837. *Studies in the Synthesis of Cortisone. Part XVII.* The Bromination of Cholestan-3-one.*

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Base-catalysed bromination of 2α-bromocholestan-3-one gives the corresponding 2 : 2-dibromo-ketone; further halogenation in such conditions yields the unstable 2 : 2 : 4β-tribromocholestan-3-one.

The rearrangement of 2 : 2-dibromocholestan-3-one into its 2α : 4α-dibromo-isomer involves hydrogen bromide as a specific promoter, by means of which molecular bromine is generated from the *gem.*-dibromo-ketone. The ensuing dehalogenation and rehalogenation eventually produce the more stable 2 : 4-dibromo-ketone. Correspondingly, in the acid-catalysed bromination of 2α-bromocholestan-3-one the first-formed 2 : 2-dibromo-compound passes into the 2 : 4-dibromo-isomer as the reversible processes oust the kinetic control.

The dehydrogenation of 3-oxo-5α-steroids to Δ^4-3-keto-steroids calls for the introduction of bromine atoms at $C_{(2)}$ and $C_{(4)}$ before a practicable dehydrobromination can be achieved.[1] In polyoxo-steroids halogenation outside ring A may complicate these stages; consequently we have tried to anticipate such difficulties in the proposed synthesis of cortisone from 5α-steroids by studying the control that may be exerted over the bromination of cholestan-3-one.

Kröhnke and Timmler [2,3] distinguished two stages in the acid-catalysed brominations of simple ketones: the first, a kinetically controlled stage, yielded a compound that might suffer change as the ensuing reversible reactions ($R{\cdot}CO{\cdot}CHBrR' + HBr \longrightarrow R{\cdot}CO{\cdot}CH_2R' + Br_2$) of the second stage reached an equilibrium in which the stable α-bromo-ketones predominated. Corey [4,5] studied similar aspects of the chemistry of α-bromoketo-steroids, and Djerassi and Scholz [6] reported attempts at avoiding these complications in the bromination of steroid ketones: to this end, for instance, they used *N*-bromosuccinimide to make 2 : 2-dibromocholestan-3-one from the 2α-bromo-ketone, so precluding the formation of hydrogen bromide, in whose presence the *gem.*-dibromo-ketone changes into 2α : 4α-dibromocholestan-3-one.[7] Acid-catalysed bromination of 3-oxo-5β-steroids yields mainly the 4-bromo-derivatives, whereas the isomeric 5α-steroids give first the 2-bromo-ketones.[8] The possibility that base-catalysed halogenation of 3-oxo-5α-steroids might be differently ordered therefore attracted us, since it could offer a means of obtaining 4-bromo-3-oxo-5α-steroids.

Our attempts at brominating cholestan-3-one in conditions favouring basic catalysis failed to yield an identifiable product. The presence of an electronegative substituent on the carbon atom next to the carbonyl group should facilitate the release of the proton and hence favour further substitution;[9] confirmation of this reasoning is provided by the bromination of acetone, which under acid catalysis generates α-bromoacetone and then slowly αα'-dibromoacetone (among other products),[10] whereas in basic conditions a haloform reaction takes place.[11] And indeed we found that 2α-bromocholestan-3-one is converted

* Part XVI, preceding paper.

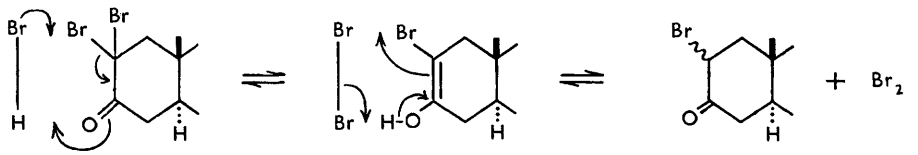
[1] Cf. following paper.
[2] Kröhnke and Timmler, *Ber.*, 1936, **69**, 614.
[3] Kröhnke, *ibid.*, p. 921.
[4] Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175.
[5] Cf. Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, p. 261.
[6] Djerassi and Scholz, *Experientia*, 1947, **3**, 107.
[7] Inhoffen and Zühlsdorff, *Ber.*, 1943, **76**, 233.
[8] Cf. Taylor, *Chem. and Ind.*, 1954, 250.
[9] Cf. Alexander, "Ionic Organic Reactions," Wiley and Sons, Inc., New York, 1950, p. 206.
[10] Hughes, Watson, and Yates, *J.*, 1931, 3318; Watson, Nathan, and Laurie, *J. Chem. Phys.*, 1935, **3**, 170; Weygand and Schmied-Kowarzik, *Chem. Ber.*, 1949, **82**, 335; Kröhnke and Lüderitz, *ibid.*, 1950, **83**, 60.
[11] Cf. Fuson and Bull, *Chem. Rev.*, 1934, **15**, 275; Bell *et al.*, *Proc. Roy. Soc.*, 1940, *A*, **176**, 88; 1949, *A*, **198**, 308.

efficiently, in acetic acid containing potassium or sodium acetate as the base, into 2 : 2-dibromocholestan-3-one, with no polarimetric or spectroscopic evidence of the formation of an isomeric 2 : 4-dibromo-compound. When sodium acetate is used only as a buffer with an acid catalyst the bromination stops at monosubstitution; [12] further substitution in these conditions is thwarted because the bromo-ketone is less easily enolised than its precursor, and it becomes possible only if the buffer is omitted or if so much of the acetate is added that a base-catalysed halogenation of the bromo-ketone occurs.

The influence of the halogen substituents on the halogenation of α-halogeno-ketones is transmitted across the carbonyl group: thus the base-catalysed bromination of ααα-trifluoroacetone is facilitated by the accumulation of halogen atoms on the seemingly remote carbon atom, and the acid-catalysed halogenation is retarded.[13] Accordingly 2 : 2-dibromocholestan-3-one affords by base-catalysed bromination an unstable tribromo-derivative, $[\alpha]_D$ +60°, which we consider to be 2 : 2 : 4β-tribromocholestan-3-one on account of its strong carbonyl absorption [14] at 1735 cm.$^{-1}$. Ellis and Petrow [15] noticed the slow acid-catalysed bromination of 2 : 2-dichlorocholestan-3-one to give a dichlorobromo-ketone, $[\alpha]_D$ +61·5°, and the similarity of the molecular rotations suggests that their product is 4β-bromo-2 : 2-dichlorocholestan-3-one; however, the survival in a solution containing hydrogen bromide of a compound with an axial C–Br bond presents an anomaly to which we shall refer later.

The acid-catalysed monobromination of a 3-oxo-5α-steroid, with subsequent base-catalysed halogenation, bids fair to yield 2 : 2-dibromo-3-oxo-5α-steroids selectively, even when there are other keto-groups in the molecule. If the rearrangement of such compounds could be kept to ring A, *i.e.*, if it is of the intramolecular type, a nice control could be exerted over the formation of the 2 : 4-dibromo-3-oxo-system in polyoxo-steroids; accordingly we examined the rearrangement.

The available information was contradictory, for Inhoffen and Zühlsdorff [7] explained it as an allylic rearrangement in the enols of the 2 : 2-dibromo-ketones, and thus of the intramolecular type, whereas Djerassi and Scholz [16] and Rubin and Hershberg [17] found that it was inhibited by sodium acetate, water, and hydrogen peroxide. These agents are of the kind that inhibit the acid-catalysed bromination of ketones,[18] and the nature of their intervention suggests that the rearrangement is of the intermolecular (pseudo-rearrangement) type,[19] involving debromination and rebromination, which we can explain on the basis of the following displacements: [20]



Our own evidence confirms this contention. In solution in acetic acid containing hydrogen bromide, 2 : 2-dibromocholestan-3-one yields the 2α : 4α-dibromo-compound at a rate proportional to the concentration of the former, and also to that of the hydrogen bromide, which is specific in promoting the change. No rearrangement occurs in refluxing acetic acid or in acetic acid containing perchloric acid or hydrogen chloride; moreover lithium bromide, ascaridole, benzoyl peroxide, or irradiation with ultraviolet light does not initiate it. We could not induce an intramolecular change in conditions that might favour general acid catalysis, *e.g.*, in chlorobenzene containing anhydrous trichloroacetic acid,

[12] Cf. Inhoffen, *Ber.*, 1936, **69**, 2141; Mattox and Kendall, *J. Biol. Chem.*, 1950, **185**, 593; ref. 1.
[13] McBee and Burton, *J. Amer. Chem. Soc.*, 1952, **74**, 3902.
[14] Jones, Ramsay, Herling, and Dobriner, *ibid.*, p. 2828.
[15] Ellis and Petrow, *J.*, 1953, 3869.
[16] Djerassi and Scholz, *J. Amer. Chem. Soc.*, 1947, **69**, 2404; *J. Org. Chem.*, 1948, **13**, 697.
[17] Rubin and Hershberg, quoted by Feiser and Fieser, ref. 5, p. 264.
[18] Cohen, *J. Amer. Chem. Soc.*, 1930, **52**, 2827.
[19] Cf. Dewar, *Ann. Reports*, 1951, **48**, 124.
[20] Cf. Newman, *J. Amer. Chem. Soc.*, 1951, **73**, 4993.

with which, for example, the Orton rearrangement of *N*-acyl-*N*-halogenoanilides can be catalysed.[21] Sodium acetate, added during the rearrangement of the 2 : 2-dibromo-keto-steroid, stops it, but quinol does not interfere.

Therefore, during the acid-catalysed halogenation of 2α-bromocholestan-3-one the immediate product is the *gem.*-dibromide, but as the kinetic control is replaced by the slower adjustments leading to a thermodynamic equilibrium the 2α : 4α-dibromo-ketone takes its place. In this way the steroid rids itself of the more confined axial C–Hal bond, since in the final product both halogens are disposed equatorially to ring A.

The stationary concentration of bromine during the rearrangement is enough hardly to colour the solution. Nevertheless the halogen can be intercepted by β-naphthol, in whose presence the rotation decreases more rapidly than in the straightforward rearrangement, but still at a rate proportional to the concentration of the steroid. The products are 1-bromo-2-naphthol and 2α-bromocholestan-3-one. We infer from these results that the fast debromination of the *gem.*-dibromide is of the first order and that it is succeeded in the rearrangement by the rate-determining bromination at the 4-position, also of the first order with reference to the steroid; the last contention accords with the kinetics of the bromination of ketones.[22] In the absence of hydrogen bromide, β-naphthol had no effect upon a solution of 2 : 2-dibromocholestan-3-one in acetic acid. In mixtures of β-naphthol and 2α-bromocholestan-3-one in acetic acid or carbon tetrachloride the naphthol outstripped the steroid as an absorber of halogen. In the presence of phenol, however, the steroid competed more successfully, so that phenol does not intervene decisively in the rearrangement.

Robinson [23] and Hurst and Macbeth [24] attributed the conversion of α- into γ-bromo-acetoacetic ester, in conditions like those in which 2 : 2-dibromo-3-oxo-5α-steroids rearrange, to the transfer of molecular halogen; the literature and the work reviewed herein contain cognate examples.[25] On the other hand, nucleophilic substitutions accompanied by rearrangements also occur in α-halogeno-ketones; [26] this type of rearrangement might be further exemplified in the elimination of hydrogen halides by means of collidine from 2-halogeno-3-oxo-5α-steroids, which affords mixtures of the Δ^1- and Δ^4-3-ketones.[27,28]

Further support for the supposition that the isomerisation of 2 : 2-dihalogeno-3-oxo-5α-steroids involves transfer of molecular halogen comes from the behaviour of the chloro-keto-steroids. Thus 2 : 2-dichlorocholestan-3-one does not rearrange in the presence of hydrogen chloride, and in 2-bromo-2-chlorocholestan-3-one only the bromine atom migrates, apparently under the specific influence of hydrogen bromide.[15,28,29] This behaviour is in accordance with the stability of α-chloro-ketones in these circumstances and with the resistance of α-bromoacetoacetic ester to hydrogen chloride.[30,31] On the other hand α-iodo-ketones are readily dehalogenated, and, as the equilibrium favours this reaction rather than iodination, rearrangement of the halogen substituent is thwarted.[32]

We tried by means of hydrogen bromide in acetic acid to invert the 4-bromo-substituent in 2 : 2 : 4β-tribromocholestan-3-one, but this failed owing to dehalogenation of the steroid; in contrast, perchloric acid in acetic acid caused no noticeable change. If the compound described by Ellis and Petrow [15] as 4-bromo-2 : 2-dichlorocholestan-3-one carries a 4β-substituent, as we suppose, the stability of this axially disposed bromine atom is remarkable,

[21] Bell, *J.*, 1936, 1154; " Acid-Base Catalysis," Oxford Univ. Press, 1941, p. 104.
[22] Hammett, " Physical Organic Chemistry," McGraw-Hill, New York, 1940, pp. 97, 109, 229; cf. Ralls, *J. Amer. Chem. Soc.*, 1938, **60**, 1744.
[23] Robinson, *Ann. Reports*, 1922, **19**, 100.
[24] Hurst and Macbeth, *J.*, 1922, **121**, 2169.
[25] *E.g.*, Altschul and Bartlett, *J. Org. Chem.*, 1940, **5**, 623; Smith, Wilson, and Woodyer, *Chem. and Ind.*, 1954, 309; cf. Kharasch, Sternfield, and Mayo, *J. Amer. Chem. Soc.*, 1937, **59**, 1655.
[26] Eastham, Fisher, Kulka, and Hibbert, *ibid.*, 1944, **66**, 26; Aston *et al.*, *ibid.*, 1951, **73**, 3900, 3902; Stevens and Lenk, *J. Org. Chem.*, 1954, **19**, 538.
[27] Cf. Djerassi, *J. Amer. Chem. Soc.*, 1949, **71**, 1003; Fieser and Romero, *ibid.*, 1953, **75**, 4716.
[28] Beereboom and Djerassi, *J. Org. Chem.*, 1954, **19**, 1196.
[29] Beereboom, Djerassi, Ginsburg, and Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 3500.
[30] Cf. Epprecht, *Annalen*, 1894, **278**, 69.
[31] Hantzsch, *Ber.*, 1894, **27**, 355, 3168.
[32] Cf. Pearson and Ross, *J. Amer. Chem. Soc.*, 1952, **74**, 2933.

since the compound survives long treatment in the presence of hydrogen bromide.[33] We presume that the ketone is so encumbered with halogen substituents that enolisation and epimerisation in these conditions are very much hindered.

Experimental

Unless it is stated otherwise, the kinetic experiments were carried out at 25° ± 1°, usually in a 2 dm.-tube shaded from bright lights; anhydrous solvents contained <0·04% (w/v) of water, and the chloroform was alcohol-free. Optical rotations and infrared absorption peaks [34] pertain to solutions of the steroids in $CHCl_3$ and CS_2 respectively, and the m. p.s were taken on a Kofler block.

2 : 2-*Dibromocholestan*-3-*one*.—2α-Bromocholestan-3-one (5 g.) was dissolved in anhydrous acetic acid (360 ml.) at 90° on the steam-bath. A solution of potassium acetate (18·5 g.; dried at 100°) in acetic acid (75 ml.) at 90° was added, followed immediately by 0·619M-bromine in acetic acid (25 ml., 1·42 mol.), added in one lot. Heating was continued on the steam-bath until the bromine colour disappeared (about 12 min. in all). The solution was then cooled as rapidly as possible to room temperature, and set aside for 30 min., during which the product crystallised as white prisms (3·34 g., 57%), m. p. 153—158°, $[\alpha]_D^{22}$ +116° (*c* 0·41), $\nu_{max.}$ 1735 cm.$^{-1}$ (Found: Br, 29·5. Calc. for $C_{27}H_{44}OBr_2$: Br, 29·4%). For this material, made by the acid-catalysed method, Djerassi and Scholz [16] give m. p. 145—147°, $[\alpha]_D^{22}$ +104°. On repeating their method, we obtained a product, m. p. 147—156°, $[\alpha]_D^{23}$ +110° (*c* 1·14). Jones, Ramsey, Herling, and Dobriner [14] give $\nu_{max.}$ 1735 cm.$^{-1}$ for material made by the earlier method.

2 : 2 : 4β-*Tribromocholestan*-3-*one*.—2 : 2-Dibromocholestan-3-one (1 g.) was similarly halogenated with bromine (1·5 mol.) in 0·5N-potassium acetate in acetic acid. The halogen was taken up in 15 min.; addition of water to the cooled solution yielded the white *tribromo-compound* (1·12 g., 98%), m. p. 35—40°, $[\alpha]_D^{20}$ +60° (*c* 0·54), $\nu_{max.}$ 1735 cm.$^{-1}$ (Found: Br, 38·7. $C_{27}H_{43}OBr_3$ requires Br, 38·3%). In spite of its low m. p. and ill-defined absorption in the "fingerprint" region of the infrared spectrum another precipitation from acetic acid did not change its properties. Attempts at crystallising this compound led to its decomposition.

A solution of the above tribromo-compound in 0·04N-hydrogen bromide in anhydrous acetic acid displayed a rapidly diminishing rotation, which stopped changing after 30 min. Isolation of the steroidal product by the addition of water and subsequent crystallisation from hexane yielded 2α : 4α-dibromocholestan-3-one, m. p. 186—189°, $[\alpha]_D^{20}$ −3° (*c* 0·43), $\nu_{max.}$ 1756 cm.$^{-1}$, which was finally identified by a mixed m. p. determination with authentic material and a comparison of the infrared spectra of the two specimens. Wilds and Djerassi,[35] and Jones *et al.*,[14] give m. p. 194°, $[\alpha]_D$ +3°, $\nu_{max.}$ 1756 cm.$^{-1}$. In the least quantity of 0·1N-hydrogen bromide in acetic acid a greater change in rotation occurred; addition of water precipitated a crude solid, m. p. 61—73°, $[\alpha]_D^{20}$ −33° (*c* 0·38), $\nu_{max.}$ 1706 and 1756 cm.$^{-1}$ (*ca.* equal intensity), that resembled the product (Found: Br, 29·9%) from the attempted acid-catalysed dibromination of 2α-bromocholestan-3-one. It must contain a hitherto unknown bromocholestan-3-one, since all the known members of this series have much higher rotations. Polarimetric evidence disclosed little change in the 2 : 2 : 4β-tribromo-compound dissolved in anhydrous 0·09N-perchloric acid in acetic acid.

Rearrangement of 2 : 2-*Dibromocholestan*-3-*one with Hydrogen Bromide as Catalyst*.—In each experiment in this series 2 : 2-dibromocholestanone (100 mg.) was dissolved in anhydrous acetic acid (20 ml.), and the rotation of the cooled solution measured. The required amount of 0·6N-hydrogen bromide in acetic acid was added, and the rotation observed at suitable intervals, corrections being made for the addition of the catalyst solution. The values of the velocity constants *k* were calculated from the equation for a first-order reaction:

$$k = [2{\cdot}303/(t_y - t_x)][\log_{10}(A_x - A_\infty) - \log_{10}(A_y - A_\infty)]$$

where A_x, A_y, and A_∞ are respectively the rotations after *x* and *y* minutes and at the end of the change. The values of *k* for different concentrations of hydrogen bromide are tabulated.

Normality of HBr	0·02	0·03	0·04	0·05	0·10
k_{mean} (min.$^{-1}$)	0·026	0·046	0·057	0·080	0·167
Standard deviation	±0·003	±0·007	±0·010	±0·024	±0·018
k_{mean}/[HBr]	1·3	1·5	1·4	1·6	1·7

[33] Cf. ref. 4.
[34] Cf. Dickson, Page, and Rogers, *J.*, 1955, 443.
[35] Wilds and Djerassi, *J. Amer. Chem. Soc.*, 1946, **68**, 1712.

Rearrangement of 2 : 2-*Dibromocholestan*-3-*one in the Presence of* β-*Naphthol.*—Two small-scale (100 mg.) experiments were performed in a similar manner to the rearrangements previously described with 0·04N-hydrobromic acid solution, except that in the first 5 mol. and in the second 1·1 mol. of β-naphthol were present. In each the rotation (corrected to 20 ml. of solution) dropped from α_D +1·10° to +0·43° in 20 min., whereas the final rotation in the absence of β-naphthol was +0·04°. The changes obeyed first-order kinetics, where $k_{mean} = 0·379$ (±0·082) min.$^{-1}$. This value was obtained at 23°.

On a larger scale, 2 : 2-dibromocholestan-3-one (933 mg.) was dissolved in warm anhydrous acetic acid (100 ml.) and cooled, and β-naphthol (purified; 1·0 mol., 247 mg.) was added and dissolved. Finally 0·6N-hydrogen bromide in acetic acid (7·0 ml.) was added, and the solution kept in the dark for 75 min. It was then poured into water, and the acid neutralised with the calculated amount of sodium hydrogen carbonate. The mixture was extracted with ether (3 × 100 ml.), and the ether extracted with N-sodium hydroxide (8 × 25 ml.). The alkaline extracts were acidified with hydrochloric acid, and the precipitated bromonaphthol was extracted with ether (3 × 50 ml.), and recovered by evaporation of the washed extract, which yielded it as a gum (356 mg., 89%). Crystallisation from hexane gave brown crystals (228 mg.), some of which were sublimed at 60—70°/10^{-1} mm. to form white 1-bromo-2-naphthol, m. p. 81° (capillary tube). The recorded m. p.[36] varies from 81° to 84°.

The original ether extract, containing neutral material, was washed three times with water, dried ($MgSO_4$), and evaporated. The crude product (790 mg., 100%) had $[\alpha]_D^{25}$ +38° (*c* 0·60). This was crystallised from ethanol–acetone (5 : 1), to yield needles (520 mg.) of 2α-bromocholestan-3-one, m. p. 164—169°, $[\alpha]_D^{26}$ +45° (*c*, 0·54), $\nu_{max.}$ 1730 cm.$^{-1}$ (Found : Br, 16·4. Calc. for $C_{27}H_{45}OBr$: Br, 17·2%). This material was identified by its infrared spectrum and by a mixed m. p. with authentic material (lit.,[14, 37] m. p. 168—169°, $[\alpha]_D$ +42°, $\nu_{max.}$ 1733 cm.$^{-1}$).

The rotation of a solution of 2 : 2-dibromocholestan-3-one in acetic acid was unchanged by the addition of β-naphthol when hydrogen bromide was absent.

Competitive Bromination Experiments.—In each of these experiments the steroid (0·10 g.) was dissolved in an anhydrous solvent (10 ml.) to which the phenolic competitors were added in equimolecular proportions with the steroid. No change in rotation was noticed when solutions of 2α-bromo- or 2 : 2-dibromo-cholestan-3-one were treated with such competitors. In series *A* cholestan-3-one was halogenated alone and in the presence of phenol and β-naphthol with bromine (2 mol.) in chloroform–acetic acid (1 : 1). In series *B* carbon tetrachloride was used as solvent instead of the mixture used in series *A*. In series *C* 2α-bromocholestan-3-one was halogenated with bromine (1 mol.) in the chloroform–acetic acid mixture, with and without competitors. The concentration of hydrogen bromide (generated by the halogenation) in series *A* and *B* was *ca.* 0·025N, whereas in series *C* it was 0·013N. The rotations of the solutions at differing times are given in the Table.

*Competitive brominations.**

	Experiment and nature of competitor	Initial rotation	Maximum rotation † (α_{max})	Time † to reach max. (min.)	Steady rotation (α)	Time to reach final val. (approx.) (min.)
A	None	0·49°	0·80°	10	0·11°	300
	Phenol	0·49	0·68	5	0·32	120
	β-Naphthol	0·49	0·56	10	0·41	180
B	None	0·46	0·86	5	0·11	300
	Phenol	0·46	0·75	5	0·57	420
	β-Naphthol	0·46	None	—	0·50	10
C	None	0·59	0·88	20	0·18	420
	Phenol	0·59	0·73	5	0·56	60
	β-Naphthol	0·59	0·65	10	0·60	300

* All rotations positive. † Approximate, as the rotation alters very quickly in the early stages.

Other Attempts to catalyse the Rearrangement.—The following agents had no effect (judged polarimetrically) on anhydrous 0·5% (w/v) solutions of 2 : 2-dibromocholestan-3-one in anhydrous acetic acid : perchloric acid or hydrogen chloride (final concentration 0·04N); anhydrous lithium bromide (which had a final concentration of *ca.* 0·03N and even at 100°

[36] *E.g.*, Fries and Schimmelschmidt, *Annalen*, 1930, **484**, 245; Hazlet, *J. Amer. Chem. Soc.*, 1940, **62**, 2156; ref. 2.

[37] Fieser and Dominguez, *ibid.*, 1953, **75**, 1705.

initiated no change); benzoyl peroxide. Irradiation of such solutions with ultraviolet light was ineffectual. Addition of benzoyl peroxide or quinol did not affect the going rearrangement, promoted with hydrogen bromide. A commercial sample of ascaridole stopped it. Treatment of a solution of 2 : 2-dibromocholestan-3-one in anhydrous chlorobenzene with anhydrous trichloroacetic acid in the same solvent (acid finally 0·03N) initiated no change, even when the solution was warmed.

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