(1 mm) in small round-bottomed flasks[2a,b] or inside the injection port of the gas chromatograph.[4] Relative yields of **3**, **4**, **5**, and **6** were determined by planimeter measurement of glpc peak areas and are reported in Scheme I. The yields of recovered **1α**, **1β**, **1γ**, and **1δ** relative to total methine were 23, 35, 98, and 96%, respectively, and their retention times were 19, 25, 25, and 26 min on the 10 ft × 0.25 in. Carbowax 20M column.[7] Under the same conditions, **3**, **4**, **5**, and **6** showed 18, 22, 20, and 19 min retention, respectively. Samples of **4** and **5** were purified by preparative gas chromatography.[7] Some spectral properties follow.

Methine **4**: ir (liquid film) 2950, 2850, 2775, 2750, 1460, 1380, 1260, 1040, 880, 845 cm^{-1}; $[\alpha]^{23}D$ +139° (*c* 0.2, $CHCl_3$); nmr[9] (neat) δ 4.8 (m, 2), 2.1 (s, 6), 2.0 (s, 2), 1.0 (d, 3, J = 6 Hz), and 0.7 (d, 3, J = 6 Hz). *Anal.* Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79. Found: C, 79.17; H, 12.82.

(9) The nmr spectra were obtained on a Varian A-60 spectrometer with tetramethylsilane as internal standard. The infrared spectra were determined with a Beckman IR-5a spectrometer.

5:[2a,b] ir (liquid film) 2950, 2850, 2775, 2750, 1650 (6.05 μ),[2b,4a] 1460, 1380, 1270, 1050, 1030, 885 (11.30 μ);[2b,4a] nmr (CCl_4) δ 4.7 (m, 2), 2.1 (s, 6), 1.65 (m, 3), 0.85 (d, 3, J = 6 Hz).[10]

Peaks from the mass spectra of **3**, **4**, **5**, and **6** are reported in Table II.

Registry No.—**1α**, 2065-32-9; **1β**, 2232-27-1; **1γ**, 23912-39-2; **1δ**, 2883-89-8; **2′α**, 23912-41-6; **2′γ**, 23912-42-7; **2′δ**, 23912-43-8; **3**, 23912-44-9; **4**, 23912-45-0; **5**, 23912-46-1; **6**, 23912-47-2.

Acknowledgment.—We thank Dr. E. L. Eliel for his advice and many helpful suggestions, and Dr. O. C. Dermer, who also read the manuscript. The partial support of the National Research Foundation through GB-5607 and the American Petroleum Institute through API Research Project 58A is gratefully acknowledged.

(10) We acknowledge a prior nmr determination by H. R. Juneja.

Bufadienolides. 1. Introduction and Base-Catalyzed Condensation of Methyl Ketones with Glyoxylic Acid[1]

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Introduction to a series of contributions pertaining to syntheses of isocardenolides, cardenolides, isobufadienolides, and bufadienolides is presented. A comprehensive study of an aldol condensation between glyoxylic acid and various methyl ketones is described. At high hydroxyl ion concentration, methyl β-naphthyl ketone gives bis(β-naphthacyl)acetic acid (**11a**), but by careful control of pH the condensation can be directed to yield the γ-ketoacrylic acid **16a** and/or a mixture of α-hydroxy-γ-oxobutyric acid (**15a**) and α-methoxy-γ-oxobutyric acid (**17a**). The reaction is applied to methyl cyclopentyl ketone, 2,5-dimethoxyacetophenone, 2,4-dimethylacetophenone, pinonic acid (**18**), and the steroidal ketones, 3β-hydroxy-20-oxo-5-pregnene (**7a**) and 3β-hydroxy-20-oxo-5α-pregnane (**24a**).

Ch'an su, the dried venom of a common Chinese toad, and extracts of the Mediterranean plant *Scilla maritima* (white squill) have received varied application in primitive medical practice for at least several millennia. The latter has been used from *ca.* 3500 B.C.[3] in the form of active glycoside extracts, principally for its diuretic and heart effects, but by the middle ages applications of the drug had gradually subsided. The heart effects were rediscovered in the early 18th century, but, with introduction of digitalis glycosides about 1785,[4] the plant was again gradually abandoned. The pioneering chemical investigations of Stoll[5] with the squill glycosides and Wieland[6] with extracts from the European toad *Bufo vulgaris* led, respectively, to structures for scillaren A,[7] bufotalin[8] (**1a**), and bufalin[9] (**1b**). The aglycones proved to be steroids bearing an α-pyrone ring at position 17 (*cf.* **1a**).[10,11]

Characteristic chemical and physiological[12] features of the plant and toad steroidal α-pyrones appear in bufalin (**1b**). In 1957, when the present study was initiated, neither bufalin nor any naturally occurring bufadienolide had yielded to total synthesis, and indeed no method was available for preparing even simpler 5-substituted 2-pyrones, such as **3**. Since then a preliminary account of the synthesis of a steroidal α-pyrone of the bufadienolide type has been reported,[13] and recently Sondheimer described a synthesis of

(1) Steroids and Related Natural Products. XLVIII. For the preceding contribution, see J. C. Knight and G. R. Pettit, *Phytochemistry*, **8**, 477 (1969). This investigation was supported by Public Health Service Research Grants CY-4074 (C3) to CA-04074-06 and CA-10115-01 to CA-10115-02 from the National Cancer Institute, and is based, in part, on the Ph.D. dissertation submitted in June 1962 by G. L. Dunn to the University of Maine.

(2) To whom correspondence should be addressed.

(3) F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworth and Co. Ltd., 1963.

(4) A. Stoll, *Chem. Ind.* (London), 1558 (1959).

(5) A. Stoll, E. Suter, W. Kreis, B. B. Bussemaker, and A. Hofmann, *Helv. Chim. Acta*, **16**, 703 (1933).

(6) H. Wieland and F. J. Weil, *Chem. Ber.*, **46**, 3315 (1913).

(7) A. Stoll and J. Renz, *Helv. Chim. Acta*, **24**, 1380 (1941).

(8) For leading references, see K. Meyer, *ibid.*, **32**, 1993 (1949).

(9) Isolation and structural determination of bufalin was reported by K. Kuwada [*J. Chem. Soc. Jap.*, **60**, 335 (1939); *Chem. Abstr.*, **34**, 1031 (1940)] and was confirmed by K. Meyer [*Helv. Chim. Acta*, **32**, 1238 (1949)].

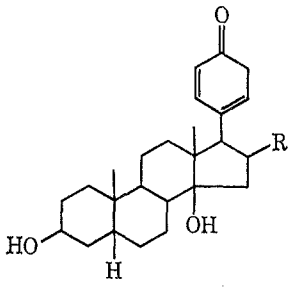
(10) In the case of hellebrigenin, the same aglycone has been found in both a plant extract and toad venom. For this and other interesting facets of bufadienolide chemistry, see ref 3 and other reviews cited therein.

(11) Subsequent extensive studies of Ch'an su, particularly by K. Meyer and colleagues, has led to location and identification of a number of related bufadienolides in this material, the most recent being 19-oxocinobufagin and 19-oxocinobufotalin: K. Meyer, *ibid.*, **52**, 1097 (1969).

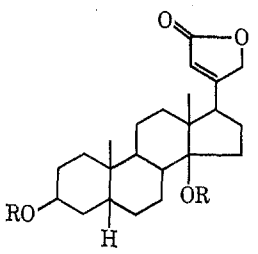
(12) The cardiac action of bufalin has been found almost equal to that of digitoxigenin (**2**) and in respect to local anesthetic potency on the rabbit cornea, *ca.* 90 times that of cocaine; see M. Okada, F. Sakai, and T. Suga, *Itsuu Kenkyusho Nempo*, **67**, 75 (1960); *Chem. Abstr.*, **55**, 16798 (1961). The bufadienolides generally display digitalis-like activity; *e.g.*, see K. K. Chen and A. Kovařikova, *J. Pharm. Sci.*, **56**, 1535 (1967); H. Murase, *Jap. J. Pharmacol.*, **15**, 72 (1965); *Chem. Abstr.*, **63**, 7517 (1965); W. Foerster, *Acta Biol. Med. Ger.*, **9**, 341 (1962); *Chem. Abstr.*, **58**, 11846 (1963).

(13) D. Bertin, L. Nedelec, and J. Mathieu, *Compt. Rend.*, **253**, 1219 (1961).

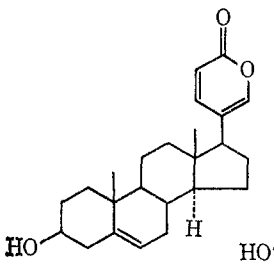
bufalin and resibufogenin.[14] With the objective of making bufadienolides more readily available for biological evaluation,[15] we decided to develop a practical synthesis of bufadienolides (*cf.* **3**) and complete a total synthesis of bufalin (**1b**). For reasons already apparent, the bufadienolide intermediates were also to be employed whenever appropriate for construction of cardenolide-type[4,16] lactones.



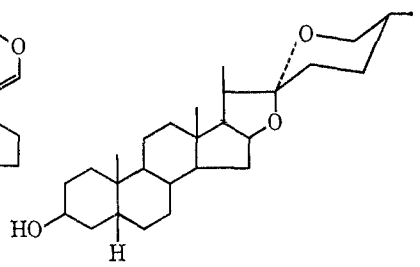
1a, R = $COOCH_3$
b, R = H



2



3



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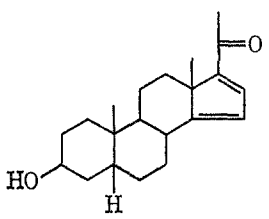

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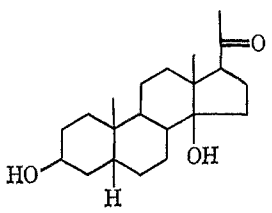

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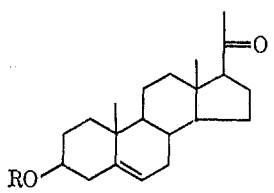
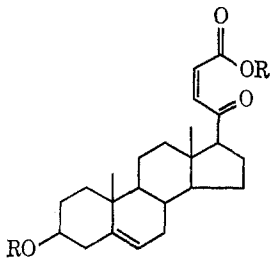


7a, R = H
b, R = $COCH_3$
c, R = $(C_6H_5)_3C$
d, R = CH_3OCH_2
e, R =



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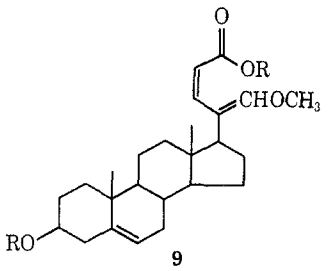


9

As originally conceived, smilagenin (**4**) was to serve as relay for obtaining diene **5** (alternatively prepared by a total synthetic sequence) and then 20-oxopregnane **6**. Simultaneously, pregnenolone (**7a**) was to be used to develop a general synthesis of bufadienolides which could be applied to bufalin intermediate **6**. Degradation of smilagenin to diene **5** was readily accomplished,[17] and, with completion of a total synthetic route to the steroidal sapogenins by Sondheimer and colleagues, formal total synthesis in turn of diene **5** was at hand. Experiments in progress to convert diene **5** into 14β alcohol **6** were discontinued when the Meister[18] and Sondheimer[19] synthesis of digitoxigenin (**2**) presented the possibility of using the glycoside digitoxin as a starting point for total synthesis of bufalin. Meanwhile, transformation of pregnenolone to γ-ketoacrylic acid **8** was being explored as summarized below, with the object of entering ketone **8** in a Wittig reaction leading to vinyl ether **9**, as noted in part 4.[20] An acidification sequence was then expected to provide the corresponding α-pyrone. Before a satisfactory procedure was uncovered for obtaining **9**, the isobufadienolide and bufadienolide syntheses described in parts 6 and 7 were completed.[21] Reduction of ketone **8** to isocardanolide and isocardenolide systems did proceed as planned and culminated in the lactone syntheses described in parts 2 and 3.[22]

The pressing requirement for an efficient route to 20-oxo-21-nor-22-cholenic acids suggested the exploration of an aldol condensation between methyl ketones and glyoxylic acid, despite the fact that no practical one-step conversion of this type had been reported. Shortly afterward, Newman[23] described the base-catalyzed condensation of a glyoxylate with the cyclic ketone α-tetralone to give an analogous product.[24] Later, Noltes and Kögl[25] found that heating the diethyl

(14) F. Sondheimer, W. McCrae, and W. J. Salmond, *J. Amer. Chem. Soc.*, **91**, 1228 (1969). A review of 2-pyrone syntheses has been prepared: N. P. Shusherina, N. D. Dmitrieva, E. A. Luk'yanets, and R. Y. Levina, *Russ. Chem. Rev.*, **36**, 175 (1967).

(15) Our interest in 1957 was strongly motivated by reports that certain α,β-unsaturated lactones inhibit cell growth: L. J. Haynes, *Quart. Rev.* (London), **2**, 46 (1948). Since then, antitumor properties have been attributed to cardenolides [S. M. Kupchan, M. Mokotoff, R. S. Sandhu, and L. E. Hokin, *J. Med. Chem.*, **10**, 1025 (1967)], bufadienolides [S. M. Kupchan, R. J. Hemingway, and J. C. Hemingway, *Tetrahedron Lett.*, 149 (1968)], and other lactones [S. M. Kupchan, R. W. Doskotch, P. Bollinger, A. T. McPhail, G. A. Sim, and J. A. Saenz Renauld, *J. Amer. Chem. Soc.*, **87**, 5805 (1965); J. E. Pike, J. E. Grady, J. S. Evans, and C. G. Smith, *J. Med. Chem.*, **7**, 348 (1964)].

(16) T. Reichstein, *Naturwissenschaften*, **54**, 53 (1967).

(17) G. R. Pettit and D. M. Piatak, *Can. J. Chem.*, **44**, 844 (1966). Results of an analogous study have recently been reported: G. Bach, J. Capitaine, and C. R. Engel, *ibid.*, **46**, 733 (1968); R. Bouchard and R. Engel, *ibid.*, **46**, 2201 (1968).

(18) P. D. Meister and H. C. Murray, U. S. Patent 2,968,596 (1961); *Chem. Abstr.*, **55**, 11,466 (1961).

(19) N. Danieli, Y. Mazur, and F. Sondheimer, *Tetrahedron*, **22**, 3189 (1966).

(20) G. R. Pettit, B. Green, G. L. Dunn, and P. Sunder-Plassmann, *J. Org. Chem.*, **35**, 1385 (1970).

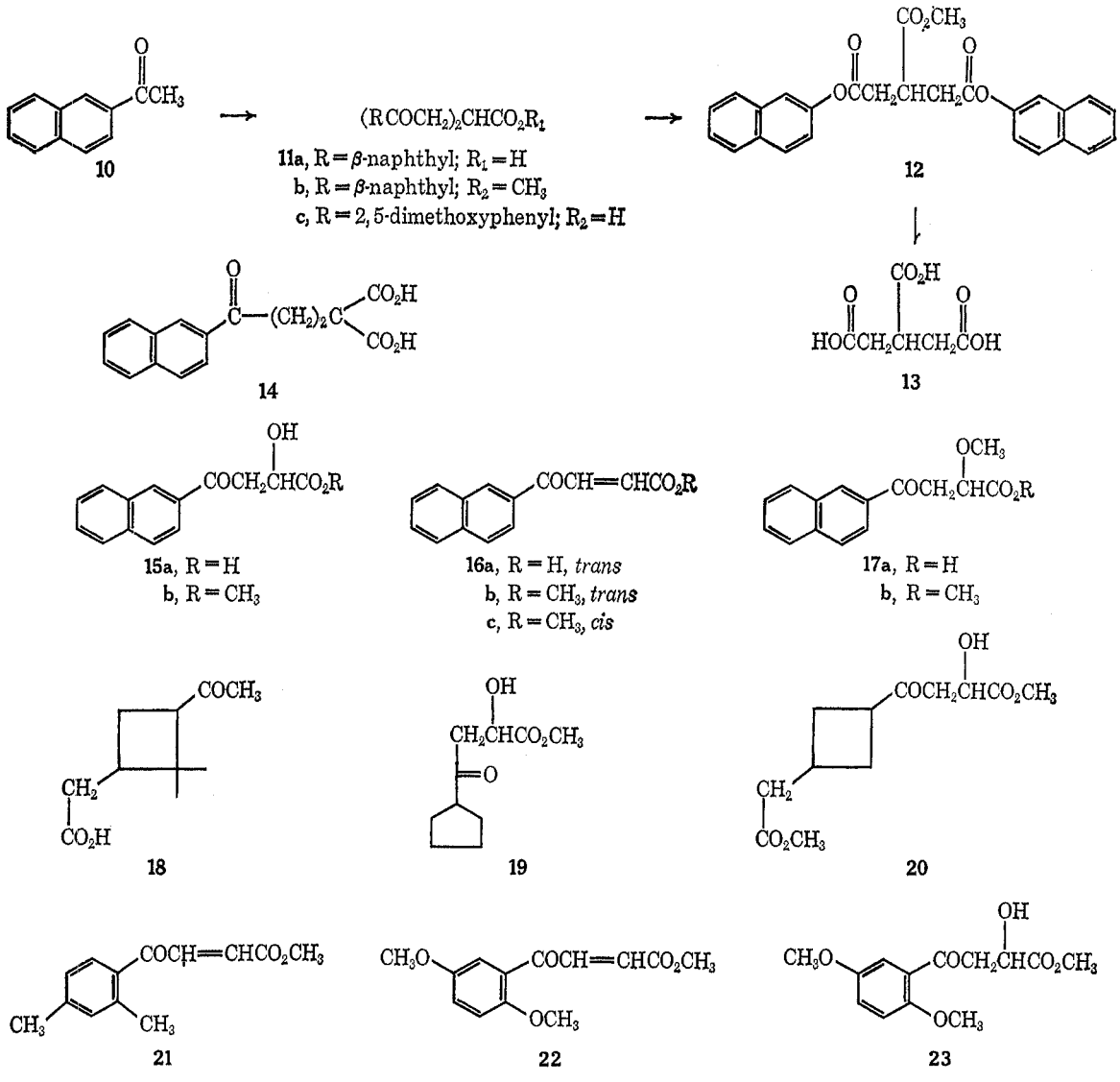
(21) (a) G. R. Pettit, J. C. Knight, and C. L. Herald, *ibid.*, **35**, 1393 (1970); (b) G. R. Pettit, D. Fessler, K. Paull, P. Hofer, and J. C. Knight, *ibid.*, **35**, 1398 (1970).

(22) (a) G. R. Pettit, B. Green, and G. L. Dunn, *ibid.*, **35**, 1377 (1970); (b) G. R. Pettit, B. Green, A. K. Das Gupta, P. A. Whitehouse, and J. P. Yardley, *ibid.*, **35**, 1381 (1970).

(23) M. S. Newman, W. C. Sagar, and C. C. Cochrane, *ibid.*, **23**, 1832 (1958).

(24) A study of the condensation of aqueous glyoxylic acid with 17-oxo-androstanes has been made: P. Kurath and W. Cole, *ibid.*, **26**, 1939 (1961). We wish to thank Dr. Kurath for allowing us to review this manuscript prior to publication.

(25) A. W. Noltes and F. Kögl, *Rec. Trav. Chim. Pays-Bas*, **80**, 1334 (1961); see also P. Kurath and W. Cole, *J. Org. Chem.*, **26**, 4592 (1961).



acetal of ethyl glyoxylate with a variety of ketones yielded α-hydroxy-γ-oxobutyric acid esters which could be dehydrated to the corresponding acrylic acids. Early attempts to condense glyoxylic acid with methyl ketones of the acetophenone type had yielded, instead of acrylic acid derivatives, bis(phenacyl)acetic acids,[26] presumably by Michael condensation of the initially formed acrylic acid with a second molecule of methyl ketone.

To determine whether a normal aldol condensation could occur, a number of reactions utilizing methyl β-naphthyl ketone[27] and glyoxylic acid or a glyoxylate were evaluated. Prior to appearance of the Newman procedure,[23] glyoxylic acid and aqueous solutions of the acid were prepared by treating barium glyoxylate with sulfuric acid. Concurrently, the more readily characterizable butyl glyoxylate (from lead tetraacetate cleavage of di-*n*-butyl tartrate) was also employed. Among a variety of acid-[28] and base-catalyzed[29] aldol conditions studied, only those reactions employing butyl glyoxylate and methyl β-naphthyl ketone, in ethyl alcohol containing 10% aqueous sodium hydroxide, gave reasonable amounts of acidic condensation products. The colorless carboxylic acid $C_{26}H_{20}O_4$ obtained was the product (**11a**) arising from Michael addition[26] of ketone **10** to the initially formed γ-ketoacrylic acid, and conclusive evidence for the bis(β-naphthacyl)acetic acid structure was obtained as follows. Acid **11a** was methylated with diazomethane and ester **11b** was treated with peroxytrifluoroacetic acid.[30] The resulting triester **12** was saponified and, following acidification, both β-naphthol and tricarballylic acid (**13**) were isolated. Assignment **11a** was further supported by an unequivocal synthesis in which diethyl malonate was condensed with ω-bromo-2-acetonaphthone and the product was saponified to provide the disubstituted malonic acid **14**, which on partial decarboxylation gave acetic acid derivative **11a**.[31]

Repeating the aldol route to acid **11a** in aqueous tetrahydrofuran–methanol at pH 14 using glyoxylic acid prepared[28] *in situ* from tartaric acid afforded bis(β-

(26) M. J. Bougault, *Compt. Rend.*, **148**, 1270 (1909).

(27) Structure of the acrylic acid **16** which would be obtained from this ketone was firmly established: G. Baddeley, G. Holt, S. M. Maker, and M. G. Ivinson, *J. Chem. Soc.*, 3605 (1952); M. Goldman and E. I. Becker, *Nature*, **170**, 35 (1952); *Chem. Abstr.*, **48**, 116 (1954).

(28) Z. Csuros, J. Petro, and P. Konig, *Acta Chim. Acad. Sci. Hung.*, **17**, 419 (1958); *Chem. Abstr.*, **53**, 17,053 (1959).

(29) For a comprehensive review of the aldol condensation, see A. T. Nielsen and W. J. Houlihan, *Org. React.*, **16**, 1 (1968).

(30) W. D. Emmons and G. D. Lucas, *J. Amer. Chem. Soc.*, **77**, 2287 (1955).

(31) An analogous sequence has been used to prepare bis(phenacyl)-acetic acid: W. Kues and C. Paal, *Chem. Ber.*, **19**, 3144 (1886).

naphthacyl)acetic acid in 65% yield. Under these strongly alkaline conditions, 2,5-dimethoxyacetophenone was easily transformed into acetic acid derivative **11c**. Application of conditions similar to those of Newman,[23] *i.e.*, lower pH, gave α-hydroxy-β-(2-naphthoyl)propionic acid (**15a**, 23%) accompanied by a lesser quantity of β-(2-naphthoyl)acrylic acid (**16a**). Heating the α-hydroxy acid in acetic anhydride with potassium hydrogen sulfate[25] gave acrylic acid **16a** in 33% yield.

Meanwhile, attempts were being made to condense aqueous glyoxylic acid obtained by the Newman method[23] with methyl ketones of the 20-oxopregnane type at various pH levels as noted below, and values (pH meter) of 13.25–13.65 were found most useful in effecting only the aldol condensation and avoiding further reaction to disubstituted acetic acids. Best conversion into acidic products was obtained at pH 13.65 (meter) in tetrahydrofuran–methanol containing 8% aqueous potassium hydroxide for 3 days at room temperature. By this means ketone **10** was transformed in up to 90% conversion into a mixture of three acids, which were esterified and separated by chromatography to give methyl esters **16b** (17%), **17b** (57%), and **15b** (10%). The unexpected ester **17b** exhibited strong infrared absorption at 1130 cm^{-1} characteristic of the carbon–oxygen bond in aliphatic ethers[32] and was deduced to be the product of addition of methanol to acrylic acid **16a**. Elemental analyses gave further support, and alternate preparation by methylation of α-hydroxy ester **15b** using diazomethane–boron trifluoride provided the necessary confirmation.[33]

Extension of the aldol condensation with glyoxylic acid to methyl cyclopentyl ketone and pinonic acid (**18**) gave comparable results, but only the α-hydroxy esters were characterized. Following methylation (diazomethane), the acid(s) from methyl cyclopentyl ketone and pinonic acid yielded α-hydroxy esters **19** (52%) and **20** (72%), respectively, as oils.

The principle objective, efficient conversion of ketone **10** into acrylic acid **16a**, was eventually achieved by allowing the aldol condensation to proceed for 12 hr at reflux temperature. The acidic products obtained in this way from β-naphthyl ketone, 2,4-dimethylacetophenone, and 2,5-dimethoxyacetophenone were methylated to furnish acrylates **16b**, **21**, and **22** in yields of 56–59%. The relative proportions of both aldol intermediates and methanol addition products were considerably smaller, as shown by careful investigation of the products from 2,5-dimethoxyacetophenone, which led to isolation of methyl α-hydroxy-β-(2,5-dimethoxybenzoyl)propionate (**23**) in 9% yield. Thin layer chromatography indicated the presence of a very small amount of the α-methoxy ester.

Shortly after the glyoxylic acid reaction with methyl ketones had reached a practical state of development, Bestmann reported[34] a valuable synthesis of γ-keto acrylic acids based on the condensation of an α-bromo ketone with carbomethoxymethylenetriphenylphosphorane. Application of this reaction to ω-bromo-2-acetonaphthone gave *trans*-methyl acrylate **16b** in 38% conversion. Irradiation of a solution of this yellow[35] product gave the colorless *cis* isomer **16c**. Side-chain olefin protons of the yellow isomer exhibited a coupling constant of 15 cps whereas the colorless isomer gave in the same region $J = 11$ cps, consistent with the assigned configurations.[36] While this general study of aldol-type reactions involving methyl ketones and glyoxylic acid was being undertaken, the model experiments now summarized were also being conducted.

Aldol condensation between benzaldehyde and 20-oxopregnenes using, *e.g.*, sodium methoxide in methanol, follows the predicted course and presents no problem.[37] However, a considerable number of experiments directed at condensing butyl glyoxylate or glyoxylic acid with 20-oxopregnanes **24a** or **7a** were quite unrewarding, leading in most cases to almost complete recovery of starting material. When the more general study of methyl ketones began to focus on aqueous glyoxylic acid prepared from tartaric acid,[23,24] it was decided to apply this method to suitable 5α- and Δ^5-20-oxopregnanes, which were chosen as models for the less readily available 3β-hydroxy-20-oxo-5β-pregnanes. It was originally deemed advisable to protect the 3β-hydroxyl group with a base-stable, acid-labile group, and those evaluated will now be discussed.

Triphenylmethyl chloride in pyridine solution generally favors reaction with a primary alcohol, but substitution of triphenylmethyl bromide can provide, in the case of secondary alcohols, greater than 80% yields of trityl ethers.[38] Modification (24-hr reaction period) of the Stegerhock procedure[38] with secondary alcohol **24a** and triphenylmethyl bromide gave reasonable conversion (53%) into ether[39] **24c**. Similarly, trityl ethers **7c** and **25b** were obtained in comparable yields, but low solubility of the trityl ethers in water–methanol–tetrahydrofuran mixtures caused rejection of this protecting group. In the expectation of a solubility increase in such protic solvent mixtures for a methoxymethyl ether,[40] a specimen of **7d** was obtained (18% yield) by treating pregnenolone (**7a**) with chloromethyl ether in the presence of silver oxide.[41] The

(32) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1958.

(33) Alcohol **15a** may represent that portion of the aldol intermediate which did not undergo dehydration, although addition of water to the α,β-unsaturated carbonyl system after dehydration would still be expected to give the α- rather than the β-hydroxy acid. Hydrolysis of methyl β-(*p*-bromobenzoyl)crotonate in hot aqueous methanolic potassium hydroxide solution has been shown to yield α-hydroxy-β-(*p*-bromobenzoyl)butyric acid: W. Koenigs and E. Wagstaffe, *Chem. Ber.*, **26**, 554 (1893). Later experiments of a similar nature with methanol gave comparable results. See, *e.g.*, E. R. H. Jones, T. Y. Shen, and M. C. Whiting, *J. Chem. Soc.*, 236 (1950).

(34) H. J. Bestmann and H. Schulz, *Angew. Chem.*, **73**, 620 (1961). Experimental details of the reaction were kindly provided by Professor Bestmann prior to publication. Later a full report and review of this useful reaction were made available: H. J. Bestmann, *Angew. Chem. Int. Ed. Engl.*, **4**, 583 (1965).

(35) Previous study of *cis–trans* isomers in β-aroylacrylic acids suggested that the yellow geometrical isomer of acid **7a** could be assigned the *trans* configuration. For a pertinent summary, refer to ref 27 (M. Goldman, *et al.*).

(36) A preliminary account of these stereochemical assignments has been summarized: G. R. Pettit, B. Green, A. K. Das Gupta, and G. L. Dunn, *Experientia*, **20**, 248 (1964).

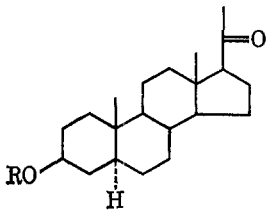
(37) I. Dory and G. Lanyi, *Acta Chim. Acad. Sci. Hung.*, **30**, 71 (1962); *Chem. Abstr.*, **58**, 564 (1963).

(38) L. J. Stegerhock and P. E. Verkade, *Rec. Trav. Chim. Pays-Bas*, **75**, 143 (1956).

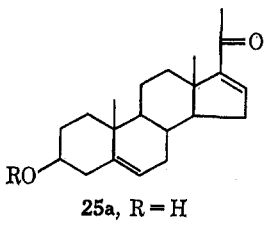
(39) For a related example, see. H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann, and R. Robinson, *J. Chem. Soc.*, 361 (1953).

(40) R. Stern, J. English, Jr., and H. G. Cassidy, *J. Amer. Chem. Soc.*, **79**, 5797 (1957). A steroid 11-methoxymethyl ether has been prepared using formaldehyde, methanol, and hydrochloric acid: R. E. Beyler, F. Hoffman, R. M. Moriarty, and L. H. Sarett, *J. Org. Chem.*, **26**, 2421 (1961).

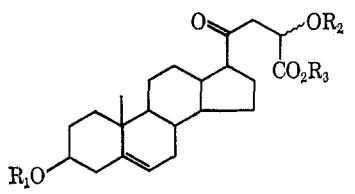
(41) G. R. Pettit and T. R. Kasturi, *ibid.*, **26**, 4553 (1961).



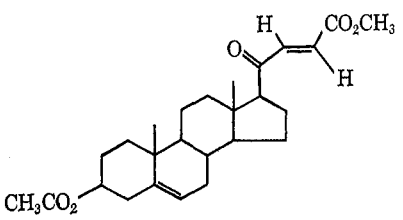
24a, R = H
b, R = $COCH_3$
c, R = $(C_6H_5)_3C$
d, R = 



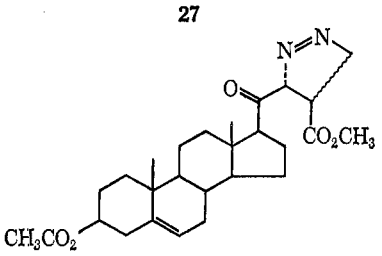
25a, R = H
b, R = $(C_6H_5)_3C$



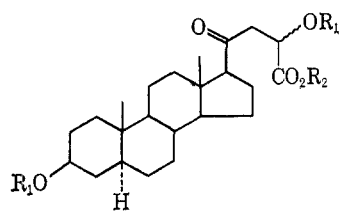
26a, $R_1 = COCH_3$; $R_2 = R_3 = CH_3$
b, $R_1 = R_2 = H$; $R_3 = CH_3$
c, $R_1 = R_2 = COCH_3$; $R_3 = CH_3$
d, $R_1 = R_2 =$  ; $R_3 = CH_3$



27



28



29a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = COCH_3$; $R_2 = CH_3$

solubility of ether **7d** and the more efficiently prepared tetrahydropyranyl ethers **24d** and **7e** proved quite favorable, but protecting-group studies were discontinued when use of blocked alcohols in the aldol reactions proved unnecessary.

Meanwhile, effects of potassium hydroxide concentration on the total yield of acidic material from reaction between pregnenolone and aqueous glyoxylic acid at various pH levels were being evaluated. The yield of acidic products increased substantially from 25% at a pH reading of 13.25 to 45% at 13.48 to 81% at 13.65. The procedure involved adding 8% aqueous potassium hydroxide to a solution composed of methanol, tetrahydrofuran, pregnenolone, glyoxylic acid, and water until the required pH scale reading was reached. The acidic product from a reaction at pH 13.48 was methylated with diazomethane and the crude mixture of methyl esters was separated by chromatography. A fraction eluted by benzene–chloroform was acetylated and rechromatographed to give methyl 3β-acetoxy-23-methoxy-20-oxo-21-nor-5-cholenate (**26a**, 20%), presumably arising by a Michael-type addition of methanol to the aldol condensation product. In addition to elemental composition and spectral data, the structure of ether **26a** was assigned using evidence already reviewed for the analogous product obtained from methyl β-naphthyl ketone.

A fraction eluted with chloroform gave methyl 3β-23-dihydroxy-20-oxo-21-nor-5-cholenate (**26b**, 30%), which was converted into both diacetate **26c** and bistetrahydropyranyl ether **26d**. Formation of these derivatives, combined with information already compiled for the aldol intermediate from methyl β-naphthyl ketone, provided structural evidence for diol **26b**.

The aldol reaction with pregnenolone and glyoxylic acid was repeated at a pH meter reading of 13.65 (optimal base concentration) and studied with respect to time and temperature. After 28 hr at room temperature, the acidic product was isolated, methylated, acetylated, and purified by column chromatography to give methyl 3β-acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (**27**),[42] methyl ether **26a**, diacetate **26c**, and an oily substance tentatively assigned pyrazoline structure **28** (formed by a 1,3-dipolar cycloaddition of diazomethane to the α,β-unsaturated ketone system).[43] Yields of the first three compounds amounted to, respectively, 5, 11, and 15%.

Extending the condensation to 72 hr increased the total yield of acidic products from 52 to 72%, and, following methylation, acetylation, and purification, olefin **27**, methyl ether **26a**, and diacetate **26c** were obtained in 8, 14, and 19% conversion, respectively. Adjusted for recovered pregnenolone, the respective yields were 15, 18, and 25% accompanied by 6% of the crude pyrazoline. It is apparent that increasing the reaction time increased the total yield of acidic products, but did not markedly affect the proportion of each constituent. Application of this procedure to 3β-acetoxy-20-oxo-5α-pregnane (**24b**) led to 3β,23-dihydroxy-20-oxo-21-nor-5α-cholanic acid (**29a**) as major product, whose structure was confirmed by preparation of the methyl ester (**29b**) and diacetate (**29c**) derivatives; no attempt was made to characterize the minor reaction constituents, which were presumably analogous to those obtained from ketone **7a**. Some indication of the necessity of controlling the base concentration was obtained by treating alcohol **29b** with 5% potassium hydroxide in methanol for a 2-hr period at reflux, at which time *ca.* 25% of the alcohol had undergone reverse aldol condensation.

(42) Evidence for the structure and stereochemistry of olefin **5** has been summarized in a preliminary communication: G. R. Pettit, B. Green, A. K. Das Gupta, and G. L. Dunn, *Experientia*, **20**, 248 (1964). A more complete summary is presented in part III.[22b]

(43) Similar reaction products have been investigated: See E. R. H. Jones, *et al.*, ref 33.

The parallel survey of reactions between glyoxylic acid and methyl β-naphthyl ketone by this time had shown that heating the aldol reaction mixture at reflux would increase acrylic acid formation. When pregnenolone was analogously condensed with glyoxylic acid, followed by methylation and acetylation, the yield of methyl ether **26a** and diacetate **26c** fell to, respectively, 1 and 8%. Substituting dimethoxypropane[44] for diazomethane in the methylation step allowed isolation of olefin **27** in *ca.* 20% yield.

Upon reaching this more promising stage for synthesis of γ-keto acrylic acid **27** by an aldol sequence, we were able to meet requirements for this compound by application of the then newly discovered Bestmann reaction.[34] However, the carefully defined experimental conditions reported herein for condensing glyoxylic acid with methyl ketones should prove of value where the α-halo ketone required for the Bestmann procedure cannot easily be obtained or where an aldol intermediate such as diol **29a** is required.

Experimental Section

Ligroin refers to a fraction boiling at 65–70°. Benzene and dihydropyran were redistilled from sodium; pyridine was redistilled from potassium hydroxide. Solvent extracts of aqueous solutions were dried over anhydrous sodium sulfate or magnesium sulfate. Acetylation reactions were conducted using 1:1 acetic anhydride–pyridine at room temperature for 14–20-hr periods. The basic (Alcoa grade F-20), neutral (E. Merck, Darmstadt), and acid-washed (Merck, Rahway, N. J.) aluminas were used as supplied. Melting points reported for analytical specimens were observed using a Kofler melting point apparatus. All other melting points were determined in open capillaries in a silicone oil bath and are uncorrected. The thin layer chromatograms were prepared on silica gel G (developed with concentrated sulfuric acid) or silica gel HF_{254} (both from E. Merck). All analytical specimens were checked for purity by thin layer chromatography. A Beckman zeromatic pH meter equipped with a Beckmann E-2 glass electrode and a calomel reference electrode was used for pH measurements.

Ultraviolet, infrared (potassium bromide pellets unless noted differently), and nuclear magnetic resonance (Varian A-60 spectrometer) spectra were recorded by Dr. R. A. Hill, University of Maine. The nuclear magnetic resonance data are expressed in parts per million (δ) downfield from tetramethylsilane. The microanalyses were provided by Dr. A. Bernhardt, Max Planck Institute, Mülheim, Germany, and by the laboratory of Dr. C. Janssen, Beerse, Belgium. Optical rotation measurements (chloroform solution) were provided by Dr. Weiler and Dr. Strauss, Oxford, England.

Glyoxylic Acid.—Unless otherwise stated, glyoxylic acid was prepared in the following manner and used immediately without further purification or isolation. To a cooled solution of tartaric acid (5.7 g, 0.038 mol) in water (9 ml) at 0° was added a solution of paraperiodic acid (8.6 g, 0.038 mol) in water (18 ml). Before this glyoxylic acid solution was used, the cleavage reaction was allowed to proceed for 12 min.

Bis(β-naphthacyl)acetic acid (11a). Method A.—To a solution of methyl β-naphtyl ketone (**10**, 2 g, 0.012 mol) in ethyl alcohol (10 ml, 95%) was added *n*-butyl glyoxylate[45] (2 g, 0.015 mol) followed by aqueous sodium hydroxide (10%, 16 ml, 0.04 mol). The mixture was heated for 6 hr at 65–70°, cooled, diluted to 100 ml with water, and extracted with diethyl ether. Acidification of the aqueous layer gave a pale yellow solid, mp 195–198°. Recrystallization from dioxane–water gave colorless plates (1.5 g, 63%), mp 198–199°. Three crystallizations from dioxane–water afforded the analytical specimen: mp 199–200°; ν_{max} 3400–2600 (carboxylic acid), 1700 (carboxyl group), and 1685 cm^{-1} (ketones).

Anal. Calcd for $C_{26}H_{20}O_4$ (mol wt, 396): C, 78.79; H, 5.10. Found: C, 78.23; H, 5.29; neut equiv, 374, 385.

Method B.—A rapidly stirred solution of methyl β-naphthyl ketone (**10**, 3.4 g, 0.02 mol) in tetrahydrofuran (35 ml)–methanol (50 ml) was treated successively with aqueous potassium hydroxide (12.6 g in 54 ml of water) and a solution of glyoxylic acid (0.012 mol) prepared by the general procedure described above. After addition of water (25 ml), a hydrogen ion measurement showed pH >14.0.

After 16 hr (with stirring) at room temperature, the solution phase was filtered to remove inorganic salts and evaporated *in vacuo* to the point of turbidity. Dilution with water (200 ml) and extraction with diethyl ether gave upon evaporation methyl β-naphthyl ketone (0.1 g). The aqueous suspension was acidified with concentrated hydrochloric acid and extracted with chloroform. Evaporation of the water-washed and dried extract gave the disubstituted acetic acid **11a** as a brown solid,[46] which crystallized from dioxane–water as leaflets (2.55 g, 65%), mp 192–193°.

Methyl Bis(β-naphthacyl)acetic Acid (11b).—To a solution of bis(β-naphthacyl)acetic acid (**11a**, 2.70 g) in dioxane (50 ml) was added excess ethereal diazomethane. The mixture was allowed to stand at room temperature for 6 hr. Diazomethane and ether were removed by warming and the remaining solution was diluted with water. The oil which separated crystallized upon trituration to yield a colorless solid (2.70 g), mp 95–97°. One recrystallization from dioxane–water raised the melting point to 116.5–117.5°. Recrystallization from the same solvent mixture gave an analytical specimen, mp 117.3–118°.

Anal. Calcd for $C_{27}H_{22}O_4$: C, 79.00; H, 5.40. Found: C, 79.05; H, 5.09.

Baeyer–Villiger Oxidation of Methyl Bis(β-naphthacyl)acetate (11b).—A solution of trifluoroperacetic acid prepared from trifluoracetic anhydride (1.7 ml, 0.012 mol) and hydrogen peroxide (90%, 0.27 ml, 0.010 mol) in methylene chloride (3 ml) was added with stirring during 15 min to a solution of methyl bis(β-naphthacyl)acetate (**11b**, 1 g, 0.0024 mol) in methylene chloride (15 ml) containing a suspension of dry disodium hydrogen phosphate (3.54 g, 0.005 mol). The yellow mixture was stirred at room temperature for 3 hr and at reflux for 7 hr. Filtration of the warm solution followed by evaporation furnished a yellow residue, which was dissolved in ethyl alcohol (95%, 5 ml) and heated at reflux for 3 hr with aqueous potassium hydroxide (20%, 4.5 ml, 0.015 mol). After evaporative removal of ethyl alcohol *in vacuo*, the aqueous solution was acidified with concentrated hydrochloric acid and the precipitated brown solid was collected (the filtrate was retained; see below) and washed with diethyl ether (two 10-ml portions). The ethereal extract was concentrated to a brown solid, mp 112–116°. One crystallization from water–methanol gave β-naphthol[46] as tan crystals (0.28 g, 40%), mp 119–121°.

The aqueous filtrate was evaporated to dryness and the residue was extracted with boiling chloroform (two 5-ml portions). Evaporation of the filtered chloroform solution furnished a tan solid (**13**, 0.10 g, 23%), mp 155–158°, which proved to be tricarballylic acid, mp 160–162°.

Alternate Synthesis of Bis(β-naphthacyl)acetic Acid (11a).—To a cooled (0°) solution of methyl β-naphthyl ketone (17 g, 0.10 mol) in dry diethyl ether (100 ml) was added, over 30 min, bromine (16 g, 0.10 mol). The brown ethereal solution was washed with water (four 75-ml portions), dried (sodium sulfate), and evaporated to a crystalline solid. Recrystallization from ethyl alcohol (95%) afforded plates (**14**, 14 g, 56%), mp 82–83°, of ω-bromo-2-acetonaphthone (lit.[47] mp 82.5–83.5°).

Absolute ethyl alcohol (38 ml) was added gradually to finely cut sodium (1.3 g, 0.057 mol). When hydrogen evolution was complete, diethyl malonate (9.1 g, 0.056 mol) was added to the vigorously stirred solution followed, during 20 min, by ω-bromo-β-acetonaphthone (14 g, 0.0562 mol) in hot absolute ethyl alcohol (100 ml). After a 2-hr period at reflux (with vigorous stirring), the ethyl alcohol was removed *in vacuo* and the oily brown residue was shaken with aqueous potassium carbonate (10%, 100 ml), followed by methyl alcohol (50 ml). The remaining residue was dissolved in hot benzene, filtered, and evaporated to a yellow oil which was heated at reflux for 2 hr with aqueous potassium hydroxide (20%, 50 ml). The mixture was cooled in ice and acidified with concentrated hydrochloric acid, and the acidic

(44) N. B. Lorette and J. H. Brown, Jr., *J. Org. Chem.*, **24**, 261 (1959).

(45) Prepared by cleavage of di-*n*-butyl tartrate with lead tetraacetate according to the method of Vogel: A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., London, 1956, p 951.

(46) The structure was confirmed by mixture melting point determination and infrared spectral comparison with an authentic sample.

(47) T. Immediata and A. R. Day, *J. Org. Chem.*, **5**, 512 (1940).

product was collected by filtration. The air-dried **bis(β-naphthacyl)malonic acid** (14, 0.70 g) melted at 137–140° with decomposition.

The crude dicarboxylic acid (0.70 g) was heated at 150° until evolution of gas ceased (15 min), and the dark residue was dissolved in benzene, filtered, and treated with ligroin (1 ml). The brown solid (0.5 g, 79%) which precipitated melted at 193–195° and was identical with the acid **11a**, obtained by condensing methyl β-naphthyl ketone with butyl glyoxylate.

Bis(2,5-dimethoxyphenacyl)acetic Acid (11c).—Using the procedure outlined above (method B), 2,5-dimethoxyacetophenone (3.6 g, 0.02 mol) was condensed with glyoxylic acid. The crude, dark solid (3.0 g, 71%), mp 110–115°, gave an analytical specimen after four recrystallizations from isopropyl ether–acetone as colorless rosettes of microneedles: mp 130–131° dec; ν_{max} 3400 (carboxylic acid), 1700 (carboxylic acid), and 1665 cm^{-1} (ketones).

Anal. Calcd for $C_{22}H_{24}O_8$: C, 63.46; H, 5.81. Found: C, 63.38; H, 5.84.

α-Hydroxy-β-(2-naphthoyl)propionic Acid (15a) and β-Naphthoylacrylic Acid (16a).—To a cooled solution of glyoxylic acid (0.04 mol, 26 ml) was added methyl β-naphthyl ketone (3.4 g, 0.02 mol) in 95% ethyl alcohol (25 ml), followed by an aqueous solution of sodium hydroxide (3 g, 0.075 mol in 54 ml of water). A mixture of 95% ethyl alcohol (50 ml) and water (150 ml) was added to produce homogeneity. The reaction was allowed to proceed for 18 hr at room temperature and at 60° for 10 min. Next the yellow mixture was cooled, diluted with water, and extracted with diethyl ether (two 300-ml portions). The aqueous solution was cooled to 10°, acidified with concentrated hydrochloric acid, and extracted with diethyl ether to provide, after drying and evaporation, a yellow solid (1.5 g). The residue was extracted with hot benzene, and insoluble material (1.1 g, 23%) was crystallized from methanol–water to give colorless crystals of acid **15a**, mp 130–132°. Four recrystallizations from the same solvent mixture yielded a pure sample of **α-hydroxy-β-(2-naphthoyl)propionic acid (15a)**: mp 132.5–133.5°; ν_{max} 1730 (carboxylic acid) and 1690 cm^{-1} (ketone).

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.53; H, 5.01.

The benzene-soluble material consisted of a yellow acid (0.4 g, 9%), mp 148–152°. Four recrystallizations from benzene gave an analytical sample of **β-naphthoyl acrylic acid (16a)**: mp 167–168°; $\nu_{max}^{CHCl_3}$ 1710 (carboxylic acid) and 1670 cm^{-1} (conjugated ketone).

Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.32; H, 4.46. Found: C, 74.10; H, 4.56.

Dehydration of α-Hydroxy-β-(2-naphthoyl)propionic Acid (15a).—A solution of α-hydroxy-β-(2-naphthoyl)propionic acid (**15a**, 0.36 g) in acetic anhydride (10 ml) was heated at 100° for 3 hr with potassium hydrogen sulfate (0.40 g). The solution was cooled, filtered, and diluted with water (10 ml). After 6 hr at room temperature the solution was evaporated to dryness *in vacuo*. The yellow residue was dissolved in saturated aqueous sodium bicarbonate, treated with Norit A, and acidified at 10° with concentrated hydrochloric acid. Upon cooling, the yellow crystalline **β-naphthoylacrylic acid (16a**, 0.12 g, 33%),[46] mp 164–165°, was collected.

Condensation of Methyl Ketones with Glyoxylic Acid. General Procedure A (Ambient).—A rapidly stirred solution of the ketone (0.032 mol) in tetrahydrofuran (250 ml)–methanol (360 ml) was treated succcessively with aqueous potassium hydroxide (100 ml, 8%) and an aqueous solution of glyoxylic acid (0.076 mol, 27 ml). The pH of the solution was adjusted to 13.65 by gradual addition of 8% aqueous potassium hydroxide. Stirring was continued for 3 days at room temperature. At this point, the yellow mixture was filtered, concentrated to 1/4 volume *in vacuo* at 50°, diluted with water (100 ml), and extracted with diethyl ether. Acidification of the aqueous solution with concentrated hydrochloric acid and extraction with chloroform provided the acidic product. Washing the chloroform solution with saturated aqueous sodium bicarbonate solution removed the acidic components and left in the chloroform neutral products whose infrared spectra indicated presence of a lactone (1780 cm^{-1}). The neutral material was formed (*ca.* 10% of the product) in all cases investigated but was not further characterized.

With Methyl β-Naphthyl Ketone.—Methyl β-naphthyl ketone (**10**, 5.4 g, 0.032 mol) was condensed with glyoxylic acid by the general procedure A given above to yield acidic (6.5 g) and neutral products (0.7 g); no starting material was recovered. A portion (3.8 g) of the crude acid was dissolved in methanol (115 ml) and heated at reflux for 3 hr with Amberlite IR-120 (H) (3.8 g).[48] The yellow solution was filtered and concentrated *in vacuo* to a yellow oil, which was dissolved in diethyl ether and washed with saturated aqueous sodium bicarbonate (three 20-ml portions) and water (two 20-ml portions). Removal of solvent gave a mobile yellow oil (2.4 g). Acidification of the sodium bicarbonate wash solution and extraction with diethyl ether gave 0.9 g of recovered acid. Repeating the esterification procedure yielded another portion of ester (0.5 g); the total yield of ester was 2.9 g. A sample of the ester (1 g) was chromatographed on acid-washed alumina (30 g) and afforded three distinct products. Elution with 2:5 ligroin–benzene led to a yellow solid (0.17 g), mp 108–109°. The melting point was raised to 112–112.5° by four recrystallizations from methanol to afford a pure sample (characterized in the sequel) of **methyl *trans*-β-(2-naphthoyl)acrylate (16b)**:[46] ν_{max} 1720 (methyl ester) and 1665 cm^{-1} (conjugated ketone). Continued elution with benzene gave a colorless, mobile oil (0.57 g): ν_{max}^{neat} 1754 (methyl ester), 1694 (ketone), and 1124 cm^{-1} (methoxyl). Distillation at 120° (0.01 mm) gave an analytical specimen of **methyl α-methoxy-β-(2-naphthoyl)propionate (17b)**.

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.56; H, 5.92. Found: C, 70.95; H, 5.74.

Elution with 1:1 benzene–chloroform afforded a colorless oil (0.10 g): ν_{max}^{neat} 3571 (hydroxyl), 1748 (methyl ester), and 1690 cm^{-1} (ketone). Distillation at 170° (0.01 mm) gave an analytical specimen of **methyl α-hydroxy-β-(2-naphthoyl)propionate (15b)**.

Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.46; H, 5.46.

When the preceding reaction sequence was repeated using 2,4-dimethylacetophenone or 2,5-dimethoxyacetophenone in place of methyl β-naphthyl ketone, examination by thin layer chromatography and infrared spectroscopy of the crude products indicated analogous results. In these examples the actual products were not further identified.

With Methyl Cyclopentyl Ketone.—The ketone (10.6 g, 0.095 mol) was condensed with glyoxylic acid by general procedure A to yield neutral (2.0 g of colorless oil) and acidic (10.0 g, 56%) fractions. Continuous (48 hr) diethyl ether extraction of the acidified reaction mixture was used to isolate the yellow, oily acidic product. A portion (3 g) of the acid was treated with ethereal diazomethane at 0°. Excess diazomethane was destroyed with glacial acetic acid and solvent was removed *in vacuo*. The resulting yellow oil (3.0 g) was chromatographed on a column of acid-washed alumina (90 g) and **methyl α-hydroxy-β-cyclopentylcarbonylpropionate (19)** was eluted by benzene–chloroform mixtures as a colorless oil (2.7 g, 52%). Distillation at 100° (0.1 mm) afforded an analytical specimen: ν_{max} 3546 (hydroxyl), 1740 (methyl ester), and 1709 cm^{-1} (ketone).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 59.63; H, 7.96.

With Pinonic Acid.—Pinonic acid[49] (**18**, 5.8 g, 0.032 mol) in tetrahydrofuran (250 ml)–methanol (360 ml) was condensed with glyoxylic acid, employing general procedure A, to give a dark, oily, acidic product (8.0 g), which was isolated by continuous extraction using diethyl ether. A portion (4.0 g) of the acid was dissolved in diethyl ether containing some methanol and treated with ethereal diazomethane. Excess diazomethane was destroyed by adding a few drops of glacial acetic acid. Removal of solvent *in vacuo* furnished a dark-colored oil (4.0 g), which was chromatographed on a column of acid-washed alumina (120 g). The product (3.3 g, 72%), **methyl α-hydroxy-β-pinonoyl propionate (20)**, was eluted by benzene–chloroform mixtures as a pale yellow oil which was purified by distillation: bp 170° (0.1 mm); ν_{max}^{neat} 3400 (hydroxyl), 1740 (methyl esters), and 1705 cm^{-1} (ketone).

Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 58.35; H, 7.65.

General Procedure B (Heating).—To a stirred solution of the ketone (0.013 mol) in tetrahydrofuran (100 ml)–methanol (150 ml) was added potassium hydroxide solution (30 ml, 8%), followed by aqueous glyoxylic acid (0.03 mole, 11 ml). The pH was adjusted as specified by addition of aqueous potassium hydroxide (8%) and the mixture was stirred for 60 min at room

(48) P. J. Mill and W. R. C. Crimmin, *Biochem. Biophys. Acta*, **38**, 432 (1957).

(49) J. B. Lewis and G. W. Hedrick, *J. Org. Chem.*, **24**, 1870 (1959). We wish to thank Dr. Hedrick for a generous supply of pinonic acid.

temperature followed by 12 hr at reflux. The acidic product(s) was isolated as summarized in general procedure A.

With Methyl β-Naphthyl Ketone.—Condensing methyl β-naphthyl ketone (**10**, 2.2 g, 0.013 mol) with glyoxylic acid using general procedure B (pH 13.20) led to 2.7 g of crude acidic product. A portion (0.5 g) of this material was dissolved in methanol (8 ml) and treated with 2,2-dimethoxypropane (Dow Chemical Co.) followed by concentrated hydrochloric acid (4 drops).[50] The yellow solution was heated to 50° and treated with four 1-ml portions of 2,2-dimethoxypropane at 1-hr intervals. The temperature was maintained at 50° for 17 hr, after which most of the solvent was removed *in vacuo* and water (50 ml) was added. Following extraction of the turbid aqueous mixture with chloroform and washing of the extract with saturated aqueous sodium bicarbonate and water, drying, and evaporating, a yellow oil (0.6 g) was obtained. Chromatography on a column of neutral alumina (18 g) and eluting with a series of hexane–benzene mixtures afforded a pale yellow solid (0.30 g, 57%): mp 108–109°; ν_{max} 1720 (methyl ester), 1665 (conjugated ketone), and 1630 cm^{-1} (double bond). Four recrystallizations from methanol gave an analytical specimen of **methyl *trans*-β-(2-naphthoyl)acrylate (15b)** as pale yellow needles: mp 112–112.5° (lit.[51] mp 112–113°); pmr (CCl_4) δ 3.74 (singlet, 3 methyl protons) and 6.61 and 6.88 (doublet, J = 15 cps, 1 proton, the second olefin proton was obscured by the aromatic proton region).

Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.04. Found: C, 74.64; H, 4.84.

With 2,4-Dimethylacetophenone.—A 1.9-g (0.013 mol) sample of 2,4-dimethylacetophenone was condensed with glyoxylic acid by general procedure B at pH 13.20 to give 2.2 g of acidic product. A portion (0.5 g) of the acidic fraction was esterified using methanol and 2,2-dimethoxypropane as described above for the preparation of methyl-β-(2-naphthoyl)-acrylate and provided a dark yellow oil (0.60 g). Column chromatography on neutral alumina (15 g) and elution with hexane yielded a yellow oil (0.30 g, 56%), ν_{max}^{neat} 1725 (methyl ester), 1670 (conjugated ketone), and 1630 cm^{-1} (double bond). The oil crystallized after 24 hr at 0°. Four recrystallizations from 2-propanol gave a yellow, crystalline, analytical specimen of **methyl β-(2,4-dimethylbenzoyl)acrylate (21)**, mp 50–50.2°.

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46. Found: C, 71.35; H, 6.44.

With 2,5-Dimethoxyacetophenone.—The acetophenone (2.3 g, 0.013 mol) was condensed with glyoxylic acid by general procedure B at pH 13.65 and the crude acidic product (2.9 g) was esterified by treatment for 3 hr with Amberlite IR-120 (H) (2.9 g) in boiling methanol (75 ml). The yellow solution was filtered and the solvent was removed *in vacuo* to yield a dark, oily residue which was dissolved in diethyl ether. The ethereal solution was washed with saturated aqueous sodium bicarbonate and water, dried, and evaporated to furnish a yellow oil (1.7 g). This residue was chromatographed on a column of acid-washed alumina (40 g). Elution with 1:1 hexane–benzene gave a yellow oil (1.0 g, 59%), which crystallized from 2-propanol in matted, yellow needles (0.9 g), mp 65–68°. Four recrystallizations from 2-propanol yielded an analytical specimen of **methyl β-(2,5-dimethoxybenzoyl)acrylate (22)**: mp 73–73.5° (lit.[52] mp 65°); ν_{max}^{Nujol} 1727 (methyl ester), 1672 (conjugated ketone), and 1636 cm^{-1} (double bond).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.40; H, 5.64. Found: C, 62.65; H, 5.80.

Further elution of the column with chloroform gave a dark oil (0.15 g). Distillation at 170° (0.01 mm) afforded **methyl α-hydroxy-β-(2,5-dimethoxybenzoyl)propionate (23)** as a pale yellow oil, ν_{max}^{neat} 3570 (hydroxyl), 1754 (methyl ester), and 1677 cm^{-1} (ketone).

Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.53; H, 6.59.

Methylation of Methyl α-Hydroxy-β-(2-naphthoyl)propionate (15b).—To a solution of methyl α-hydroxy-β-(2-naphthoyl)-propionate (**15b**, 0.5 g) in diethyl ether (5 ml) at −10° was added 1 drop of boron trifluoride etherate followed dropwise by an ethereal solution of diazomethane from 1.2 g of nitrosomethylurea during 5 min.[53] Cooling was maintained until the yellow color had disappeared (15 min). A gelatinous precipitate was removed by filtration and the filtrate was washed with saturated aqueous sodium bicarbonate, dried, and concentrated to a colorless oil (0.2 g). The residue was chromatographed on acid-washed alumina (15 g), and **methyl α-methoxy-β-(2-naphthoyl)-propionate (15b**, 0.1 g, 18%) was obtained, eluted by benzene, as a colorless oil.

Alternate Synthesis of Methyl *trans*-β-(2-Naphthoyl)acrylate (16b).—To a stirred solution of ω-bromo-2-acetonaphthone (2.4 g, 0.01 mol) in dry tetrahydrofuran (20 ml) was added in one portion a warm solution of carbomethoxymethylenetriphenylphosphorane[54] (6.7 g, 0.02 mol) in dry tetrahydrofuran (30 ml). After 24 hr at room temperature the solution was filtered to remove carbomethoxymethyltriphenylphosphonium bromide (2.6 g, 64%). The filtrate was evaporated to a dark oil, which was diluted with dry benzene and treated with methyl iodide for 2 hr at 5°. Filtration and evaporation yielded a dark residue which was chromatographed (column) on acid-washed alumina (30 g). The hexane–benzene fractions yielded a yellow solid **16**,[46] which recrystallized from methanol as pale yellow plates (0.91 g, 38%), mp 110–111°.

Methyl *cis*-β-(2-Naphthoyl)acrylate (16b).—Methyl *trans*-β-(2-naphthoyl)acrylate (**16a**, 0.20 g) in benzene (10 ml) was irradiated with a sun lamp (GE 110–125 V) at a distance of 4 ft for 48 hr, at which time tlc examination showed almost complete conversion into the more polar *cis* isomer. Evaporation of solvent gave an orange oil which slowly crystallized on trituration with hexane. The crude product was heated with hexane and the hot solution was decanted from an oily by-product. The product, which crystallized upon cooling, was recrystallized three times from hexane to give cream-colored crystal clusters (0.06 g): mp 92–95°; pmr (CCl_4) δ 3.41 (singlet, 3 methyl protons) and 5.94, 6.13, 6.58, and 6.77 (quartet, J = 11 cps, 2 protons, *cis* isolated double bond).

3β-Triphenylmethoxy-20-oxo-5α-pregnane (24c).—A solution of 3β-hydroxy-20-oxo-5α-pregnane (**24a**, 3.6 g, 11 mmol) and triphenylmethyl bromide (5.4 g, 17 mmol) in dry pyridine (100 ml) was heated at 100° for 12 hr. The yellow reaction mixture was cooled and poured onto ice, and the resulting yellow precipitate was collected by extraction with chloroform. The chloroform extract was washed twice with water, dried, and evaporated to yield a yellow gum which solidified on trituration with diethyl ether. Filtration provided a cream-colored solid (3.87 g), mp 216–220°. Recrystallization from chloroform–methanol gave cream-colored needle clusters in two crops of 2.2 g, mp 222–225°, and 1.3 g, mp 218–223°. Recrystallization of the second crop from the same solvent mixture gave 1.19 g, mp 223–227°. Yield (of almost pure material) was 3.39 g (53%). An analytical specimen was prepared by three recrystallizations from the same solvent mixture: mp 227–230°; ν_{max} 1695 (ketone) and 1030–1050 cm^{-1} (ether); $[\alpha]^{22}D$ +39.2° (*c* 1.46).

Anal. Calcd for $C_{40}H_{48}O_2$: C, 85.66; H, 8.63. Found: C, 85.11; H, 8.26.

3β-Triphenylmethoxy-20-oxo-5-pregnene (7c).—Treatment of 3β-hydroxy-20-oxo-5-pregnene (**7a**, 5.0 g, 16 mmol) with triphenylmethyl bromide in pyridine was performed exactly as described above for the 5α analog **24c** to yield a brown, glasslike crude product (11.4 g). A solution of the residue in 5:1 hexane–benzene was chromatographed on basic alumina (250 g). The benzene–hexane eluate gave a colorless solid which crystallized from chloroform–methanol as needles (4.7 g, 53%), mp 180–185°. An analytical specimen was prepared by trituration with boiling methanol followed by six recrystallizations of the insoluble material from chloroform–methanol: mp 188–191°; $[\alpha]^{22}D$ +23.2° (*c* 1.29); ν_{max} 1690 (ketone) and 1040 cm^{-1} (ether).

Anal. Calcd for $C_{40}H_{46}O_2$: C, 85.98; H, 8.30. Found: C, 85.49; H, 8.05.

3β-Triphenylmethoxy-20-oxo-5,16-pregnadiene (25b).—A 5.0-g (16 mmol) sample of 3β-hydroxy-20-oxo-5,16-pregnadiene (**25a**) was treated with triphenylmethyl bromide in hot pyridine for 24 hr as described above for **24c**. The product was a dark, viscous oil (10 g). Column chromatography on basic alumina (250 g) and elution with hexane–benzene mixtures gave a colorless solid which crystallized from chloroform–methanol as glistening needles (4.5 g, 51%), mp 190–194°. Three recrystal-

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lizations from acetone gave an analytical sample: mp 195–197°; $[\alpha]^{22}D$ −21.4° (*c* 1.215); ν_{max} 1665 (conjugated ketone) and 1040 cm^{-1} (ether).

Anal. Calcd for $C_{40}H_{44}O_2$: C, 86.27; H, 7.97. Found: C, 86.22; H, 7.98.

3β-Methoxymethyloxy-20-oxo-5-pregnene (7d).—A solution of 3β-hydroxy-20-oxo-5-pregnene (**7a**, 7.5 g, 24 mmol) in refluxing chloromethyl methyl ether (75 ml, Eastman) containing suspended Drierite (20 g) was treated in portions with freshly prepared, dry silver oxide (17 g) during 90 min. Heating was continued for 4 hr. The solvent was reduced in volume and filtered, and the inorganic residue was washed well with chloroform. The residue (9.0 g) obtained upon removal of solvent *in vacuo* was chromatographed on basic alumina (200 g). Elution with benzene gave a colorless solid (1.5 g, 18%), mp 95–100°. Four recrystallizations from methanol gave a pure specimen as colorless microneedles: mp 103–104°; $[\alpha]^{22}D$ 0°; ν_{max} 1700 (ketone), 1150, 1100, and 1040 cm^{-1} (ether).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.64; H, 10.07. Found: C, 77.23; H, 9.94.

Elution of the column with chloroform yielded unreacted 3β-hydroxy-20-oxo-5-pregnene (5.5 g).

Condensation of 3β-Hydroxy-20-oxo-5-pregnene (7a) with Glyoxylic Acid at Readings of pH 13.25–13.48. Experiment A. pH 13.25.—A vigorously stirred solution of 3β-hydroxy-20-oxo-5-pregnene (**7a**, 2.0 g, 6.3 mmol) in tetrahydrofuran (50 ml)–methanol (75 ml) was treated successively with potassium hydroxide solution (8% aqueous, 20 ml), and a solution of glyoxylic acid (23 mmol, 6 ml) prepared as described above. Potassium hydroxide (8% aqueous) was then gradually added until the pH meter scale reading was 13.25. Stirring was continued for 3 days at room temperature, and the solution was filtered, concentrated *in vacuo* to 1/5 volume, and diluted with water (100 ml). Extracting the basic mixture with chloroform followed by washing with water, drying, and concentration furnished unreacted 3β-hydroxy-20-oxo-5-pregnene (**7a**, 1.3 g).[46] Acidification of the aqueous solution with concentrated hydrochloric acid gave a gelatinous, acidic product which was collected by chloroform extraction to yield a colorless, amorphous, acidic product (0.63 g, 25%): mp 160–170° dec; ν_{max} 3400 (broad, acid) and 1750–1690 cm^{-1} (carboxylic acid and ketone).

Experiment B. pH 13.48.—Experiment A was repeated with ketone **7a** (3 g, 9.5 mmol) exactly as above except that the pH reading was adjusted to 13.48. The neutral extract gave starting material (1.3 g), and the acidic fraction yielded a colorless, amorphous solid (1.6 g, 45%), mp 155–175° dec.

Methyl 3β,23-Dihydroxy-20-oxo-21-nor-5-cholenate (26b).—Condensation of 3β-hydroxy-20-oxo-5-pregnene (**7a**, 20 g, 63.4 mmol) with glyoxylic acid was carried out at pH 13.48 exactly as described above (experiment B) to yield starting material (8.5 g) and amorphous acid (12.3 g, 50%), mp 155–175° dec. A portion (11 g) of the acidic material, dissolved in methanol, was treated with ethereal diazomethane at 0°. Excess diazomethane was decomposed immediately with a few drops of glacial acetic acid, and the solvent was removed *in vacuo*. The yellow, viscous oil (11.5 g) was chromatographed on acid-washed alumina (250 g). A pale yellow solid (4 g) was eluted by 1:1 benzene–chloroform; purification of this material will be described below (see **26a**). Elution with chloroform furnished a pale yellow solid (7 g, 30%), mp 154–164°, which was homogeneous as evidenced by thin layer chromatography. Four recrystallizations from isopropyl ether–methanol afforded an analytical sample of diol **26b** as colorless plates: mp 170–174°; $[\alpha]^{22}D$ +9.0°; ν_{max} 3400 (hydroxyl), 1740 (methyl ester), and 1700 cm^{-1} (ketone).

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.18; H, 8.80.

A sample (2.3 g) of the diol was acetylated, and the crude diacetate (**26c**, 2.6 g) was decolorized by two treatments with Norit-A in methanol. Recrystallization from aqueous methanol gave the diacetate (2.2 g, 79%) as colorless plates, mp 105–107°. An analytical specimen of methyl 3β,23-diacetoxy-20-oxo-21-nor-5-cholenate (**26c**) was prepared by five recrystallizations from aqueous methanol: mp 105–108°; $[\alpha]^{22}D$ +23.2° (*c* 1.242); ν_{max}^{Nujol} 1754 (sh, methyl ester), 1738 (acetates), 1709 (ketone) and 1250 cm^{-1} (acetates).

Anal. Calcd for $C_{28}H_{40}O_7$: C, 68.82; H, 8.25. Found: C, 68.90; H, 7.96.

Methyl 3β,23-Ditetrahydropyranyloxy-20-oxo-21-nor-5-cholenate (26d).—To a magnetically stirred suspension of 3β,23-dihydroxy-20-oxo-21-nor-5-cholenate (**26b**, 1.25 g) in dry benzene (40 ml) and dihydropyran (7.5 ml, distilled from sodium) was added *p*-toluenesulfonic acid monohydrate (75 mg). After 2 min the solution became homogeneous, and stirring was continued at room temperature for 30 min.[55] The pale yellow solution was washed with sodium hydroxide solution (1% in 1:1 methanol–water) and water. Removal of solvent gave a yellow oil (2.0 g) which was chromatographed on neutral alumina (30 g). Elution with 1:1 benzene–hexane gave a colorless oil (1.25 g, 70%) which solidified, mp 70–75° (vacuum dried) upon trituration with cold (ice-bath) methanol. An analytical sample was prepared by three recrystallizations from methanol, followed by two from aqueous acetone: mp 70–78°; ν_{max} 1750 (methyl ester), 1705 (ketone), and 1030 cm^{-1} (split, ethers).

Anal. Calcd for $C_{34}H_{52}O_7$: C, 71.29; H, 9.15. Found: C, 71.53; H, 9.10.

Methyl 3β-Acetoxy-23-methoxy-20-oxo-21-nor-5-cholenate (26a).—A portion (1.5 g) of the material (4 g) eluted in 1:1 benzene–chloroform (see **26a** above) during isolation of methyl 3β,23-dihydroxy-20-oxo-21-nor-5-cholenate (**26a**) was acetylated. The oily acetate (1.2 g) was chromatographed on acid-washed alumina (30 g). A 0.3-g quantity of 3β-acetoxy-20-oxo-5-pregnene (**7b**) was eluted by 1:1 benzene–hexane. Elution with benzene gave a colorless solid (0.7 g), mp 102–103°. Three recrystallizations from diethyl ether–hexane gave a pure specimen as colorless plates: mp 104–105°; $[\alpha]^{20}D$ +20.5° (*c* 2.879); ν_{max}^{Nujol} 1754 (methyl ester), 1733 (acetate), 1709 (ketone), 1250 (acetate), and 1136 cm^{-1} (methoxy); pmr δ 3.24 (3 methoxy protons) and 3.58 (3 methyl ester protons).

Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.40; H, 8.76. Found: C, 70.80; H, 8.68.

Condensation between 3β-Hydroxy-20-oxo-5-pregnene (7a) and Glyoxylic Acid at pH 13.65. Method A. Room Temperature.—Reaction between 3β-hydroxy-20-oxo-5-pregnene (**7a**, 20 g, 63.4 mmol) and glyoxylic acid at pH 13.65 was accomplished as described above (*cf.* **26b**). After 28 hr, half of the reaction mixture was taken for isolation studies and the other half was allowed to proceed for an additional 48 hr at room temperature. Isolation work with the first half was complicated by emulsion formation (during extraction of the basic solution with chloroform), and caused inefficient separation into neutral and acidic fractions. The neutral extract furnished 3β-hydroxy-20-oxo-5-pregnene (0.6 g, **7a**), and the acidic portion was obtained as a pale yellow foam (10 g). The acid (10 g) was dissolved in 10:1 chloroform–methanol and treated with ethereal diazomethane at ice-bath temperature. Excess diazomethane was destroyed at once with a few drops of glacial acetic acid. The solution was concentrated to a yellow oil (11 g). Acetylation gave a yellow, viscous oil (11.5 g) which was chromatographed on acid-washed alumina (300 g). Elution with 1:1 hexane–benzene gave **3β-acetoxy-20-oxo-5α-pregnane (7b**, 4.3 g), and benzene gave a mixture of two components, separable by crystallization from methanol, to give first the less soluble **methyl 3β-acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (27**, 0.60 g, 5%), mp 153–156°. Three recrystallizations from methanol gave long yellow needles: mp 157–158.5°; $[\alpha]^{20}D$ +37.5° (*c* 1.27); ν_{max} 1735 (methyl ester), 1730 (acetate), 1690 (conjugated ketone), and 1628 cm^{-1} (m, conjugated double band).

Anal. Calcd for $C_{26}H_{36}O_5$: C, 72.86; H, 8.47. Found: C, 73.34; H, 8.43.

The second component eluted by benzene was identical[46] with **methyl 3β-acetoxy-23-methoxy-20-oxo-5-cholenate (26a**, 1.6 g, 11%), mp 102–104°. Further elution of the column with 2:1 benzene–chloroform gave **methyl 3β,23-diacetoxy-20-oxo-21-nor-5-cholenate (26c**, 2.3 g, 15%),[46] mp 96–99°, and a pale yellow, viscous oil (1.0 g). An infrared spectrum suggested that the oil represented **pyrazoline 28:** ν_{max} 1745 (methyl ester), 1701 (ketone), and 1577 cm^{-1} (pyrazoline). Continued elution with 10:1 and 4:1 benzene–chloroform gave mixtures (shown by thin layer chromatography) of the 23-acetoxy (**26b**) and 23-methoxy (**26d**) esters.

After 72 hr the second half of the reaction product was methylated and acetylated in the same way to give 3β-hydroxy-20-oxo-5-pregnene (**7a**, 0.8 g) as the initial neutral fraction and a mixture of methyl esters (9.0 g) from the initial acid fraction. Chromatography of the methyl ester mixture as before gave 3β-

(55) Normal reaction time (3 hr) for tetrahydropyranyl ether formation produced a mixture of products. After several experiments over various periods, the 30-min procedure was found most satisfactory.

acetoxy-20-oxo-5-pregnene (**7b**, 1.6 g), methyl 3β-acetoxy-20-oxo-21-nor-5,22-choladienate (**27**, 1.0 g, 8%), methyl 3β-acetoxy-23-methoxy-20-oxo-21-nor-5-cholenate (**26a**, 2.0 g, 14%), methyl 3β,23-diacetoxy-20-oxo-21-nor-5-cholenate (**26c**, 3.0 g, 19%), and pyrazoline **28** (0.4 g).

Method B. Reflux Temperature.—Here, 3β-hydroxy-20-oxo-5-pregnene (**7a**, 20 g, 63.4 mmol) was condensed with glyoxylic acid as described above at pH 13.65 except that the reaction was heated at reflux temperature (60°) for 8 hr. Despite an inefficient separation because of emulsification, 2.4 g of unreacted starting material and 19.5 g of acidic material (as a pale yellow foam) were isolated. Methylation (see method A) and acetylation gave a dark oil (20 g) which was chromatographed on acid-washed alumina (500 g). Elution with the same solvents as described in the preceding experiment gave 3β-acetoxy-20-oxo-5-pregnene (**7b**, 3.56 g), methyl 3β-acetoxy-20-oxo-21-nor-5,22-choladienate (**27**, 2.1 g, 8%), methyl 3β-acetoxy-23-methoxy-20-oxo-21-nor-5-cholenate (**26a**, 0.3 g, 1%), methyl 3β-23-diacetoxy-20-oxo-21-nor-5-cholenate (**26c**, 2.8 g, 9%), and pyrazoline **28** (5.5 g).

In another experiment[56] a portion (17 g) of the acidic product prepared by method B (reflux, 8 hr) in methanol (170 ml) was treated with 2,2-dimethoxypropane (17 ml) and warmed to 50° with concentrated hydrochloric acid (5 ml). After 1 hr, more dimethoxypropane (17 ml) was added, and this operation was repeated twice more at hourly intervals. One day later the brown solution was filtered and concentrated *in vacuo*. Addition to water and extraction with chloroform furnished the crude product. Acetylation led to a pale yellow solid (17 g). Chromatography on acid-washed alumina (450 g) and elution with benzene gave methyl 3β-acetoxy-20-oxo-21-nor-5-*trans*-22-cholanate (**27**, 5.0 g),[46] mp 154–155°. In this case the other products were not isolated.

Condensation between 3β-Acetoxy-20-oxo-5α-pregnane (24a) and Glyoxylic Acid.—Using method A (see above with ketone **7a**, pH 13.65), 3β-acetoxy-20-oxo-5α-pregnane (**24a**, 10 g, 28 mmol) was condensed with glyoxylic acid. A period of 3 days at room temperature afforded starting material (5.1 g) after reacetylation and acidic product (4.82 g), mp 198–205° dec, collected by filtration. A sample of the acid was recrystallized five times from aqueous ethyl alcohol to give the analytical specimen of **3β,23-dihydroxy-20-oxo-21-nor-5α-cholanic acid (29a)** as colorless plates: mp 227–229° dec; ν_{max} 3350 (hydroxyl), 2700–2300 (w, carboxyl), 1730 (carboxyl), and 1698 cm^{-1} (ketone).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24; O, 20.38. Found: C, 70.80; H, 9.00; O, 20.20.

A solution of the crude acid (mp 198–205° dec, 4.8 g) in 1:1 chloroform–methanol (200 ml) was converted into the methyl ester with ethereal diazomethane. Excess reagent was quickly destroyed with acetic acid, and the solution was washed with saturated sodium bicarbonate solution followed by water. Removal of solvent furnished a yellow, oily residue. The crude ester was chromatographed on acid-washed alumina (140 g). Elution with 7:3 benzene–chloroform gave a yellow oil (1.1 g) which slowly solidified and showed two closely positioned spots on a thin layer chromatogram. Elution with 1:1 benzene–chloroform led to a colorless solid (2.0 g), mp 147–157°. Recrystallization from diethyl ether containing a trace of methanol gave colorless needles (1.0 g), mp 165–167°. Three recrystallizations from the same solvent gave **methyl 3β,23-dihydroxy-20-oxo-21-nor-5α-cholanate (29b)** as needles: mp 177–179°; $[\alpha]^{20}D$ +91.8° (*c* 1.381); ν_{max} 3200, 3100 (hydroxyls), 1739 (methyl ester), and 1697 cm^{-1} (ketone).

Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42; O, 19.68. Found: C, 70.84; H, 9.24; O, 20.16.

Acetylation of a sample of the dihydroxymethyl ester (0.09 g), mp 174–176°, gave diacetate **29c** (0.12 g), mp 109–113°, and successive recrystallization from hexane and aqueous ethyl alcohol gave the analytical specimen of **methyl 3β,23-diacetoxy-20-oxo-21-nor-5α-cholanate (29c)** as colorless plates: mp 113–114.5°; $[\alpha]^{21}D$ +71.1° (*c* 0.82); ν_{max} 1725–1750 (acetates and methyl ester) and 1695 cm^{-1} (ketone).

Anal. Calcd for $C_{28}H_{42}O_7$: C, 68.54; H, 8.63; O, 22.83. Found: C, 68.52; H, 8.79; O, 22.92.

Conversion of Methyl 3β,23-Dihydroxy-20-oxo-21-nor-5α-cholanate (29b) into 3β-Hydroxy-20-oxo-5α-pregnane (24a).—A solution of methyl 3β,23-dihydroxy-20-oxo-21-nor-5α-cholanate (**29b**, 0.1 g) in methanol (20 ml) containing potassium hydroxide (1 g) was heated at reflux for 2 hr. Concentration *in vacuo* to a small volume, followed by dilution with water, three extractions with chloroform, and evaporation of solvent gave a colorless, crystalline solid (25 mg) identical[46] with **3β-hydroxy-20-oxo-5α-pregnane (24a)**. Acidifying the alkaline solution provided a 0.072-g acid fraction.

Registry No.—Glyoxylic acid, 298-12-4; **7c**, 23328-04-3; **7d**, 23328-05-4; **11a**, 23349-18-0; **11b**, 23389-68-6; **11c**, 23349-19-1; **14**, 23349-20-4; **15a**, 23359-85-5; **15b**, 23349-21-5; **16a**, 23328-06-5; **16b**, 23328-07-6; **17b**, 23349-22-6; **19**, 23349-23-7; **20**, 23349-24-8; **21**, 23349-25-9; **22**, 23349-26-0; **23**, 23349-27-1; **24c**, 23328-08-7; **25b**, 23328-09-8; **26a**, 23328-10-1; **26b**, 23328-11-2; **26c**, 23328-12-3; **26d**, 23328-13-4; **27**, 23330-45-2; **28**, 23328-15-6; **29a**, 23328-16-7; **29b**, 23328-17-8; **29c**, 23328-18-9.

(56) Performed by Dr. A. K. Das Gupta.