obtained was recrystallized from diglyme–CH_3CN to give 2.3 g of **7**, mp 186–188°, and having nmr and ir spectra essentially identical with those of the product obtained by the first method.

Treatment of (*N,N,N',N'*-Tetramethylformamidinium)-phenylphosphinate (7) with *N,N,N'N'*-Tetramethylchloroformamidinium Chloride (1).—A mixture of 4.1 g (0.017 mol) of **7** and 1.45 g (0.0085 mol) of **1** in 10 g of dry CH_3CN was stirred under N_2 at room temperature for 22 hr. Nmr measurements on the resulting clear, slightly yellow solution showed a ^{31}P signal at −19.0 ppm and ^1H signals at δ 2.73 (s, 12), 3.43 (s, 24), and 7.6–8.4 (m, 10). The ^1H signal at δ 2.73 was enhanced by addition of tetramethylurea. Stripping of the reaction mixture at reduced pressure and extraction of the residue with ether left a gum having a ^{31}P nmr signal at −19.0 ppm and ^1H nmr signals at δ 3.45 (s, 24) and 7.6–8.4 (m, 10). It could not be induced to crystallize. Tetramethylurea was isolated from the ether extract and identified by mass spectra.

***N,N,N',N'*-Tetramethyl(diphenylphosphinyl)formamidinium Chloride (8).**—Ethyl diphenylphosphinite, 6.9 g (0.03 mol), was added dropwise to a stirred mixture of 5.1 g (0.03 mol) of **1** in 20 g of CH_3CN under N_2. All of **1** dissolved during the addition, and then another solid separated. The reaction mixture was stirred at room temperature overnight and then filtered to give 9.6 g (94% yield) of **8**, mp 137–138.5°. Recrystallization from acetonitrile gave a white solid: mp 137.5–138.5°; ^{31}P nmr −28.8 ppm; ^1H nmr δ 3.46 (s, 12, CH_3), 7.5–8.3 (m, 10, C_6H_5); ir (KBr) 2.9 (m), 6.3 (s), 6.95 (m), 7.15 (m), 8.3–8.4 (s), 8.95 (s).

Anal. Calcd for $C_{17}H_{22}ClN_2OP$: C, 60.62; H, 6.58; Cl, 10.53; N, 8.32; P, 9.20. Found: C, 60.33; H, 6.65; Cl, 10.54; N, 8.20; P, 9.07.

Registry No.—**1**, 13829-06-6; **2**, 34959-65-4; **5**, 34959-66-5; **6**, 34982-10-0; **7**, 34959-67-6; **8**, 34982-11-1.

Degradation of Penicillin G Methyl Ester with Trifluoroacetic Acid[1]

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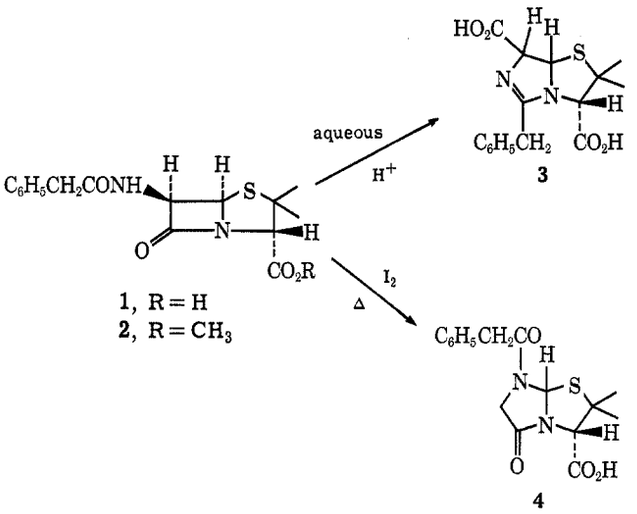
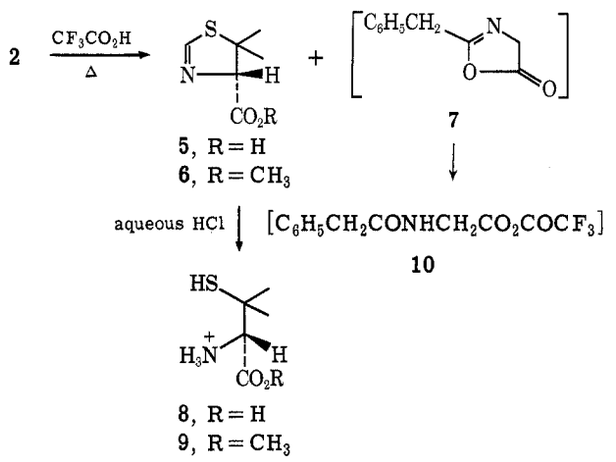
Penicillin G methyl ester (**2**) is degraded to methyl D-5,5-dimethyl-Δ^2-thiazoline-4-carboxylate (**6**) in trifluoroacetic acid. The *N*-phenylacetylglycyl fragment was isolated by conversion to its *N*-benzylamide. Methicillin and penillonic acid methyl esters were also degraded to **6**. A mechanism for the degradation is presented with special emphasis on the relationship to the penillic acid and penillonic acid rearrangements.

The penillic acid and the penillonic acid rearrangements are two well-known rearrangements of benzylpenicillin (**1**).[2] These rearrangements may be carried out by exposure of **1** to dilute aqueous mineral acid or by heating **1** in toluene with iodine, processes which respectively yield penillic acid (**3**) and penillonic acid (**4**).



We have discovered a new and potentially useful degradation of benzylpenicillin which we believe is closely related in mechanism to the penillic acid and penillonic acid rearrangements.

The nmr spectrum of a solution of either benzylpenicillin (**1**) or its methyl ester (**2**) in trifluoroacetic acid (TFAA) which had been briefly warmed exhibited the characteristic nmr signals of the thiazolines **5** or **6**. To facilitate isolation of the thiazoline, degradation was



performed on the ester **2**. Optically active D-thiazoline ester could be obtained easily in 50–60% yield. That the configuration at C-4 has been retained was shown by comparison of its melting point with that reported in the literature[3] and by hydrolysis to D-penicillamine (**8**).[4]

The fate of the phenylacetylglycyl portion of **2** is not known with certainty. The fragment has clearly retained the capacity to acylate, since addition of the reaction mixture to an excess of benzylamine in pyridine led to the isolation of the benzylamide of *N*-phenylacetylglycine. As a result there appear to be at least three choices among monomeric species for the structure of the phenylacetylglycyl fragment: the oxazolone **7**, the mixed anhydride **10**, and the acylaminoketene **11**. An analogous ketene has been pro-

$C_6H_5CH_2CONHCH{=}C{=}O$

11

(1) A preliminary communication has been published: M. R. Bell, J. A. Carlson, and R. Oesterlin, *J. Amer. Chem. Soc.*, **92**, 2177 (1970).

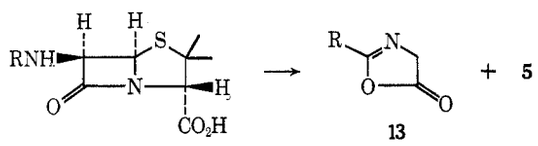
(2) (a) A. H. Cook in "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, p 126; (b) R. L. Peck and K. Folkers, ref 2a, p 188.

(3) Merck Report No. 63, p 18, April 1945, cited by H. M. Crooks, Jr., in ref 2a, p 1057.

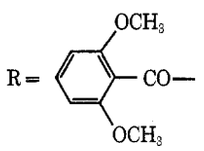
(4) "The Merck Index," P. G. Stecher, Ed., Merck and Co., Rahway, N. J., 1968, p 789.

posed as an intermediate to account for the products observed upon irradiation of an aqueous solution of 6-aminopenicillanic acid,[5] but it seems unlikely that **11** would have an appreciable lifetime in trifluoroacetic acid.

The nmr spectrum of the reaction mixture from **2** does not show the characteristic signals of the oxazolone **7**, although this compound is reasonably stable alone or in the presence of the thiazoline in hot trifluoroacetic acid. Addition of authentic benzyloxazolone **7** to the reaction mixture from **2** resulted in a rapid loss of its characteristic nmr signals. We do not have a satisfactory explanation for the instability of **7** under these circumstances. Possibly ring opening of **7** is promoted by side products generated in the degradation of **2**. We favor, therefore, the mixed anhydride structure **10** for the *N*-phenylacetylglycyl fragment, since this is the simplest alternative to the oxazolone which would retain the capacity to acylate a nucleophile. In contrast, oxazolone **13** was clearly present in



12 **13** **5**



the reaction mixture from methicillin (**12**);[6] this reaction appears to be quantitative.

The trifluoroacetic acid degradation is apparently limited to those penicillins which possess an acyl side chain, since 6-aminopenicillanic acid failed to yield detectable amounts of thiazoline. A few cephalosporin structures were examined but the results were not considered promising. Penillic acid (**3**) was stable in boiling trifluoroacetic acid, but penillonic acid (**4**) as the methyl ester was quantitatively transformed to the oxazolone **7** and the thiazoline **6**. The nmr spectrum of the reaction mixture showed that equal parts of **6** and **7** had been formed. Thiazoline **6** was isolated and the *N*-phenylacetylglycyl fragment was characterized as the benzylamide.

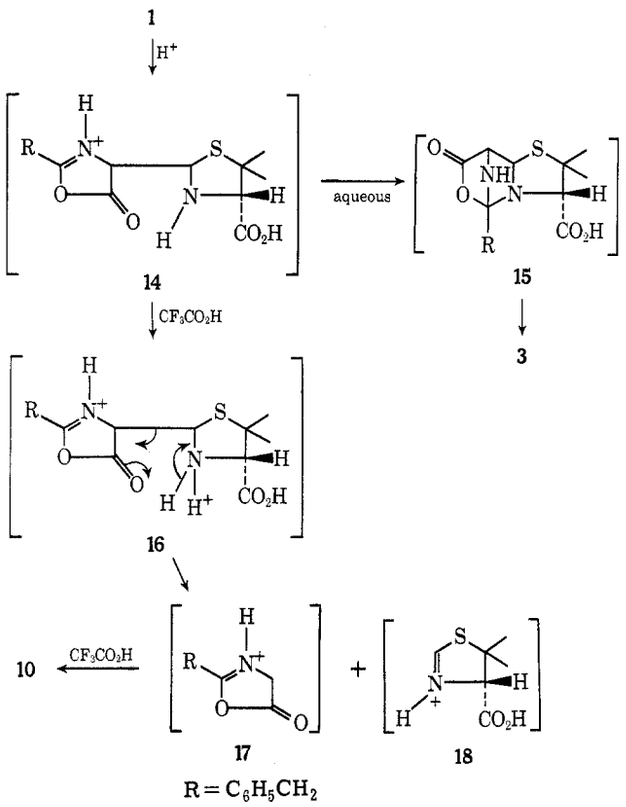
Our proposal for the mechanism of the trifluoroacetic acid degradation and its relationship to the penillic acid rearrangement is outlined in Scheme I. The intermediate **14** is identical with that which has been proposed for the penillic acid rearrangement.[7] This rearrangement is carried out in dilute aqueous mineral acid, and under these conditions it was suggested that nucleophilic addition of the thiazolidine ring amino function to the imino ether function of the oxazolone in intermediate **14** gave **15**, which then yields penillic acid (**3**). We suggest that in trifluoroacetic acid the intermediate **14** is diverted from this course by protonation of the thiazolidine ring nitrogen followed by fragmentation of the new intermediate **16** to give **17** and **18**.

(5) W. O. Godtfredsen, W. von Daehne, and S. Vangedal, *Experientia*, **23**, 280 (1967).

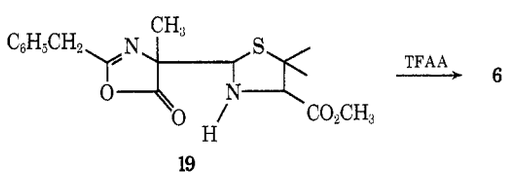
(6) F. P. Doyle, K. Hardy, J. H. C. Nayler, M. J. Soulal, E. R. Stove, and H. R. J. Waddington, *J. Chem. Soc.*, 1453 (1962).

(7) R. B. Woodward, ref 2a, pp 445–446.

SCHEME I



Where R is benzyl, the oxazolone is solvolyzed to the mixed anhydride **10**. Support for the step **16** → **17** + **18** is provided by the observation that synthetic oxazolone–thiazolidine[8] **19** is cleaved in trifluoroacetic acid to thiazoline **6**.



19

Jansen and Robinson have reported that penillonic acid methyl ester is formed by the condensation of oxazolone **7** with thiazoline **6** in benzene and on this basis proposed that the penillonic acid rearrangement proceeds by dissociation of penicillin to oxazolone and thiazoline followed by recombination to penillonic acid.[9] Although the degradation of penicillin to the thiazoline under acid conditions provides support for the first step of the Robinson pathway, it does not exclude the mechanisms proposed by Bird[10] and Woodward.[11]

The simplicity of the process for the preparation of the D-thiazoline[12] may be of some practical importance

(8) M. R. Bell, S. D. Clemans, R. Oesterlin, and J. A. Carlson, Abstracts, 23rd International Congress of Pure and Applied Chemistry, Boston, Mass., July 1971, p 74.

(9) A. B. A. Jansen and R. Robinson, *Monatsh. Chem.*, **98**, 1017 (1967).

(10) C. W. Bird, *Tetrahedron*, **22**, 2489 (1966).

(11) R. B. Woodward, ref 2a, p 447.

(12) A. K. F. Bose, G. Spiegelman, and M. S. Manhas, *J. Amer. Chem. Soc.*, **90**, 4506 (1968). These workers reported that DL-**6** could be prepared by heating DL-*N*-formylpenicillamine with boron trifluoride etherate in methanol. Prior to their publication we had synthesized DL-**6** by hydrogen chloride catalyzed esterification of DL-**5** in the presence of trimethyl orthoformate. The Merck group[3] prepared D-**6** by the reaction of ethyl formimidate hydrochloride and D-penicillamine methyl ester (**9**).

in view of the need to develop methods for the synthesis of pencillins with a modified nucleus. Our initial efforts to synthesize a 6-substituted penicillin utilizing the D-thiazoline **6** as a relay have recently been reported.[8] Sheehan has reported that a DL and L penicillin have respectively one-half and negligible antibacterial activity when compared with the corresponding D isomer. This underlines the importance of the absolute configuration of a penicillin for maximum biological activity.[13] The advantages of the D-thiazoline as a starting material for penicillin total syntheses are that it is readily available and inexpensive, and that it has the correct absolute configuration.

Experimental Section

All melting points were taken in capillary tubes in an oil bath and are uncorrected. Nmr spectra were determined under the supervision of Dr. R. K. Kullnig with a Varian Model A-60 spectrometer; TMS was used as the internal standard.

Penicillin G Methyl Ester (2).—A suspension of 344 g (0.9 mol) of penicillin G potassium salt (Chas. Pfizer) in 2 l. of anhydrous DMF (distilled, then stored over molecular sieves) was stirred at room temperature for 6 hr with 59 ml (0.9 mol) of methyl iodide. The clear solution was left under nitrogen at room temperature overnight. It was poured slowly into 6 l. of ice–water with vigorous stirring. The white solid was filtered and washed with cold water. The solid was dissolved in 2.5 l. of methylene dichloride and washed (cold H_2O, brine). The dried (Na_2SO_4) filtrate was evaporated at 40° and the residual oil was triturated with *ca.* 1 l. of absolute ether. The solid was filtered to afford 250 g (80%) of ester, mp 95–96.5° (lit.[14] mp 97–98°). Concentration of the mother liquor gave a second crop, 21 g (7.5%): mp 94–95°; ir ($CHCl_3$) 5.61 (β-lactam C=O), 5.73 (ester C=O), and 5.99 μ (amide C=O); nmr ($CDCl_3$) δ 1.45(s, 3), 1.5 (s, 3), 3.6 (s, 2, $ArCH_2$), 3.7 (s, 3, OCH_3), 4.4 (s, 1, $CHCO_2CH_3$), 5.5 (d, 1, J = 4 Hz, CHS) 5.6 (dd, 1, J = 4, 10 Hz, NCHCO), 6.3 (d, 1, J = 10 Hz, NH), and 7.3 ppm (5, ArH).

Methyl D-5,5-Dimethyl-Δ^2-thiazoline-4-carboxylate (6).—Penicillin G methyl ester (150 g, 0.43 mol) was added to 1.5 l. of TFAA and the solution was heated on a steam bath in a nitrogen atmosphere for 20 min. The excess TFAA was recovered by distillation *in vacuo* (water aspirator, pot temperature not to exceed 40°) and was used in subsequent reactions. The residual yellow oil was dissolved in 1.5 l. of dry methylene dichloride and added slowly during 1 hr to a vigorously stirred, ice-cooled solution of 600 ml of concentrated ammonium hydroxide in 3 l. of ice–water. The organic phase was separated. The aqueous layer was extracted once with chloroform. The combined organic fractions were washed (H_2O, brine). The dried (Na_2SO_4) filtrate was evaporated at 40° and the residual brown gum was distilled twice to afford 43 g (58%) of thiazoline **6**: bp 74° (0.3 mm); mp 50.5–51.5° (lit.[3] mp 50°); $[\alpha]^{25}D$ +51.9° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 1.35 (s, 3), 1.73 (s, 3), 3.8 (s, 3, OCH_3), 4.6 (d, 1, J = 3 Hz, $CHCO_2CH_3$), and 8.15 ppm (d, 1, J = 3 Hz, N=CHS); nmr (TFAA) δ 1.7 (s, 3), 1.9 (s, 3), 3.95 (s, 3), 5.15 (d, 1, J = 2 Hz), and 8.15 ppm (d, 1, J = 2 Hz).

D-Penicillamine Hydrochloride (8).—Two grams of the thiazoline **6** dissolved in 21 ml of 2.5 *N* HCl and 11 ml of H_2O was heated at reflux for 16 hr under nitrogen and evaporated *in vacuo*. The amorphous residue was crystallized from acetonitrile to give 1.3 g (61%) of **8**: mp 177–179.5° dec; $[\alpha]^{25}D$ −48.6° (*c* 1, 1 *N* NaOH) [lit.[4] mp 177.5° dec, $[\alpha]^{25}D$ −55° (*c* 1, 1 *N* NaOH)]. An additional recrystallization left the melting point unchanged but raised the rotation to $[\alpha]^{25}D$ −49.8°. Its isopropylidene derivative was obtained in 57% yield: mp 199–201° dec; $[\alpha]^{25}D$ +92.0° (*c* 1, H_2O) [lit.[15] 198°, $[\alpha]^{17}D$ +94° (*c* 1, H_2O)].

Commercial D-penicillamine (Aldrich Chemical Company) was converted to its hydrochloride, mp 177–180° dec, $[\alpha]^{25}D$ −50.6° (*c* 1, 1 *N* NaOH). Its isopropylidene derivative was obtained in 72% yield, mp 199–200° dec, $[\alpha]^{25}D$ +92.8° (*c*, 1, H_2O).

***N*-Benzyl-2-(2-phenylacetamido)acetamide.**—Penicillin G methyl ester (5 g) in 50 ml of TFAA was heated at reflux for 15 min in a nitrogen atmosphere. After cooling, the solution was added slowly with stirring to ice-cooled benzylamine (80 ml) in 100 ml of pyridine. Stirring was continued for 1.5 hr at room temperature. The mixture was poured into 2 l. of water and extracted with ethyl acetate. The organic fractions were washed (H_2O, 10% H_3PO_4 until acidic, H_2O, saturated brine), dried (Na_2SO_4), and evaporated to yield a yellow solid. Recrystallization from THF afforded 1.1 g (27%) of the amide, mp 173–175°, identical with a sample (mixture melting point, ir) prepared from phenylacetylglycine, benzylamine, and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate.

TFAA Degradation of Methyl Benzylpenillonate (4-Methyl Ester).—A solution of methyl benzylpenillonate (8 g) in 38 ml of TFAA was allowed to stand at room temperature in a nitrogen atmosphere. After 30 hr the nmr spectrum of this solution indicated that an equimolar mixture of thiazoline **6** and oxazolone **7** had formed. The acid was evaporated *in vacuo* at room temperature.

Most of the oxazolone **7** initially present in the reaction mixture was destroyed during this evaporation, as evidenced by nmr. An aliquot (1.03 g) was added to 2 g of benzylamine in 15 ml of pyridine. After standing at room temperature for 2 hr, the phenylacetylglycyl benzylamide was isolated by the above procedure, yield 63 mg, mp 173–174.5°, mixture melting point with an authentic sample was undepressed. The thiazoline **6** was isolated from the remaining reaction mixture by the above procedure, yield 1.6 g, mp 49–51°.

TFAA Degradation of Penicillin G (1).—Penicillin G (1 g) prepared from Potassium Penicillin G (Chas. Pfizer) was dissolved in 5 ml of TFAA. The nmr spectrum indicated essentially complete conversion to thiazoline **5** within 5 min after mixing. Heating the solution at reflux for 15 min completed the degradation. The nmr spectrum of this solution exhibited sharp signals at δ 1.7 (s, 3), 2.0 (s, 3), 5.35 (d, 1, J = 2 Hz, $CHCO_2H$), and 9.75 ppm (d, 1, J = 2 Hz, NCHS), characteristic of thiazoline **5** in addition to broad undefined absorptions at δ 1.7, 4.3, and 7.5 ppm (ArH).

2-Benzyl-2-oxazolin-5-one (7)[9].—This compound was prepared from phenylacetylglycine by dehydration with dicyclohexylcarbodiimide: bp 92–98° (0.003 mm) [lit.[9] bp 90–100° (0.005 mm)]; nmr (TFAA) δ 4.35 (t, 2, J = 1.5 Hz, $ArCH_2$), 4.8 (t, 2, J = 1.5 Hz, NCH_2CO), and 7.3–7.6 ppm (5, ArH). The nmr spectrum of **5** was essentially unchanged after heating the TFAA solution at reflux for 30 min.

Stability of Oxazolone 7 to TFAA Degradation.—Penicillin G methyl ester (**2**) (350 mg) and benzyloxazolone **7** (175 mg) were dissolved in 3 ml of TFAA. After heating at reflux for 30 min the nmr spectrum of this solution exhibited signals at δ 1.65 (s, 3), 2.0 (s, 3), 3.95 (s, 3), 5.15 (d, 1, J = 2 Hz), and 9.75 ppm (d, 1, J = 2 Hz) characteristic of thiazoline **6**. Additional undefined signals at δ 1.3–2.1, 3.6–3.8, 4.1–4.5, and 7.2–7.6 ppm (ArH) were also present.

TFAA Degradation of Methicillin (12).—Sodium methicillin (200 mg, Bristol-Myers) was heated at reflux in 1 ml of TFAA for 30 min. The nmr spectrum of this solution exhibited signals at δ 1.75 (s, 3), 2.05 (s, 3), 5.2 (d, 1, J = 2 Hz), and 9.75 ppm (d, 1, J = 2 Hz) characteristic of thiazoline **6** in addition to signals at δ 4.2 (s, 6, OCH_3), 4.6 and 4.7 (s, AB, NCH_2CO), 7.0 (d, 1, J = 10 Hz, ArH), 7.05 (d, 1, J = 9.5 Hz, ArH), and 9.75 ppm (dd, 1, J = 9.5 10 Hz, Ar*H*) characteristic of oxazolone **13**.

TFAA Degradation of Adduct 19.—Adduct **19**[8] (100 mg) was dissolved in 0.3 ml of TFAA and heated at 60° for 15 min. The nmr spectrum of this solution exhibited signals characteristic of **6** at δ 1.7 (s, 3), 1.9 (s, 3), 3.95 (s, 3), 5.15 (d, 1, J = 2 Hz), and 9.75 ppm (d, 1, J = 2 Hz) in addition to broad undefined resonances at δ 1.4–1.8, 3.8–4.2, and 7.3–7.8 (ArH).

Registry No.—**2**, 653-89-4; **6**, 27494-11-7; trifluoroacetic acid, 76-05-1; *N*-benzyl-2-(2-phenylacetamido)-acetamide, 15440-34-3.

(13) J. C. Sheehan and J. R. Henry-Logan, *J. Amer. Chem. Soc.*, **81**, 3089 (1959).

(14) O. Wintersteiner, W. R. Boon, H. C. Carrington, D. W. MacCorquodale, F. H. Stodola, J. L. Wachtel, R. D. Coghill, W. C. Risser, J. E. Philip, and O. Touster, ref 2a, p 93.

(15) E. P. Abraham, W. Baker, W. R. Boon, C. T. Calam, H. C. Carrington, E. Chain, H. W. Florey, G. G. Freeman, R. Robinson, and A. G. Sanders, ref 2a, p 26.