of them to question the validity of the overall Houben-Weyl approach. Who will actually use the selected experimental procedures as printed without reference to the primary literature? If any of them on repetition cause a disaster, the safety police may say it was irresponsible of the victims not to check original authorities, especially as the publishers repeat their disclaimers so often. It is difficult to feel that the effort and cost behind reproducing so many experimental procedures was really worthwhile. It seems most improbable that any laboratory with enough funds to buy these five volumes will be remote from a major library in which full and original experimental detail could be found. Similarly, although the four volumes of E 22a-d are a rich data-mine, and E 22e is a powerful tool for excavating their treasures, specific questions about the literature are these days surely more swiftly answered, and more exhaustively, through services such as SciFinder Scholar®, my favourite. This is not to imply that the five volumes of E 22a-e are not a cost-effective investment. They most emphatically are. My feeling is that they could have been even more cost-effective by cutting out most of the experimental procedures; the value of volumes E 22a-d lies in the critical discussion and leading references given.

Each section contains critical introductory material (often concise and rather original first-time reviews), with carefully selected protocols and a corresponding bibliography. Stabbing more or less at random takes us to a typical Section, 10.6, by S.Ro, on the *Synthesis of Peptides Containing C/O Amide Bond Replacements*. It runs for 26 pages, gives 95 references, and some 25 experimental procedures. The synthesis of dipeptide building blocks containing the $\psi[CH_2O]$-, $\psi[CH(OH)CH_2]$-, $\psi[CH_2CH(OH)]$-, $\psi[CH(OH)CH(OH)]$-, $\psi[C(=O)CH_2]$-, and $\psi[CH(O)CH]$-peptide bond isosteres is covered, all well elucidated and illustrated with clear formulae.

The Editors themselves have not merely presided and shirked the front-line work, but have earned their wages and contributed large sections themselves; distinguished as they all are, that adds greatly to the authority of the work. So does the inclusion of contributions from such luminaries of the subject as Professors Ugi, Jakubke, Stewart, Merrifield, Atherton, Meldal, Barany, Benoiton, Sakakibara, Ivanov, Carpino, Martinez, Offord, Mutter, Jung, Hruby, Giralt, Albericio, Atherton, Houghten, Rivier, Kessler. No doubt I have missed some stars in this arbitrary recitation, but I offer as a lame excuse that there is no convenient single overall checklist of contributors. Come to think of it, my earlier military metaphor may not be as apposite as I had fancied — we have an army of generals here, and few foot soldiers. The ordinary soldiers who were recruited should reflect on Napoleon's dictum, and those who declined the opportunity may rue the day. One contributor's name I see is poignant: my friend the late Arno Spatola, who as long ago as 1983 was one of the first to recognise the emerging importance of peptidomimetics in a seminal review*, which made me for one start to wake up to a coming shift in emphasis for peptide chemistry. He died suddenly shortly after the publication of the new Houben-Weyl was completed, at the height of his powers as Secretary of the APS, aged only 59.

The five volumes are priced separately, and so can presumably be bought separately, but the conception is a unified one, and the indexes are all in E 22e. Although each of E 22a-d has an extended contents list, E 22e, with its exhaustive author, keyword, and preparation indexes, is in my opinion an indispensable tool for their use. Picking and choosing among the volumes would appear to be ill advised. Despite the cost — 9500 Euros for the full set at the regular price — everyone engaged in the area will want easy access, and for peptide research groups of any size it will be a time-saving, thought-provoking, and worthwhile investment, not a luxury.

JOHN JONES
Editor-in-Chief
Balliol College
Oxford
[john.jones@balliol.ox.ac.uk]

* "Peptide Backbone Modifications" in *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, **3**, pp. 267–357