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A brief encounter on steroids between Robinson and Woodward in 1951

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Dedicated to Robinson and Woodward, eventual founding co-Chairmen of the Tetrahedron Journal.

ABSTRACT

A supposed apocryphal encounter between Robert Robinson and R. B. Woodward was found to be confirmed in Sir Robert's handwritten memoirs. The current article examines what lay behind this strained meeting of two of the greatest protagonists of organic chemistry from the last century, and its aftermath in the context of what became a race to publish the first total synthesis of a non-aromatic steroid.

Sir Derek H. R. Barton in his 1991 autobiography 'Some Recollections of Gap Jumping', regaled a jaw dropping tale of an encounter between two of the most distinguished organic chemists of the last century, Sir Robert Robinson (RR, Oxford, UK) [1] and R. B. Woodward (RBW, Harvard, USA) [2]: 'By pure chance, the two great men met early on a Monday morning on an Oxford train station platform in 1951. Robinson politely asked Woodward what kind of research he was doing these days; Woodward replied that he thought that Robinson would be interested in his recent total synthesis of cholesterol. Robinson, incensed and shouting, "Why do you always steal my research topics?", hit Woodward with his umbrella.' [3] (!) While Barton then added 'This story must be true, because Woodward told me about it several days later', the anecdote, or even that this meeting between RR and RBW happened, has been considered doubtful [4,5]. However, Robinson in his unpublished and unfinished (due to his death in 1975) second volume of memoirs wrote (in a draft chapter entitled: Synthesis in the group of the Steroids): 'At this time I encountered R. B. Woodward on the platform of the Oxford railway station and learned that he had come to England in order to deliver a lecture on the synthesis of cholesterol.' [6] The current article examines the events that led to this chance meeting between RR and RBW, why it might have been a strained one, and its aftermath particularly in the context of publication precedent in non-aromatic steroid total synthesis.

The third Waynflete Professor of Chemistry at Oxford, W. H. Perkin, Jr, died in post at age 69 on September 17, 1929 and Robinson was appointed in November that year to replace him. Robinson was widely considered a natural and obvious successor to his doctoral supervisor (when they were both at Manchester): aged 43 he had a stunning record of academic achievement and in 18 years had already held professorships at five major universities (Sydney, Liverpool, St Andrews, Manchester, and University College London), moreover he was familiar with Oxford having carried out very productive work with Perkin continuously since his graduate studies [7]. Robinson's time in Oxford has been well documented elsewhere [8–10] and only aspects pertinent to the current focus are summarised here; it was a productive period but not without its difficulties. Nevertheless, while Robinson's rapid turnover of university chairs eventually led somebody to ask when next he would be moving, he replied that 'since the only better place to be was Heaven, he intended to stay in Oxford' [8]; his tenure at Oxford lasted a quarter of a century until retirement. His steroid studies commenced in 1932 and were towards the simpler partially aromatic systems and were sustained (albeit with some reduction during the war years) through to stereochemically more complex non-benzenoid targets, resulting in 53 papers over two decades [11,12].

In early 1951 Robinson was 64, his work had been recognised by the Nobel Prize in 1947 (sole recipient, 'for his investigations on plant products of biological importance, especially the alkaloids') and by the Order of Merit in 1949. Among the many and increasing calls on his time outside of Oxford, he had been President of the Royal Society 1945–1950. Due to retire as Waynflete Professor later in 1951, he had applied in 1950 for extension of tenure to 1955. Dalziel Hammick, a contemporary long-standing academic colleague of his in the Dyson Perrins Laboratory, said at the time "sheer eminence will get it for him" [10]; it was formally granted by the University on March 6, 1951. By then the steroid studies were finally closing in on non-aromatic targets, mainly being driven by John Cornforth [13] - a man who Robinson profiled in his unfinished memoirs, saying 'the synthesis (of the Köster–Logemann ketone, Scheme 1) was far from easygoing and I make bold to say the success was entirely due to Cornforth's personal bench work and the skill with which he attacked and overcame formidable obstacles as they arose. In my experience only R. B. Woodward could equal his pertinacity.' [6] Cornforth had arrived in Oxford in late 1939 along with his eventual wife Rita Harradence, both from Sydney and each holding a prestigious 1851 Scholarship; they both carried out their

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graduate studies with Robinson. Cornforth completed his doctoral studies on steroid synthesis in 1942. His initial results laid the foundation for the ultimately successful approach almost a decade later. After his DPhil he made significant contributions to the joint UK/US wartime project on penicillin. In 1946 he moved, with the support of Robinson, to the National Institute for Medical Research, run by the Medical Research Council (M.R.C.), and resumed steroid research in collaboration with RR.

The steroid work of Woodward (and Robinson) [11,14–18], as well as Woodward's rise to prominence [19,20], have been reviewed elsewhere, and again only material pertinent to the 1951 encounter with RR is discussed here. Woodward's interest in steroid chemistry was deep-rooted, tracing back as far as his second year as an undergraduate at MIT, when at the end of a lecture in which the difficulty of synthesising estrone from carbon was mentioned, he proposed a way that impressed both the lecturing Professor and the Department. Both his BS thesis and PhD thesis (submitted only a year later in 1937), focused on this problem; in the introduction to the latter, he mentions probable structure determinations of the steroids and then presciently wrote 'the problem must be considered unfinished, however, until the present views have been confirmed by the total synthesis of one or more of these important substances.' [21] Steroid studies continued at Harvard, after an initial period there as research assistant to Kohler. This followed a summer teaching position at Illinois, where Roger Adams had raised Robinson's estrone work in his reply to RBWs application in 1936. In 1940, three steroid related papers were published by Woodward, as sole author; one of which related to his graduate study work. Thereafter focus shifted – with wartime-related studies, including penicillin, a famous quinine synthesis and structure elucidation of strychnine being notable highlights. In the late 1940s, worldwide interest in access to steroids was significantly ramping up with reports on cortisone to treat rheumatoid arthritis. Woodward returned to the field in a characteristically intense period of research on the synthesis of non-aromatic steroids, commencing in autumn 1949 and culminating in four communications 1951 and a classic full paper in 1952 [22].

Prior to their crescendo of activity on non-aromatic steroid synthesis, Robinson and Woodward had mutual history albeit in structure elucidation, of penicillin (where Edward Abraham's proposed structure, supported by Woodward, was shown to be correct) and latterly strychnine (another long-standing interest of RR). Both episodes have been reviewed in detail [8,23,24]. RR and RBW met at least twice to discuss strychnine, one of these being in New York in August 1947, and there was frequent, respectful correspondence between the two. Indeed, Woodward's sole-authored paper on the 'biogenesis of the strychnos alkaloids' (eventually shown to be incorrect) [25], written in December 1947 and submitted to the journal *Nature*, appeared in July 1948 with, unusually, two paragraphs added at the end from Robinson supporting the article [26]. This happenstance arose, as Woodward wrote to Robinson with a copy of the manuscript in March 1948, 'through an extraordinary error on the part of the Editors of Nature … They sent to me, at my address, the original copies of the manuscript, together with a note to you, at my address {Woodward's underlining}, requesting your opinion.'[27] Woodward also lectured on strychnine at Oxford in June 1948 and at the lecture 'Robinson was very complimentary, saying that he had scrutinised Woodward's {biogenesis} paper very carefully but could find no fault!' [28]. This was despite Robinson greeting 'him there with the question: "Dr. Woodward, why can't you work on your own problems?"' [25]. RBW was visiting England at the time as a side trip on his first visit to Europe, as American Swiss Foundation Lecturer following the invitation of Ruzicka at the ETH. In the audience at RBWs mesmerising London lecture, on the structure of santonic acid, were Derek Barton [29] and Franz Sondheimer [30], both Hofmann Prize winners as the top Imperial College students in their graduating years (1940 and 1945, respectively), and both research fellows at Imperial College at the time of the lecture. Barton and Sondheimer would go on to form close associations with Woodward: Barton initially in Harvard in 1949-50 to cover a sabbatical year for Woodward (who remained in Harvard) and where Barton wrote his famous *Experientia* paper on conformational analysis - instrumental in his 1969 Nobel Prize; Sondheimer, inspired by Woodward's London lecture, became a leading post-doc in the subsequent steroid work at Harvard.

The relationship between Robinson and Woodward deteriorated later in 1948 when Robinson angrily broke correspondence off following his reading of Woodward's claim of priority of assignment of the true structure of strychnine [31]. As Robinson wrote to Vladmir Prelog at the ETH, an academic respected by both RR and RBW, in August 1948: 'Altogether a very bad paper and exceedingly foolish from the Woodward point of view. It cannot harm me but any reaction will not be good for him.' [32] Prelog, who came to regard Woodward as his best personal friend [33], made efforts to bridge the differences. This included pursuing a note he drafted on the constitution and configuration of strychnine, with himself, Robinson and Woodward as authors and that he first wrote to Robinson about at the end of April 1950. Woodward even wrote directly to Robinson in May 1950 to say: 'I wish once again to reaffirm to you with all sincerity my respect and admiration for you and for your work, and to ask if it is too much to expect that you air your grievance with me directly, with a view to resolving our differences, and returning to the cordial relations which we once enjoyed.' [34].

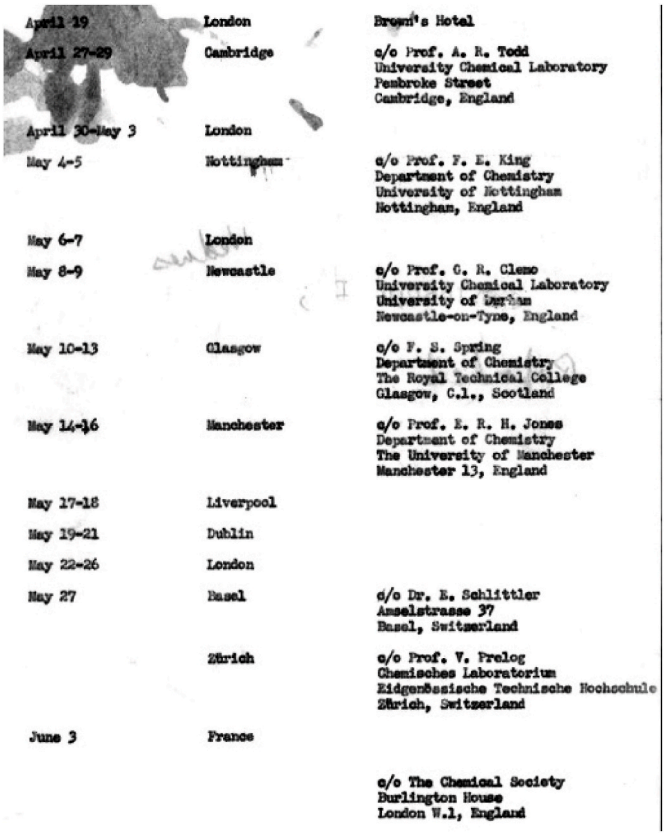
The centenary celebrations of the Chemical Society, due to take place in 1941, were postponed until after the war and the associated endowed lectures have run in an unbroken series since 1949. In the minutes of the Chemical Society of January 19, 1950 concerning endowed lectures, it was reported that 'provided the Society agreed to share the cost, the University of London would consider extending an invitation to Professor R. B. Woodward to lecture in the UK during the forthcoming session. It was agreed that Professor Woodward should be appointed … [as Centenary Lecturer for the session 1950/51 …] and that the Society would refund to the University of London half of the expenses involved.' [35] It seems likely that Sir Ian Heilbron was instrumental in this arrangement. Heilbron was President of the Chemical Society 1948–1950, held the Chair of Organic Chemistry at Imperial College at the time of Woodward's 1948 visit and had been a doctoral supervisor to both Barton and Sondheimer.

Woodward had a strong sense of history and was a showman; when in spring 1950 he accepted the Centenary Lecture invitation, the possibility of announcing the total synthesis of steroids within the hallowed walls that housed one of the oldest chemical societies in the world would have been appealing. Moreover, with Sondheimer and three other postdocs (Karl Heusler, W. M. McLamore and David Taub) he 'could hardly have had a more able and devoted workforce' [30]. By early April 1950 a key *anti*, *trans* BCD trieneone (Scheme 2) had been made and by that autumn a tricyclic enone acetonide [22]. Nevertheless, synthesis of complex natural products takes time – even with those co-workers, supplementation of building blocks from industry, and Woodward's strategic brilliance together with his intense and inspirational leadership. Despite severed communications with Robinson in 1949, Woodward was certainly aware that Robinson, substantially aided by the skilful Cornforth, was gradually closing in on a non-aromatic steroid total synthesis [36]. For example, on his return to London from Harvard in June 1950 and to a faculty position at Birkbeck (initially as Reader),

Barton wrote to Woodward, 'From Sir John {Simonsen} I learn that the great Sir Robert has been making rude remarks about you in connection with strychnine. Apparently you stole his idea! or some nonsense like that. It seems that Sir Robert is an irascible old man. I visited the M.R.C. the other day and learnt that he is planning to synthesise cortisone in seven stages.' [37].

Prelog chased up the joint strychnine note with Robinson in late August 1950, but by late November was writing to Woodward with bad news: 'Sir Robert finally answered me. He still seems very angry with you and didn't want to sign the note with you. I wrote him a very nice letter about 6 weeks ago and tried to change his mind, but he didn't answer me at all. We could now publish the message alone, it is perhaps superfluous, as you will certainly write something about strychnine soon and you can then highlight the essentials in your message. Sir Robert actually disappointed me a lot.' [38] Woodward's reply to Prelog in February 1951 gives a good indication of his thoughts on the matter, less than two months before his Centenary Lecture trip: 'I too was again disappointed to learn of Sir Robert's continuing bad behaviour; perhaps most of all I feel sorry for him, who seems to live in a world in which he must bear the unpleasant burden of ill-will against a colleague who admires his work with perhaps better reason than most, and who has certainly done him no wrong. May we be less irascible and jealous of our fancied prerogatives in our old age!' [39].

This was the state of affairs then when Woodward once again took a stratocruiser from New York to London to lecture in the UK and Europe, although the geographical focus this time during the two-month sojourn in 1951 was very much the UK. Arriving in London on Thursday 19th of April, he took up residency at the magnificent Browns Hotel, ahead of his main Centenary Lecture at Burlington House a week later. The UK itinerary subsequently encompassed lecture visits to Cambridge, Nottingham, Newcastle, Glasgow, Manchester, Liverpool and Dublin; Oxford was noticeably absent from the list (Fig. 1)!



April 19	London	Brown's Hotel
April 27-29	Cambridge	c/o Prof. A. R. Todd University Chemical Laboratory Pembroke Street Cambridge, England
April 30-May 3	London	
May 4-5	Nottingham	c/o Prof. F. E. King Department of Chemistry University of Nottingham Nottingham, England
May 6-7	London	
May 8-9	Newcastle	c/o Prof. C. R. Clemo University Chemical Laboratory University of Durham Newcastle-on-Tyne, England
May 10-13	Glasgow	c/o F. S. Spring Department of Chemistry The Royal Technical College Glasgow, C.1., Scotland
May 14-16	Manchester	c/o Prof. E. R. H. Jones Department of Chemistry The University of Manchester Manchester 13, England
May 17-18	Liverpool	
May 19-21	Dublin	
May 22-26	London	
May 27	Basel	c/o Dr. E. Schlittler Anselstrasse 37 Basel, Switzerland
	Zürich	c/o Prof. V. Prelog Chemisches Laboratorium Eidgenössische Technische Hochschule Zürich, Switzerland
June 3	France	
		c/o The Chemical Society Burlington House London W.1, England

Fig. 1. Woodward's personal itinerary for his 1951 visit to the UK and Europe; Oxford is noticeably absent [40].

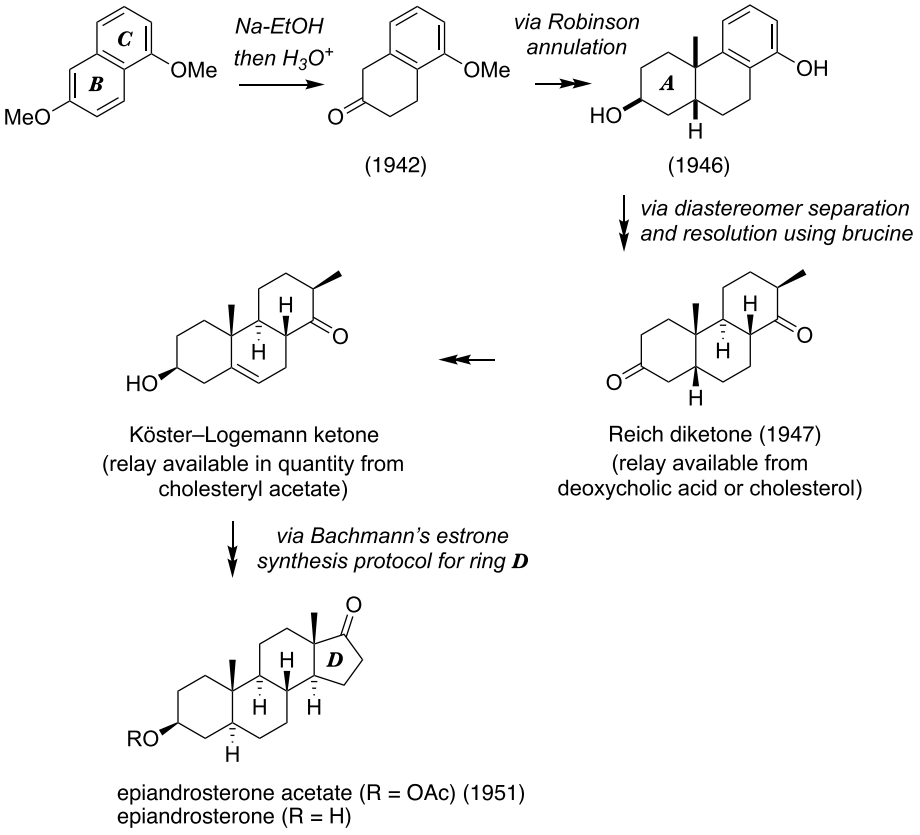
At the time of Woodward's arrival in the UK in 1951, he had just turned 34, had risen the academic ranks at Harvard being recently promoted to full Professor. His list of published academic achievements were substantial, although at that stage they were arguably more notable in the area of structure elucidation than synthesis (aside from quinine). Before crossing the Atlantic in April 1951, a key intermediate, racemic methyl 3-keto-4,9(11),16-etiatrienate (Scheme 2), had been reached, 'at 3 a.m., March 30, 1951, in ample time for Woodward to prepare his Chemical Society Centenary Lecture of April 26, 1951.' [22] It contained the full steroid ABCD tetracyclic system with the correct relative stereochemical array and functionality present to lead on to the major steroid targets. Although short of a total synthesis, it represented a major step forward and the story of its elegant assembly would indeed be announced at the Centenary Lecture, under the usual generic title Woodward gave for all his talks, 'Some Recent Advance in the Chemistry of Natural Products'. Efforts to link the intermediate through to naturally occurring steroids, including cholesterol and ultimately cortisone, would continue at Harvard while RBW was abroad. In preparation for the lecture, Woodward familiarised himself with a copy of the Centenary Lecture given by Prelog from two years previously. RBWs drafts of his own lecture, archived at Harvard, indicate the typical detail he took including timings for each section of the presentation [41]. A press announcement on the intermediate would be made at Harvard on the eve of the talk, with faculty colleague Paul Bartlett fielding questions.

Woodward possessed an incredible work ethic and was not a tourist. Although his wife had joined him on the 1951 UK visit and there were some small gaps in his program following the main London lecture, it seems certain that he remained abreast of his many chemistry projects. He gave additional lectures in London: at University College and on patulin synthesis at Birkbeck [42]. Regarding the encounter with Robinson, Woodward's itinerary together with both the wording of the anecdote from Barton and Robinson's reminisces, suggest Woodward visited Oxford in the week after his arrival in the UK and prior to giving his main Centenary Lecture in London. If indeed the encounter occurred early on a Monday morning, then that would have been 23rd of April, the first day of the undergraduate Trinity (summer) term. Robinson was nominally timetabled to give a second-year undergraduate lecture at 9 a.m. in the Dyson Perrins Laboratory that day [43], so could have been travelling back to Oxford to deliver it. However, Robinson had been involved in that lecture course for 20 years, and his rising external commitments through that period, particularly post-war, would have meant that he increasingly delegated such matters to his junior staff members; more likely he and Woodward met while waiting for a London train (than both stepping off one). Why might Woodward have visited Oxford? He had good scientific contacts with academics such as Edward Abraham and Harold Worrall Thompson (at St John's College) who were involved in the transatlantic wartime penicillin project, but a more likely host was the crystallographer and future Nobel laurate Dorothy Hodgkin. In the latter's "Memories of RB Woodward" solicited by Harvard following RBW's death, she wrote: 'Bob Woodward and I first met at MIT: where I came to give a lecture on penicillin during my first visit to the United States {1947}. After the lecture he came to discuss it and invited me to his home for lunch next day. I was charmed by his and his

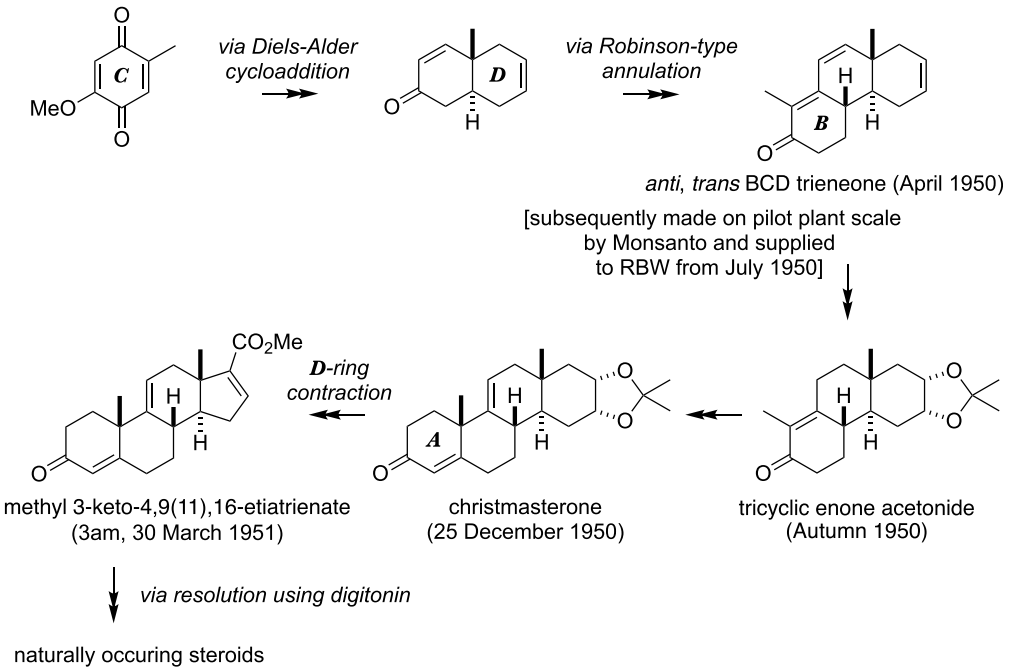
wife's hospitality, the family circle, children coming and going from school, and most of all by our afternoon talking together of our experiences in the study of penicillin. After that, visit to Harvard was never complete without a call on Bob and the chemistry laboratory – somehow he seemed always to find time to tell me what was happening. Intermittently, we met elsewhere." [44] Hodgkin would certainly have been in Oxford at that time for the start of term – but had unavoidable (unlike Robinson) lecturing that morning and laboratory demonstrating that afternoon [43]; moreover, in the close-knit Oxford academic chemistry community and as a collaborator on crystal structures with Robinson (including many steroid-related ones), she could well have been aware of Robinson's regular travel routines …

Woodward was a meticulous planner and did not do things by accident. No doubt RBW did not visit Oxford with the express intention of encountering the man he had long admired, who he was in direct competition with and who had rebuffed his efforts at reconciliation. Perhaps the meeting was indeed an accident, but if the opportunity of a meeting arose why not take it? As Barton wrote in his autobiography: 'Woodward was always interested in the psychology of human behaviour. In particular, he liked to observe the reaction of someone to a mild stress imposed by himself.' [3] The renowned chemist Gilbert Stork has provided some stronger views about his old Harvard colleague: "He {Woodward} was quite capable of viciousness, but it was a highly intellectual, structured viciousness. It was not emotional. When he was rude, he knew he was rude and was rude for a purpose." [45] Although Robinson was prone to strong outbursts at times, we only have Woodward's word via Barton that Robinson raised an umbrella in ire (unsurprisingly, Robinson doesn't mention anything about that in his unpublished memoirs!). Ranganathan, a close postdoc of Woodward, has commented:' he {[RBW} had a fountain of stories to tell, some perhaps invented' [46]. William S. Johnson, an academic colleague of Woodward, and who also made substantial contributions to steroid synthesis, wrote in his autobiography: 'without finding out anything about Bob Woodward's steroid synthesis, Robinson accused him of thievery. Bob, who related this to me, seemed to be more amused than hurt.' [47].

Regardless of any physical interaction, Woodward's verbal assertion to Robinson concerning his synthesis of cholesterol was a little ahead of actual progress in his Converse Memorial Laboratory at Harvard. Remarkable as it may seem, the implication from Robinson's memoir is that prior to his encounter with RBW at Oxford railway station he wasn't even aware that Woodward was lecturing in the UK. However, the meeting may have backfired on Woodward, prompting Robinson and Cornforth to disclose their synthesis of epiandrosterone acetate as a communication, grandly entitled 'total synthesis of androgenic hormones', in *Chemistry and Industry* (*C&I*) [48]. Unfortunately, the journal did not indicate the date of receipt of communications, but Robinson stated in his subsequent full paper (published in 1953) [49] that 'the submission of our preliminary note on the synthesis of the androgenic hormones was quickly followed by a verbal disclosure of the very different synthesis by R. B. Woodward and his colleagues'. Although Robinson's synthesis was a tour de force, it was lengthy, made use of relays to make the final target, and lacked stereocontrol (production and separation of diastereomers at various stages, Scheme 1). The use of relays reduces the torment of the 'chemical Sisyphus', as described by Cornforth in his consummate 1954 review on 'total synthesis of steroids': 'To symbolise eternal torment the Greeks imagined Sisyphus, who rolls his rock forever upwards to an unattainable summit. The chemical Sisyphus sees the rock grow smaller at every step; he must reach the top before it crumbles away, or start again from the bottom.' [11] Significantly, the Robinson-Cornforth achievement did represent the first synthesis of an



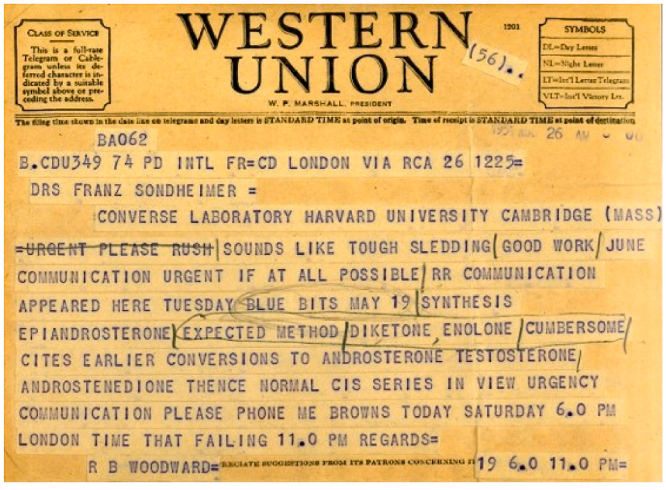
Scheme 1. Outline of the Robinson-Cornforth ***BC→ABC→ABCD*** epiandrosterone synthesis.



Scheme 2. Outline of Woodward's ***CD→BCD→ABCD*** steroid synthesis.

androgenic hormone; indeed, it constituted the first published synthesis of a non-aromatic steroid from simple starting materials (Sarett's ~40-step synthesis of cortisone, completed in 1944 and reported in 1946, was from steroidal bile acids [16]). Strictly speaking, Robinson and Cornforth initially reported the synthesis of the acetate of the natural product epiandrosterone (Scheme 1).

The omission of the acetate hydrolysis step in their communication could be considered an indication of a rush to submit the work. Robinson subsequently reported the acetate hydrolysis in his 1953 full paper, marginalising it as a 'punctilio' {a fine or petty point of procedure} [49]. [The abstract at the start of the full paper erroneously refers to the synthesis in the *C&I* article being that of epiandrosterone.] However, and although not referenced in the 1951 communication (nor in the 1953 full paper), acetate hydrolysis of naturally derived epiandrosterone acetate to epiandrosterone *had* already been reported, by Wenner and Reichstein in 1944 [50]. In any event, the 1951 *C&I* note appeared in the Saturday 19 May edition and Woodward became aware of the article a few days later on his return to London from Dublin at the end of his UK lecture tour. RBW was clearly concerned, as indicated in the telegram he sent from Browns Hotel to Sondheimer on Saturday May 26th, the eve of his departure to Europe (Fig. 2).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=URGENT PLEASE RUSH SOUNDS LIKE TOUGH SLEDDING GOOD WORK JUNE COMMUNICATION URGENT IF AT ALL POSSIBLE RR COMMUNICATION APPEARED HERE TUESDAY BLUE BITS MAY 19 SYNTHESIS EPIANDROSTERONE EXPECTED METHOD DIKETONE ENOLONE CUMBERSOME CITES EARLIER CONVERSIONS TO ANDROSTERONE TESTOSTERONE ANDROSTENEDIONE THENCE NORMAL CIS SERIES IN VIEW URGENCY COMMUNICATION PLEASE PHONE ME BROWNS TODAY SATURDAY 6.0 PM LONDON TIME THAT FAILING 11.0 PM REGARDS=

R B WOODWARD= 19 6.0 11.0 PM=

Fig. 2. Woodward's turn to feel the pressure: his telegram to Sondheimer following Robinson's 'total synthesis of androgenic hormones' publication [51].

The subject of RBW's Centenary Lecture, the synthesis of the ABCD steroid skeleton in racemic form (Scheme 2), was received by the *JACS* the day after the lecture, subsequently appearing as a "communication to the editor" a few days later in the 8th of May issue [52]. Although titled 'the total synthesis of a steroid', Woodward would have been well aware that this fell short of a steroidal natural product total synthesis. By the time Woodward spoke to Sondheimer on May 26th, the ABCD steroid skeleton had been resolved and converted to known intermediates linking to a variety of steroid natural products. Sondheimer duly wrote to Marshall Gates (an assistant editor at *JACS*) that day enclosing a draft manuscript containing this information. The cover letter effectively assumed Marshall's rapid approval, adding in a ps that acknowledged 'the imperfect appearance of the communication, but we'll retype it before giving it to Bliss {managing editor of *JACS*, based in Boston, who would arrange publication} on Monday morning.' [53] Despite this, the article 'the total synthesis of some naturally occurring steroids' just missed the June edition, appearing in the July issue (*JACS* was published monthly in those days), with a May 27th receipt date [54]. It appeared alongside another Woodward communication entitled 'the total synthesis of cholesterol', received on June 20th [55]. As with Robinson's synthesis, Woodward's syntheses relied on relays to reach targets and were similarly strictly *formal* total syntheses – in the sense that they also linked up to intermediates used by other researchers to reach the final natural products. While Robinson in his later full paper described his 'synthesis of epiandrosterone' as a 'formal' one, Woodward, as Johnson noted: 'would never use the term formal total synthesis; indeed, he steadfastly refused to recognise that there was any difference between a synthesis that was carried all the way through from simple chemicals and one that relied on relays. Bob and I used to have heated arguments on this issue presenting each other with absurd

Scientists Break Down Another Secret

AFTER 18 years of painstaking research, a team of British scientists working in an Oxford laboratory has unravelled one of nature's most important secrets.

They have, for the first time, completed a total chemical synthesis of male sex hormones, the internal gland secretions which, on absorption into the bloodstream, influence the action of various organs of the body.

Their achievement, which has so far defied other scientists all over the world, is regarded as an advance of the greatest magnitude, particularly in consolidating the chemical theory of the steroids, which include many substances of medical importance.

The medical profession also believes that the discovery has opened up new vistas regarding the treatment of other grave diseases.

The British team has been working in the Dyson Perrins Laboratory at Oxford under the leadership of Professor Sir Robert Robinson, O.M., one of the most distinguished figures in the scientific world. A most important part was also played by Dr. J. W. Cornforth, formerly of Oxford University and now of the National Institute of Medical Research at Mill Hill.

ANOTHER TEAM AT WORK

When he talked to a "News of the World" representative yesterday in the laboratory at Oxford Sir Robert Robinson spoke with the care and reserve of the scientist. He said:

"We have effected something which, I think, must be regarded as a tour de force in chemical synthesis—that the male sex hormones, which are themselves of importance in practical medicine, have the essential skeleton of cortisone."

Cortisone, or "Compound E," is the rare and expensive drug used in the treatment of rheumatoid arthritis.

"I don't want you to think," Sir Robert went on, "that we have reached the stage of methods of factory production. It is rather a question of dotting the 'i's' and crossing the 't's' of the scientific aspect.

"We started work on this away back in 1933, and we reached a partial synthesis some time ago, but it is only now that we have done the complete job."

Supported by the Nuffield Foundation, another team of scientists is attacking yet another problem—that of how to make synthetic cortisone.

Experiments began last year, and Sir Robert said of them: "We are getting a lot further, but I would not describe the results as startling from the point of view of actual production.

"It is a long-term research and, therefore, a little too early just now to make any optimistic pronouncement."

Cortisone, which is made principally from ox bile, has been used to a considerable extent in America where it now costs £9 per gramme. In Britain, it is estimated that the treatment of one patient would cost more than £400 a year. It is reckoned that rheumatism attacks 200,000 British children annually and that every year some 25,000 people die from disorders of rheumatic origin.

Fig. 3. Publicity in *News of the World* (June 3, 1951) for Robinson's steroid synthesis [60].

hypothetical cases, such as if you affect a completely total synthesis of testosterone acetate, then saponify the acetate prepared from natural material, are you obliged to label this as a formal total synthesis of testosterone? Neither of us ever convinced the other … ' [47] The 'hypothetical case' appears rather close to the real case of Robinson's epiandrosterone acetate.

Woodward finally developed a route that linked through to the main prize, cortisone. His communication was received by *JACS* on July 9. This appeared in the August 6th issue [56] along with, remarkably, three other cortisone syntheses by other groups. The communication with the earliest received date was actually that by Djerassi at Syntex in Mexico [57]. Djerassi reported a synthesis from a readily available plant source, diosgenin in Mexican yams (unlike Sarett's earlier synthesis from bile acids). Also significantly, that communication specifically outlined how their work provided a link, albeit convoluted, between epiandrosterone and cortisone, thereby being able to state a formal total synthesis of cortisone (from simple starting materials) had now been achieved. The story of Djerassi's notable synthesis and the apparent shenanigans in the publication process leading to the simultaneous publication of the 4 communications have been described in detail by Djerassi [58] and will not be further discussed here.

Woodward's Centenary lecture gained good publicity in the USA [14]; following the press announcement orchestrated at Harvard it was the focus of an article in the 26 April *New York Herald Tribune*, it also appeared on May 1st on American radio, and in the UK it was reported in a leading medical journal, *The Lancet* in its May 19th issue [59]. Robinson's note in *C&I* also gained some publicity, being picked up by the *News of the World* newspaper in an article published on Sunday June 3rd under the headline 'scientists break down another secret' (Fig. 3) [60].

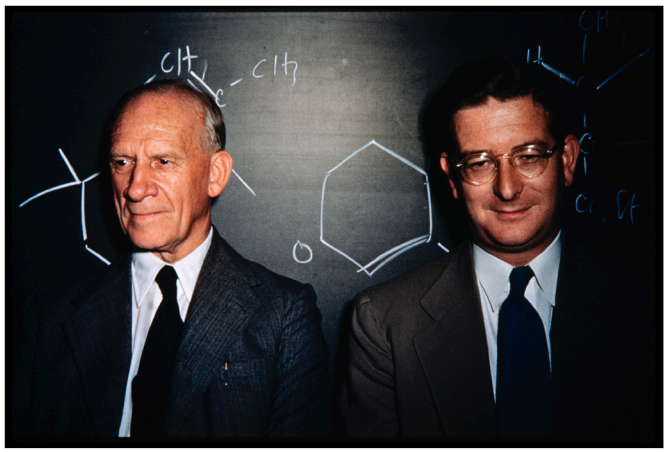

Fig. 4. Showing the strain. Robinson and Woodward 'together' at MIT in fall 1951 [64].

The appearance of the article in *News of the World* led Barton to comment in a letter to Woodward, dated July 15th, that: 'Your old friend Robinson continues to misbehave in a childish manner. The enclosed cutting from England's lowest Sunday paper will illustrate my point. Perhaps I should mention that the 'News of the World', from which this extract comes, is devoted to a summary of the more unsavoury court cases - particularly divorces – the title is a complete misnomer. I hope that at the Symposium on the total synthesis of Steroids {Gordon Research Conference, New Hampton, 12–16 August 1951} you will be able to reply and place everything in the correct historical perspective.' [42] While Barton was quite dismissive of the News of the World, in the 1950s it was the biggest-selling newspaper in the world (over 8 million copies per Sunday edition), so not bad in terms of what would be considered today as 'public engagement with research'!

Robinson, like Woodward, was very much concerned with publication priority [61]. With regard to steroid synthesis this is indicated in a reply from Djerassi to Robinson, dated 20 July 1951: 'From a priority standpoint, the total synthesis of cortisone by way of epiandrosterone and pregnenolone is certainly the first one, since your total synthesis of epiandrosterone appeared before Woodward's etioacid synthesis.' [62] Prior to Woodward's work, the etioacid had already been demonstrated to lie on a path (from epiandrosterone) to a variety of steroid natural products, and now to cortisone as described in Djerassi's communication. Djerassi could rightfully claim the first formal total synthesis of cortisone, as his Syntex group achieved a link to cortisone from known advanced intermediates that had previously been made from simple starting materials. In his letter to Robinson, he was attempting to placate the latter's concerns over priority by indicating that the early steps in that formal total synthesis sequence could be first attributed to Robinson (following the latter's *C&I* note).

Robinson and Woodward met at least once more in 1951. Robinson had been invited to the 75th anniversary celebrations of the American Chemical Society, held at their fall meeting in New York City 3rd-7th September. During this visit to the USA, Robinson lectured on his steroid work at MIT, with Woodward in the audience. The enduring tension between them is immortalised in a famous photograph that J. D. Roberts managed to get of the two of them together (Fig. 4) [63].

Woodward's desire to be first even extended to the now classic full paper describing his steroid work in detail. He wrote in the cover letter to Gates with his manuscript on April 3, 1952: 'I think it is fair to estimate that a large number of readers is looking forward to its appearance with more than ordinary interest, and that this may justify expedited treatment. There is also a certain competitive element; I have no exact knowledge of the publication plans of our English friends, but the British Journal gets papers out very fast nowadays particularly if there are special reasons for doing so, and I should not like to see the American

team lose.' [65] The manuscript appeared in *JACS* at the start of September that year [66], a rapid publication time for a *JACS* full paper. Robinson's full paper, which included the links to cholesterol and cortisone formal syntheses, was received by the *Journal of the Chemical Society* on September 12th, 1952, and was published at the start of 1953 [49].

Towards the end of his life Robinson still wished to emphasise his place in the history of steroid synthesis. At the close of his chapter on steroids in his unpublished and unfinished memoir, and immediately before his sentence on the meeting between himself and RBW, he noted: 'The stages from epiandrosterone to cholestanyl acetate {the latter's conversion to cholesterol 'had already been effected'} were not mentioned in our preliminary note {*C&I* paper} because we were still making efforts to improve the details.' Immediately after the sentence on the meeting with RBW, RR gave a qualified approval to Woodward's route: 'The method was highly original although it is also true that ring A was introduced by condensation of a cyclohexanone derivative with vinyl ethyl ketone {i.e., what is now called a Robinson annulation}, RR then wrote 'our preliminary note proceeded all other papers on the synthesis of androgenic hormones.' [6] He was, perhaps, more generous in another section of his memoirs specifically devoted to an overall appraisal of Woodward. It began: 'Through the work of Woodward and his important collaborators – organic synthesis reached its highest level –and I would certainly describe Woodward himself as the best organiser of the total synthesis in the history of science.' [67] Few would disagree!

Declaration of competing interest

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2025.134516.

Data availability

No data was used for the research described in the article.

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