Journal of Peptide Science
J. Pept. Sci. 2006; **12**: 563–568
Published online 19 May 2006 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/psc.766

JOURNAL OF PEPTIDE SCIENCE

Historical Essay

Peptide chemistry at Oxford before the Second World War

RACHEL CURTIS and JOHN JONES*
Chemistry Research Laboratory, University of Oxford, OX1 3TA, UK

Received 4 April 2006; Accepted 4 April 2006

Abstract: The largely unnoticed and unpublished peptide science interests of Nobel Laureate Sir Robert Robinson at Oxford during the period 1936–1939 are outlined. Copyright © 2006 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: Robinson; Sir Robert; Rockefeller Foundation; peptide chemistry; history of

Peptide chemistry has recently celebrated its centenary [1], and its history, entwined with the development of molecular biology as it is, has become an area of interest to historians of science [2,3].

The early roots of the subject are found in Germany, spreading to the United States, especially in the person of Max Bergmann, who was driven out by Hitler but enabled to continue his work – with Leonidas Zervas, the inventor of the Z group [4] – by the support of the Rockefeller Foundation. Guided by Warren Weaver from 1932 [5], the Foundation took an inspired interest in the application of physical science to biology, especially anything to do with proteins [6–8].

X-ray diffraction observations were made in England during the thirties by W. T. Astbury on protein fibres in Leeds, and on crystalline pepsin by J. D. Bernal and Dorothy Crowfoot (later Hodgkin) in Cambridge, and by her, publishing alone, on insulin in Oxford. Important enabling advances in chromatography were described by A. J .P. Martin and R.L.M. Synge soon after the War broke out. During the War, there was an intensive UK-USA programme directed at solving the structure of and synthesising penicillin, which is a peptide of sorts. This work, driven by its military significance and consequently secret, was only reported confidentially within a very limited circle, and did not enter the public domain until 1948, only in a condensed form [9]. The literature records then practically nothing else of note in the peptide field from English laboratories until well after the Second World War, when, in the late forties and early fifties, the synthetic schools of G. W. Kenner, H. N. Rydon [10] and G. T. Young [11] were established, and Frederick Sanger laid the foundations of sequence analysis.

It was therefore quite a surprise to discover, during the compilation of a history of Oxford's Dyson Perrins Laboratory 1914–2004, that in the thirties Robert Robinson, Waynflete Professor of Chemistry at Oxford 1930–1955, had entered the fray with a Rockefeller-funded grant aimed at 'protein synthesis'. This work has hardly been noticed because it was abruptly abandoned in 1939, and was never taken up again or published. Robinson, who contributed to organic chemistry in diverse ways – mechanistic theory, biosynthetic ideas, natural product structure and synthesis – was one of the great all-time geniuses of the subject, on a par with Emil Fischer and R. B. Woodward. Robinson would have had a major impact on peptide science of he had returned to it after the War.

Kenner and Rydon were pre-War associates of Robinson, although they were not working on peptides at the time, and Friedrich Weygand [12] was another of his co-workers who became well known in the field during the fifties and sixties. And, although she never worked under his immediate direction, Robinson encouraged Dorothy Crowfoot in the mid-thirties, by using his influence to obtain Rockefeller funding for X-ray equipment for her, and it was through him that she obtained her first insulin crystals.

Robinson was very active in Oxford efforts to organise suitable jobs and other help for Jewish academics displaced by the Nazis [13]. Support for two of them, which he obtained from the Rockefeller Foundation in 1933 [14] began a relationship between him and the Foundation that was to continue until the end of his tenure.

Dorothy Wrinch also became known to the Rockefeller Foundation at about this time, through separate recommendations by the physiologist J. B. S. Haldane and the physicist F. A. Lindemann [15].

Wrinch was a mathematician based in Oxford without a Faculty position or College Fellowship, having moved to Oxford to join her husband, John Nicholson. He was a mathematician too, a Fellow of Balliol of considerable distinction who had come close to anticipating Niels Bohr's atomic theory, but in 1930 he was certified insane and confined for the remaining 25 years of his life. This left Wrinch to support herself and their

*Correspondence to: J. Jones, Chemistry Research Laboratory, University of Oxford, OX1 3TA, UK; e-mail: john.jones@balliol.ox.ac.uk

daughter by service mathematics teaching for women's colleges.

The first woman to be awarded an Oxford DSc degree, Wrinch developed an interest in the application of mathematics to biology, and in 1935 she was awarded a 5-year Rockefeller grant to relieve her of the need to maximise her income from teaching drudgery so that she could develop her ideas [16]. As an early result, by the application of topological and numerological arguments, she arrived at a novel hypothesis of protein structure.

Wrinch envisaged that proteins were not composed of linear chains of amino acid residues as in the simple peptides made by Emil Fischer and others, but of peptide chains with further 'cyclol' connections resulting from (we would now say) nucleophilic addition of peptide bond nitrogens to the carbonyl groups of other peptide bonds (Figure 1).

The two-dimensional networks of six-membered rings assembled in this way formed sheets of protein 'fabric', which could be moulded into hollow structures like (another anachronism) the fullerenes. She was not abashed by the fact that cyclol connections were counter-intuitive to experienced organic chemists, who in any case could not immediately refute her proposition. Little was known for certain about protein structure at that time. They were macromolecules, composed of amino acids condensed together, but evidence on how the units were linked was thin.

So the cyclol hypothesis was not damned at the outset. Wrinch was a woman with a forceful personality, forceful enough to persuade Robinson, the dominant force in Oxford and indeed British chemistry, to take her seriously despite his doubts. His genius included advanced chess talents, symptomatic perhaps of a turn of mind, which made him receptive to mathematical argument. The upshot was that Robinson decided to attempt to explore the validity of the hypothesis experimentally, and sought a Rockefeller grant to enter the field. After considerable correspondence and personal visits by Rockefeller scouts, the Foundation was informed [17] as follows:

> *Professor R. Robinson ... is the outstanding organic chemist of England and ranks very near the top among the organic chemists of the world ... Professor Robinson's project for a five year study of the proteins is direct result of the work of Professor W. T. Astbury of Leeds and more particularly of Dr Dorothy Wrinch of Oxford, both of whom are pursuing their investigations with Rockefeller Foundation assistance ... Dr Wrinch, in her mathematical analysis of the proteins, ... [has] arrived at a new and most promising view of protein structure.*
>
> *The development of this new theory was an unexpectedly prompt result of the recent grant to Dr Wrinch. She discussed her ideas at length with Professor Robinson who has written "As a preliminary I ought to say that I think Dr Wrinch's views on protein structure, whether they are fully substantiated in the future or not, certainly provide a working hypothesis, and indicate a fresh mode of entry into the field of protein investigation ... It seems to me that the ordered arrangement of the polypeptide chains contemplated by Dr Wrinch represents an extremely natural marshalling of the units, and I am particularly impressed by number of the numerical coincidences, which she has disclosed, and by the way this conception explains many of the most puzzling properties of the proteins. My own ideas in this field are but loosely connected with the more precise conceptions of Dr Wrinch, but my attention having been drawn to the subject, I have formulated a number of schemes for the synthesis of polypeptides of high molecular weight, and I am of the opinion that these schemes should be tested, and that there are splendid opportunities in this purely synthetic field ...*

A major grant was made, of $40 800 over 5 years 'for researches in the Dyson Perrins Laboratory of Organic Chemistry on the SYNTHESIS OF PROTEINS under the direction of Professor R. Robinson'.

The programme undertaken from 1936 to 1939 involved L. J. Goldsworthy [18] and F. E. King as Robinson's lieutenants supervising research by junior associates including E. P. Abraham. It comprised the attempted synthesis of oligopeptides with a view to investigating cyclol formation by them; the copolymerisation of *N*-carboxy (Leuchs) anhydrides to generate protein models; and the study of film formation from amino acids and simple peptides acylated by fatty acids. By 1939, a substantial volume of work had been more or less completed, but apart from a brief note with Abraham on the first crystallisation of lysozyme [19] none of it was ever published under Robinson's name. The record of his role only survives in passing acknowledgements [20,21], in theses [22,23], in unpublished research reports to him by Goldsworthy [24], and by Robinson himself to the Rockefeller Foundation [25].

The protein analogue work can be seen as anticipating later results, especially by Woodward and Schramm [26], which opened the way to diverse studies of

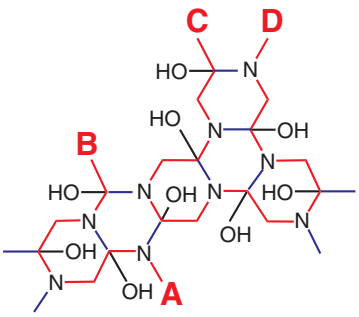

Figure 1 A fragment of Wrinch's cyclol fabric. Side chains are omitted for clarity. The fabric is formed from two sections of peptide backbone, shown in red, cross-linked by amide N to amide CO 'cyclol' connections, shown in blue. An infinite two-dimensional network can be formed in this way, and appropriately sized pieces of fabric can be shaped into completely enclosed structures with no edges.

DOI: 10.1002/psc

polypeptide properties in simplified but high molecular weight models, which helped in the understanding of native proteins.

The synthesis of the linear oligopeptides required for the work did not take advantage of the Z group for *N*-protection, which is not easily compatible with acid chloride activation, and which at that time could only be cleaved reductively. The phthaloyl group, independently developed and published by Sheehan and Frank [27] after the War, was used instead, building on the observation a decade or so before [28] that phthalimides were smoothly cleaved by hydrazine. The synthesis shown in Figure 2 [29] exemplifies what Robinson's people were able to achieve.

Their success with 'PhtGlyGlyCl' is testimony to their skill, which anyone who has tried acid chloride activation of protected peptides will admire. A perfect chlorine analysis was obtained for the protected dipeptide chloride, but it was very probably actually the isomeric oxazolone hydrochloride, like 'hippuryl chloride', which has properties pointing that way [30].

The cyclol hypothesis stimulated a lot of debate for a while, and for that reason alone has a place in the history of peptide and protein science, but by 1938 the only prominent chemist supporting Wrinch was Irwin Langmuir [31].

The theory was comprehensively debunked by Linus Pauling in the following year [32]. Wrinch thought herself a woman wronged by the male scientific establishment, but did herself no favours by lack of tact and appearing to twist the evidence in her direction. There is absolutely no evidence that she was the victim of any anti-feminist attitudes; so far as Oxford chemists were concerned, it can be pointed out that there were several women being accorded professional status and respect among them, not least Robinson's wife and Dorothy Crowfoot. Wrinch's biographers have tended to be sympathetic, and she deserves that because her private life was traumatic. But she was a difficult, pushy, blinkered and manipulative person at this stage. And the cyclol hypothesis was in fact a rather mad theory judged from a chemical perspective. In retrospect, it is surprising that it had as much credence, albeit short-lived, as it did.

In 1940, Wrinch emigrated to the USA, clinging to the delusion that there was something in her ideas, and as late as 1965 she published a book on the subject [33]. A cyclol-like motif does occur in some alkaloids such as ergotamine, and at least one artificial cyclol structure has been generated (Figure 3) and proven by X-ray crystallography [34,35], but this is evidently a very special case.

Robinson concluded that the cyclol hypothesis was untenable and fell out with Wrinch [36] not long after his programme had begun, and it may be that the declaration of War gave him an escape route to terminate his work. Whatever the background, that was where his peptide studies ended, and the Rockefeller Foundation agreed for its support to be diverted to his other research [37–39], as well as largely funding a major extension to the Dyson Perrins Laboratory, which was completed in 1940 notwithstanding the War.

Within a short while, however, fate threw more peptide-related chemistry into Robinson's lap. Penicillin was shown by Florey and his colleagues, by this time including Abraham, in the Oxford Dunn School of Pathology just along the road from the Dyson Perrins Laboratory, to be a wonder-drug. Its structure, and hopefully synthesis, became of enormous human (and soon military) importance. This developed into a major transatlantic project, with Robinson as the British driving force. Wilson Baker and John Cornforth were also involved, along with Abraham and others. Ironically, as the structural solution loomed into sight, Robinson was a slightly retarding influence, because he would not easily give up on an oxazolone structure for the correct but uncomfortably novel β-lactam structure (Figure 4) favoured by some of his co-workers and eventually proved by Dorothy Hodgkin's X-ray work [40].

After the War, Robinson's energies were taken up in manifold ways beyond peptide chemistry, which he never revisited. In 1947, he gave G. T. Young laboratory space, but Young's appearance on the Oxford scene had nothing to do with Robinson. He was elected to a Fellowship at Jesus College, by the independent powers

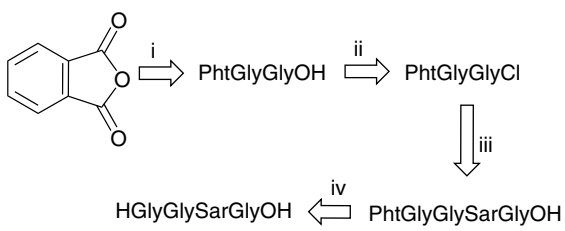

Figure 2 Pthaloyl protection.
Conditions: i, HGlyGlyOH, heat; ii, PCl_5-$POCl_3$, rt, 80–90%, rext. ex $CHCl_3$ by addition of Et_2O, mp 152°, good chlorine analysis; iii, HSarGlyOH; iv, NH_2NH_2.

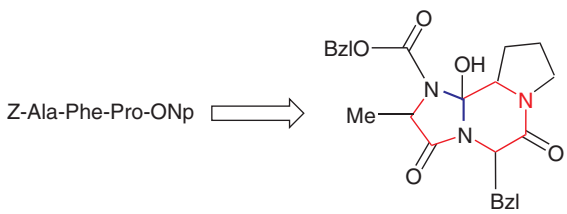

Figure 3 A cyclol synthesis.
Conditions: aq. $NaHCO_3$-Na_2CO_3 buffer-dioxan, room temp. The original peptide backbone is shown in red and the cyclol connections in blue. Actually, this well-characterised compound is an [amide N + imide CO] cyclol rather than an [amide N + amide CO] cyclol as conceived by Wrinch.

DOI: 10.1002/psc

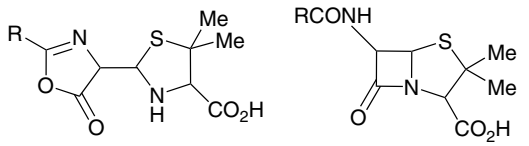

Figure 4 Penicillin. The oxazolone and (correct) β-lactam structures proposed by Robinson and Abraham respectively.

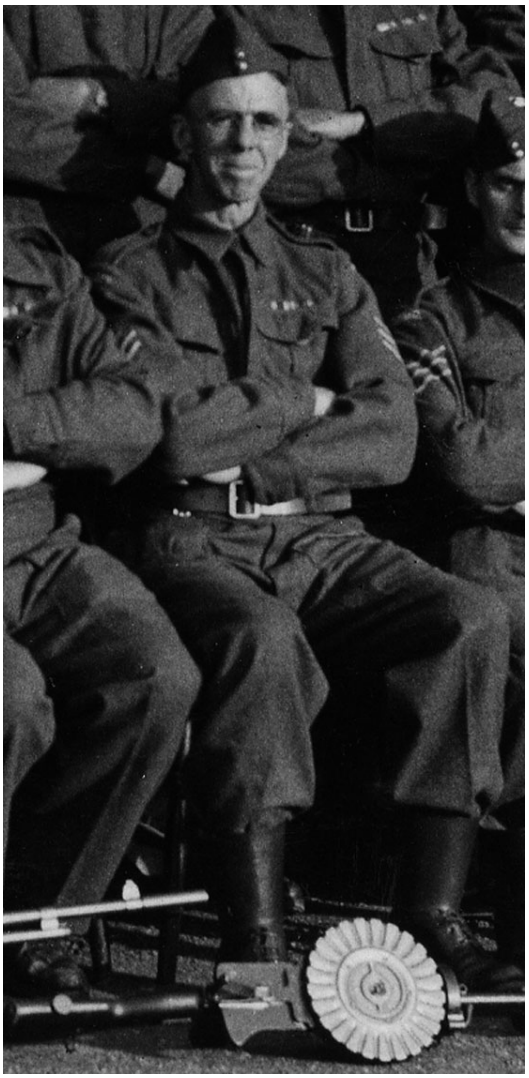

Figure 5 Sergeant (intelligence) L. J. Goldsworthy of the North Oxford home guard, about 1942.

of that College, whose eyes would have been more on their teaching needs in organic chemistry than anything else. He came from the University of Bristol, with a background in carbohydrate chemistry, but with the imagination to see that amino acid peptide and protein work was timely. Robinson did not actively discourage him, but the school of peptide chemistry that Young established in Oxford, and which one of us had the great privilege of joining in its heyday, was his child, not Robinson's.

Figure 6 F. E. King, 1946.

A NOTE ON SOURCES

The great majority of the individuals named above were elected to the Royal Society, and several were awarded Nobel Prizes. For them, detailed biographical information can easily be located through *Biographical Memoirs of Fellows of the Royal Society* or the *Oxford Dictionary of National Biography* or Nobel Prize related sources. Accordingly, biographical sources are only cited below for less well-recorded people.

Much has been written about Dorothy Wrinch. *The Oxford Dictionary of National Biography* article gives more respect to the cyclol hypothesis than it deserves, but is very useful for the other biographical accounts it cites. For a more robust recent judgement, which coincides with ours, refer to Tanford and Reynolds [41].

DOI: 10.1002/psc

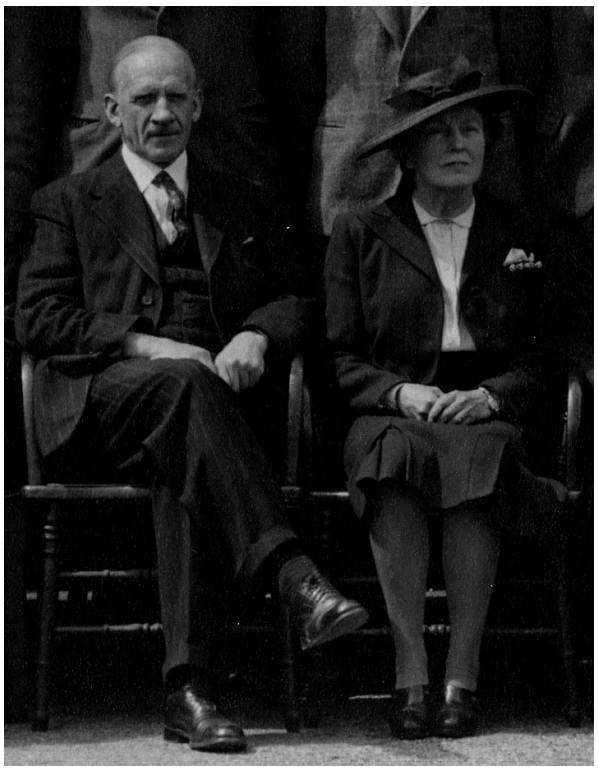

Figure 7 Sir Robert and Lady Robinson, 1946.

There is extensive documentary material relevant to the subject of this brief note in the Rockefeller Archive Center (Sleepy Hollow, New York); in the Archives of the University of Oxford; and in the personal papers of Dorothy Wrinch (Sophia Smith Collection, Smith College), Sir Robert Robinson (Royal Society Library, London), Sir Edward Abraham (Bodleian Library, Oxford), and Dorothy [Crowfoot] Hodgkin (Bodleian Library, Oxford).

During our research, we had occasion to pursue to source some references to the secret wartime reports on penicillin. These, the 695 so-called CPS Reports, are listed in *The Chemistry of Penicillin* [9]. It was recorded [42] that sets of the CPS Reports had been placed in various publicly accessible repositories, but it is unfortunately the case that most of these sets cannot presently be traced in the places where they were said to have been deposited. It may therefore be helpful to note that an apparently complete set is to be found in the personal papers of Sir Edward Abraham.

Acknowledgements

We are grateful to many correspondents for help and comment, especially Dr A. S. Bailey, Sir John Cornforth, Mrs J. M. Curtis, Mr H. W. Goldsworthy, and Dr G. T. Young. Archivists at the National Institute for Medical Research, the Royal Society, our own Oxford University Archives, the Bodleian Library and the Rockefeller Archive Center all gave us far better service than we could reasonably have expected.

Figure 5 is reproduced by courtesy of Mr H. W. Goldsworthy; Figures 6 and 7 are from a photograph saved from the Dyson Perrins Laboratory; Figure 8 is reproduced by permission of Associated Press/EMPICS.

Figure 8 Dorothy Wrinch showing a cyclol model to Katherine Blodgett, an associate of Langmuir's. *c* 1940.

DOI: 10.1002/psc

REFERENCES

1. Jones JH. A peptide centenary celebration. *J. Pept. Sci.* 2003; **9**: 531–533.
2. Naider F, Goodman M. 100 years of peptide synthesis. *Houben-Weyl* 2002; **E22a**: 1–16.
3. Wieland T, Bodanszky M. *The World of Peptides. A Brief History of Peptide Chemistry*. Springer-Verlag: Berlin, 1991.
4. Bergmann M, Zervas L. Uber ein allgemeines verfahren der peptid-synthese. *Berichte* 1932; **65**: 1192–1201.
5. Warrren Weaver (1894–1978). Obituary notice; *New York Times* 25 November 1978.
6. Kohler RE. *Partners in Science. Foundations and Natural Scientists 1900–1945*. University of Chicago Press: Chicago, 1991.
7. Kay LE. *The Molecular Vision of Life: Caltech, the Rockefeller Foundation and the Rise of the New Biology*. Oxford University Press: New York, 1992.
8. Glass B. The Rockefeller Foundation: Warren Weaver and the launching of molecular biology [a review essay on G Jonas "The circuit riders: Rockefeller money and the rise of modern science", New York, 1989]. *Q. Rev. Biol.* 1991; **66**: 303–308.
9. Clarke HT, Johnson JR, Robinson R. *The Chemistry of Penicillin*. Princeton University Press: Princeton, 1949.
10. Henry Norman Rydon (1912–1991). Obituary notice: Ridge B. *Chem. Br.* 1992; 732.
11. Geoffrey Tyndale Young (1915–). Founding Chairman of the European Peptide Society.
12. Friedrich Weygand (1911–1969). Obituary notice: Simon H, Steglich W. *Z. Naturforsch. B* 1970; **25**: 126–133.
13. Morrell J. *Science at Oxford 1914–1939*. Oxford University Press: Oxford, 1997; 380.
14. Miller HM. Diary entry, 25 September 1933; Rockefeller Foundation Archives, Rockefeller Archive Center, RG12.1, box 44.
15. Miller HM. Diary entry, "Miscellaneous gossip with Prof. Haldane," 14–15 March 1934; Rockefeller Foundation Archives, Rockefeller Archive Center, RG12.1, box 44.
16. Miller HM. Diary entry, 26 October 1934; Rockefeller Foundation Archives, Rockefeller Archive Center, RG12.1, box 44.
17. Rockefeller Foundation Archives, Rockefeller Archive Center, RG1.1, series 401D, box 38, folder 497.
18. Leonard James Goldsworthy (1890–1960). Obituary notices: (a) Robinson R. *Nature* 1960; **188**: 536; (b) Smith JC. *Proc. Chem. Soc.* 1961; 181–183; (c) Peacock DH. *The Times* 1960; (d) Jones ERH. *The Times* 1960.
19. King FE, Kidd DAA. A new synthesis of glutamine and of γ-dipeptides of glutamic acid from phthalylated intermediates. *J. Chem. Soc.* 1949; 3315–3319.
20. Abraham EP, Robinson R. Crystallization of lysozyme. *Nature* 1937; **140**: 24.
21. Koebner A. Palmitoyl and stearoylglycylglycine and -diglycylglycine. *J. Chem. Soc.* 1941; 564–566.
22. Bowman A. *Investigations on the cyclisation of peptide chains*, DPhil Thesis, Oxford, 1940.
23. Abraham EP. *Part 1. Some substituted peptides. Part II. Experiments with lysozyme*. DPhil thesis, Oxford, 1938.
24. Goldsworthy LJ. Reports and drafts submitted to Sir Robert Robinson, c1939. Robinson Papers, Royal Society Library, B285 & 286.
25. Robinson R. Report for the Rockefeller Foundation on work supported by it 1936–1938, sent with his letter to WE Tisdale dated 6 December 1938. Rockefeller Foundation Archives, Rockefeller Archive Center, RG1.1, series 401D, box 37, folder 472.
26. Woodward RB, Schramm CH. Synthesis of protein analogs. *J. Am. Chem. Soc.* 1947; **69**: 1551–1552.
27. Sheehan JC, Frank VS. A new synthetic route to peptides. *J. Am. Chem. Soc.* 1949; **71**: 1856–1861.
28. Ing HR, Manske RHF. Modification of the Gabriel synthesis of amines. *J. Chem. Soc.* 1926; 2348–2351.
29. Goldsworthy LJ. Experimental detail drafted for a paper which was never published, *c*1939. Robinson Papers, Royal Society Library, B286.
30. Karrer P, Bussmann G. Einwirkung von diazomethan auf hippursäurechloride. *Helv. Chim. Acta* 1941; **24**: 645–646.
31. Wrinch DM, Langmuir I. The structure of the insulin molecule. *J. Am. Chem. Soc.* 1938; **60**: 2247–2255.
32. Pauling L, Niemann C. The structure of proteins. *J. Am. Chem. Soc.* 1939; **61**: 1860–1867.
33. Wrinch D. *Chemical Aspects of Polypeptide Chain Structures and the Cyclol Theory*. Plenum Press: New York, 1965.
34. Lucente G, Romeo A. Synthesis of cyclols from some small peptides *via* amide-amide reaction. *Chem. Commun.* 1971; 1605–1607.
35. Cerrini S, Fedell W, Mazza F. *X*-ray crystallographic proof of a cyclol structure in a tripeptide. *Chem. Commun.* 1971; 1607–1608.
36. Tisdale WE. Diary entry, May 3, 1938. Rockefeller Foundation Archives, Rockefeller Archive Center, RG1.1, series 401D, box 37, folder 472.
37. Robinson R. Letter to H. M. Miller, 6 October 1939. Rockefeller Foundation Archives, Rockefeller Archive Center, RG1.1, series 401D, box 37, folder 473.
38. Robinson R. Letter to the Registrar of the University of Oxford, 25 September 1939. Oxford University Archives UR/6/CHE/5 file 1.
39. Weaver W. Letter to Sir Robert Robinson, 15 December 1939. Rockefeller Foundation Archives, Rockefeller Archive Center, RG1.1, series 401D, box 37, folder 473.
40. Abraham EP. Sir Robert Robinson and the early history of penicillin. *Nat. Prod. Rep.* 1987; 41–46.
41. Tanford C, Reynolds J. *Nature's Robots. A History of Proteins*. Oxford University Press: Oxford, 2003; 115–117, paperback edition.
42. ANON. Reports on penicillin. *Nature* 1947; **159**: 565–566.

DOI: 10.1002/psc