(75 ml.) and then shaken with constant boiling hydriodic acid (10 ml.). When the evolution of nitrogen had ceased, the resultant dark red chloroform solution was removed and successively washed with water (3 × 50 ml.), saturated sodium thiosulfate solution (50 ml.), saturated sodium bicarbonate solution (50 ml.), and again with water (50 ml.). On drying (Na_2SO_4) and removal of the solvent, a yellowish white mobile oil (1.70 g.) was obtained. It no longer showed the diazo, the diazocarbonyl or the anhydride bands. The infrared spectrum is in fact a composite picture of dimethyl succinate and methyl levulinate. In this connection it is interesting to note that the carbonyl CO and the ester CO of an authentic sample of methyl levulinate (prepared from levulinic acid and diazomethane) show in the infrared (film) spectrum only a single band (strong and somewhat broad) at 1725 $cm.^{-1}$. The above oil gave a 2,4-dinitrophenylhydrazone, (0.21 g., crude: m.p. ~130°) which crystallized from ethanol into shiny orange-yellow platelets, m.p. 133°, mixed melting point with the authentic sample of the 2,4-D.N.P. of methyl levulinate was the same. The infrared spectra of the two dinitrophenylhydrazones are also identical. The material left after the removal of the 2,4-D.N.P. was worked up in the usual way and dimethyl succinate was isolated. The remaining products of reactions were not examined.

As the investigation was on'y incidental to the author's main work on the tetracyclines, and as it did not yield the desired results, the study was not further pursued. For the same reason yields of the reaction products are not specified.

Acknowledgment. The author thanks the University Court and Professor R. A. Raphael for the award of a Pfizer Research Fellowship.

GLASGOW W. 2., SCOTLAND

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

α-Halo Ketones. I. The Reaction of 2α,4α-Dibromocholestan-3-one with *N*,*N*-Dimethylaniline[1]

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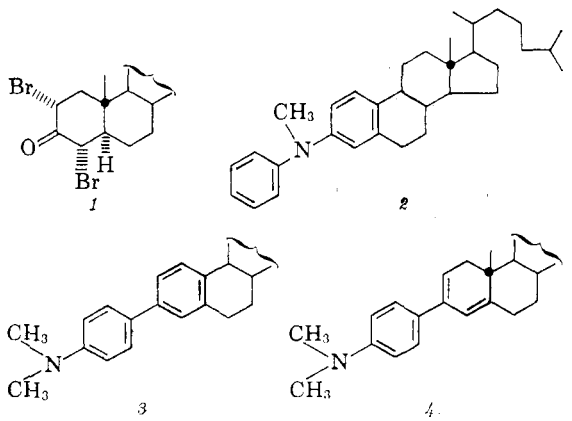
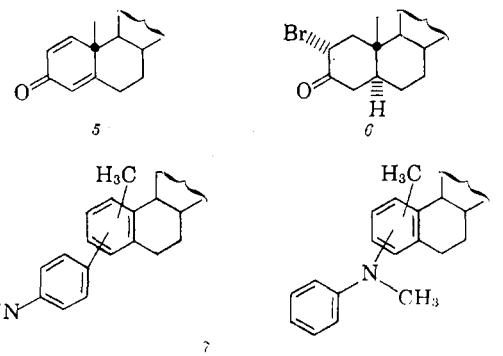
The product obtained earlier from reaction of the title compounds at *ca.* 200° has been shown to be the conjugated indole (*17*). The first step in the reaction sequence is apparently dehydrobromination to 2α-bromo-Δ⁴-cholesten-3-one (*23*) and dimethylaniline hydrobromide which reacts with dimethylaniline to give *N*-methylaniline and phenyltrimethylammonium bromide. The indole (*17*) could result from reaction of *N*-methylaniline with (*23*) or one of its transformation products. Several indoles incorporating the steroid nucleus have been prepared and evidence for their structures is presented.

In 1937 Schwenk and Whitman[3] while studying the dehydrobromination of bromo-3-keto steroid derivatives refluxed 2α,4α-dibromocholestan-3-one (*1*) with *N*,*N*-dimethylaniline (b.p. 193°). A crystalline product, m.p. 230–232°, whose analysis corresponded to $C_{33-34}H_{47-49}N$, was isolated in small yield. The compound in alcohol–acetic acid solution was reported to give a red color with *p*-nitrobenzenediazonium ion and was presumed to be an amine for which three structures *2*, *3*, and *4* were tentatively suggested. Although dehydrobromination of *1* would give dimethylaniline hydrobromide, a fairly strong acid in refluxing dimethylaniline, the loss of an angular methyl group required by *2* or *3* seemed unlikely under the relatively mild reaction conditions. From experience with the acid-catalyzed and thermal reactions of Δ¹,⁴-3-keto dienones (*5*), loss of a methyl group is observed only under pyrolysis at 325–600°.[4] Formula *4* or a double bond isomer was more reasonable since Schwenk and Whitman also observed





(1) Taken in part from a thesis presented by Paetong NaNonggai to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree Master of Science.

(2) On leave of absence from Chulalongkorn University, Bangkok, Thailand.

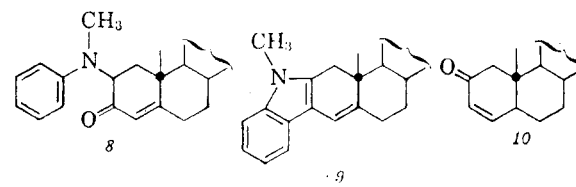
(3) E. Schwenk and B. Whitman, *J. Am. Chem. Soc.*, 59, 949 (1937).

that 2α-bromocholestan-3-one (*6*) was reduced in part to cholestan-3-one (*21*) by dimethylaniline; structure *4* could arise from condensation of dimethylaniline and Δ⁴-cholesten-3-one (*16*) formed by reduction of 2α-bromo-Δ⁴-cholesten-3-one (*23*). However, the reported analytical figures do not agree well with *4*. Furthermore, structures *3* and *4* are rendered suspect by the extraction of the compound from hydrochloric acid into ether. *A priori* there were other conceivable reaction paths leading by rearrangement with retention of the methyl group to such formulas as *7*.

When the reaction was repeated according to the directions of Schwenk and Whitman, a crystalline product, m.p. 221–223° dec., $[\alpha]D$ −24°, was obtained in up to 10% yield.[5] The analytical data fitted best the formula $C_{34}H_{49}N$ (mol. wt. 471), and this was confirmed by the mass spectrum[6] which had its parent peak at 471 mass units. However, the compound was insoluble in dilute hydrochloric acid and did not give a precipitate from ether when hydrogen chloride gas was added. Moreover it gave no color with *p*-nitrobenzenediazonium ion in ethanol–acetic acid solution. Nevertheless, the product isolated in the present work is probably identical with Schwenk and Whitman's compound.[7]

The ultraviolet spectrum of the compound, λ_{max} 242 mμ (ε 24,000), 254 mμ (ε 22,000), 260 mμ (ε 21,000), 286 mμ (ε 7130), and 304 mμ (ε 5880), was reminiscent of a carbazole.[8] This observation coupled with the lack of basic properties excluded arylamine, diarylamine, and aminodiphenyl formulas, leaving indole structures for consideration. In agreement the infrared spectrum had in the region 670–900 cm.$^{-1}$ only one strong peak at 738 cm.$^{-1}$, the position expected of a benzene ring with four adjacent hydrogen atoms. The presence of an indole nucleus was confirmed by hydrogenation in benzene with palladium. One equivalent of hydrogen was absorbed with the formation of a dihydro compound, m.p. 196°, $[\alpha]D$ −7.4°, whose ultraviolet spectrum, λ_{max} 232 mμ (ε 35,400), 287 mμ (ε 6650), and 294 mμ (ε 6400), was recognized as that of a typical indole.[9] The reduced double bond had been conjugated with the indole nucleus since the ultraviolet spectrum changed markedly on hydrogenation. The presence of an *N*-methyl group was verified by the Herzig-Meyer determination and the absence of NH absorption in the infrared region. The necessity of accommodating an *N*-methylindole with a conjugated double bond restricted the number of reasonable possibilities for Schwenk's compound.

It was originally assumed that the indole nitrogen must be fused at the 2- or 4- position of the steroid skeleton because the most likely reaction seemed an alkylation of the dimethylaniline nitrogen by the α-bromo ketone analogous to the reaction of pyridine with 2α-bromocholestan-3-one.[10] Since, however, 2α,4α-dibromocholestan-3-one is rapidly dehydrobrominated to 2α-bromo-Δ⁴-cholesten-3-one (*23*) by reagents such as refluxing collidine,[11] this could reasonably precede the alkylation which would consequently take place exclusively at C-2. Demethylation (phenyltrimethylammonium bromide was also isolated) would give *8* the cyclization of which to *9* could be catalyzed by dimethylaniline hydrobromide. This view appeared to be strengthened by the NMR spectrum[12] of Schwenk's compound which clearly had only one vinyl hydrogen centered at δ = 6.15 p.p.m. (tetramethylsilane = 0) although the splitting pattern was not apparent.



8 *9* *10*

To check this interpretation dihydro Schwenk's compound was compared with an *N*-methylindole from an available steroid ketone. The crystalline hydrogenation product was not identical with the indole (*13*), m.p. 185°, $[\alpha]D$ +71°, prepared by the Fischer method from cholestan-2-one (*12*) and α-methylphenylhydrazine. The structure *13* follows from the facts that cyclization in the Fischer synthesis normally occurs in the direction of enolization of the ketone and cholestan-2-one is known to give the Δ²-enol.[13] The same compound was formed by reaction of *N*-methylaniline and 2α-bromocholestan-3-one (*6*). Dihydro Schwenk's compound

(4) For a brief discussion and references see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, 1959, pp. 327–329 and 479–480. However, see also K. Tsuda, E. Ohki, S. Nozoe, and N. Ikekawa, *J. Org. Chem.*, 26, 2614 (1961).

(5) The noncrystalline remainder of the product is mostly conjugated ketone from dehydrobromination to judge from spectra.

(6) Kindly determined by Dr. R. I. Reed and Dr. J. M. Wilson, Chemistry Department, The University, Glasgow, Scotland.

(7) *N,N*-Dimethylaniline gives a red coupling product with *p*-nitrobenzenediazonium ion in ethanol–acetic acid solution. Possibly the sample of the high-melting compound tested in ref. 3 contained a trace of dimethylaniline.

(8) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," J. Wiley and Sons, Inc., New York, 1951, no. 338.

(9) Ref. 8, no. 193 and 194.

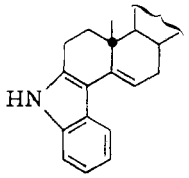
(10) A. Butenandt and A. Wolff, *Ber.*, 68, 2091 (1935).

(11) C. Djerassi, *J. Am. Chem. Soc.*, 71, 1003 (1949).

(12) The NMR spectra were kindly determined by Dr. J. B. Stothers through the courtesy of Professor P. de Mayo, Department of Chemistry, University of Western Ontario, Canada, and by Dr. Lois Durham through the courtesy of Dr. E. J. Eisenbraun, Department of Chemistry, Stanford University.

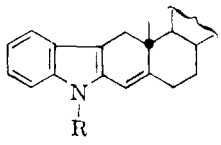
(13) C. Djerassi and T. Nakano, *Chem. & Ind.*, (London) 1385 (1960).

might more likely have been the 5β-epimer of *13*, but rather than make this A/B *cis* derivative it appeared simpler to prepare *9*. Dehydrogenation of *13*, which could lead directly to *9*, with one equivalent of chloranil gave a crude product containing some carbazole chromophore, but none of the desired dihydrocarbazole could be isolated. A more promising approach to *9* appeared to be a Fischer indole reaction with Δ³-cholesten-2-one (*10*).[14] There was precedent for the Fischer synthesis with a conjugated ketone of this type in the reported reaction of Δ⁴-cholesten-3-one (*16*) with phenylhydrazine to give a conjugated indole formulated without evidence as *11a*.[15] As a model reaction



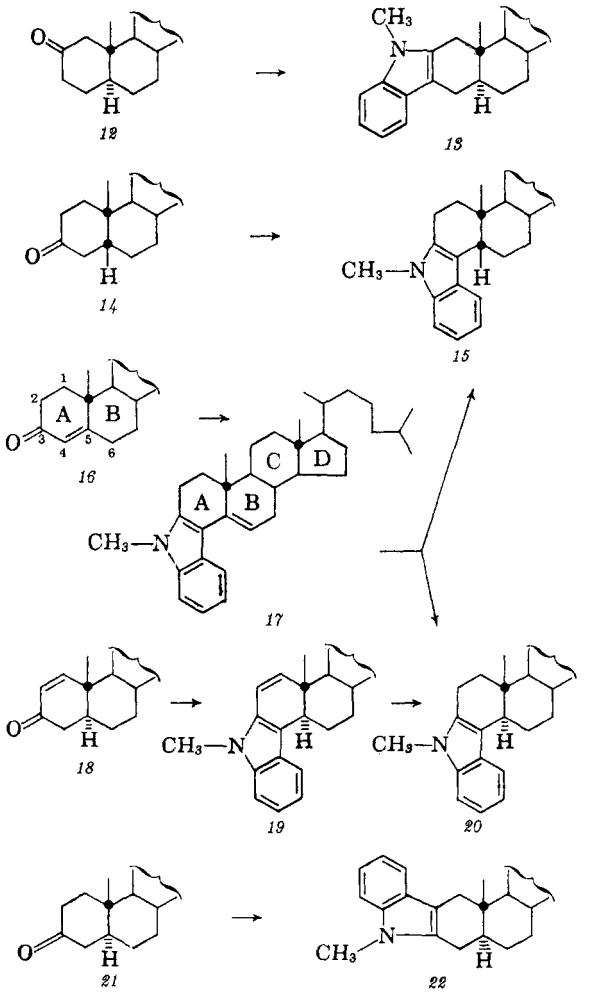
i

and a check on the literature report α-methylphenylhydrazine and Δ⁴-cholesten-3-one (*16*) were heated with polyphosphoric acid. There was obtained an 11% yield of a crystalline substance, m.p. 223° dec., $[\alpha]_D$ −22.4°, which was identical (m.p., m.m.p., $[\alpha]_D$, infrared, ultraviolet) with Schwenk and Whitman's compound! This unexpected result fixed the location of the indole nitrogen, but left for consideration two structures *11b* or *17* with a conjugated double bond bearing one vinyl hydrogen. According to the enolization of Δ⁴-cholesten-3-one toward C-6[16] structure *17* would be anticipated from the Fischer synthesis, but *11b* is not rigorously excluded.



11a, R = H
11b, R = CH_3

A choice between *11b* and *17* was made through the dihydro compounds. Reinvestigation of the hydrogenation of Schwenk and Whitman's compound revealed in the mother liquors from the crystalline product a second, oily dihydro compound, $[\alpha]_D$ +121°, formed in about 14% yield. These two dihydrocompounds constituted one of the two pairs of C-5 epimers corresponding either to the 2,3(*N*)-indolo steroid skeleton (*11b*) or else the 3(*N*),4-indolo steroid skeleton (*17*). Comparison of both reduction products with one known isomer from each series would necessarily reveal two of the compounds identical and permit structural assignments. A known representative of each type was prepared from α-methylphenylhydrazine and two steroid ketones at hand. Cholestan-3-one (*21*) which enolizes preferentially toward C-2 gave an indole assigned the 2,3(*N*)-indolo structure (*22*), while coprostan-3-one (*14*) which enolizes toward C-4 gave an indole assigned the 3(*N*),4-indolo structure (*15*).[17] The derivative *22* from cholestan-3-one, m.p. 217°, $[\alpha]_D$ +67°, was not identical with either of the hydrogenation isomers. On the other hand, the A/B *cis* coprostan-3-one derivative (*15*), m.p. 153°, $[\alpha]_D$ +149°, had an infrared spectrum identical with that of the impure oily dihydro Schwenk's compound. This tentative correlation was confirmed and unequivocal evidence provided for the previously assumed structures of the Fischer indole synthesis products in the following way:



Δ¹-Cholesten-3-one (*18*) on reaction with α-

(14) Cyclization to C-1 was considered unlikely because of the severe steric crowding of the indole system with the steroid C-ring.

(15) W. Rossner, *Z. physiol. Chem., Hoppe-Seyler's*, **249**, 267 (1935). In view of the results described here the formula of Rossner's indole must be revised to *i*. Furthermore the indole from coprostanone and phenylhydrazine described in ref. 25 must be (15, N—CH_3=NH).

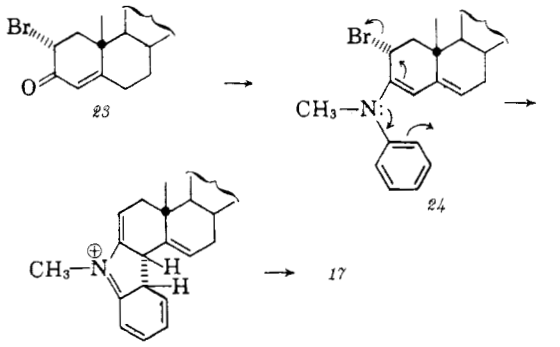
(16) Ref. 4, pp. 288–290.

(17) For evidence regarding the direction of enolization see ref. 4, p. 282.

methylphenylhydrazine gave a dihydrocarbazole (*19*), m.p. 214°, $[\alpha]D$ +153°. Hydrogenation of *19* in benzene solution with palladium produced the identical (m.p., m.m.p., $[\alpha]D$, infrared, ultraviolet) crystalline dihydro compound *20* obtained by reduction of Schwenk and Whitman's compound. Therefore the conjugated indoles from Δ^1-cholesten-3-one and Δ^4-cholesten-3-one have the same skeleton. If this skeleton had the indole ring fused at C-2:C-3 as in *11b*, in addition to the difficulty of devising a plausible path from *18* to *11b*, the two conjugated indoles would have to be identical which they are not.[18a] Consequently Schwenk's compound, the *N*-methylindole from Δ^4-cholesten-3-one, must have the Δ^5-3(*N*),4-structure (*17*). The hydrogenation isomer of m.p. 196° must be *20* with the A/B *trans* arrangement since its preparation from Δ^1-cholesten-3-one could not affect the 5α-H of that ketone. The indole from cholestan-3-one, not being identical with *15* or *20*, by elimination must be *22* with the heterocyclic ring attached at C-2:C-3 and rings A/B *trans*.

The path by which *17* is formed presents an interesting problem. There is no way for the tertiary nitrogen of dimethylaniline to react with a C-3 carbonyl group. Instead *17* must have come from *N*-methylaniline which could add to a C-3 carbonyl group. However, the amount of *N*-methylaniline contaminating the *N*,*N*-dimethylaniline as determined by quantitative isolation of the *p*-toluenesulfonamide was 0.112% or 0.50 mmole in the 50 ml. used, considerably less than the maximum isolated yield (0.935 mmole) of Schwenk's compound. This fact suggested that *N*-methylaniline was being formed by reaction of dimethylaniline with dimethylaniline hydrobromide resulting from dehydrobromination. Such a disproportionation would also account for the high yields of phenyltrimethylammonium bromide. It was found that reflux of dimethylaniline hydrobromide in dimethylaniline did lead to good yields of *N*-methylaniline (isolated as the *p*-toluenesulfonamide) and the quaternary salt (isolated as the perchlorate).[18b] Furthermore a quantitative study of the reaction in which Schwenk's compound is formed showed the amount of quaternary ammonium perchlorate (7.00 mmoles) isolated to be close to the amount of *N*-methylaniline formed (8.07 mmoles).[19]

The indole *17* must then arise from reaction of *N*-methylaniline with some C-3 ketone intermediate. Boiling γ-collidine (b.p. 172°, $pK_a^{H_2O}$ 7.5) removes 1.2 equivalents of hydrogen bromide from 2α,4α-dibromocholestan-3-one within 40 seconds to give 2α-bromo-Δ^4-cholesten-3-one (*23*). If, as seems likely, boiling *N*,*N*-dimethylaniline (b.p. 193°, $pK_a^{H_2O}$ 5.0) does the same, then *17* might be formed by addition of *N*-methylaniline to the carbonyl group of *23*,[20] followed by dehydration to the enamine *24* and cyclization with SN2′ type displacement of bromide from C-2. That *17* is not



formed directly from the dibromo ketone (*1*) was proved by its reaction with *N*-methylaniline from which no crystalline product was obtained by trituration and seeding or by chromatography. Spectra of the crude reaction product and chromatogram fractions indicated a mixture of indole and arylamine with little (<*ca.* 6%) if any *17* present. In order to explain why *17* was not formed *via* *23* arising from dehydrobromination it is necessary to postulate that *N*-methylaniline reacts with the dibromo ketone (*1*) to give other products more rapidly that it is dehydrobrominated to *23*. This is not unreasonable; for example *N*-methylaniline reacts with 2α-bromocholestan-3-one (*6*) giving *13*, the result of a Bischler indole synthesis, as the major product. A more serious objection to the reaction path suggested above is the failure to isolate *17* from a small scale reaction of *N*-methylaniline with 2α-bromo-Δ^4-cholesten-3-one although spectra of the crude product were consistent with the presence of *17*. The fact that *17* could not be crystallized directly does not necessarily exclude its presence, for it was observed that occasionally *17* could not be crystallized from the dibromo ketone–dimethylaniline reaction although it was undoubtedly present to judge from spectra. As yet the mechanism of formation of *17* remains uncertain and must await further work.

EXPERIMENTAL

General. Melting points were taken on a microscope hot stage and are corrected. Optical rotations were observed

(18a) Rearrangement in any of these reactions is excluded by interrelation of the indoles from *14*, *16*, and *18*.

(18b) It has long been known that dimethylaniline hydrobromide on heating decomposes to these products even at 150°. W. Staedel, *Ber.*, **19**, 1947 (1886).

(19) Part of the difference is due to the difficulty of quantitative isolation of the quaternary ammonium perchlorate. The figure 8.07 was obtained by adding the *N*-methylaniline *p*-toluenesulfonamide isolated (7.93 mmoles) to the amount of 17 formed (0.64 mmole) and subtracting the amount of *N*-methylaniline present in the dimethylaniline (0.50 mmole).

(20) Δ^4-Cholesten-3-one reacts with boiling *N*-methylaniline to give a noncrystalline product whose ultraviolet and infrared spectra are consistent with formulation as (*24*, Br = H)—no carbonyl absorption, conjugated double bond, five adjacent hydrogens on a benzene ring, λ_{max} 248 and 294 mμ.

in chloroform solution in a 1-dm. tube with a Rudolf Model 18 polarimeter. Ultraviolet spectra were taken in 95% ethanol on a Cary Model 14 PM recording spectrophotometer. Infrared spectra were recorded with a Perkin-Elmer Model 137 Infracord spectrophotometer. Proton magnetic resonance spectra were determined in deuteriochloroform solution on a 60 mc. Varian HR-60 or A-60 spectrometer. Line positions are in δ units where $\delta = \Delta_{Me_4Si}$ in c.p.s./60 p.p.m. (tetramethylsilane = 0). Alumina for chromatography was Merck reagent grade; activity was determined by the method of Brockmann and Schodder.[21]

Reagents. (a) Cholestan-3-one (*21*), m.p. 129–131°, was prepared according to the directions of Bruce.[22]

(b) 2α,4α-Dibromocholestan-3-one (*1*) was prepared from cholestan-3-one by the procedure of Wilds and Djerassi.[23] From 30.4 g. of *21* was obtained 32 g. (75%) of the dibromo ketone, m.p. 187–191° dec. (reported,[23] m.p. 194–194.5° dec.); from 18.5 g. of *21* was obtained 13.0 g. (50%) of *1*, m.p. 191–193.5° dec.

(c) Cholestan-2-one (*12*), m.p. 130–131°, $[\alpha]^{23}D$ + 51° (*c*, 2.32) [reported,[24] m.p. 128–129°, $[\alpha]D$ +50° (chloroform)] was prepared in 68% yield by chromic acid oxidation of cholestan-2β-ol according to the procedure of Barton and Alt.[24] The 2β-ol was made by the sequence of reactions used by these authors.

(d) Coprostan-3-one (*14*) was prepared by atmospheric pressure hydrogenation of 2.000 g. of Δ^4-cholesten-3-one (*16*) in ethyl acetate solution with 200 mg. of 10% palladium-on-carbon catalyst. Chromatography on activity II alumina and recrystallization gave 50% of the ketone, m.p. 59.5–61.5° (reported,[25] m.p. 63°).

(e) Δ^4-Cholesten-3-one (*16*), m.p. 79.5–80.5° (reported,[26] m.p. 79.5–80.5°), was made by Oppenauer oxidation of cholesterol according to Eastham and Teranishi.[26]

(f) Δ^1-Cholesten-3-one (*18*) was prepared from 2α-bromocholestan-3-one (*6*) according to the semicarbazide procedure of Djerassi.[11] From 1.66 g. of *6* was obtained 35% of not quite pure conjugated ketone, m.p. 93–100°. A sample recrystallized from 95% ethanol had m.p. 99–100°, λ_{max} 232 mμ (ϵ 10,500) [(reported,[27] m.p. 98–100°, λ_{max} 231 mμ (log ϵ 3.99)].

(g) *N,N*-Dimethylaniline (Eastman, mono-free) was distilled under reduced pressure and tested by the procedure described below. It was found to contain 0.112% of *N*-methylaniline.

(h) *N*-Methylaniline was Eastman Kodak redistilled grade.

Reaction of 2α,4α-dibromocholestan-3-one with N,N-dimethylaniline. (a) A solution of 5.00 g. (9.20 mmoles) of 2α,4α-dibromocholestan-3-one, m.p. 187–191° dec., in 50 ml. of *N,N*-dimethylaniline was refluxed for 5 hr. under an atmosphere of nitrogen. The clear yellow solution turned blue within 10 min., became wine-red within 0.5 hr. and finally turned orange. A white solid formed in the condenser. The cooled reaction mixture was treated with 30 ml. of 10% sodium bicarbonate solution, and dimethylaniline was removed by steam distillation. The residue was taken up in 200 ml. of ether which was then washed with water, saturated sodium chloride solution, dried over magnesium sulfate, filtered, and evaporated almost to dryness. The thick amber sirup was chilled and scratched. There was obtained after filtration and washing with cold ether 439 mg. (0.93 mmole, 10%) of slightly yellow crystals, m.p. 209–210° dec. Three recrystallizations from chloroform–ethyl acetate gave long slightly yellow needles of *17*, m.p. 221–223° dec., $[\alpha]^{22}D$ −23° (*c*, 1.40), $[\alpha]^{24}D$ −24° (*c*, 2.16) (reported,[3] m.p. 230–232°). Removal of the trace of colored impurity by sublimation at 160° (<0.01 mm.) did not change the melting point.

Anal. Calcd. for $C_{34}H_{49}N$ (471.74): C, 86.56; H, 10.47; N, 2.97; (N)—CH_3, 3.18. Found: C, 86.57; H, 10.67; N, 2.90; (N)—CH_3, 3.88; mol. wt. (mass spectrometer[6]), 471.

Ultraviolet spectrum. λ_{max} 242 mμ (ϵ 24,000), 254 mμ (ϵ 22,000), 260 mμ (ϵ 21,000), 286 mμ (ϵ 7130), and 304 mμ (ϵ 5880).

Infrared spectrum. $\nu_{max}^{CS_2}$ 1650 cm.$^{-1}$ (w) (conjugated C=C) and 738 cm.$^{-1}$ (s) (four adjacent hydrogens on benzene ring).

Nuclear magnetic resonance spectrum. δ = 3.55 p.p.m. (3H, N—CH_3), 6.15 p.p.m. (1H, C=C—H), and 7.18–7.83 p.p.m. (4H, ArH).

The white solid in the condenser was dissolved in a few milliliters of water and made basic with potassium hydroxide. Dimethylaniline was removed by ether extraction. On addition of perchloric acid to the aqueous solution crystals precipitated. Four recrystallizations from 95% ethanol gave colorless needles of phenyltrimethylammonium perchlorate, m.p. 179–181°. On admixture with an authentic sample prepared as described below the melting point was 178–181°.

Anal. Calcd. for $C_9H_{14}NO_4Cl$ (235.66): C, 45.87; H, 5.97. Found: C, 45.91; H, 6.07.

An authentic specimen was prepared by treatment of *N,N*-dimethylaniline with methyl iodide. The resulting methiodide was dissolved in water and perchloric acid added to precipitate the quaternary perchlorate. Four recrystallizations from 95% ethanol gave long white needles, m.p. 179–181°.

(b) When the reaction of 5.00 g. of the dibromo ketone (*1*) with 50 ml. of *N,N*-dimethylaniline was carried out according to the procedure of Schwenk and Whitman[3] and the excess amine removed by hydrochloric acid, there was obtained 240 mg. (0.51 mmole, 5.5%) of *17*, m.p. 216°.

(c) In another reaction with 5.000 g. (9.20 mmoles) of 2α,4α-dibromocholestan-3-one carried out as described in (a) except that the reflux period was 2 hr. there was isolated 303 mg. (0.64 mmole, 7%) of crude *17*. From the acidified (nitric acid) aqueous steam distillation residue was precipitated 1.426 g. of silver bromide equivalent to 7.60 mmoles of bromide ion. The filtrate from separation of the silver bromide was concentrated at room temperature to *ca.* 20 ml., treated with excess solid sodium perchlorate, and chilled to precipitate 1.642 g. (7.00 mmoles) of phenyltrimethylammonium perchlorate, m.p. 171–181°.

The steam distillate was extracted with ether and the dried ethereal solution stirred (magnetic bar) with *p*-toluenesulfonyl chloride overnight. Dimethylaniline was removed from the ether solution by extraction with dilute hydrochloric acid. The excess *p*-toluenesulfonyl chloride was removed by stirring (magnetic bar) the ether solution with potassium hydroxide solution at room temperature until no odor of sulfonyl chloride remained. Evaporation of the water-washed and dried solution left 2.071 g. (7.93 mmoles) of *N*-methylaniline *p*-toluenesulfonamide, m.p. 92–95.5°. One recrystallization from 95% ethanol gave m.p. 94.5–96°. The mixture melting point with an authentic sample, m.p. 95–96.5°, was 94.5–95°.

(d) The pure compound *17* was insoluble in 10% aqueous hydrochloric acid. When anhydrous hydrogen chloride was passed into an ethereal solution of *17*, no precipitate formed.

A solution of *17* in acetic acid–ethanol solution gave no color on addition of a solution of diazotized *p*-nitroaniline in

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acetic acid. However, under these conditions *N,N*-dimethylaniline gave a deep wine-red color.

Hydrogenation of the $C_{34}H_{49}N$ compound. A solution of 191 mg. of the $C_{34}H_{49}N$ compound, m.p. 221–223°, in 6 ml. of reagent grade benzene was hydrogenated with 65 mg. of 10% palladium-on-carbon catalyst at atmospheric pressure and room temperature. The minimum amount of hydrogen absorbed was 8.8 ml. (77% of one equivalent). After filtration and evaporation of benzene there was obtained 185 mg. of crude product, $[\alpha]^{23}D$ +14.3° (*c*, 2.02). Recrystallization from ethyl acetate gave a first crop of 134 mg., m.p. 189–195.5°, and a second crop of 16 mg., m.p. 187–193.5° bringing the total yield of one isomer *20* to 150 mg. (78%). Further recrystallization of the first crop gave 122 mg. of colorless needles of *20*, m.p. 194–196°, $[\alpha]^{24}D$ −7.4° (*c*, 2.03).

Anal. Calcd. for $C_{34}H_{51}N$ (473.75): C, 86.19; H, 10.85. Found: C, 86.41; H, 10.79.

Ultraviolet spectrum. λ_{max} 232 mμ (ε 35,400), 287 mμ (ε 6650), and 294 mμ (ε 6400).

Infrared spectrum. $\nu_{max}^{CS_2}$ 737 cm.$^{-1}$ (s) (four adjacent hydrogens on benzene ring).

From the mother liquor of the second crop of crystals above was obtained 36 mg. of an oil which was dissolved in petroleum ether and passed through activity II alumina. The eluate was evaporated to give 20 mg. (11%) of crude *15* as a colorless glass, $[\alpha]^{24}D$ +121° (*c*, 2.05).

Ultraviolet spectrum. λ_{max} 232 mμ (ε 28,000), 286 mμ (ε 5570), and 294 mμ (ε 5600).

Infrared spectrum. $\nu_{max}^{CS_2}$ 732 (s) and 738 cm.$^{-1}$ (s) (one peak presumably from four adjacent hydrogens on a benzene ring).

A calculation based on the optical rotations of the crude product (double bond reduced completely) and the two pure reduction products indicates that 86% of the A/B *trans* 5α-isomer and 14% of the A/B *cis* 5β-isomer were formed.

General procedure for Fischer indole syntheses.[28] To a mixture of each ketone and α-methylphenylhydrazine in the molar ratio 1:3 was added an amount of polyphosphoric acid equal to twice the weight of ketone. The reaction mixture was then gradually heated over a period of 30 min. in an oil bath. After reaching the maximum temperature the reaction mixture was cooled, diluted with water, and extracted with ether. The ethereal solution was washed with water until the wash solution was neutral. The dried ether solution was evaporated to dryness and the product recrystallized.

Indole (13) from cholestan-2-one. From 1.11 g. (2.88 mmoles) of cholestan-2-one (*12*), m.p. 130–131°, and 1.20 g. (9.9 mmoles) of α-methylphenylhydrazine gradually heated with 2.46 g. of polyphosphoric acid to 216° was obtained 7.04 mg. (51%) of indole, m.p. 178–182°, which had been recrystallized once from ethyl acetate. Three more recrystallizations from the same solvent gave colorless plates of *13*, m.p. 183–185°, $[\alpha]^{23}D$ +71.0° (*c*, 2.24), $[\alpha]^{23}D$ +72.7° (*c*, 2.54). On admixture with the hydrogenation product of *17*, m.p. 194–196°, the melting point was depressed to 154–186°.

Anal. Calcd. for $C_{34}H_{51}N$ (473.75): C, 86.19; H, 10.85; N, 2.96. Found: C, 86.41; H, 10.90; N, 3.08.

Ultraviolet spectrum. λ_{max} 232 mμ (ε 38,000), 286 mμ (ε 7760) and 292 mμ (ε 7260).

Infrared spectrum. $\nu_{max}^{CS_2}$ 738 cm.$^{-1}$ (s) (four adjacent hydrogens on benzene ring).

Indole (22) from cholestan-3-one. From 644 mg. (1.67 mmoles) of cholestan-3-one (*21*), m.p. 129–130°, and 875 mg. (7.1 mmoles) of α-methylphenylhydrazine gradually heated with 1.85 g. of polyphosphoric acid to 210° was obtained 504 mg. (64%) of crude indole, m.p. 174–200°. Seven recrystallizations from chloroform–ethyl acetate gave 137 mg. (17%) of long white needles, m.p. 215–217°, $[\alpha]^{24}D$ +67.7° (*c*, 1.70).

Anal. Calcd. for $C_{34}H_{51}N$ (473.75): C, 86.19; H, 10.85. Found: C, 85.78; H, 10.95.

Ultraviolet spectrum. λ_{max} 232 mμ (ε 35,400), 284 mμ (ε 5830), and 293 mμ (ε 5630).

Infrared spectrum. $\nu_{max}^{CS_2}$ 738 cm.$^{-1}$ (s) (four adjacent hydrogens on benzene ring).

Indole (15) from coprostan-3-one. From 438 mg. (1.14 mmoles) of coprostan-3-one (*14*), m.p. 59.5–61.5°, and 450 mg. (3.7 mmoles) of α-methylphenylhydrazine gradually heated with 1.30 g. of polyphosphoric acid to 210° was obtained 554 mg. of non-crystalline product which was chromatographed on activity II alumina. Elution with benzene–petroleum ether (1:19) gave 329 mg. (61%) of crude crystalline indole *15* and then 25 mg. of crude conjugated indole (*17*) apparently formed from *15* by oxidation. Six recrystallizations from ethyl acetate–ethanol gave 86 mg. (15%) of colorless plates, m.p. 151–153°, $[\alpha]^{24}D$ +149° (*c*, 1.67).

Anal. Calcd. for $C_{34}H_{51}N$ (473.75): C, 86.19; H, 10.85. Found: C, 86.54; H, 11.00.

Ultraviolet spectrum. λ_{max} 233 mμ (ε 36,400), 286 mμ (ε 6360), and 294 mμ (ε 6260).

Infrared spectrum. $\nu_{max}^{CS_2}$ 732 cm.$^{-1}$ (s) and 738 cm.$^{-1}$ (s) (one peak presumably from four adjacent hydrogens on benzene ring).

Indole (17) from Δ⁴-cholesten-3-one. From 566 mg. (1.47 mmoles) of Δ⁴-cholesten-3-one (*16*), m.p. 78.5–79.5°, and 0.80 g. (6.5 mmoles) of α-methylphenylhydrazine gradually heated with 1.62 g. of polyphosphoric acid to 150° was obtained the crude indole which after four recrystallizations from ethyl acetate gave 80 mg. (11.5%) of slightly yellow needles of *17*, m.p. 221–223° dec., $[\alpha]^{24}D$ −22.4° (*c*, 2.01).

Anal. Calcd. for $C_{34}H_{49}N$ (471.74): C, 86.56; H, 10.47. Found: C, 86.14; H, 10.98.

Ultraviolet spectrum. λ_{max} 242 mμ (ε 23,620), 253 mμ (ε 21,590), 260 mμ (ε 20,800), 285 mμ (ε 6570), and 304 mμ (ε 5520).

Infrared spectrum. $\nu_{max}^{CS_2}$ 1655 cm.$^{-1}$ (w) (conjugated C=C), 738 cm.$^{-1}$ (s) (four adjacent hydrogens on benzene ring).

The mixture melting point with the compound isolated from the dimethylaniline-dibromocholestanone reaction was undepressed, 220–223° dec.

Indole (19) from Δ¹-cholesten-3-one. From 645 mg. (1.68 mmoles) of Δ¹-cholesten-3-one (*18*), m.p. 97–102°, and 0.93 g. (7.6 mmoles) of α-methylphenylhydrazine gradually heated with 1.89 g. of polyphosphoric acid to 180° was obtained 703 mg. of crude indole. Five recrystallizations from chloroform–ethyl acetate gave 160 mg. (28%) of white plates of *19*, m.p. 210–214°, $[\alpha]^{24}D$ +153° (*c*, 1.62).

Anal. Calcd. for $C_{34}H_{49}N$ (471.74): C, 86.56; H, 10.47. Found: C, 86.30; H, 10.72.

Ultraviolet spectrum. λ_{max} 247 mμ (ε 22,000) and 321 mμ (ε 10,300); $\lambda_{shoulder}$ 251 mμ (ε 21,000), 310 mμ (ε 8660), 338 mμ (ε 6960), and 352 mμ (ε 6100).

Infrared spectrum. $\nu_{max}^{CS_2}$ 728 cm.$^{-1}$ (m), 736 cm.$^{-1}$ (m), 744 cm.$^{-1}$ (m), and 765 cm.$^{-1}$ (m).

Hydrogenation of indole (19) from Δ¹-cholesten-3-one. A solution of 100 mg. (0.212 mmole) of the indole *19*, m.p. 208–214°, in 5 ml. of reagent grade benzene was reduced with 30 mg. of 10% palladium-on-carbon catalyst at atmospheric pressure and room temperature. The minimum amount of hydrogen absorbed was 4.5 ml. (72% of one equivalent). The solution was filtered and evaporated to leave 95 mg. of partially crystalline product. Recrystallization from chloroform–ethyl acetate gave 79 mg. (79%) of the indole *20*, m.p. 912–194°, $[\alpha]^{24}D$ −6.6° (*c*, 2.13). The melting point was unchanged after the second recrystallization. On admixture with the hydrogenation product of Schwenk's compound, m.p. 193–195°, the melting point, 193–196°, was not depressed.

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Anal. Calcd. for $C_{34}H_{51}N$ (473.75): C, 86.19; H, 10.85. Found: C, 85.86; H, 10.81.

Ultraviolet spectrum. λ_{max} 233 mμ (ε 35,000), 286 mμ (ε 6480), and 294 mμ (ε 6310).

Reaction of 2α-bromocholestan-3-one (6) with N-methylaniline. A solution of 300 mg. (0.645 mmole) of 2α-bromocholestan-3-one in 4 ml. of *N*-methylaniline was refluxed for 1 hr. under an atmosphere of nitrogen. The reaction mixture was diluted with ether and the excess amine removed by extraction with dilute hydrochloric acid. Evaporation of the dried ether layer left 295 mg. (97%) of colorless glass, λ_{max} 232 mμ (ε 25,300), 286 mμ (ε 5600), and 292 mμ (ε 5270), whose infrared spectrum had no carbonyl absorption. Four recrystallizations from ethyl acetate gave 112 mg. (37%) of colorless needles of *13*, m.p. 181–185°, $[\alpha]^{24}D$ +69.5° (*c* 2.36).

Ultraviolet spectrum. λ_{max} 232 mμ (ε 40,000), 286 mμ (ε 7300), and 293 mμ (ε 6800).

Infrared spectrum. $\nu_{max}^{CS_2}$ 738 cm.$^{-1}$ (s) (four adjacent hydrogens on benzene ring).

The mixture melting point with the *N*-methylindole (*13*) from cholestan-2-one was undepressed, m.p. 181–185°, but the mixture melting point with the indole *22* from cholestan-3-one was depressed to 145–179°.

Estimation of N-methylaniline in N,N-dimethylaniline. (a) A solution of 19.043 g. of the *N,N*-dimethylaniline used for dehydrobromination in 50 ml. of ether was stirred (magnetic bar) overnight with 1 g. of *p*-toluenesulfonyl chloride. Dimethylaniline was then removed by extraction with dilute hydrochloric acid; excess sulfonyl chloride was removed by stirring (magnetic bar) the ethereal solution with 10% potassium hydroxide solution. The dried ether solution was evaporated to leave 52.0 mg. of *N*-methylaniline *p*-toluenesulfonamide which corresponded to 0.112% of *N*-methylaniline contaminating the dimethylaniline.

(b) To prove that no hydrolysis of the sulfonamide was taking place 113 mg. of *N*-methylaniline *p*-toluenesulfonamide in 85 ml. of ether was stirred (magnetic bar) with 15 ml. of 10% potassium hydroxide solution for 22.5 hr. at room temperature. Evaporation of the washed and dried ether solution left 111.7 mg. (98.5% recovery) of starting material.

(c) To show that the reaction of *N*-methylaniline with *p*-toluenesulfonyl chloride was essentially complete, 9.390 g. of *N,N*-dimethylaniline containing 16.7 mg. of added *N*-methylaniline was treated as in (a). There was obtained 59.3 mg. (90%) of *p*-toluenesulfonamide. The total amount of *N*-methylaniline calculated to be present was (16.7) + (9.390 × 0.00112) = 27.2 mg. equivalent to 66.3 mg. of *p*-toluenesulfonamide.

Disproportionation of N,N-dimethylaniline hydrobromide. A solution of 480 mg. (2.38 mmoles) of anhydrous *N,N*-dimethylaniline hydrobromide and 37.8 mg. (2.10 mmoles) of water in 6.686 g. of *N,N*-dimethylaniline was refluxed under nitrogen for 1 hour. A white solid appeared in the condenser. The reaction mixture was distributed between ether and dilute sodium bicarbonate solution. From the aqueous layer was precipitated 361 mg. (1.53 mmoles, 64%) of phenyltrimethylammonium perchlorate by addition of sodium perchlorate. Recrystallization from water gave 305 mg., m.p. 179–181.5°. The ether layer was dried and allowed to react with *p*-toluenesulfonyl chloride as described in part (*a*) above. The yield of *N*-methylaniline *p*-toluenesulfonamide was 552 mg. After allowance for the *N*-methylaniline in the dimethylaniline (6.686 × 0.0011) the amide formed by disproportionation was 534 mg. (2.04 mmole, 86%). One recrystallization from 95% ethanol gave 499 mg., m.p. 95.5–96.5°, undepressed on admixture with an authentic specimen. When the same reaction was carried out without addition of water to the reaction mixture, the disproportionation still occurred.

Reaction of N-methylaniline with 2α,4α-dibromocholestan-3-one (1). A solution of 1.000 g. (2.60 mmoles) of *1* in 10 ml. of *N*-methylaniline was refluxed (oil bath 210°) under nitrogen for 2 hr. Excess amine was removed by steam distillation after addition of sodium bicarbonate. The residue was taken up in ether, washed with dilute hydrochloric acid, water, and saturated sodium chloride solution. Evaporation of the dried ether solution left 734 mg. of an amber colored glass, λ_{max} 231 and 289 mμ, with no more than *ca.* 6% of *17* present. The infrared spectrum had no carbonyl absorption but did have peaks corresponding both to four and five adjacent hydrogens on a benzene ring. No crystalline material could be obtained from the crude product. Chromatography on activity II alumina gave no fractions that could be crystallized. Furthermore, infrared spectra showed that the material containing four adjacent aromatic hydrogens had not been separated from that with five adjacent aromatic hydrogens.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Rearrangements of Certain α-Alkoxy-α-hydroperoxyacophenones. Alcoholysis of Acetic Benzoic Anhydride

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The decompositions of four different α-alkoxy-α-hydroperoxyacophenones in hot ethanol and methanol were studied. The decompositions were shown to occur by three different simultaneous routes, two of which (87%) apparently involve concerted rearrangement of the hydroperoxides with migration of the acyl group. Incidental to this was a study of the alcoholysis of acetic benzoic anhydride. The major nucleophilic attack occurred at the acetyl carbonyl group giving benzoic acid and acetates.

α-Alkoxy-α-hydroperoxyacophenones (I) are products obtained from ozonolysis of certain 1,2-dibenzoylalkenes[1,2] and phenylacetylenes.[3] Since, as shown in the accompanying paper,[3] it is not always possible to isolate these (I) from the phenyl-

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