A Memoir

The Merck Bile Acid Cortisone Process: The Next-to-Last Word

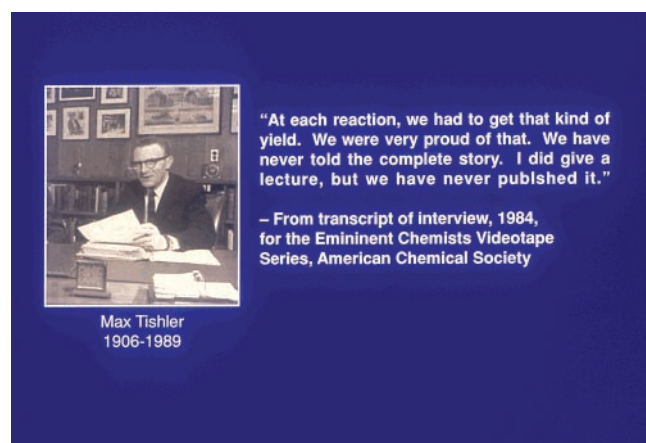Seemon H. Pines[†]

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Abstract:
A personal account of the process research and development effort at Merck and Company, leading to the first commercial process for the manufacture of cortisone acetate, is described.

Introduction

"...At each reaction, we had to get that kind of yield. We were very proud of that. We have never told the complete story. I did give a lecture, but we have never published it.[1a,b]"

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– From transcript of interview, 1984, for the Emininent Chemists Videotape Series, American Chemical Society

Max Tishler
1906-1989

Max Tishler, had he been alive, most assuredly would have been invited to participate in the International Symposium on the History of Steroid Chemistry, August 1991,[2] and would have found it the forum, after all these years, to tell the story of the process development of the first cortisone

manufacturing process. The commercial conversion of desoxycholic acid to cortisone bore his imprint not only from the standpoint of design of some of the laboratory experiments but also from his unique managerial style. No task was too large, no mountain too high, no effort beyond reason. That was how he led. He inspired by giving and demanding total dedication from his subordinates *and* also from associates outside his R&D arena. On the other side of the coin, he would go out of his way to help solve a personal problem if it arose amongst his people. In many regards he was a warm and compassionate friend. You could see it in the twinkle in his eyes.

Dr. Tishler was honored and praised frequently and deservedly by scientists the world over, and even by a U.S. President,[3] for his many remarkable contributions to science, both academic and industrial; his memory needs no tribute from me. Nevertheless, he was a role model for my 40 years at Merck, and once I had seen his words with which I started this story, I was determined to record all that I could recall, and all that I could glean from Merck Archives. In that regard, this augments the Symposium Proceedings cited above. Then, too, some of our chemistry is worth recording for its historical and still-utilitarian value.

It is interesting, but not remarkable, that in the many lectures delivered in the early 1950s by Dr. Tishler on the general topic of progress towards cortisone, there was no hint of what was being done in his organization on the existing process. Merck refrained from publishing developmental results in those days; there was no sure way to protect an economic advance other than by silence.

The adrenal corticoids had been recognized as early as 1927, and their properties had drawn interest from animal studies in academic circles. Synthetic efforts, especially toward Kendall's Compound E, which was cortisone, were undertaken by a group of cooperating laboratories,[4] both academic and industrial, under the sponsorship of the National Research Council with the objective of supplying

[†] Merck and Company, Inc., Process Research and Development, Retired.
(1) (a) Quotation from Dr. Max Tishler in videotaped interview conducted in 1984. From *Max Tishler*; Eminent Chemists Video Series; American Chemical Society: Washington, DC, 1986. The interview was also published: *The Life of Max Tishler*; The Kitasato Institute: Tokyo, Japan, 1991. (b) Max Tishler, b. 1906. B.S. Chemistry, Tufts University; Ph.D., Harvard University. Employed at Merck & Company, Inc., 1937−1970. Among his numerous achievements was leadership of research teams resulting in the development of practical processes for ascorbic acid, riboflavin, penicillin, streptomycin, vitamin B₁₂, sulfaquinoxaline, and commercialization of cortical steroids. He was the first president of the Merck Sharp & Dohme Research Laboratories, as well as President of the American Chemical Society in 1972. He retired from Merck at age 64 and joined the ranks of academia at Wesleyan University, where he continued to pursue research with graduate students until his death in 1989. He was a recipient of the Priestley Medal, the highest honor which the American Chemical Society can bestow upon a chemical scientist, and was named one of the top 75 "Contributors to Chemical Enterprise" by *Chemical and Engineering News* in 1998.
(2) The proceedings have been published in *Steroids* **1992**, *57*.

(3) Awarded The National Medal of Science by President Ronald Reagan in 1987.
(4) Fieser, L. F.; Fieser, M. *Steroids*; Reinhold Publishing Corp.: New York, 1959; particularly Chapter 19, provides a thorough summary of the field of cortical hormones and cortisone up to the point of its publication. Thorough coverage is precluded, other than to show further development and touch upon key early literature citations. The Fiesers were unstinting in their praise of some of that development especially that of J. van de Kamp and S. M. Miller, without whose herculean effort Merck might not have been the first on the market. Their efforts are also documented and contributions likewise praised: Kendall, E. C. *Cortisone*; MacMillan Publishing Company: New York, 1971.

sufficient quantities of this cortical hormone in order to evaluate its possible medical utility. Most routes at that time started from desoxycholic acid from cattle bile. Agricultural starting materials were not found in quantity until the 1950s.

When I was recruited by Merck in 1951, I was informed that my initial assignment would involve participation in the factory demonstration of the then still-under-development bile acid process in a new plant being established in Danville, Pennsylvania. It became clear during my first days in Rahway, New Jersey, that the demonstration was only a portion of it. Praise she had, but if Merck were to achieve financial success, the process would require considerable change and improvement. My exposure to steroid chemistry before that July 16 had come from one seminar at the University of Illinois and from an article in a popular magazine, *The Saturday Evening Post*.

Background

Before describing and discussing the nature of the process development, an understanding of the times during which the work was undertaken, the state of the technology at the time pertaining to the compound, and the prior studies reported up to that time must be considered. It was our initial belief that every intermediate that we would invoke was known and had been characterized to some degree by earlier researchers. Our goal was truly cost reduction; the new plant had been designed and nearly completed. Our mission was to improve what had been achieved up to that point. While new chemistry was not summarily dismissed, the timeline imposed was indeed challenging and required dealing with ca. 30 steps involving 18 isolations and factoring in time which may be required to perform the occasional rework for purity considerations. Also, we could not ignore the fact that modest ongoing "production" in Rahway utilized many reactions which could not be effectively scaled to manufacturing-level production, while other reactions seemingly had to be improved and scaled up.

The Rahway team was to go on to other tasks although they continued to offer suggestions—some good, some otherwise.

The nature of chemical development in 1950 was carried out without the aid of NMR, mass spectrometry, modern chromatographic methods, and other tools common to today's laboratory environment. These tools would have provided us valuable information regarding side reactions leading to byproducts, information critical to reaction optimization.

Six of us[5] took up residence in central Pennsylvania near the end of 1951. We had departed Rahway with the Preliminary Operating Instructions committed to paper. The start-up, which was set back a couple of months due to

equipment delays, commenced in March 1952 with the Second Phase (vide infra) using methyl 12-bromo-3,9-epoxy-11-ketocholanate (**12**), supplied from Rahway.[6] The idea was to remove Second-Phase production from the Rahway pilot plant as quickly as possible. Simultaneously, we continued the laboratory development, some of which went directly into the factory without piloting as the start-up for that specific step was initiated.

"First Phase" referred to the first 11 chemical transformations, *the sole purpose of which was to transpose oxygen from position 12 to 11 of the C-ring*. This phase carried with it six isolations plus a step to recycle an otherwise useless isomer. The "Second Phase" required 14 reactions with nine isolations to transform the cholate side chain to the ultimate dihydroxyacetone moiety, while the "Third Phase" required three chemical transformations to introduce unsaturation to the A-ring. Economics dictated that some second crops be taken and recycled to the process stream, a requirement which was eventually relaxed as the process was improved.

Demonstration was completed by the end of 1952, at which time an overall yield of 12% from desoxycholic acid to cortisone acetate had been achieved. There will be more discussion regarding both individual step- and overall yields; suffice it to say here that 12% was a greater than 50% improvement compared to the December 1951 Rahway campaign. By April 1953, a 15% overall yield, the target for the end of 1953, was in hand, thereby doubling the performance in the year that Danville had operated. This was not only laudable, it was probably influential in Merck management's decision to proceed long-term with this process. On the horizon were Upjohn's competitive advantages which were to arise as a result of commercialization of the unique microbial 11-hydroxyation of progesterone.[7]

progesterone → *Rhizopus* → 11α-hydroxyprogesterone
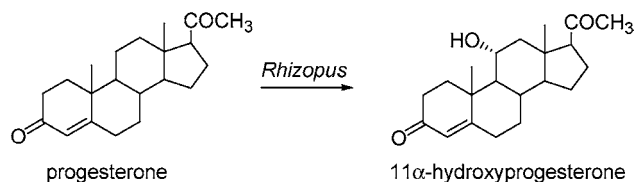
The latter is readily attainable from diosgenin, which became less expensive and more available than desoxycholic acid. This advance permitted circumvention of the entire First Phase of Merck's process by allowing for the substitution of a less costly microbiological route.

One purpose of this article is to demonstrate the merits of process development, especially under the competitive gun, and the outcome of this particular body of work under the guidance of Max Tishler. It would be less likely to occur today with the more rigorous requirements for process definition by regulatory agencies.

In describing the major process advances, references have been cited for the most relevant literature preceding the then

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(5) Edith Chase, George Hazen, Willard Jones, Frederick Kocher, George Krsek, and I. As time passed, some went, others came, notably James Grier and John Day. John had contributed much to the Third Phase in Rahway; he replaced George Krsek who led us initially. I do not intend to attribute the individual achievements to specific members of the group; it would be inappropriate and unfair to others who might, in fact, have generated ideas but were too preoccupied with other steps at the specific time to pursue them. Additionally, some of our inspiration came from our erstwhile colleagues in Production. Those contributions were by no means inconsequential. Thus, the whole will be considered as a team effort, which, indeed, was the case.

(6) First-Phase and Third-Phase production would continue in Rahway until the Danville, PA, plant was fully up and running. During that time, considerable progress would be achieved there towards development of the latter, the bromination, and subsequent dehydrobromination of the 3-ketone.

(7) The picture on this front is well described in the contributions made by John Hogg and Carl Djerassi to the International Symposium cited earlier; see *Steroids* **1992**, *57*, 593−616 and 631−641, respectively.

current "state of Merck art" as manufacture commenced, as well as the existing process at shutdown in 1966. Sufficient detail is likewise provided to assess the results. As process efficiency increased, the cost contribution of the desoxycholic acid lessened relative to the total, while labor, auxiliary raw materials, and overhead took on greater significance. A counterintuitive change crept into the acceptable thinking at that time: in some cases, modest yield sacrifice could be endured for the sake of overall cost reductions. Thus, most of the accomplishments delineated in this article occurred during the initial process demonstration and in the following three years.

While cost improvements from the pre-Danville "production" until shutdown in 1966 are not really comparable for a number of reasons, the terminal inventory cost was approximately 100-fold less than that of the initially produced cortisone.

Experimental results (and quality) were gauged by the tools in use at that time. Purity was judged by rigorously determined reproducible melting points, optical rotation, and UV absorbance where applicable. An occasional phase-solubility analysis was sought in special cases, but that was a rather time-consuming analysis for routine use. The utilization of NMR spectroscopy after it became commercially available was of minimal value due to its relatively low sensitivity and resolution. Utilitarian quantitative chromatographic technologies were not yet available at that time. When the USP introduced the requirement that steroids be examined by thin-layer chromatography, low-level impurities were observed which had eluded prior detection. The advent of that technique, coupled with the availability of high-pressure liquid chromatography a decade later, would have been of inestimable value for development work. Each generation of chemists witnesses the fruits of technological advancements, many of which come too late for their use.

Process Development

I do not recall any grand plan which had been established to guide development of the individual steps. If Dr. Tishler or anyone else had arranged the strategy, it was kept well hidden. We felt that, as a group, we were responsible to define our own approach within the boundaries of good sense—as long as we did not ignore factory problems that, if deferred, might impact product commitments. This is not to imply that we were without management oversight—far from it. In many respects, we were in a fishbowl: costs and production were on the minds of many people in Danville and Rahway. Priorities were different to different observers, and local production managers were frequently on our doorstep with enticing suggestions to improve their steps. There was even an undercurrent of rivalry between Rahway and Danville production people while the First and Third Phases were being operated at both sites by ostensibly the same processes. Neither factory wished to be seen as less efficient than the other.

Below is the process in its normal sequence, with the major specific fruits of our development described. The myriad use-tests and trouble-shooting are not detailed although they consumed a large part of our time.

First Phase. *Conversion of Desoxycholic Acid (DCA) 1 to 2 (Scheme 1).* The ester was formed in methanol at modest temperature, initially catalyzed by hydrogen chloride, later by sulfuric acid. While yields were recorded, the purity of the starting material was a significant determinant. Kendall's group reported, "With highly purified material, the yields are almost quantitative."[8] They utilized 3.6 mL of methanol per gram, taking successive crops to achieve the yield. Less solvent was used at Merck, and rather than take multiple crops, controlled dilution with water depressed the solubility and permitted high recovery in a single crop. During the early years of processing, mother liquor values were recovered via the magnesium salt of DCA. This practice ceased when the cost of recovery exceeded its (falling) purchase price.

Conversion of 2 to 4b. At start-up, Merck had already combined these two reactions and was achieving 94% yield, overall. Kendall's published chemistry[8] was very similar; however, it included an intervening isolation of **3**. Had a modest excess of benzoyl chloride been used, his yield on the step **2** to **3** would most likely have been higher. He reported yields of 86% and 96.5%, respectively.

Soon, the benzoyl protecting group was changed to the ethoxy-carbonyl moiety, based in part on a claim by Fieser et al.,[9] that the "cathyl" group at position **3** is "the exclusive product of reaction even when a large excess of ethyl chloroformate is used...". The new intermediate was labeled "DLIV" (**4b**). The cathyl group also permitted simplification of the isolation of the subsequent intermediate, **7** (see below). Other than that, these two reactions ran pretty much as described throughout the years.

Conversion of 4b to 7. Direct introduction of oxygen at position **11** via bromination of the 12-ketone, hydrolysis, and removal of the 12-ketone was a goal long sought by many steroid chemists dating back to the early 1940s. No productive route was found,[10] and a new strategy necessarily evolved, requiring formation of the Δ-9,11-unsaturated hydroxyl at C-12. Reflecting dissatisfaction with bromination—dehydrobromination as the means to that end, Kendall's group[8] developed the findings of Schwenk and Stahl[11] that selenium dioxide would accomplish that transformation in one step. The product **7** was isolated by crystallization after hydrolysis. Kendall's reported yield was 84%; Merck brought it to the low 90s before long.

After the demonstration, however, the cost and scarcity of SeO_2 (a necessity for the burgeoning electronics industry and thus required for the Korean war effort) forced the reinvestigation of the previously failed bromination—dehydrobromination approach to the 9-11 double bond. It was found that by conducting the bromination in benzene/methanol, product was obtained arising from virtually total attack at the 11-β position, critical to the subsequent 9-11 dehydro-

(8) McKenzie, B. F.; Mattox, V. R.; Engel, L. L.; Kendall, E. C. *J. Biol. Chem.* **1948**, *173*, 271−281.
(9) Fieser, L. F.; Herz, J. E.; Klohs, M. E.; Romero, M. A.; Utne, T. *J. Am. Chem. Soc.* **1952**, *74*, 3309−3313.
(10) Gallagher, T. F.; Long, W. P. *J. Biol. Chem.* **1946**, *162*, 521−532. This paper reports introduction of the 11-hydroxyl, but the authors were unable to achieve acceptable yields in a Wolff−Kishner reduction of the still present 12-ketone.
(11) Schwenk, E.; Stahl, E. *Arch. Biochem.* **1975**, *14*, 125−129.

Scheme 1. First phase
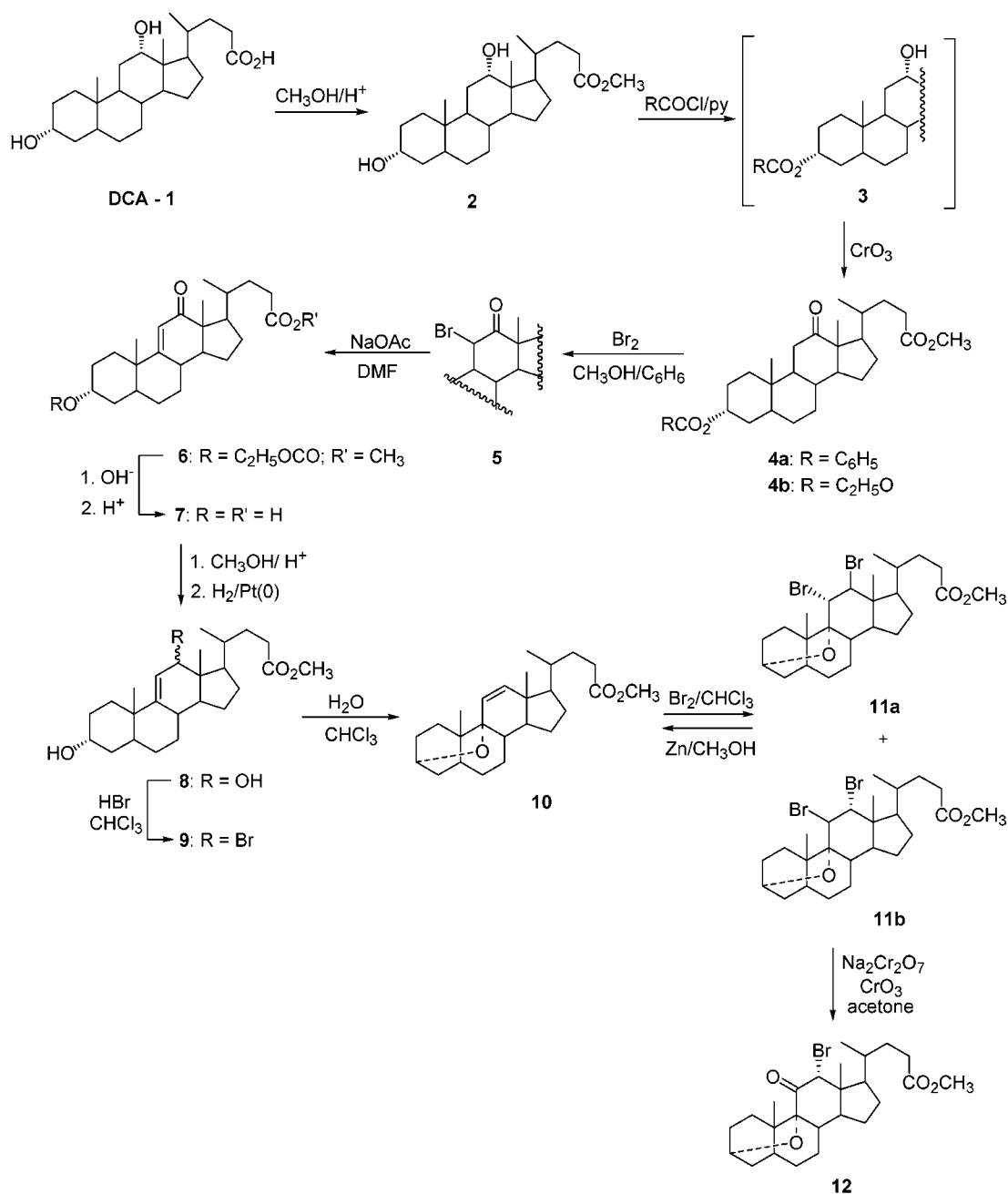
bromination which followed. That dehydrobromination via sodium acetate/DMF at 100 °C provided a two-step yield of >93%. The success was significant in many regards: shorter reaction time, processing simplicity, elimination for the need of a noxious reagent requiring recycle, cost, and elimination of the requirement for royalty payments pertaining to the use of the patented procedure of Schwenk and Stahl.

Conversion of 7 to 11b. Kendall and co-workers' seminal elucidation[12] of the C-ring chemistry leading to the 3,9-epoxide and its stereoselective bromination was the key to the First Phase. Building on it, Merck fashioned a facile process, which eliminated one step and the isolation of all the intermediates between **7** and **11b**. That latter compound,

the 11-β-12-α dibromide, and its 11-α-12-β epimer (**11a**), produced in an approximate 3:1 ratio, possessed similar but not identical solubilities. In all of our experience, optimum yields of high-quality **11b** required rigorously controlled crystallization conditions (vide infra), which relied on the *initial* crystallization of **11b** and the somewhat slower crystallization of **11a**. That experience was unanticipated from Kendall's protocol. Unless the melting point met a minimum 138 °C criterion, **11b** was purified by slurrying in acetone. Second crops from the initial and (occasional) reslurried mother liquors were debrominated by zinc dust in methanol to intermediate **10** for subsequent rebromination.

Process improvements after introduction at the Danville site were few. Sodium borohydride was examined as a substitute for Pt-catalyzed hydrogenation of **7**, but it provided

(12) Mattox, V. R.; Turner, R. B.; Engel, L. L.; McKenzie, B. F.; McGuckin, W. F.; Kendall, E. C. *J. Biol. Chem.* **1946**, *164*, 569−596.

no advantage. Epoxide formation was changed; initially, the 12-hydroxyl was converted to the corresponding chloride and then treated with pyridine to provide **10**. Use of anhydrous HBr instead of HCl gave a better leaving group, and the same epoxide could be formed simply by washing the solution with water in lieu of pyridine.[13]

Another area of interest was the optimization of bromination conditions to improve the ratio **11b** to **11a**. Other than a modest 2% which could have been gleaned by a rather expensive refrigeration upgrade to achieve at least −75 °C, efforts proved unsuccessful. This was puzzling since the product of bromination of the similar 3-α-hydroxy-Δ-11-cholenic acid in chloroform at +4 °C had been reported to afford only the 11-β-12-α epimer.[14]

For **11b**, however, it was observed that adding sodium hydroxide to the sodium bisulfite quench of the excess bromine played a role in minimizing loss to acid-initiated side reactions.

The sequence **7** to **11b** was demonstrated at 70% and ultimately reached 76.6%.

*Conversion of **11b** to **12***. The efficient conversion of the higher-melting isomer **11b** (compared to the lower-melting **11a**) to an 11-ketocholanate ended the long search in many laboratories for the Phase 1 objective, transposition of oxygen from C-12 to C-11. Kendall's group[15] reported a 94% yield of methyl 3,9-epoxy-11-keto-12-bromocholanate from treatment of **11b** suspended in acetone with silver chromate and chromic acid, followed by sulfuric acid. This process, with minor modification, ran smoothly at 96% yield until time was available to challenge its cost. Silver salts, even with optimal recovery of the silver, were expensive raw materials.

Earlier, it had been shown that the 11-β bromine of **11b** could be displaced with sodium acetate in good yield,[12] providing the 11-β acetate. Guided by this observation, it was found that, indeed, lead oxides and even sodium and potassium chromates and dichromates reacted with **11b** in acetone to provide the desired 11-ketone. Optimization with sodium dichromate, the least expensive reagent, afforded a less costly and higher-yielding process. The 98.5% yield was due, in part, to modifications which eliminated the need for filtration of inorganic salts and concomitant attendant handling losses. Additionally, since the starting material was of low solubility in acetone, reaction concentration and temperature were significantly increased, thereby minimizing labor and solvent costs.

First-Phase Summary. The major results (see Table 1) of the First-Phase effort appear scant, indeed, if viewed by structural formulas of the intermediates: a changed blocking

Table 1. First-phase yields, %

steps	best literature yield (%)	Danville demonstration (%)	ultimate performance (%)
1 to **2**	"near quant"	92.5	94
2 to **4b**	83	95.6	95.5
4b to **7**	83	93.5	91
7 to **11b**	60.4	67.5	76.6
11b to **12**	94	95.8	98.5
overall		53.5%	61.6%

group at the 3-position, and a leaving group at C-12. On the other hand, economic improvement was significant as a result of yield increases of nearly 60% over the starting Kendall process, a quarter of which followed the demonstration. Notable and specific nonyield savings came from the new **4b** to **7** process and from substituting sodium dichromate for silver chromate. Also of significance, but less perceptible for this story, were the benefits from solvent, labor, and overhead reduction through a variety of individual changes. Obviously, many of these were unique to the physical plant [and for its potential concurrent use on other steps, or other projects].

One goal, better stereochemical control of the 11,12-dibromination, still remains elusive.

Second Phase. While the First Phase had been established at the Rahway site turning out **12** throughout 1951, the Second Phase saw continuing development activity prior to taking up the task in Danville. That effort was put in large part into the ongoing modifications of the Sarett process dealing with the construction of the corticoid side chain at C-17.[16] However, there were significant drawbacks, including the use of ozone, cyanide, and osmium tetroxide. The latter reagent was highly toxic, very costly, and in short supply. Research had even hired an inorganic chemist specifically to design and oversee a process for its recovery. It was, in fact, the acknowledged future bottleneck in production should that chemistry not be circumvented.

Simultaneously, a parallel effort that would utilize Gallagher's 17,20-epoxide[17] and ultimately avoid those three reagents was under intensive study (see Scheme 2).

A linkage to the then current intermediates was not firm; thus, design and construction of the Danville Plant moved forward with anticipation of last-minute changes. Neither time nor larger-scale pilot facilities were to be available for most of the new steps beyond 12- and 22-L flasks. In the current vernacular, this operating style might be dubbed: "Just in time!".

*Conversion of **12** to **13**; **13** to **14***. The functionality of **12** was ideal for the phenyl Grignard reaction and the multistep Miescher Degradation[18] for excising most of the

(13) This idea is actually reported[14] wherein the "Kendall Process" is described as proceeding through the 12-methoxy- and the 12-chloro-intermediates to the 3,9-epoxide. Why neither Kendall nor Merck introduced the technique for large scale earlier remains unexplained.

(14) Engel, L. L.; Mattox, V. R.; McKenzie, B. F.; McGuckin, W. F.; Kendall, E. C. *J. Biol. Chem.* **1946**, *162*, 565−570. The authors state that "...only one of the possible isomeric dibromides could be isolated"; however, a more careful reading showed that the reported yield amounted to only 61%. The *probable* configuration was reported in Mattox, V. R.; Turner, R. B.; McKenzie, R. F.; Engel, L. L.; Kendall, E. C. *J. Biol. Chem.* **1948**, *173*, 283−294.

(15) Turner, R. B.; Mattox, V. R.; Engel, L. L.; McKenzie, B. F.; Kendall, E. C. *J. Biol. Chem.* **1946**, *166*, 345−365.

(16) Fieser, L. F.; Fieser, M. *Steroids*; Reinhold Publishing: New York, 1959; pp 645ff.

(17) Kritchevsky, T. H.; Gallagher, T. F. *J. Biol. Chem.* **1949**, *174*, 507−508. Koechlin, B. A.; Garmaise, D. L.; Kritchevsky, T. H.; Gallagher, T. F. *J. Am. Chem. Soc.* **1949**, *71*, 3262−3263.

(18) Meystre, C.; Frey, H.; Wettstein, A.; Miescher, K. *Helv. Chim. Acta* **1944**, *27*, 1815−1824.

Scheme 2. Second phase
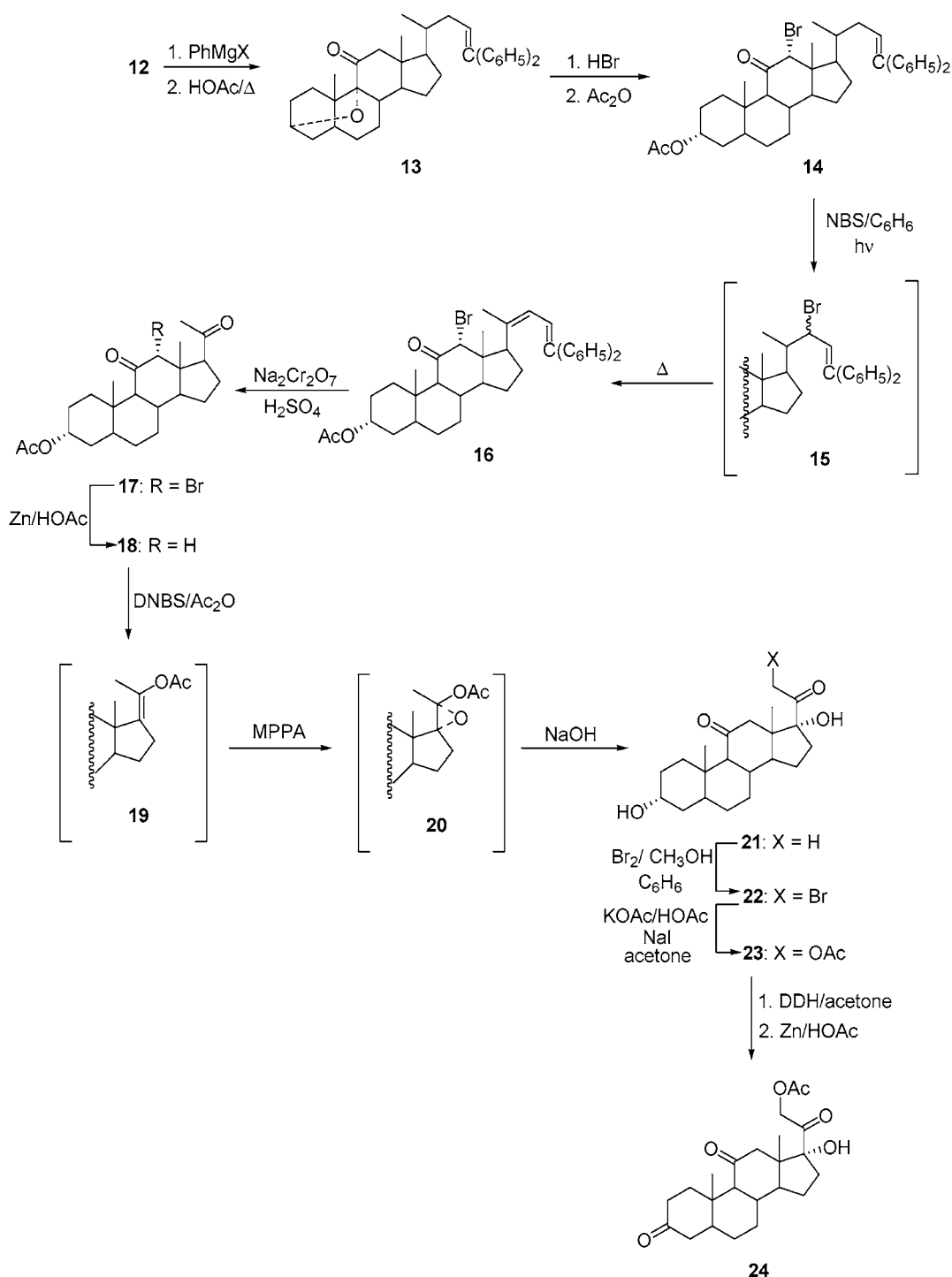
side chain (**12** → **17**). Genesis of that process is well reviewed by the Fiesers.[16] Mattox and Kendall[19] published a protocol for the Grignard step, dehydration, and the subsequent hydrogen bromide opening of the 3,9-epoxide, **12** to **14**, all of which were mirrored in our start-up reaction conditions. For the former, they cited an 88% yield (two crops), for the cyclic ether cleavage and acetylation, 90%. Our second crop recovery for the former step was soon abandoned due to the erosive nature of the steam distillation to the vessel, coupled with its minimal value. Later,

phenylmagnesium chloride was substituted for the corresponding bromide when it was found that the former could be readily made in tetrahydrofuran.[20] That change was welcomed for reasons of safety (avoidance of diethyl ether) and cost impact. It also provided a slightly higher yield and quality, as measured by melting point and yield through the next step. This is illustrated in Table 2; the data came from the Demonstration Report.

(19) Mattox, V. R.; Kendall, E. C. *J. Biol. Chem.* **1950**, *185*, 589−592.

(20) Ramsden, H. E.; Balint, A. E.; Whitford, W. R.; Walburn, J. J.; Cserr, R. *J. Org. Chem.* **1957**, *22*, 1202−1206. Tetrahydrofuran was not readily available in bulk early on.

Table 2. Demonstration results phenylmagnesium chloride vs bromide

	bromide		chloride	
12 to **13**	84.2%	151−153.6 °C	87.0%	152.7−153.9 °C
13 to **14**	91.5%		92.7%	

Other modest changes were introduced shortly thereafter: a change from benzene to toluene for dissolution of the substrate, an increase in the reaction temperature to ambient rather than 0−5 °C, and a shortening of reaction time.

During the Grignard reaction, the reagent reduced the bromine atom at C-12. It is an interesting quirk of fate that Mattox and Kendall found precedence for this unexpected reduction in Max Tishler's Ph.D. work at Harvard.[21]

The conversion, **13** to **14**, was carried out by stirring a solution of **13** and anhydrous hydrogen bromide in chloroform at 0 °C and 85−90 psig for 40 h. The resulting carbinol was converted to its crystalline acetate by workup in acetic anhydride. Little improvement came from the modest development effort put into the step other than to recover and reuse a major portion of the anhydrous HBr.

Conversion of 14 to 16. These two reactions set the stage for the completion of the Miescher Degradation, C-22 bromination followed by dehydrobromination without intervening workup. The originally published procedure[18] for the bromination had been improved within a year through the use of light activation.[22] In Rahway, the sequence was applied to **14** and studied in glassware preparatory to the upcoming introduction.[23]

It is still exciting to recall the start-up. Twenty-gallon reactors fitted with glass thimbles containing projection lamps and controlled by a "Flexo-Timer" were fed sequentially from weigh tanks containing carefully determined amounts of **14** dissolved in CCl_4. The reactors were automatically heated to reflux, the illumination started, and another feed tank containing hot slurry of *N*-bromosuccinimide was drained into **14**. Heat was evolved, the solution turned reddish-brown, and then paled. After 20 min, the lights were automatically extinguished, the bottom valve opened and the reaction drained to a large vessel in which dehydrobromination occurred at reflux over 6 h. About 35 drops constituted one batch. Compared to today's electronics, the automation was rudimentary but proved effective.

The product, isolated from ethyl acetate after removing succinimide by filtration and evaporating the carbon tetrachloride was obtained as an impure solvate, but good enough for the next step. The crude contained approximately 10−14% ethyl acetate, some starting material, and very likely some spuriously brominated congeners. A second crop was mainly a mixture of **14** and **16** for which a nonchromatographic separation method was not available on start-up. A simple installation was provided, and a process was designed

to fit it. The "true" first crop yield was about 73%; with the recycle, the overall yield reached approximately 80%. These values are an approximation since they reflect a purity factor based upon UV extinction coefficients, which did not account for any response from the byproducts. In fact, the purity factors were found to be affected by the manner of sample preparation. At any rate, yields over the two steps, **14** to **17**, were valid, and the progress of the process could be followed and problems could be diagnosed when necessary.

Even with this minor yield uncertainty, it was, nevertheless, clear that the light-initiated reaction was a good subject for development. Wohl−Ziegler brominations such as this one had most frequently been carried out in carbon tetrachloride with *N*-bromosuccinimide, and they made use of either a chemical initiator (usually a peroxide) or light activation, usually the former. Examination of other reagents and peroxide initiators provided no leads. Surprisingly, a change to benzene gave a much more rapid reaction and a very clear yield improvement. Rather than the usual 7−15 min for the bromination, it was complete in one minute in benzene. The vigorous boiling upon mixing the reactants and the rapidity of the color changes evidenced this rate increase. We also found out that total light intensity was a factor; all attempts to find an optimal wavelength were to no avail. Increased intensity was most readily achieved by batch dilution; we had already put as many lamps in the thimbles as would fit.

Those lamps created their own problem. In the case of the carbon tetrachloride process, passing air over them cooled them. In a system containing benzene, there would be a severe fire hazard should a thimble break, not an unknown occurrence. To circumvent this hazard, deionized, low-conductivity water was passed through the thimbles in direct contact with the lamps, bare electrical contacts and all! This system addressed our hazard prevention concerns and operated uneventfully for many years.

The workup with the new reaction was simplified. Dehydrobromination was more rapid, requiring only 2−3 h. The succinimide, which was soluble in benzene, was removed by a water wash, and the product was crystallized from benzene−hexane. Benzene formed a solvate, as did the prior ethyl acetate; the first crop yield was approximately 80%, and with recycle the overall yield was about 86%. The yield over both the **14** to **16** and **16** to **17** conversions substantiated this breakdown.

Two unrelated postscripts deserve mention. First, this new light reaction was now so rapid that a glass coil, which would fit in a conventional 30-gal galvanized garbage pail, could have provided the total factory production if run around the clock. We rigged such a setup, and while it ran long enough to prove the principle, it never went commercial.

Second, as we much later found, we were not the first to use benzene in this chemistry. In 1946, Fieser[24] published some unsatisfactory results of an attempt to carry out the Wohl−Zieger bromination on a steroid side chain in benzene. Had he repeated his experiment under more productive conditions, i.e., with illumination, the scheme might have been known today as the Fieser Degradation.

(21) Kohler, E. P.; Tishler, M. *J. Am. Chem. Soc.* **1932**, *54*, 1594−1599.
(22) Meystre, C.; Ehmann, L.; Neher, R.; Miescher, K. *Helv. Chim. Acta* **1945**, *28*, 1252−1257.
(23) For ongoing production, Rahway used a further modification of the scheme wherein C-21 was brominated and the bromine displaced by acetate prior to oxidation. Ozone was used for that cleavage and was considered for use at the new plant as late as the first half of 1951.

(24) Ettlinger, M. G.; Fieser, L. F. *J. Biol. Chem.* **1946**, *164*, 451−453.

Conversion of 16 to 17. While the initial results for the actual cleavage of the diene were not unacceptable, it should be remembered that chromic acid oxidations had been more practiced than understood. Early literature citations with a variety of nucleus-substituted steroids were sometimes followed by complex workup procedures including chromatography, semicarbazone formation, and even Girard's Reagent to achieve pure products. Yields generally ranged from 50 to 75%. After some study it was decided to use dichromate in acetic acid at the lowest possible temperature, 17 °C, on the basis of the observation that better performance was obtained in that "buffered" system than with the traditional CrO_3. After most of the reaction had subsided, sulfuric acid was added to complete the oxidation, at which time the Cr(VI) concentration was considerably diminished, and the over-oxidation minimized. Ironically, even this system proved troublesome during the initial batches at Danville. Heat transfer surface in the vessel was inadequate to permit maintenance of the time−temperature conditions desired, and over-oxidation still occurred. The problem was solved by dilution of the acetic acid with benzene (required for the product workup, in any event) and lowering the reaction temperature. While the change seemed trivial, it made a difference. Further improvement resulted from the improved quality of **16** from the benzene process and fine-tuning the stoichiometry and reaction composition. These gains, combined, allowed a simplified second-crop procedure to be instituted, which replaced the last chromatography in the plant. The ultimate overall yield rose to about 93%, or 81% for the **14** to **17** conversion versus the demonstrated yield of 57%.

Conversion of 17 to 18. It was now time to remove, once and for all, the bromine atom, which had occupied the C-12 position off and on since being placed there during the bromination of Intermediate **10**. It was part of the scheme required for the introduction of the 11-ketone; the Grignard reagent leading to Intermediate **13** unintendedly removed it; it returned during the epoxide opening, leading to **14**. Its presence undoubtedly played a role in preventing unwanted reaction during the formation of **16** and **17**. As with other α-bromoketones, its removal was readily achieved by zinc and acetic acid reduction.

Initial conditions were not stringent. The reaction was carried out with plenty of zinc in an unnecessarily large volume of acetic acid, and the water-precipitated product was even recrystallized. Due to the facility of this chemistry, this step was optimized only when there was time available to look at it. The amounts of zinc and acetic acid were reduced, and the yield rose from 94 to over 99%, mainly through elimination of the recrystallization. No impact was observed in the subsequent steps, and the volume change allowed a quadrupling of the batch size.

Conversion of 18 to 21. Insertion of the 17-hydroxyl by a modified Gallagher[17] route was next. Three reactions were required: formation of an enol acetate at C-20 (to the D-ring), epoxidation of the so-formed double bond, and regeneration of the C-20 ketone along with the 3-α-17-α-diol.

Gallagher had utilized chromatographically purified enol acetates, which were formed by slow distillation of an acetic anhydride solution of substrate containing *p*-toluenesulfonic acid.[25] Their benzene solutions could be epoxidized with 2 M perbenzoic acid in an hour. While the products could be isolated in a pure state, it was not necessary since saponification gave the 17-α-ol-20-ketones directly. In a "through process",[26] the Sloan-Kettering group reported 72.1% overall yield, including product resulting from chromatography of the mother liquors. That amounts to an average of 90% for each reaction on (essentially) our same substrate. It had been determined from the start to use monoperphthalic acid (MPPA) rather than perbenzoic. While the reaction was slower, it was intrinsically safer, and the MPPA could be made in-house and used without isolation in an operating area behind a steel barrier.

Optimization was postponed until after the demonstration was completed. In fact, the demonstration in the manufacturing plant was accomplished at the then expected 80% overall yield, 8% of which came from recycle of the mother liquors. That achievement required many hours of intense plant oversight and concurrent laboratory work.

The approach to understanding and development began with the first step of the sequence. While many laboratories were learning much about that reaction during the early 1950s,[25,27−30] a unified picture was not yet in place. It should be re-emphasized that Merck was seeking improvements to what was considered an already reasonable series of reactions. Available analytical methods were neither sufficiently accurate nor determinative to find the distinctions desired. For example, as interesting as was the kinetics of acetic acid formation during enol acetylation or peracid uptake during the oxidation and despite the nice data plots, they taught little about minor byproducts or over-reaction. We were fairly confident that a goodly amount of the dienol diacetate was formed that, when separately purified and subjected to peracid reaction, was shown to give a 95% isolated yield of good quality **21**. That implied that little peracid attack occurred at the 9(11)-double bond, in accord with Gallagher's view[16] when working with perbenzoic acid. On the other hand, Hirschmann and Wendler[28] had shown that a different 9(11) enol acetate could be smoothly oxidized at 40 °C in the same reaction medium. Surely a small amount of **19** *might* follow that path. Further, it was shown[30] that the dienol diacetate reacted faster than the mono, a point used to argue in favor of utilizing greater forcing enol acetylation conditions. We were not distilling the low-boiling acetic acid away from the reaction as did the inventors of the procedure, and there were questions from Max Tishler as to whether substrate was lost to an enol acetate between C-20 and C-21

(25) Marshall, C. W.; Kritchevsky, T. H.; Lieberman, S.; Gallagher, T. F. *J. Am. Chem. Soc.* **1948**, *70*, 1837−1839.

(26) Kritchevsky, T. H.; Garmaise, D. L.; Gallagher, T. F. *J. Am. Chem. Soc.* **1952**, *74*, 483−486.

(27) Vanderhaeghe, H.; Katzenellenbogen, E. R.; Dobriner, K.; Gallagher, T. F. *J. Am. Chem. Soc.* **1952**, *74*, 2810−2813.

(28) Hirschmann, R.; Wendler, N. L. *J. Am. Chem. Soc.* **1953**, *75*, 2361−2364.

(29) Anderson, H. V.; Garrett, E. R.; Lincoln, F. H., Jr.; Nathan, A. H.; Hogg, J. A. *J. Am. Chem. Soc.* **1954**, *76*, 743−746.

(30) Cutler, F. A.; Fisher, J. F. Merck, 1954. Unpublished.

which might have formed and eluded our scrutiny, especially after the somewhat related findings of Gallagher, published in 1952.[31]

Absolute answers were not found and are still unknown. We acquired experimental evidence, however, that forcing the enol acetylation by raising the temperature by as little as 7 °C had a clearly deleterious effect on yield, melting point, and product color. Influenced by that, an improved enolization catalyst was sought and found which was active at lower temperature. It was shown that 3 mol % of 3,5-dinitrobenzenesulfonic acid (DNBS) would give "complete" enol acetylation at room temperature at C-20 without measurable involvement of the C-11 ketone, in contrast to the 96 °C conditions used with 30 mol % of *p*-toluenesulfonic acid. Many other acids were examined; their relative rates were measured, and DNBS was selected for plant use. It was available at modest price as its sodium salt and could be converted to the acid via ion exchange. Implementation on plant scale provided **21** first-crop yields of 88.7% versus the then current 79.8%. The overall yield which included the recycle rose to 94%, and the quality, as judged by yields in the next step also rose significantly.

In almost every development throughout the process, performance on the following step(s) was a key measure of quality. Melting point was not sufficient by itself. I suspect that even with modern instrumentation, which would have gained us precious time (and allowed us to satisfy our Rahway friends sooner), we would still have carried out those "use-tests".

Conversion of 21 to 22; 22 to 23. These two reactions can be conveniently covered together and represented the preferred functionalization of C-21. It will be recalled that with the modified Sarett cyanohydrin process prior to the Gallagher chemistry, C-21 acetoxylation was accomplished along with side chain diene formation.

Having devised an efficient process for the introduction of the 17-hydroxyl, the Gallagher group continued on to form the complete dihydroxyacetone side chain. Their definitive paper[26] appeared as our demonstration got underway; the authors chose bromination at C-21 in chloroform and obtained 81% yield after a conventional workup and purification from ethyl acetate. Starting material was recovered by reduction of the mother liquor solids. Their preferred route to acetoxylation was base hydrolysis followed by acetylation with acetic anhydride. Because of that choice, oxidation at C-3 preceded manipulation of the 21-bromide. Had this path not been taken, some 3,21-diacetate would have likely resulted upon acetylation, thereby lowering the overall yield to cortisone.

The Merck choice to acetoxylate first was pragmatic since it was believed that it was not prudent to carry a reactive bromoketone through subsequent steps where (especially on a large scale and consequently over longer exposure) unplanned chemistry might ensue.

Our bromination was found to give a nicely crystalline, stable solvate with acetonitrile, but yields were modestly lower when run in the factory with recovered chloroform as solvent until we traced the cause to stabilization of the solvent with methanol instead of with ethanol. An appropriate change returned the yield of the first crop to the mid-80% range. Once again, a precise number was not routinely available because of the acetonitrile of solvation; however, that was dealt with as in the case of **16**; performance was measured over both preparations of **22** and **23**. Demonstration of those two gave 85.4%, including the recycle from debromination of the **22** mother liquors.

Improvement continued. A less expensive, more productive, and simpler process was devised. Compound **21** was brominated in 10:1 benzene−methanol(!) containing anhydrous HBr. Crystallization of 95% yield ensued upon quench with aqueous sodium bicarbonate. An additional 2% could be recovered by crystallization of the mother liquor residues from acetonitrile without reduction and rebromination.

The acetoxylation to **23** changed little over the years other than to increase the concentration and decrease the charge of sodium iodide. The latter could probably have been reduced further; it was present as a catalyst, over 40 mol % based on substrate. The pennies involved were not enough to put that project on anyone's priority list.

Conversion of 23 to 24. By rights, this step formally belongs with the Third Phase since it initiates the preparation of the A-ring enone. As an offshoot of the Gallagher chemistry, where it was run before the 21-acetoxylation, it wound up here.

Reich and Reichstein[32] were probably the first to use *N*-bromoacetamide (NBA) for the oxidation of steroid alcohols; they found that *tert*-butyl alcohol served their purpose as solvent as did Gallagher in later years. For large-scale work, however, methanol was preferred since it was less expensive and easier to recover, was already used in other parts of the process, and was less viscous. With a melting point above 20 °C, *tert*-butyl alcohol would surely be troublesome in cold weather. The protocol that was first demonstrated involved room-temperature oxidation for 16 h with 2.3 mol of NBA (prepared in situ) per mole of steroid in methanol containing approximately an equivalent of pyridine. Results from attempts to replace the latter with, for example, triethylamine proved unsatisfactory. The product was obtained in 94% yield by dilution with water after quenching excess oxidant. The quality, however, was not optimal; it could be improved by zinc−acetic acid treatment to remove spurious brominated impurities with a concomitant cost of a 6% yield loss. Logic suggested that the major byproduct would be **26**, the next intermediate; however, the overall yield through **26** was depressed when the zinc treatment was bypassed.

In a search for improvement, dibromodimethyl hydantoin was commercially available, cheaper than NBS, and worked equally well. A process evolved with acetone as solvent. The zinc dust purification was added before isolation, and direct crystallization after removal of the zinc residue gave acceptable quality **24** in 93.6%, superior to all found in the literature.

(31) Belleau, B.; Gallagher, T. F. *J. Chem. Soc.* **1952**, *74*, 2816−2819.

(32) Reich, H.; Reichstein, T. *Helv. Chim. Acta* **1943**, *26*, 562−585.

Table 3. Second-Phase Yields, %

steps	best literature yield (%)	Danville demonstration (%)	ultimate performance (%)
12 to **13**	88[a]	85.7[b]	87[b]
13 to **14**	90	91	92.7
14 to **16**	67.5[c]	80	87.4
16 to **17**	63.5[c]	71.3	93
17 to **18**	27,[c] 90[d]	94	99
18 to **21**	72.1	80	94
21 to **22**	81	84	97
22 to **23**	70[e]	95	95
23 to **24**	71[d]	88	93.6
	overall	23.5%	52.6%

[a] Includes second crop. [b] Without second crop. [c] From U.S. Patent 2,598,559. [d] Slightly different structured substrate. [e] Via two steps on 3-ketone.

Second-Phase Summary. The First Phase had seen factory implementation in Rahway before its introduction to Cherokee. That was not true for the Second Phase, save for the first two steps. It was, therefore, remarkable that the unpiloted chemistry fell into place with relative ease. Among other things, it spoke well for the quality of work, upon which it was based, and the prior collaboration of the Merck R&D chemists with the Sloan-Kettering and Mayo Foundation groups. I suspect their footnotes of thanks to Dr. Tishler and his research team were sincere.

Prior to that, Max showed courage in taking on what had to be the technological responsibility for factory introduction of this chemistry. Decisions to go ahead with large-scale manufacturing were made long before the process was available and before he knew who would back him up "in the field". This being a new plant, there were to be all new and inexperienced chemical operators and supervisors as well as mostly new chemists to provide guidance and to solve problems. Of the six named earlier,[5] only two had more than a year of experience with the Merck steroid program when the first reactor was charged.

From a developmental standpoint, the 14 chemical reactions that comprised the Second Phase were introduced at 23.4% overall yield, and wound up at 52.6%, an average in excess of 95% per reaction. Short cuts were taken, but not at the expense of **24** purity, which was to be crucial for the Third-Phase performance and the cortisone product quality (Table 3).

The most gratifying advances included the change to benzene for the formation of **16**, the discovery of DNBS as a superior enolization catalyst for the formation of **19** as an intermediate, and the solvent system for the bromination of **21**, which permitted such process simplification. With benzene, we actually considered it benificent in that carbon tetrachloride was a known liver toxin. Little did we know at the time that we were exchanging it for what would many years later be labeled a carcinogen!

Third Phase. The Third Phase required the smallest molecular change: removal of two vicinal hydrogen atoms. Occurring after a long synthesis and demanding product of the highest chemical purity in addition to pharmaceutical elegance, it received a disproportionately large effort. The

First-Phase conversions from **2** to **8** comprised seven chemical reactions: cathylation of the 3-OH, oxidation at C-12, bromination at C-11, dehydrobromination, hydrolysis, re-esterification, and 12-ketone hydrogenation, the net effect of which was also the removal of two vicinal hydrogen atoms (see Scheme 3). That was surely no more difficult. This ultimate processing was, indeed, the ultimate economic challenge.

Sarett[33] used pyridine dehydrobromination of the 4-bromosteroid (reduced and acetylated at C-20) in his first synthesis of cortisone, the usual method[34] to introduce the double bond. The scheme was first devised by Butenandt and Schmidt,[35] but a casual perusal of its application shows both variable and invariably poor yields by all who used it. The Fiesers, in discussing the Merck production of Compound A (11-dehydrocorticosterone) in 1944 note, "Jacob van de Kamp, Stewart M. Miller, and one part time assistant working under the direction of Max Tishler [...] completed the task in sixteen months."[36] Of various improvements introduced, the most striking was in the terminal dehydrobromination to produce the 4,5 double bond, for which the best previous yield was about 10%. By skillful development work, Miller raised the yield to 30%.

A better solution to this problem was widely sought; Mattox and Kendall[37] were the first to put in print a new scheme, dehydrobromination of **25** through the agency of dinitrophenylhydrazone formation and subsequent hydrazone hydrolysis.

Conversion of 24 to 25. A great deal of development was still required as the demonstration with an incompletely developed process was initiated in the new plant. Some improvements were made on an ad-hoc basis, at times prematurely, with production at sub-optimal performance better than no production at all. For better and for worse, such a modus operandi is no longer practiced, courtesy of FDA and cGMP regulations.

The start-up bromination was run in acetic acid below 20 °C with the isolated product requiring purification. That the best dehydrobromination occurred via hydrazone formation strongly supported the view that the bromine was attached to the β-face. While not definitive proof, it was then believed that the mechanism for that reaction was cis elimination; however, other materials convertible to product were also present. Tedious separation, chemical instability, and the lack of physical chemical methodology made the identification of the congeners difficult. Possibilities included the epimer, isomers (2-position), polybrominated species, and total unpredictables. Instability of one or more of them was obvious. There was literature suggesting such results with analogous substrates. Obtaining yields ranging from 75 to 80% at that stage was quite gratifying.

An early key finding suggested that "epimerization" of the minor 4-α-bromo epimer in the crude **25** could be

(33) Sarett, L. H. *J. Biol. Chem.* **1946**, *162*, 601−631.
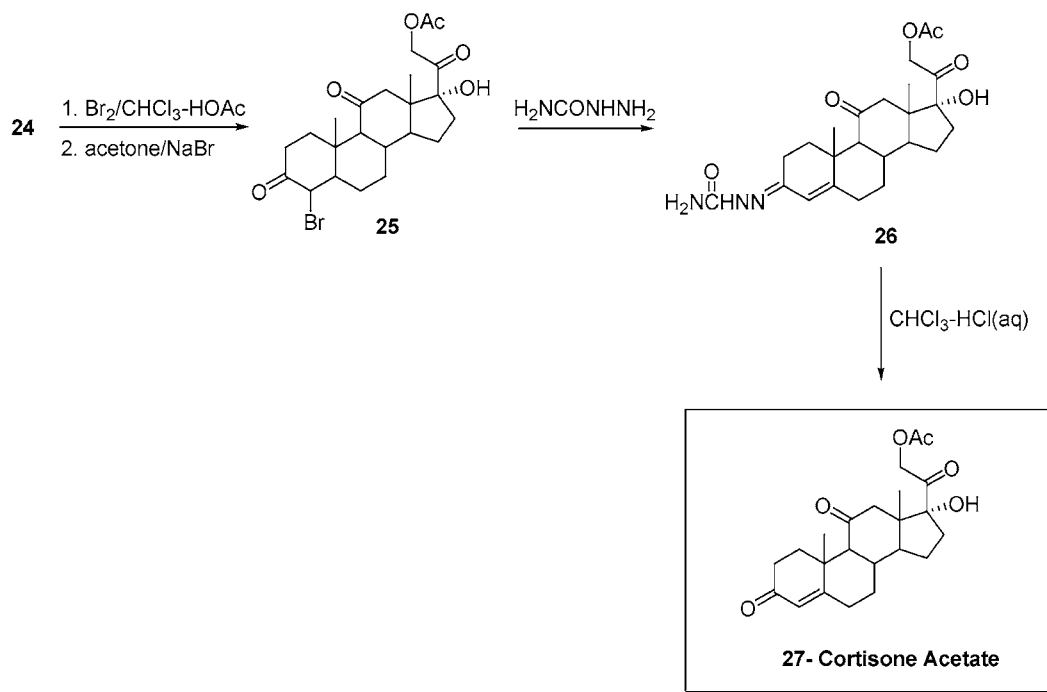(34) Djerassi, C. *J. Am. Chem. Soc.* **1949**, *71*, 1003−1010.
(35) Butenandt, A.; Schmidt, J. *Chem. Ber.* **1934**, *67*, 1901−1904.
(36) Reference 18, p 645.
(37) (a) Mattox, V. R.; Kendall, E. C. *J. Am. Chem. Soc.* **1948**, *70*, 882−883.
    (b) Mattox, V. R.; Kendall, E. C. *J. Biol. Chem.* **1951**, *188*, 287−297.

Scheme 3. Third phase

achieved by heating the entire crude product with sodium bromide in acetone. Whether it was epimerization or the result of some other subtle change was not immediately relevant; the product showed an increase in optical rotation from the mid 90° to 109−112°, higher than hitherto reported. Research from Upjohn[38] which appeared as these results were being implemented in the plant revealed a different solution to the same problem, achieving the same +112° specific rotation by carrying out the bromination in dimethylformamide and recrystallizing from acetone. While evidence supporting the 4-β configuration was also provided, it was stated, "these data suggested that the stereochemistry of bromination in buffered acetic acid was different from that in the dimethylformamide system; and, the formation of the 4-β-bromo isomer was favored in dimethylformamide."

The dehydrobromination yield improved, as well. Moreover, when the bromination was performed in chloroform−acetic acid at −55 to −51 °C instead of buffered acetic acid at about room temperature as was done originally, even higher yields (above 92%) were obtained, and that product was still amenable to upgrading by our method. Now, the **25** overall process had reached 95% yield while halving the amount of steroid requiring recycle through **24**.

Conversion of 25 to Cortisone Acetate (27). Product elegance has long been an ethereal objective of ethical pharmaceutical companies; it is sometimes an expensive one. Planning for the last step has to include concerns of color and appearance as well as chemical purity. It is annoying to some synthetic chemists to see a difficultly won, elegant, white crystalline material subjected by pharmacists to granulation, sometimes coloration, and compression to an unnatural form. Nevertheless, reproducibly effective dosage

forms are the ultimate goal**.** We strove for both chemical purity and that elegance with cortisone. Neither came free.

The start-up employed semicarbazide for the dehydrobromination of **25**, a wonderful improvement over dinitrophenylhydrazine—if only from the standpoint of color. The reaction was carried out at room temperature in acetonitrile and the semicarbazone, **26**, isolated from water. Conversion to the enone was carried out in 70% acetic acid with pyruvic acid. Transfer of the product to chloroform (which had been washed free of acid), passage over alumina, and a solvent exchange into acetone was a lengthy operation. The acetone concentrate was diluted with ether and the product isolated in 81.4% yield.

Continuing study revealed the partial reversal of **26** in 70% acetic acid in the absence of pyruvic acid. An equilibrium was apparent. It was thus reasonable that complete reversal would be possible by conditions which prevented recondensation and did not allow undesired side reaction. First, it was shown that a clean hydrolysis could be carried out in chloroform−dilute hydrochloric acid. The released semicarbazide (predominantly as its hydrochloride) did not react with free **27** in the chloroform layer. Both acetic and pyruvic acids could be removed from the process; the latter was expensive and required a difficult purification. Then, the formation of **26** was improved by running it dry. To achieve that, semicarbazide free base was required, and a supplier was found. The solvent system was changed for **26** and its isolation eliminated. Product crystallization was also changed when it was found that cortisone acetate formed a solvate with dimethylformamide, which aided in its separation, and could be desolvated by simple means. The ultimate process reached an average of 88% in the plant; very pure **25** could provide 94%.

(38) Holysz, R. P. *J. Am. Chem. Soc.* **1953**, *75*, 4432−4437.

Table 4. Third-phase yields, %

steps	best literature yield (%)	Danville demonstration (%)	ultimate performance (%)
24 to **25**	89	84.5	95
25 to **27**	92[a]	81.4	92
overall	68.8%	87.4%

[a] Not of pharmaceutical quality.

Third-Phase Summary. In a rather evolutionary way, the Third Phase was reduced to a much simpler as well as a higher-yielding process (see Table 4). The latter rose from 68.7% to 87.4%, cutting the losses by 2.5-fold. Much of the equipment originally planned for recovery, recycle, and repurification became redundant by the end of 1953. Surely Dr. Tishler had every right to express his pride, as noted in my opening paragraph. One can only contemplate the pressure on him in the late 1940s when Merck made the decision to proceed with this unproven entity, two of whose close structural analogues had proven to be biologically uninteresting. The trust placed in him was well rewarded.

The Last Word

It remains for me to explain the "The Next-To-Last Word" in the title. Reflection after all these years is nostalgic. Moreover, it reveals how much progress has been made in the way we undertake and accomplish developmental chemistry. What stimulated us then would still, however, stimulate us today: scientific and economic challenges leading to new products in the market place for the betterment of human health.

Some questions from the project nag, however, now that they have resurfaced. Would reexamination of the procedures today, with our new tools, reveal ways to improve reactions? Could we raise the yields? Would we have changed our purifications if we had had HPLC analysis? There are even stereochemical questions to which I have alluded which have not been conclusively answered. The list goes on...

But development is like raking leaves from the lawn in mid-autumn, where we usually settle for less than 100% removal. More will appear shortly, anyway. To the Development mindset, more questions will appear even though we have raked most of them into the "answered" pile.

Experimental Section

Each step of the cortisone acetate process is recorded below. The quantities are scaled down from the production level to amounts considered appropriate for meaningful use tests that were run to evaluate raw materials, intermediates, or alternate conditions. The procedures are those that were in use when the process closed down in 1966.

Preparation of 2. To a slurry of DCA (167.0 g, 0.43 mol) in methanol (288 mL) stirred at 30−35 °C was added 3.2 mL of sulfuric acid. The batch was aged 4 h during which the acid dissolved and the ester crystallized. The slurry was cooled and held 1 h at 0−5 °C and maintained at that temperature while 151 mL of water at the same temperature

was added slowly. The product was filtered and washed with a cold solution of 240 mL of methanol and 122 mL of water. Drying was optional if the product was to be converted to **4b**; $y = 93−95\%$.

Preparation of 4b. A stirred solution of methanol-solvated ester **2** (100.0 g dry basis, 0.25 mol) in ca. 500 mL of benzene was distilled atmospherically until the vapor temperature reached 80 °C and the residual methanol was removed to a final batch volume of 395 mL. The solution was cooled to ambient temperature; pyridine (22.8 mL, 22.3 g, 0.28 mol) was added, followed by the dropwise addition at 20−23 °C of ethyl chloroformate (25.4 mL, 28.8 g, 0.27 mol) over a 30-min period. After 2 h of aging, 297 mL of acetic acid was added, followed by the dropwise addition of chromic acid (18.8 g, 0.16 mol) dissolved in 17.8 mL of water, again holding the temperature at 20−23 °C.

After the addition, the reaction was heated at 60 °C for 1 h and cooled, and the dark acidic layer was removed. The benzene layer was washed essentially free of acid, combined with acid-free extracts of the aqueous layers, and concentrated, and the residual benzene was removed by flushing with methanol. The final slurry was cooled and aged at −5 to 0 °C, filtered, and washed with cold methanol. Compound **4b** showed a mp 155−156 °C; $y = 95−96\%$.

Preparation of 7. *Bromination and Dehydrobromination.* To a 1-L, three-neck flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel was charged **4b** (150.0 g, 0.30 mol), 185 mL of benzene, and 165 mL of methanol. A total of 17 mL of bromine (53.0 g, 0.33 mol, ca. 1.05 mol per mol of **4b**) was placed in the addition funnel. After heating to reflux, 20 mL of freshly prepared 3 N hydrogen bromide in methanol was added to the slurry. Addition of 2-mL increments of bromine was initiated immediately, maintaining reflux and awaiting decolorization between additions. The last 5 mL was added in one portion. The addition funnel was rinsed into the reaction with 10 mL of benzene, and reflux was continued for 15 min. The slurry was cooled to 50 °C, and allyl alcohol (1 mL, 0.85 g, 0.01 mol) was added to quench excess bromine, giving a negative test to starch-iodide test paper. The bromoketone was not isolated. Anhydrous sodium acetate (64.5 g, 0.79 mol) and dimethylformamide (179.5 mL) were added to the mixture. The batch was concentrated in vacuo until the temperature reached 100 °C at 16 in. vacuum. The temperature and vacuum were maintained for 2 h to complete the dehydrobromination, after which the slurry was cooled to 50 °C. Methanol (225 mL) was added in a thin stream, and when thoroughly mixed, the slurry was cooled to 5 °C and aged for 1 h. The product, **6**, was filtered, washed with ice-cold methanol until the filtrate was essentially colorless, and then dried at 60 °C to constant weight (139.1 g, 93.1%, mp 162.5−166 °C; UV 2400 Å, A1%/1 cm = 236).

Hydrolysis of both ester and cathyl moieties was carried out in less than 4 mL per gram of methanol containing 4.2 equiv of sodium hydroxide by refluxing the slurry for 2 h, diluting with two volumes of water based on methanol, and carefully crystallizing by slow addition (with seeding) of a slight excess of acetic acid; $y = 97.6\%$.

Preparation of 11b. A solution of **7** (77.6 g, 0.20 mol) in methanol (140 mL) was treated with 2.59 g of Nuchar at 50−55 °C for 1 h. After filtering and washing with methanol (2 × 60 mL) into a hydrogenation bottle, 1.55 mL of concentrated HCl was added, and the solution stirred for 5 h at 25−30 °C to effect esterification. Hydrogenation was then carried out over Adams catalyst (1.54 g Pt equiv) at 40 psig and at 15−18 °C. Usually, less than 2 h was required to reduce the starting material to less than 1% as determined by UV measurement.

The catalyst was removed by filtration and sequentially washed with chloroform (205 mL), methanol (32 mL), and water (65 mL). Extractive workup, followed by concentration of the chloroform layers in vacuo to a total volume of 216 mL gave **8**, ready for conversion to **10**.

While stirring at −15 to −10 °C, anhydrous HBr (21.6 g, 0.27 mol) was rapidly added to the solution, which was then aged 1 h. The chloroform solution was extracted three times by stirring vigorously with 3% brine, each extract in turn being back-extracted with chloroform which was added to the batch. This final solution of **10** was azeotropically dried while concentrating to a total volume of 375 mL.

A stirred solution of chloroform (253 mL), ethanol (4.1 mL), sodium bicarbonate (4.0 g, 4.76 mmol), and bromine (21 mL, 0.41 mol) was cooled to −62 °C. The intermediate **10** solution from above was added to it, slowly maintaining a temperature of −59 to −60 °C. After an additional 30 min at that temperature, the batch was added with stirring to a solution of water (453 mL) containing sodium bisulfite (236.0 g, 2.27 mol) and sodium hydroxide solution (80 mL, 23%). After extractive workup, the chloroform solution was concentrated to a volume of 147 mL in a pre-marked 1-L, three-neck flask. The temperature was adjusted to 25−30 °C, and 500 mL of methanol was added in a thin stream while seeding the batch. As crystallization ensued, the rates of addition and agitation were increased. After the completion of the methanol addition (5 min), the slurry was filtered and washed with methanol (2 × 100 mL). When dried without heat, the **11b** showed mp 138 °C or higher; $y = 60\%$ for the **7** → **11b** sequence, crop I.

Isolation of 11a. Mother liquors and washes were concentrated in vacuo to a total volume of 65 mL, diluted with methanol (130 mL), and concentrated again to the same volume to ensure removal of chloroform. After cooling to 0 °C, **11a** was filtered and washed with methanol, and dried as above. This crop amounted to ca. 20% direct yield, but was valued at only 75% since it required debromination and rebromination.

Debromination of 11a. To a stirred slurry of **11a** (109.0 g, 0.20 mol) in methanol (521 mL) at 50 °C was gradually added zinc dust (21.9 g, 0.33 mol) while maintaining the temperature range. After the addition was complete (15 min), the temperature was raised to reflux for 90 min, and then the slurry was cooled, filtered, washed with methanol; the filtrate was then partitioned between chloroform and water containing sufficient HCl to bring the pH to 2−3. After completion of the extractions, the concentrated solution of **10** was ready for bromination as before.

Preparation of 12. To a 2-L flask containing acetone (600 mL), sodium dichromate (41.5 g, 0.16 mol), and a solution of chromic acid (36.8 g, 0.37 mol) in water (32.2 mL) was added intermediate **11b** (100.0 g, 0.18 mol). The mixture was stirred and heated at reflux for 5 h, after which it was cooled to 30−35 °C. Hydrochloric acid (concentrated, 27.4 mL) was added over 15 min, and the slurry stirred another 45 min. The mixture was then cooled to 13 °C, vacuum was applied carefully, and the volume was reduced by distillation to 600 mL. Distillation was continued, maintaining the same volume by gradual addition of 242 mL of water as needed. A Karl Fischer titration at the end of the concentration showed the desired 55−60% water content. The slurry was then cooled to 0−5 °C, held 1 h, filtered, and washed with chilled 1:1 acetone−water. The product when dried at 50 °C showed mp 113−115 °C.

Preparation of 13. To a 1-L, three-neck flask was added magnesium turnings (15.4 g, 0.63 mol), and the apparatus was heated to 60 °C while passing a slow stream of nitrogen through it for 15 min. The heat was removed, the nitrogen flow decreased, and a crystal of iodine was added, followed by bromobenzene (1 mL). At this point, a 15-mL portion of a solution of chlorobenzene (69 mL) and tetrahydrofuran (165 mL) was added in one portion. In most cases, the reaction started immediately; if not, the application of heat was required for initiation.

The remainder of the reagent chlorobenzene solution was added dropwise at a rate to sustain continuous reflux without applied heat. At the end of the addition, heating at reflux was continued for an additional 2 h. The batch was then cooled to 0−5 °C.

Meanwhile, **12** (59.0 g, 0.12 mol) in toluene (98 mL) was stirred with Nuchar (0.6 g) and filter aid for 15 min, filtered, and washed with toluene (4 × 30 mL).

The steroid solution was added to the Grignard reagent, maintaining the 0−5 °C temperature, was rinsed in with 50 mL of toluene, and was then heated to and held at 23−30 °C for 3 h. The batch was poured into a stirred mixture of water (140 mL), hydrochloric acid (concentrated, 69 mL), and cracked ice (350.0 g). The flask residue was washed into the quench mixture with toluene (150 mL) at 35−40 °C. After extractive workup, the organic layer was concentrated in vacuo to dryness, the residual toluene was flushed out with acetic acid, and the final residue was taken up to reflux in acetic acid (144 mL). After reflux for 2 h, the solution was cooled to 85−90 °C, seeded with intermediate **13**, and allowed to crystallize in that temperature range for 30 min. The thin slurry was cooled slowly to 17−20 °C, held for 3 h, filtered, washed with a minimal amount of cooled acetic acid, and dried at 60 °C; $y = 87\%$, mp > 150 °C.

Preparation of 14. Since most laboratories for synthetic chemistry do not have autoclaves, the procedure of Mattox and Kendall[19] is recommended which gives the same results. A 1-gal autoclave, approximately half filled, was charged with 1.2 mL of chloroform per g of **13**, pressured to 85−90 psig with anhydrous HBr at 0 °C, and aged for 40 h at those conditions. The workup volume in acetic anhydride was

approximately double that used by Mattox and Kendall. The final product was washed by displacement with acetic acid before drying; $y = 92.7\%$, mp > 175 °C.

Preparation of 16. A solution of **14** (277.5 g, 0.44 mol) in benzene (2 L) was stirred with Nuchar (27.7 g) for 30 min and filtered, and the cake was washed with benzene (2 × 500 mL). The clear solution was placed in a 12-L flask with five ground-glass joints. The central (large) joint contained a glass thimble fitted with a 500-W projection lamp which was submerged in low conductivity water. Two of the other fittings held condensers, another, a nitrogen sparger, and the last was used for introduction of the *N*-bromosuccinimide (NBS) solution. That solution was prepared by heating NBS (85.4 g, 0.48 mol) to reflux in benzene (3.3 L).

The steroid solution was heated to reflux with a slow flow of nitrogen serving as agitation. When the NBS solution reached boiling, the projection lamp was illuminated, and the NBS was transferred to the light reactor all at once through a wide Tygon tube. The reaction turned bright red and then returned to a light amber. The lamp was turned off after 1 min (the solution gave a negative starch-iodide test), and the batch refluxed for 3 h with a good flow of nitrogen to sparge the evolving hydrogen bromide. After cooling to at least 50 °C, the solution was washed with water (750 mL), and the benzene solution was concentrated in vacuo to a total volume of 555 mL. An equal volume of hexane was added to the slurry which was then aged for 3 h at 0−5 °C. The product was filtered, washed with hexane (555 mL), and then dried at 50 °C (243.8 g).

Second-Crop Mixture. The mother liquors were concentrated to dryness and taken up in acetone (150 mL). To the solution were added potassium acetate (15.0 g, 0.15 mol), acetic acid (5 mL), and sodium iodide (2.5 g, 0.02 mol), and the slurry refluxed for 4 h. The solids were removed by filtration while hot, and washed with hot acetone (2 × 10 mL). To the reheated filtrate was added methanol (170 mL), and then the solution was cooled slowly during which time the solids crystallized. After 4 h at 0−5 °C, they were collected and washed with 50 mL of cold 3:1 methanol−acetone and then 50 mL of cold methanol. When dry, the cake weighed 36.6 g, and assayed 28% **16** by UV measurement. (The purpose of the reagents was to convert any 21-brominated diene to its acetate, thereby rendering it more soluble and more easily separated from the desired **14** and **16**.)

Second-Crop Separation. The solids were heated to solution with stirring in benzene (30 mL) and then cooled slowly and stirred at ambient temperature overnight. An equal volume of hexane was added to the **16** solvate slowly; the product was then filtered and washed with 72 mL of hexane. A total of 6.91 g (2.5%) product was obtained after drying and was of quality suitable for the next step (even if not quite as pure as first crop **16**).

Recovery of 14. The above mother liquors were again concentrated in vacuo to a residue, taken up in benzene (30 mL) at reflux, and slowly diluted with methanol (90 mL) while maintaining reflux. The solution was then cooled

Table 5. Yield estimation

14 charged	277.5 g	
14 recovered	24.5 g	
net charge		253.0 g
16 crop 1	243.8 g	
16 crop 2 @ 95% value	6.56 g	
gross yield	250.36 g	
assuming 12% solvation		220.3 g, 87.4%

slowly to room temperature, then to 0−5 °C, and aged 4 h. The product was filtered and washed with cold methanol (15 mL), providing after drying **14** (24.5 g, 8.8% of initial charge), mp 176.1−177.2 °C (see Table 5). This responded well to recycle through the light reaction.

Preparation of 17. To a stirred 2-L, three-neck flask with thermometer and dropping funnel were added solvated **16** (50.0 g; 44.0 g on solvate-free basis, 0.07 mol), acetic acid (52 mL) and benzene (32 mL), and the slurry was cooled to 5 °C. A cooled solution of sodium dichromate (47.5 g, 0.18 mol) in acetic acid (92 mL), which had been prepared by heating at about 70 °C, was added while controlling the temperature in the 13−17 °C range. That temperature was maintained until the reaction was quenched. After 30-min aging, a cooled solution of sulfuric acid (54.0 g, 0.55 mol) in acetic acid (18.3 mL) was added over 45 min, and then the reaction was aged an additional hour. The reaction was terminated by adding benzene (200 mL) and water (216 mL). The two-phase mixture was worked up via aqueous extraction to remove essentially all acid, the appropriate back extracts of the water layers being added to the batch. The organic phase was treated with sodium hydroxide solution (9.5 mL at 25%) with vigorous mixing to extract any "nor-acid" formed from oxidation of unreacted **14** in the **16.** The mixture was filtered through filter aid, the solids were washed with benzene, and any aqueous layer was cut off. The filtrate was washed with ca. 15% brine containing sufficient acetic acid to ensure removal of residual base. The benzene solution was distilled atmospherically to 82 mL and diluted with methanol to 180 mL. Distillation was resumed, maintaining the volume constant by appropriate addition of methanol, until the internal temperature reached 60 °C. The batch was seeded with **17**, and the azeotroping continued until the temperature reached 65 °C. The slurry was cooled slowly, aged for 2 h at 0−5 °C, filtered and washed with cold methanol (20 mL), and dried to provide **17** (27.9 g, 88%), mp > 188 °C.

Second-Crop Semicarbazone Formation of 17. Mother liquors from five such batches were treated with acetic acid (5 mL), semicarbazide free base (7.2 g, 0.1 mol), and water (19 mL), stirred to solution, then seeded with **17** semicarbazone, and allowed to crystallize for at least 3 d. The product was recovered by filtration, washed with methanol (25 mL), and dried to provide the semicarbazone (12.0 g, 6.7% based on charge), mp 260−266 °C.

Recovery of 17 from the Semicarbazone. A stirred mixture of benzene (300 mL), water (100 mL), hydrochloric acid (concentrated, 130 mL), and ground **17** semicarbazone (40.0 g, 0.08 mol) was refluxed for 1 h and then cooled to

room temperature; the aqueous layer was extracted with benzene (275 mL). After washing the organic phase to neutrality with dilute sodium bicarbonate, it was worked up to **17** in the same distillative manner as the first crop to provide acceptable product (31.0 g, 87%), mp 187−190 °C.

Preparation of 18. To a slurry of **17** (100.0 g, 0.22 mol) in acetic acid (167 mL) was added zinc dust (11.0 g, 0.17 mol) portionwise, maintaining the temperature between 40 and 45 °C. The batch was aged an additional 30 min at that temperature and then cooled to 25 °C and filtered through filter aid. After washing with warm acetic acid (40 mL), the combined filtrate was diluted slowly with water to the cloud point and stirred for 20 min. Water addition was continued slowly until a total of 565 mL had been added over ca. 1 h. The slurry was aged 2 h at 0−5 °C, filtered, washed free of acid with water, and dried to provide **18** (81.8 g, 99%), mp 132.5−134.1 °C.

Preparation of 21. To a solution of **18** (50.0 g, 0.13 mol) in acetic anhydride (300 mL) was added 3,5-dinitrobenzenesulfonic acid (1.67 g, 0.67 mol). After stirring at 25−28 °C for 6 h, the catalyst was neutralized by the addition of sodium acetate (3.4 g, 0.04 mol), and the solvent was removed by vacuum distillation below an internal temperature of 45 °C. The residual gum was dissolved in ethyl acetate (278 mL) and extracted with saturated sodium bicarbonate solution (1 × 510 mL, 1 × 232 mL), each aqueous phase being back-extracted with ethyl acetate (75 mL) that was combined with the batch. After a final water wash, the ethyl acetate was concentrated to 125 mL in vacuo, and to it were added water (4.5 mL) and powdered phthalic acid (3.0 g, 0.02 mol). The flask was placed in an ice−water bath, and to it was added an ethyl acetate solution of MPPA (33.9 g, 0.19 mol) (see below for its preparation). The reaction was allowed to proceed overnight, and the temperature allowed to rise to ambient. (Normal plant practice was to carry out the reaction for 12 h at 25−30 °C.)

The batch was then cooled to 0 °C, and water (128 mL) containing sodium bisulfite (11.1 g, 0.11 mol) was added, keeping the temperature below 30 °C, followed by 25% sodium hydroxide (110 mL) below 20 °C. After the normal aqueous workup, the ethyl acetate was removed in vacuo and flushed with methanol to ensure removal of the former. The volume was adjusted to 236 mL with methanol and the temperature adjusted to 15 °C. Sodium hydroxide (75 mL) was added slowly, maintaining the temperature at 25−30 °C. After 30 min, the batch was again cooled and acidified by dropwise addition of 20% sulfuric acid below 25 °C until the pH < 3. Approximately 100 mL of acid was required. Following that, water (100 mL) was added slowly, and the methanol was then removed by concentration (28 in. Hg vacuum) until the internal temperature reached 35 °C. The volume of concentrate was not above 127 mL. Water (200 mL) was added, and the slurry was cooled to 5−10 °C and filtered after a 1-h aging. It was washed free of sulfate with water and dried at 60 °C.

The dry, crude product was taken up in methanol (26 mL) and benzene (200 mL) and distilled at atmospheric pressure until the internal temperature reached 80 °C. The volume was adjusted to 164 mL, and the slurry was cooled and held 12 h at 10−15 °C. After filtering and washing with benzene (35 mL), the product was dried at 60 °C (41.3 g, 88.7%), mp > 198 °C.

Chloroform extracts of the aqueous mother liquors from the isolation of the crude product were combined with the benzene mother liquors from the recrystallization, and the whole was subjected to recycle through the entire process; the overall yield rose to 95%.

Preparation of Monoperphthalic Acid. The synthesis was carried out below 10 °C. To a cooled slurry of powdered phthalic anhydride (222.0 g, 1.50 mol) in water (804 mL) was added sodium perborate (305.0 g, 3.73 mol) with stirring. After 2 h and with cooling, sulfuric acid (105 mL) dissolved in water (320 mL) was added. The peracid was extracted after adding ethyl acetate (1040 mL) and ammonium sulfate (9.6 g, 0.07 mol); it was further washed twice with a solution of ammonium sulfate (192.0 g, 1.45 mol) in water (680 mL). The resulting ethyl acetate solution was dried to no more than 2.5% water content by treating it portionwise with magnesium sulfate (requiring ca. 150.0 g). The peracid molarity was determined by titration with thiosulfate before use in the process and was generally 0.9 M.

Preparation of 22. A stirred slurry of **21** (150.0 g, 0.43 mol) in benzene (750 mL) and methanol (75 mL) was warmed to 46 °C, and to it was added methanolic HBr (15 mL of a 2.75 N solution), followed by bromine (23.7 mL, 0.46 mol) over a 0.5 h period, holding the temperature at 46 ± 2 °C. After a 5-min age, about 30 mL of a solution of sodium bicarbonate (52.5 g, 0.63 mol) in water (630 mL) was added rapidly, enough to initiate crystallization. After 30 min, addition was resumed and the remainder of the bicarbonate solution added over another 30 min with agitation. The slurry was cooled to and held at 25 °C for 1 h, then filtered, washed with water, and air-dried to provide **22** (174.8 g, 95%), mp > 192 °C.

Second-Crop Isolation of 22. The organic layer was removed from the mother liquors, washed with a fifth volume of water, then concentrated in vacuo to near dryness. The residue was taken up in acetonitrile (100 mL), and after warming to solution, the volume was reduced by half. The batch was seeded, if necessary, and allowed to crystallize for at least 24 h; it was then cooled to 0−5 °C for 4 h. The solids were filtered, washed with cold acetonitrile, and dried to provide acceptable material (3.9 g. 2.1%).

Preparation of 23. To a solution of **22** (100.0 g, 0.23 mol) in acetone (417 mL) were added anhydrous potassium acetate (115.0 g, 1.17 mol) and acetic acid (35.1 mL). With stirring, the solution was heated to distill off 50 mL of solvent. Sodium iodide (16.3 g, 0.11 mol) was then added along with fresh acetone (50 mL) and the solution heated at reflux for 4 h. After cooling to 50 °C, water (125 mL) was added, and the batch then distilled at atmospheric pressure with water added to maintain the volume, until the temperature reached 77 °C. The remainder of the acetone was then removed by distillation in vacuo and the volume adjusted to approximately 520 mL with water. After cooling to and aging

1 h at 0−5 °C, the product was collected on a filter, washed with water (2 × 200 mL), and dried to provide **23** (90.4 g, 95%), mp > 220 °C.

Preparation of 24. To a stirred flask containing **23** (50.0 g, 0.12 mol) in acetone (550 mL), water (150 mL), and pyridine (11 mL) at 35 °C and covered with cloth to exclude light, was added 1,3-dibromo-5,5-dimethylhydantoin (30.7 g, 0.011 mol). A temperature rise occurred in about 10 min, after which the reaction was aged at 40−45 °C for 4 h. That temperature range was maintained until the filtration of the zinc and Nuchar (vida infra). Acetic acid (50 mL) was added followed by zinc dust (5.0 g, 0.08 mol). In 10 min additional zinc dust (1.0 g, 0.02 mol) was added, and then 30 min later, Nuchar (3.0 g) was added. After 15 min more, the solids were filtered and washed with a solution of acetone/water (100 mL, 9:1 v/v). To the stirred filtrate was added water (200 mL) gradually, while cooling to 20 °C.

The batch was concentrated in vacuo to remove acetone until the internal temperature rose to 35−40 °C resulting in a volume of ca. 415 mL. Acetic acid (216 mL) was added and then water (440 mL) over a 30-min period, still maintaining 35−40 °C. After the addition, the slurry was cooled and held 1 h at 0−5 °C, filtered, washed free of acid with water, and air-dried at 60 °C to provide **24** (46.6 g, 93.6%), mp > 228 °C.

Preparation of 25. Compound **24** (100.0 g, 0.25 mol) was dissolved in a mixture of chloroform (2 L) and acetic acid (222 mL) contained in a 5-L, three-neck flask premarked at 600 mL. When dissolved, the batch was cooled to −55 to −51 °C; 1 N HBr in acetic acid (9 mL) was added, followed directly by the bromination solution [bromine (121 mL, 0.24 mol) added to 1 N HBr in acetic acid (255 mL)] over 60−70 min. The temperature was maintained at −55 to −51 °C during the bromination and for 1 h thereafter. A solution of sodium acetate (40.0 g, 0.49 mol) in water (316 mL) was added rapidly, and ca. 1 g of sodium bisulfite was added if bromine color remained.

The two-phase mixture was concentrated in vacuo to 600 mL, keeping the temperature in the range of 25 °C by adjusting the vacuum. Towards the end, the temperature was allowed to rise to 30 °C, at which time water (1010 mL) was added gradually, maintaining the same temperature and pressure with the intent to complete the removal of chloroform. A subsequent 1010 mL of water was added directly, and the slurry was cooled and held at 0−5 °C for 1 h. The crude **25** was filtered, washed with water (185 mL), ether (325 mL), and water (55 mL) in that sequence. A sample of **25** showed [α]$_D$ +95°, minimum.

The ether wash was retained with the ca. 100 mL of chloroform used for extraction of the combined aqueous layers for the mother liquor workup (see below).

Purification of 25. The crude **25** was stirred and heated at reflux in acetone (2080 mL) and water (183 mL) containing sodium bromide (23.0 g, 0.19 mol). The water charge was adjusted for that which was present in the wet **25** and the acetone. After 5 h, the batch was cooled to ambient and concentrated at an internal temperature of 25 °C to a final volume of 393 mL. Control of the temperature

as noted allowed for proper crystal growth and final solvent composition (ca. 40% water). After the concentration, ether (876 mL) was added over 30 min. The slurry was cooled to and held at 0−5 °C for 1 h and then was filtered and washed by slurry treatment with ether (2 × 63 mL) and water (3 × 126 mL). The product, when dried to constant weight at 55 °C, showed [α]$_D$ +108° or greater (97.5 g, 81.6% from **25** direct or 95.2% overall, considering the recrystallized **25** recovered, below).

Recovery Procedure for 25. The ether wash and the chloroform extracts from the crude step were combined with the mother liquors from the epimerization, concentrated, and worked up by extraction into chloroform. After thorough water wash and reconcentration to 63 mL, residual chloroform was flushed out with acetic acid and the volume brought to 522 mL with that same solvent. Zinc dust (9.4 g, 0.14 mol) was added with stirring at 30−35 °C, followed by acetic anhydride (9.5 mL) and Nuchar (4.29 g) 15 min later. After 1 h, the batch was filtered and washed with acetic acid and then concentrated to 225 mL below 40 °C. Addition of water was begun slowly to the cloud point, stopped to permit crystal growth for 10 min, and then continued slowly for a total of 406 mL. After that, another 621 mL was added rapidly. The product was filtered and washed with water after aging for 1 h at 0−5 °C. Drying was carried out at 55 °C.

Recrystallization Procedure for Recovered 24. A slurry of recovered **24** (10.0 g, 25 mmol) in ethyl acetate (182 mL), water (16 mL), and Nuchar (2.0 g) was heated and stirred at 70 °C for 15 min and then filtered and washed with hot ethyl acetate (2 × 18 mL). The filtrate was distilled at atmospheric pressure to 60 mL, cooled to 15 °C, and diluted with 100 mL of ether while stirring. After 1 h at 0−5 °C, the product was filtered, washed with ether (2 × 6 mL), and dried. The recovered **24** showed a mp ≥ 227 °C.

Cortisone Acetate Procedure. To a 2-L, three-neck flask fitted with a thermometer, stirrer, and nitrogen/vacuum purging valve were added chloroform (380 mL), dimethlyformamide (160 mL), and anhydrous sodium sulfate (48.3 g, 0.34 mol). After thorough purging, and with a low nitrogen flow, **25** (48.3 g, 0.10 mol) was added, followed by semicarbazide free base (16.5 g, 0.22 mol). The system, at 15−20 °C, was purged again and held at that temperature for 3 h. At the completion of the reaction, water was added (200 mL) and the batch heated at reflux for 10 min. A solution of concentrated HCl (46.5 mL), in water (300 mL) was added, and reflux continued for 90 min. After phase separation, the organic layer was treated again similarly with concentrated HCl (36.2 mL) in water (355 mL). Each time, chloroform back extracts of the aqueous layer were added to the batch. After the second treatment, the chloroform layer was passed over and washed through a bed of 50 g of alumina. To the effluent was added 25 mL of dimethlyformamide (to minimize decomposition which can occur in anhydrous chloroform), and the solution was concentrated to 97 mL in vacuo. The DMF solvate of the product crystallized; the slurry was slowly diluted with 2-propanol (294 mL) with stirring. After aging 1 h at 0−5 °C, the product was filtered and washed with cold isopropanol (2

× 30 mL). After sucking dry, the solvate was slurried in 200 mL of water to remove the DMF. After drying, cortisone acetate was obtained (37.0 g, 92%), mp 242−245 °C.