[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroidal Sapogenins. XXXVIII.[1] Synthesis of Cortisone from Botogenin[2]

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11α-Hydroxydiosgenin (mixture of C-25 epimers), readily derivable from botogenin, has been converted by a multi-step sequence into 21-desoxycortisone and thence by iodination followed by treatment with potassium acetate into cortisone acetate.

Various chemical routes from diosgenin to cortisone and related cortical hormones have been accomplished[3] but these did not find any large scale, commercial application, since the chemical introduction of an oxygen atom at C-11 of such a ring C-unsubstituted steroid could not compete in efficiency with the microbiological hydroxylation procedures[4] which were developed almost concurrently. On the other hand, the chemical synthesis of cortisone from the steroidal sapogenin hecogenin (I with 5,6-double bond reduced), first reported in this Laboratory[1,5] has been improved to such an extent by the Glaxo group[6] that it is now used on a commercial scale.

A third steroidal sapogenin representing a potentially useful starting material for the synthesis of 11-oxygenated cortical hormones is botogenin (I),[7] for which Marker established the structure 12-keto-diosgenin (I). Attempts in our laboratories to locate Marker's plant source[7] failed, but recently there was reported the rediscovery of 12-ketodiosgenin as well as its C-25 epimer from *Dioscorea spiculiflora*.[8] In view of certain discrepancies in physical constants, the new names "gentrogenin" and "correlogenin" have been suggested[8] for 12-ketodiosgenin (botogenin) (I) and its C-25 epimer. By the use of methods developed originally in the hecogenin series for shifting the 12-keto function to C-11,[6a,9] Rothman and Wall[10] succeeded in transforming I into 11-ketodiosgenin (II) and 11α-hydroxydiosgenin (IV).[11,12]

Recent work in the cortical hormone field[13,14] has shown that substitution at C-6 increases biological activity and it seemed of interest to develop completely chemical syntheses (lacking microbiological steps) for such steroids. Botogenin (I) is particularly suited for such purposes because of the presence of the 5,6-double bond and we have examined the feasibility of employing this sapogenin as a new raw material for cortical hormones. The present paper is concerned with the description of a successful synthesis of cortisone from botogenin (I) while subsequent papers will deal with transformations of I to various substituted cortical hormones.

No difficulty was encountered in repeating the literature directions[8,10] for the isolation of botogenin (I) from *Dioscorea spiculiflora* Hemsl[15] and its transformation by the standard route[9] to the ketol diacetate III. In agreement with Rothman and Wall,[10] it was preferable to employ the mixture of C-25 epimers rather than to attempt their laborious separation since this center of asymmetry is destroyed in the subsequent side chain degradation step. The deacetoxylation of III with calcium–ammonia[6a,10] was conducted in the presence of methanol so as to lead directly to 11α-hydroxydiosgenin (IVa), which was characterized further as its 3,11-diacetate IVb.[12] Both products showed a fairly wide melting point range because of admixture with the corresponding C-25 epimer. Degradation of the side chain was accomplished in the conventional manner[16] by heating for 5 hours with acetic anhydride at 195°, the only modification being that the intermediate "11α-acetoxydiosone" was cleaved by heating with potassium hydroxide in aqueous acetone. The resulting $\Delta^{5,16}$-pregnadiene-3β,11α-diol-20-one (Va) was not purified, but for purposes of characterization it was transformed into the 3,11-diacetate Vb and hydrogenated catalytically to the known[17] allopregnane-3β,11α-

(1) Paper XXXVII, C. Djerassi, H. J. Ringold and G. Rosenkranz, THIS JOURNAL, **76**, 5533 (1954).

(2) Presented at Symposium IV (Biochemistry of Steroids) of the 4th International Biochemical Congress, Vienna, September 2, 1958.

(3) For pertinent reviews see: (a) C. Djerassi, "Vitamins and Hormones," Academic Press, Inc., New York, N. Y., 1953, Vol. XI, pp. 205–238; (b) G. Rosenkranz and F. Sondheimer, "Progress in the Chemistry of Organic Natural Products," Springer, Vienna, 1953, Vol. X, pp. 274–389; (c) G. Rosenkranz, F. Sondheimer, O. Mancera, J. Pataki, H. J. Ringold, J. Romo, C. Djerassi and G. Stork, "Recent Progress in Hormone Research," Academic Press, Inc., New York, N. Y., 1953, Vol. VIII, pp. 1–25. For the most recent synthesis see A. J. Lemin and C. Djerassi, THIS JOURNAL, **76**, 5672 (1954).

(4) For recent reviews see: (a) A. Wettstein, *Experientia*, **11**, 465 (1955); (b) S. H. Eppstein, P. D. Meister, H. C. Murray and D. H. Peterson, "Vitamins and Hormones," Academic Press, Inc., New York, N. Y., 1956, Vol. XIV, pp. 359–432.

(5) C. Djerassi, H. J. Ringold and G. Rosenkranz, THIS JOURNAL, **73**, 5513 (1951).

(6) For leading references see: (a) J. H. Chapman, J. Elks, G. H. Phillipps and L. J. Wyman, *J. Chem. Soc.*, 4344 (1956); (b) R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, A. G. Long, J. F. Oughton, L. Stephenson, T. Walker and B. M. Wilson, *ibid.*, 4356 (1956).

(7) R. E. Marker and J. Lopez, THIS JOURNAL, **69**, 2397 (1947).

(8) H. A. Walens, S. Serota and M. E. Wall, *ibid.*, **77**, 5196 (1955); *J. Org. Chem.*, **22**, 182 (1957).

(9) C. Djerassi, H. Martinez and G. Rosenkranz, *ibid.*, **16**, 303 (1951).

(10) E. S. Rothman and M. E. Wall, THIS JOURNAL, **79**, 3228 (1957).

(11) The formation of 11α-alcohols from 11-ketones by metal-ammonia reduction in the presence of alcohol has already been reported by F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, *ibid.*, **75**, 1282 (1953), and it has been shown (ref. 6a, 10) that the presence of a proton source in the calcium-ammonia deacetoxylation of 11-keto-12-acetates (*e.g.*, III) results in the direct formation of the 11α-ol.

(12) The corresponding 3,11-diacetate IVb had already been prepared earlier from diosgenin (J. Romo, *Bol. inst. quim. nacl. anton. Mex.*, **7**, 53 (1955)).

(13) (a) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, THIS JOURNAL, **78**, 6213 (1956); (b) A. Bowers and H. J. Ringold, *ibid.*, **80**, 3091 (1958).

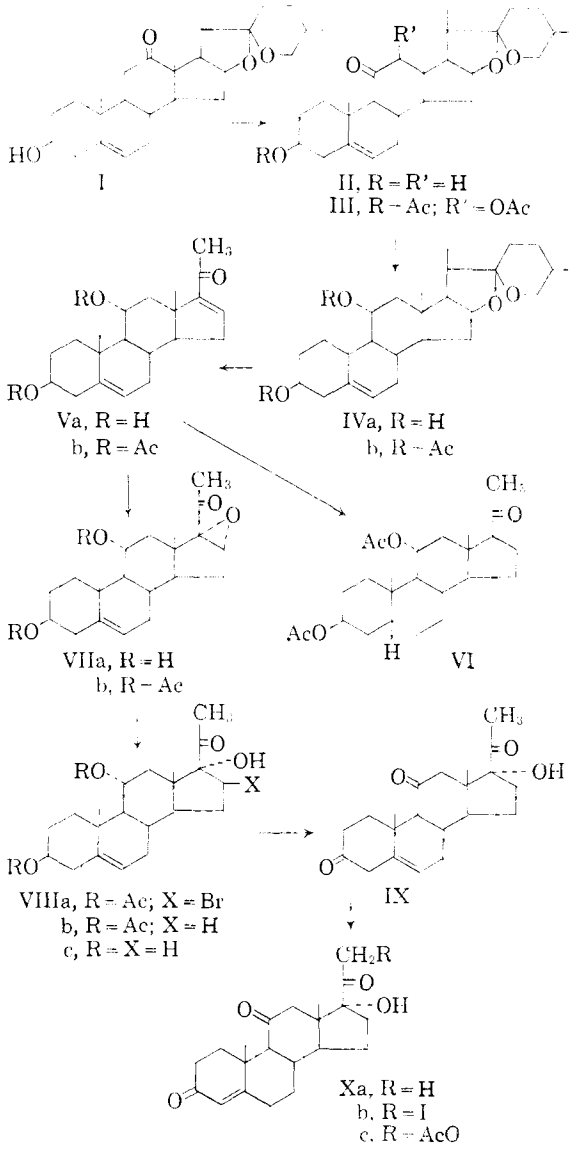
(14) A. Bowers and H. J. Ringold, *ibid.*, **81**, 424 (1959).

(15) D. K. Cox, A. Hernandez, E. Matuda and J. G. González, *Bol. Soc. Botanica Mex.*, No. 22, 1 (1958). We are indebted to Dr. D. K. Cox of our botanical section for the collection of the plant material.

(16) See R. E. Marker, THIS JOURNAL, **62**, 3350 (1940).

(17) C. Djerassi, E. Batres, J. Romo and G. Rosenkranz, *ibid.*, **74**, 3634 (1952).

diol-20-one diacetate (VI). The crude degradation product Va was epoxidized directly with alkaline hydrogen peroxide to the crystalline 16α,17α-epoxide VIIa and acetylated to the 3,11-diacetate VIIb. The requisite 17α-hydroxy group was introduced in the usual manner[18] by hydrogen bromide opening of the epoxide VIIb followed by catalytic debromination of the bromohydrin VIIIa and saponification of the acetate functions of the 3β,11α,17α-triol 3,11 diacetate VIIIb. Δ⁵ Pregnene-3β,11α,17α-triol-20-one (VIIIc) thus obtained, was oxidized with chromium trioxide in acetone solution[19,20] to the non-conjugated ketone IX, which did not exhibit any ultraviolet or infrared absorption corresponding to an α,β-unsaturated carbonyl moiety. Isomerization of the double bond could be accomplished with hydrogen chloride–acetic acid whereupon the known[21] 21-desoxycortisone (Xa) was produced. The synthesis of cortisone acetate (Xc) from botogenin (I) was completed by subjecting 21-desoxycortisone (Xa) to the recently described[22] iodination–potassium acetate procedure.



Experimental[23]

11α-Hydroxydiosgenin (IVa).—A solution of 59.5 g. of the ketol diacetate III[10] (m.p. 213–216°, [α]D −118° derived from botogenin contaminated with its C-25 epimer) in 700 cc. of dioxane–ether (1:1) was added with vigorous stirring over a period of 10 min. to 25 g. of calcium metal dissolved in *ca.* 2 l. of liquid ammonia. As the blue color disappeared, a second 10-g. portion of calcium was added followed by 170 cc. of methanol and the solution was stirred for an additional 15 min. Excess reagent was decomposed with a slurry of 250 g. of ammonium chloride in 250 cc. of water and most of the ammonia was allowed to evaporate. The remaining ammonia was removed under reduced pressure by warming on the steam-bath, 1 l. of warm water and 200 cc. of acetic acid were added and the solution was extracted thoroughly with methylene dichloride. The extracts were washed with water, dried and evaporated to yield a crystalline residue which was heated under reflux for 30 min. with 700 cc. of 2% methanolic sodium hydroxide solution containing 5% of water. Upon cooling, a colorless, crystalline precipitate of 11α-hydroxydiosgenin (IVa), mixed with the corresponding C-25 epimer, separated. The solid was collected and the filtrate was concentrated to provide a second crop, m.p. 204–233°, amounting to a total of 40 g. (84%) of material suitable for the next step. Recrystallization from benzene–methylene dichloride led to an analytical sample, m.p. 246–252°, [α]D −105°.[24]

Anal. Calcd. for $C_{27}H_{42}O_4 \cdot {}^1/_2H_2O$: C, 73.76; H, 9.86; O, 16.38. Found: C, 73.77; H, 9.42; O, 16.19.

Acetylation of the crude diol IVa with acetic anhydride–pyridine and recrystallization from methanol afforded in over 80% yield the 3,11-diacetate IVb, m.p. 199–209°, [α]D −116°.

Anal. Calcd. for $C_{31}H_{46}O_6$: C, 72.34; H, 9.01; O, 18.65. Found: C, 72.66; H, 8.97; O, 18.63.

Δ⁵,¹⁶-Pregnadiene-3β,11α-diol-20-one (Va).—A 38.5-g. sample of crude 11α-hydroxydiosgenin diacetate (IVb) was heated with 155 cc. of acetic anhydride for 5 hr. in a sealed tube at 195° and then poured in 1.5 l. of water. After stirring for 1 hr., the water was decanted, the brown gummy furosten derivative was extracted with methylene dichloride, washed with sodium bicarbonate and water, dried and evaporated. The residue was taken up in 385 cc. of 80% acetic acid, cooled to 8° and to it was added in one portion a cold solution of 16.2 g. of chromium trioxide in 210 cc. of 90% acetic acid. The temperature rose to 17° and the solution was stirred at 10–15° for an additional 10 min., diluted with 1 l. of water and the crude 11α-acetoxydiosone was cleaved by heating under reflux for 5 hr. with a mixture of 230 cc. of acetone, 115 cc. of water and 20 g. of potassium hydroxide. The semi-crystalline, pale yellow residue, consisting largely of the desired ketone Va (λ_{max}^{EtOH} 236–238 mμ, log ε 3.8), contaminated with partially acetylated material was converted without purification into the epoxide VIIa.

A small sample of crude Va was acetylated with acetic anhydride-pyridine (1 hr., steam-bath); the diacetate Vb crystallized from acetone–hexane in large prisms, m.p. 156–159°, [α]D −85°, λ_{max}^{EtOH} 236–238 mμ, log ε 4.01.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.11; H, 8.42.

(18) *Cf.* P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, THIS JOURNAL, **72**, 5145 (1950); F. B. Colton, W. R. Nes, D. A. van Dorp, H. L. Mason and E. C. Kendall, *J. Biol. Chem.*, **194**, 235 (1952).

(19) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(20) C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956), have shown that this reagent can be used for the direct oxidation of a steroidal Δ⁵-3β-alcohol to the corresponding Δ⁵-3-ketone.

(21) This substance has been prepared by at least six different methods and the relevant literature is reviewed in ref. 13b.

(22) H. J. Ringold and G. Stork, THIS JOURNAL, **80**, 250 (1958).

(23) Melting points were determined on the Kofler block. Unless noted otherwise, all rotations were measured in chloroform solution. We are indebted to Dr. L. Throop and staff for these determinations as well as for all infrared and ultraviolet spectroscopic measurements.

(24) The reported constants (ref. 10) for 11α-hydroxydiosgenin uncontaminated by 11α-hydroxy-yamogenin are m.p. 233–235°, [α]D −116°.

The diacetate Vb (63 mg.) was hydrogenated in methanol solution with 10% palladized charcoal catalyst and since the hydrogen consumption (14.36 cc.) indicated the uptake of nearly 3 equivalents of hydrogen and hence reduction of the keto group, the total hydrogenation product was oxidized in acetone solution with a standard chromium trioxide–sulfuric acid solution[19] and then recrystallized from acetone–hexane. The resulting colorless crystals, m.p. 169–173°, were shown to be identical with allopregnane-3β,11α-diol-20-one diacetate (VI) by mixture melting point determination and infrared spectral comparison with an authentic sample.[17]

16α,17α-Oxido-Δ^5-pregnene-3β,11α-diol-20-one (VIIa).—The entire crude side chain degradation p oduct from the preceding experiment was dissolved in 460 cc. of chloroform and 1080 cc. of methanol, cooled to 0° and then treated dropwise with stirring with 65 cc. of 30% hydrogen peroxide and with a solution of 25 g. of sodium hydroxide in 310 cc. of water. After stirring for an additional 30 min. at 0–5°, the mixture was left overnight at room temperature and then diluted with water. Extraction with chloroform provided a product which still exhibited a small acetate band in the infrared—apparently due to incomplete hydrolysis at C-11 during the diosone cleavage— and the total material was heated under reflux for 30 min. with 15.4 g. of potassium hydroxide, 38.5 cc. of water and 385 cc. of methanol. The mixture was neutralized with acetic acid, diluted with water and the precipitated epoxide VIIa (20 g., m.p. 195–207°) was used directly in the next step. The analytical sample was recrystallized from aqueous methanol whereupon it exhibited m.p. 209–211°, $[\alpha]_D$ −11°, no high selective absorption in the ultraviolet, λ_{max}^{KBr} 2.89 and 5.89 μ.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73; O, 18.47. Found: C, 72.37; H, 8.82; O, 18.47.

A portion (12.85 g.) of the crude dihydroxy epoxide VIIa was acetylated with 15 cc. of acetic anhydride and 25 cc. of pyridine at room temperature for 70 hr., poured into water and stirred for 1 hr. The precipitate was collected, washed well until the washings were neutral, dried and recrystallized from aqueous methanol and then from acetone–hexane; yield 10.5 g. of colorless prisms, m.p. 147–149°. The combined mother liquors were purified by chromatography on 165 g. of ethyl acetate–washed alumina to provide an additional 2.95 g. of material of equal purity, raising the yield of pure **16α,17α-oxido-Δ^5-pregnene-3β,11α-diol-20-one** diacetate (VIIb) to 84%. The analytical sample was obtained from acetone–hexane, m.p. 147–149°, $[\alpha]_D$ −37°; λ_{max}^{KBr} 5.78, 5.90 and 8.08 μ.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96; O, 22.30. Found: C, 69.53; H, 7.89; O, 21.64.

Δ^5-Pregnene-3β,11α,17α-triol-20-one (VIIIc).—To 1.82 g. of 16α,17α-oxido-Δ^5-pregnene-3β,11α-diol-20-one diacetate (VIIb) dissolved in 20 cc. of acetic acid was added 1.1 cc. of a saturated solution of hydrogen bromide in acetic acid and after standing for 30 min. at room temperature, the mixture was poured into water. The bromohydrin VIIIa was filtered, washed with water until neutral and a small sample was recrystallized from aqueous methanol; m.p. 143–149° sl. dec., $[\alpha]_D$ −41°; λ_{max}^{KBr} 2.94, 5.78 and 5.88 μ.

Anal. $C_{25}H_{35}O_6Br$. Calcd. C, 58.71; H, 6.90; Found: C, 58.20; H, 7.10.

The moist cake of the bromohydrin VIIIa was dissolved in 50 cc. of methanol, 100 mg. of 10% palladized charcoal catalyst and 515 mg. of ammonium acetate were added and the suspension was stirred in an atmosphere of hydrogen for 2 hr., whereupon hydrogen consumption had ceased. Since the debromination product had precipitated in part, the solution was filtered and the precipitate was washed with methylene dichloride. The combined filtrate and washings were evaporated to dryness and recrystallized twice from aqueous methanol to yield 1.16 g. of **Δ^5-pregnene-3β,11α,17α-triol-20-one 3,11-diacetate (VIIIb)**, m.p. 244–254° (sl. decomposition when taken on Kofler block), m.p. 229–230° (sealed capillary), $[\alpha]_D$ −15°, λ_{max}^{KBr} 2.86, 5.79 and 5.87 μ. The mother liquors consisted largely of unreacted epoxide VIIb and after retreatment with hydrogen bromide and catalytic debromination afforded an additional 540 mg. of VIIIb, thus raising the yield to 94%.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.61; H, 8.45.

The saponification of the diacetate VIIIb (3.8 g.) was performed by suspending the material in 50 cc. of methanol, adding a solution of 1.5 g. of potassium hydroxide in 100 cc. of methanol and stirring at room temperature until all the solid had dissolved (*ca.* 30 min.). After standing at room temperature for 60 hr., the solution was poured into saturated salt solution, the product was extracted with ethyl acetate and the extracts were concentrated until precipitation occurred. Upon cooling, there was obtained a first crop (1.82 g.) of crystals, m.p. 262–265°, while concentration afforded an additional 0.67 g., m.p. 260–264°. The substance sublimed very readily as could be observed during melting point determination on the Kofler block and an analytical sample of **Δ^5-pregnene-3β,11α,17α-triol-20-one (VIIIc)** was prepared by sublimation at 250° and 0.1 mm. The sublimed material exhibited m.p. 262–265° (Kofler), m.p. 248–252° (sealed capillary), $[\alpha]_D$ −14°, λ_{max}^{KBr} 3.00 and 5.93 μ.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: 71.90; H, 9.12.

Δ^5-Pregnene-3,11,20-trione-17α-ol (IX).—Δ^5-Pregnene 3β,11α,17α-triol-20-one (VIIIc) (200 mg.) was suspended in 25 cc. of acetone (distilled from permanganate), cooled to 10–15° and 0.4 cc. of chromium trioxide–sulfuric acid reagent[19,20] was added in an atmosphere of nitrogen. Within 3 min., all of the suspended material had dissolved and a new precipitate had appeared. The suspension was poured into saturated salt solution, extracted with ethyl acetate and dried. Upon concentration, a precipitate separated which was collected and recrystallized from acetone–hexane; colorless plates (144 mg.), m.p. 210–225° dec., $[\alpha]_D$ +5°, no ultraviolet absorption maximum in the 240 mμ region, λ_{max}^{KBr} 2.91 and 5.88 μ.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19; O, 18.58. Found: C, 72.87; H, 8.31; O, 19.17.

21-Desoxycortisone (Xa).—The oxidation of 200 mg. of Δ^5-pregnene-3β,11α,17α-triol-20-one (VIIIc) was performed exactly as described above but the crude oxidation product was dissolved in 6 cc. of acetic acid and hydrogen chloride gas was passed through the solution for 45 min. at 0°. After standing for an additional hour at 0°, saturated salt solution was added and the product was extracted with ethyl acetate. The solution was subjected to decolorization with charcoal, evaporated to dryness, the residue was dissolved in benzene and filtered through a short column of washed alumina. Recrystallization from hexane–acetone afforded 120 mg. of colorless crystals, m.p. 236–240°, with loss of solvent at 210° and change of crystal form near 228°, λ_{max}^{EtOH} 238–240 mμ, log ϵ 4.20. No depression in melting point was observed upon admixture with an authentic sample[13b] of 21-desoxycortisone (Xa) prepared from cortisone and the infrared spectra were identical.

Cortisone Acetate (Xc).—To a stirred solution of 400 mg. of 21-desoxycortisone (Xa) in 3 cc. of old[25] tetrahydrofuran and 1.8 cc. of methanol was added 600 mg. of finely powdered calcium oxide followed by 600 mg. of iodine. When the iodine color had disappeared (*ca.* 3 hr.), methylene dichloride was added, the solution was filtered and the filtrate was washed successively with aqueous sodium iodide solution, sodium thiosulfate solution, water, dried and evaporated *in vacuo* without applying heat. The residual 21-iodo derivative Xb was dissolved in 10 cc. of dry acetone and heated under reflux for 18 hr. with 1.0 g. of anhydrous potassium acetate. Most of the solvent was distilled off, water was added and the product was extracted with methylene dichloride. After washing with water, drying and evaporating, there was obtained 297 mg. of cortisone acetate (Xc). The needles, obtained by recrystallization from methanol or from acetone–hexane, exhibited m.p. 235–237°, undepressed upon admixture with an authentic sample of cortisone acetate (Xc). Identity was confirmed further by infrared spectral comparison.

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(25) Tetrahydrofuran having a peroxide content equivalent to 0.01 g. of iodine/cc. of tetrahydrofuran (titration with potassium iodide and thiosulfate). Alternatively tetrahydrofuran distilled from calcium oxide is exposed to sunlight in an open bottle until the peroxide content reaches the above value.