in 20 cc. of water was mixed with 7.3 g. (0.02 mole) of Amberlite IRA-400(OH$^-$) having a capacity of 2.8 meq./dry g. and agitated for 10 min. at 20°. Then the resin was filtered off and washed thoroughly with water on the filter. The filtrate was evaporated to dryness under reduced pressure to recover unconverted 0.88 g. (52%) of cyanoacetamide. Thus, 0.82 g. of cyanoacetamide had exchanged with the hydroxyl ion of the resin during the course of the reaction. The entire washed resin was treated with 2.4 g. (0.02 mole) of allyl bromide in 20 cc. of ethanol for 0.5 hr. at room temperature under shaking. The corresponding 2,2-diallylcyanoacetamide (0.58 g.) was thereby obtained. On the other hand, when treated with 1.66 cc. (0.02 mole) of concentrated hydrochloric acid in ethanol for 10 min., the resin regenerated 0.45 g. of cyanoacetamide unchanged.

Acknowledgment.—The authors wish to express their appreciation to Mr. T. Sakan and to Mr. S. Matsuura for their able technical assistance. They are also indebted to the Tokyo Organic Chemical Industries Ltd., for supplying Amberlite IRA-400 throughout this work.

Studies on Resin Acids. 1-Ketonordehydroabietane

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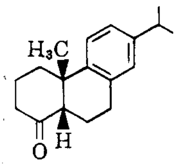
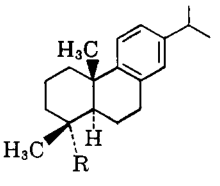
The preparation of 1-ketonordehydroabietane (I) from dehydroabietic acid has been reinvestigated. When the original preparation was repeated it was found that the olefinic precursor of I was contaminated with the tertiary alcohol (IIc), and a modified approach *via* the Cope reaction was employed. Oxidation of III with permanganate–manganese sulfate–pyridine gave 1-α-carboxy-9-ketonordehydroabietane (IV), which was also synthesized by an alternate route. Ozonization of the olefin from the Cope reaction gave I in good yield. I was shown to have a *cis* A-B ring fusion, based on its optical rotatory dispersion curve.

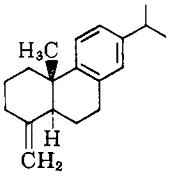
The preparation of 1-ketonordehydroabietane (I) either from dehydroabietic acid[2,3] or by total synthesis[4] has received considerable attention in the past few years. The need for rather large quantities of I has led us to reinvestigate in detail the preparation of this compound. Of the several methods reported for obtaining this material the most attractive, in spite of rather poor yields, appeared to be that of Zeiss and Martin.[2] Conversion of dehydroabietic acid (IIa) to the secondary amine (IIb) proceeded as reported; however, the Hofmann elimination product, reported to be the olefin (III), showed distinct hydroxyl absorption in the infrared, and on chromatography could be separated into a mixture of the olefin (40%) and a substance having the properties expected of the tertiary alcohol (IIc, 31%). The modification of the Hofmann reaction employed, using potassium carbonate and methyl iodide,[2] is one which would not be expected to afford high yields of olefin,[5] and the formation of alcohols in the Hofmann reaction is not without precedent.[5] When the secondary amine was converted to the corresponding tertiary amine (IId), and the quaternary hydroxide pyrolyzed,[2] the product still showed distinct hydroxyl absorption in the infrared, and this method was not investigated in any greater detail. Good yields of pure exocyclic olefin were ultimately obtained by converting the tertiary amine to the N-oxide (IIe) with peracetic acid,[6] followed by pyrolysis. Direct thermal treatment of the N-oxide gave much charring, and consequently the N-oxide was boiled in dimethylformamide, whereupon the olefin was smoothly produced in good yield. The choice of dimethylformamide as a solvent was based on the observation of Cram, *et al.*,[7] that the rate of many elimination reactions are enhanced by the use of the very polar solvent, dimethyl sulfoxide. It was felt that a similar polar solvent, dimethylformamide, would also show this rate-enhancing effect, and would provide a suitable alternative to direct pyrolysis. Although the possibility of contamination of the exocyclic olefin formed in this manner with double bond isomers cannot be *a priori* excluded, the definitive experiments of Cope on monocyclic systems,[8] combined with the conversion of the olefin thus formed to a crystalline diol in high yield (*vide infra*) makes this possibility seem most unlikely.



I



IIa. R = CO_2H
b. R = $NHCH_3$
c. R = OH
d. R = $N(CH_3)_2$
e. R = $N(CH_3)_2$ → O



III

When an attempt was made to oxidize the olefin, prepared by the Hofmann elimination, to the desired ketone (I), using permanganate–manganese sulfate–pyridine,[9] a complex mixture of products was obtained, which could be separated into acid and neutral fractions. The multicomponent neutral fraction was devoid of the desired ketone and was not investigated further. The acid fraction showed carbonyl absorption in the infrared at 5.85 and 5.97 μ, indicating that the material was a keto acid, with a conjugated ketonic carbonyl.

Analysis of the dinitrophenylhydrazone of the ethyl ester of this keto acid indicated that the parent compound had the empirical formula, $C_{19}H_{24}O_3$. This

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[1] Abstracted from the thesis presented by R. F. Stockel in partial fulfillment of the requirements for the Ph.D. degree, June, 1962.

[2] H. H. Zeiss and W. B. Martin, *J. Am. Chem. Soc.*, **75**, 5935 (1953).

[3] (a) A. Brossi, H. Gutman, and O. Jeger, *Helv. Chim. Acta*, **33**, 1730 (1950); (b) R. P. Jacobsen, *J. Am. Chem. Soc.*, **75**, 4709 (1953).

[4] G. Stork and A. W. Burgstahler, *ibid.*, **73**, 3544 (1951).

[5] A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 317 (1960).

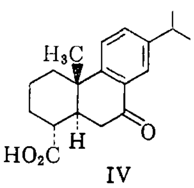
[6] A. C. Cope and H. H. Lee, *J. Am. Chem. Soc.*, **79**, 964 (1957).

[7] D. J. Cram, D. A. Scott, and W. D. Nelson, *ibid.*, **83**, 3696 (1961). Following the completion of our work at room temperature Cope elimination in dimethyl sulfoxide was reported by D. J. Cram, R. V. Sahyun, and G. R. Knox, *ibid.*, **84**, 1734 (1962).

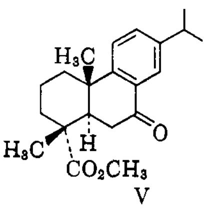
[8] A. C. Cope and C. L. Bumgardner, *ibid.*, **79**, 960 (1957).

[9] K. Yamakawa, *J. Org. Chem.*, **24**, 897 (1959).

compound was tentatively assigned the structural formula IV, 1-α-carboxy-9-ketonordehydroabietane.[10] Confirmatory evidence for this structure was obtained from the following data. The ultraviolet spectrum of IV is very similar to that of methyl-9-ketodehydroabietate (V) and in addition the 2,4-dinitrophenylhydrazones of IV and V show similar ultraviolet spectra. This spectral data is summarized in Table I. The oxidation of methyl dehydroabietate with the permanganate–manganese sulfate mixture afforded the 9-keto compound (V) in good yield.



IV



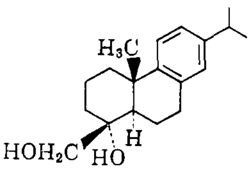
V

TABLE I

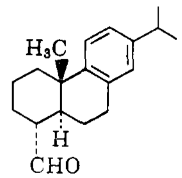
ULTRAVIOLET SPECTRA

	λ_{max}, mμ	log ε
Methyl-9-ketodehydroabietate V	252	3.93
IV	253	3.36
2,4-Dinitrophenylhydrazone of V	383	4.56
2,4-Dinitrophenylhydrazone of IV	386	4.40
2,4-Dinitrophenylhydrazone of 1-keto-3,4,4-trimethyldihydronaphthalene	405	4.49
2,4-Dinitrophenylhydrazone of VIII	402	4.47

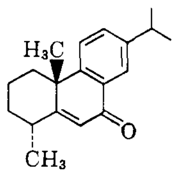
The keto acid was prepared by an independent route from the olefin (III) obtained by the Cope reaction. Treatment of the olefin with osmium tetroxide afforded 1β-hydroxymethyl-1α-hydroxydehydroabietane (VI)[11] which on boiling in formic acid gave the aldehyde (VII).



VI



VII



VIII

Oxidation with chromic acid, followed by Fischer esterification gave a keto ester, identical in all respects to the material obtained from the acid fraction of the permanganate oxidation.

Ozonization of the olefin (III) prepared by the Cope reaction, or periodic acid oxidation of the glycol (VI) gave good yields of rather pure 1-ketonordehydroabietane (I). On the other hand ozonization of the olefin prepared by Zeiss's method gave a 38% yield of I and 15% of a second ketone of empirical formula $C_{19}H_{24}O$. The infrared spectrum of this compound, and the ultraviolet spectrum of its dinitrophenylhydrazone (Table I) were very similar to those of 1-keto-3,4,4-trimethyldihydronaphthalene,[12] and it is probable that this compound is the dienone (VIII). The feasibility of oxidation at C-9 by ozone was demonstrated when methyl-9-ketodehydroabietate was obtained from the ozonization of methyl dehydroabietate.

Although it has been suggested that 1-ketonordehydroabietane exists with either an exclusively or largely *cis* A-B ring fusion,[13] there is little published definitive evidence on this point. The optical rotatory dispersion curve of I shows a strongly positive Cotton effect,[14] and since the absolute stereochemistry about the angular methyl group in the resin acids is the same as that in the steroids,[15] application of the octant rule[16] confirms the conclusion that I has a *cis* ring fusion.

Experimental[17]

N-Methyl-1-aminodehydroabietane.—This compound was prepared from dehydroabietic acid using the method of Zeiss.[2] From 63 g. of dehydroabietic acid 45 g. (75%) of crude amine was obtained. This was purified *via* the hydrochloride, m.p. 199–201° dec., lit.,[2] m.p. 199–202° dec. The hydrobromide, m.p. 240–241° dec., was also used to effect purification.

Anal. Calcd. for $C_{20}H_{32}BrN$: C, 65.57; H, 8.74; N, 3.82. Found: C, 65.38; H, 8.63; N, 4.13.

N,N-Dimethyl-1-aminodehydroabietane.—This compound was best prepared by the following modification of Zeiss's procedure.[2] A mixture of 3.77 g. of 90% formic acid, 2.8 g. of formalin, and 4.1 g. of N-methyl-1-aminodehydroabietane was heated under reflux for 4 hr. The excess water, formaldehyde, and formic acid were removed *in vacuo*, the residue made basic with 10% sodium hydroxide and extracted with ether. The ether layer was washed with water, dried, and the solvent removed to give 3.90 g. (91%) of tertiary amine. This material was sufficiently pure for the following step, and was characterized as the picrate, m.p. 199–200°.

Anal. Calcd. for $C_{27}H_{36}N_4O_7$: C, 61.34; H, 6.86; N, 10.59. Found: C, 61.51; H, 6.88; N, 10.47.

Δ^1-*exo*-Dehydroabietene.—(a) The secondary amine was treated with potassium carbonate and methyl iodide in ethanol as described by Zeiss to give a pale yellow oil, which showed infrared absorption at 2.90, 6.10, and 11.3 μ. From 3.2 g. of amine 2.8 g. of product was obtained, 2.25 g. of which were taken up in hexane and chromatographed on Merck alumina. Elution with hexane gave 1.10 g. of colorless oil, having an infrared spectrum identical to that of the olefin prepared by the Cope reaction (*vide infra*). Elution with benzene gave 0.23 g. of oil showing multiple bands in the infrared between 5.78 and 6.05 μ, and which gave no precipitate with 2,4-dinitrophenylhydrazine reagent. This oil was not investigated further. Finally, elution with chloroform afforded 0.86 g. of colorless oil, which showed infrared absorption at 2.90 μ. Although we were unable to obtain any solid derivatives of this compound, it is almost certainly 1-hydroxydehydroabietane.

(b) To a solution of 1.56 g. of the dimethylamine in 20 ml. of ether was added 24 g. of methyl iodide, and the reaction mixture kept in the refrigerator for several days. The solvent was decanted, and the resulting viscous material dissolved in methanol and treated with 1.0 g. of freshly prepared silver oxide. The resulting slurry was stirred 2 hr. at room temperature, the silver

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[10] Although we have no direct evidence for the stereochemistry of the carboxyl group, it seems probable that it would be in the more stable α (equatorial) configuration.

[11] Although there is no proof of the stereochemistry of this material it would be expected that osmium tetroxide would attack the olefin from the least hindered side, to afford VI.

[12] J. W. Huffman and T. W. Bethea, unpublished work.

[13] (a) G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **84**, 284 (1962); (b) N. N. Saka, B. K. Ganguly, and P. C. Dutta, *ibid.*, **81**, 3670 (1959).

[14] We would like to thank Dr. Werner Herz of Florida State University for carrying out the optical rotatory dispersion studies on this compound.

[15] E. Kyburz, B. Riniker, H. R. Schenk, H. Heusser, and O. Jeger *Helv. Chim. Acta*, **36**, 1891 (1953).

[16] C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill, New York, N. Y., 1960, p. 178.

[17] Melting points were determined on a Hershberg melting point apparatus and are corrected. Infrared spectra were carried out in chloroform solution, as liquid films, or in potassium bromide pellets on a Perkin-Elmer Model 137 spectrophotometer. Ultraviolet spectra were carried out in ethanol or chloroform on a Perkin-Elmer Model 4000A spectrophotometer. Rotational values were run in ethanol or chloroform using a Rudolph Model 70 polarimeter.

salts filtered off, washed with methanol, and the solvent removed at 55–60° and water pump pressure. The distillate was collected in a cold trap, and on treatment with alcoholic picric acid gave 0.44 g. of trimethylamine picrate, m.p. 223–224° dec. The oily residue which remained after removal of the methanol weighed 1.1 g. (87%) and showed infrared absorption at 2.90 μ (alcohol), in addition to the peaks present in the pure olefin.

(c) To 3.5 g. of the tertiary amine at 0° was added slowly 5.36 ml. of 40% peracetic acid,[18] and the mixture allowed to stand at 0° for 30 min., and then overnight at room temperature. The reaction mixture was neutralized with iced 10% potassium hydroxide, extracted with ether, the ether layer washed with water, dried, and the solvent removed at reduced pressure to give 3.4 g. of oily amine oxide. This material was dissolved in 50 ml. of dimethylformamide and the reaction mixture heated 3 hr. under reflux in a nitrogen atmosphere. Removal of the solvent *in vacuo* gave a brown oil which was dissolved in hexane and passed through a column of Merck alumina to give 2.16 (89%) of colorless olefin. This material showed no infrared absorption in the 2.8–3.1-μ region and showed clearly absorption at 3.30 μ, 11.30, 7.05, and 6.10 μ which may be associated with olefins of the type $CR_2 = CH_2$.[19] The olefin had $\alpha^{25}\text{D}$ +224° (c 0.973, $CHCl_3$) and $n^{25}\text{D}$ 1.5527. Zeiss[2] gives values of $[\alpha]\text{D}$ +196° and $n^{27}\text{D}$ 1.5500.

Permanganate–Manganese Sulfate–Pyridine Oxidation of Zeiss's Olefin.—To a solution of 14.5 g. of the unchromatographed olefin from procedure a in 350 ml. of pyridine containing 17 g. of manganese sulfate at 0° was added over a period of 90 min. 27 g. of potassium permanganate. The resulting black solution was stirred at 0° for 2 hr. and then at room temperature for five more. The manganese dioxide was removed by filtration through Celite and the solvent removed *in vacuo* to give a dark oil which was dissolved in ether, washed well with water and dilute hydrochloric acid, dried, and the solvent removed at reduced pressure leaving 10.74 g. of yellow oil which showed infrared absorption at 2.90, 5.85, and 6.00 μ. This oil was redissolved in ether, extracted twice with 5% sodium bicarbonate, washed with water, dried, and the solvent removed *in vacuo* to give 6.29 g. of yellow oil. This oil was dissolved in benzene and chromatographed on Bio-Rad AG-7 neutral alumina, to give small quantities of at least five oily compounds, which resisted characterization. The bicarbonate extracts were washed with ether, acidified with dilute hydrochloric acid, and extracted with ether. The ethereal solution was washed with water, dried, and the solvent removed at the water pump to give 3.12 g. of yellow oil, which showed infrared absorption at 5.85 and 5.97 μ. A solution of 0.3 g. of this material in 10 ml. of ether was treated with 10 ml. of ethereal diazomethane (from 0.3 g. of nitrosomethylurea) to give 0.3 g. of 1-α-carbomethoxy-9-ketonordehydroabietane, which showed infrared absorption at 5.78 and 5.97 μ. The keto ester gave a 2,4-dinitrophenylhydrazone, m.p. 179–180°, from ethanol; $\lambda_{\max}$ 386 mμ, log ϵ 4.40.

Anal. Calcd. for $C_{27}H_{32}N_4O_6$: C, 64.52; H, 6.41; N, 11.12. Found: C, 64.67; H, 6.41; N, 10.91.[20]

Cleavage of this derivative with pyruvic acid–hydrobromic acid[21] in the usual fashion and filtration of the crude product through alumina gave the free keto ester as a colorless oil, $[\alpha]^{25}\text{D}$ −12.7° (c 1.89, $CHCl_3$); $\lambda_{\max}$ 253 mμ, log ϵ 3.03.

Methyl 9-Oxodehydroabietate.—(a) To a solution of 1.0 g. of methyl dehydroabietate in 25 ml. of pyridine was added 1.2 g. manganese sulfate and 1.9 g. of potassium permanganate. The reaction was carried out and the product isolated as described in the oxidation of the exocyclic olefin. By this procedure 0.65 g. (65%) of keto ester was obtained. The infrared spectrum was identical to a sample prepared by chromic acid–acetic acid oxidation,[22] and showed $\lambda_{\max}$ 252 mμ, log ϵ 3.93. The 2,4-dinitrophenylhydrazone melted at 184–185°,[23] was undepressed on mixing with an authentic sample, and showed $\lambda_{\max}$ 383 mμ log ϵ 4.40.

(b) A solution of 0.20 g. of methyl dehydroabietate in 20 ml. of ethyl acetate was ozonized at −60° for 15 min., and then swept with oxygen to remove excess ozone. The solvent was removed *in vacuo*, the residue dissolved in 40% aqueous ethanol, and heated under reflux 3 hr. After cooling, the reaction mixture was extracted with ether, the ethereal extracts washed with water, dried, and the solvent removed at the water pump to leave 0.17 g. of oil which showed infrared absorption at 2.90, 5.84, and 5.97 μ. This oil was dissolved in benzene, and chromatographed on Merck acid-washed alumina to give the keto ester which had an infrared spectrum identical to that obtained in part a above. The 2,4-dinitrophenylhydrazone had m.p. and mixed m.p. 181–183°.

1β-Hydroxymethyl-1α-hydroxynordehydroabietane.—To a solution of 0.5 g. of exocyclic olefin, prepared *via* the Cope reaction, in 13 ml. of dry pyridine was added with stirring 0.5 g. of osmium tetraoxide. The reaction mixture was stirred 3 days at room temperature, 15 ml. of water, 1.0 g. of sodium bisulfite, and 6.6 ml. of pyridine were added, and stirring continued 20 min. The mixture was extracted with chloroform, the extracts washed with water and dilute hydrochloric acid, dried, and the solvent removed under reduced pressure to leave 0.55 g. (96%) of white solid. Recrystallization from ether–hexane gave white crystals, m.p. 101–102°; $[\alpha]^{25}\text{D}$ +51.7 (c 0.848, EtOH)

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.73. Found: C, 79.16; H, 9.58.

1α-Carbethoxy-9-ketonordehydroabietane.—A solution of 0.5 g. of the diol in 20 ml. of 97% formic acid was heated at reflux 1 hr. The solvent was removed at reduced pressure, the residue taken up in ether, washed with 5% sodium bicarbonate, and water. The ethereal solution was dried over magnesium sulfate, and the solvent removed *in vacuo* to leave a dark brown oil, which was dissolved in benzene, and chromatographed on alumina. Elution with benzene gave 0.45 g. of colorless oil which showed infrared bands at 3.78 and 5.79 μ, indicative of an aldehyde. Without further purification 0.25 g. of this oil was dissolved in 2 ml. of acetic acid and 0.28 g. of chromic acid in 5 ml. of 4:1 acetic acid–water were added. The solution was allowed to stand at room temperature overnight, 25 ml. of saturated sodium chloride was added and the mixture extracted with chloroform. The chloroform extracts were washed with water until colorless, then extracted with 5% aqueous sodium bicarbonate. The bicarbonate extracts were washed with ether, acidified, and extracted with ether. After drying and removal of the ether 0.17 g. of crude keto acid were obtained. This acid was dissolved in 10 ml. of benzene, 3 ml. of ethanol, 4 mg. of p-toluenesulfonic acid were added, and the mixture heated 12 hr. at reflux under a Dean–Stark water separator. The reaction mixture was washed with 5% sodium bicarbonate, dried over magnesium sulfate, and the solvent removed *in vacuo* to give a yellow oil, the infrared spectrum of which was identical to that of the keto–ester isolated from the permanganate oxidation. The 2,4-dinitrophenylhydrazone had m.p. and mixed m.p. 179–180°.

1-Ketonordehydroabietane.—(a) A solution of 8.0 g. of exocyclic olefin, prepared by the Cope reaction in 100 ml. of ethyl acetate at −60° was ozonized for 20 min. The reaction mixture was allowed to warm to room temperature, the solvent removed at reduced pressure, the residue taken up in 200 ml. of 50% aqueous ethanol and 40 g. of zinc dust added. The resulting mixture was heated at reflux 5 hr., the zinc dust filtered off, and the solvent removed at reduced pressure, leaving 7.2 g. of yellow oil. This oil was dissolved in benzene, and chromatographed on Merck alumina. Elution with benzene gave 6.29 (65%) of colorless oil which showed a single carbonyl band at 5.86 μ. α_{700} +70; α_{589} +85; α_{312} +8000; α_{280} +2100.

The 2,4-dinitrophenylhydrazone had m.p. 91–92°, from ethanol.[24]

Anal. Calcd. for $C_{24}H_{28}N_4O_4$: C, 65.76; H, 6.25; N, 12.74. Found: C, 66.05; H, 6.42; N, 12.84.

When the olefin prepared by Zeiss's method[2] was ozonized, the desired ketone was obtained in 38% yield, and 15% yield of a second ketone, which showed carbonyl absorption at 6.05 μ was obtained on elution of the column with benzene–chloroform mixtures. This material gave an almost black 2,4-dinitrophenylhydrazone, m.p. 230–231°, and showed $\lambda_{\max}$ 402 mμ, log ϵ 4.47.

Anal. Calcd. for $C_{25}H_{28}N_4O_4$: C, 66.94; H, 6.28; N, 12.49. Found: C, 66.82; H, 6.10; N, 12.35.

(b) To a solution of 1.5 g. of glycol from the osmium tetroxide

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[18] We would like to thank the Becco Chemical Division of the FMC Corp. for the gift of a quantity of this material.

[19] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1954, p. 31.

[20] This is actually the derivative of the ethyl ester, ester interchange apparently having taken place during formation of the derivative.

[21] C. Djerassi, *J. Am. Chem. Soc.*, **71**, 1003 (1949).

[22] H. H. Zeiss and W. J. Considine, *J. Org. Chem.*, **24**, 253 (1959).

[23] P. F. Ritchie, T. F. Sanderson, and L. F. McBurney, *J. Am. Chem. Soc.*, **75**, 2610 (1953), give m.p. 184–185° for this derivative.

[24] H. H. Zeiss, ref. 2, gives m.p. 94–96° for this compound.

oxidation in 30 ml. of methanol was added 1.87 g. of periodic acid in 5 ml. of water, and the resulting solution stirred 15 hr. at room temperature. The solvent was removed at reduced pressure, the residue taken up in benzene and filtered through alumina to give 1.11 g. (83%) of 1-ketonordehydroabietane, the infrared spectrum of which was identical to that prepared by ozonization. The 2,4-dinitrophenylhydrazone had m.p. and mixed m.p. 90–91°.

Acknowledgment.—This work was supported by grant RG-7817 from the Division of General Medical Sciences of the National Institutes of Health. We would like to express our thanks to the Hercules Powder Company for generous gifts of dehydroabietonitrile from which the dehydroabietic acid was prepared.

A Synthesis of 5-Chloro-6-ethoxypyrimidines[1]

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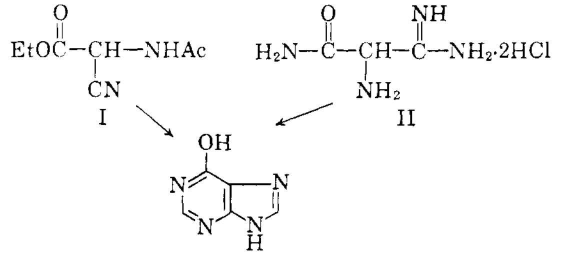
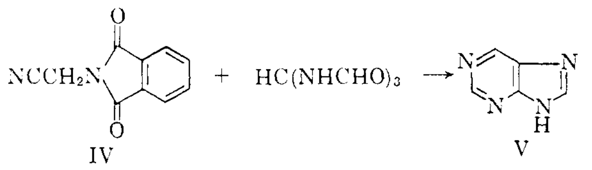
Frick Chemical Laboratory, Princeton University, Princeton, New Jersey

Received July 9, 1962

Condensation of ethyl α-chloro-β,β-diethoxyacrylate with amidines in the presence of sodium ethoxide has been found to give 2-substituted 4-hydroxy-5-chloro-6-ethoxypyrimidines in high yield. An intermediate conjugate addition compound, ethyl α-chloro-β,β-diethoxy-β-guanidinopropionate (IX), was isolated when guanidine was employed. An analogous series of 2-substituted 4-amino-5-chloro-6-ethoxypyrimidines was prepared by the condensation of α,β,β-trichloroacrylonitrile or the imino ether of α-chloro-β,β-diethoxyacrylonitrile with amidines. These 5-chloro-6-ethoxypyrimidines did not react further with amidines to give purines.

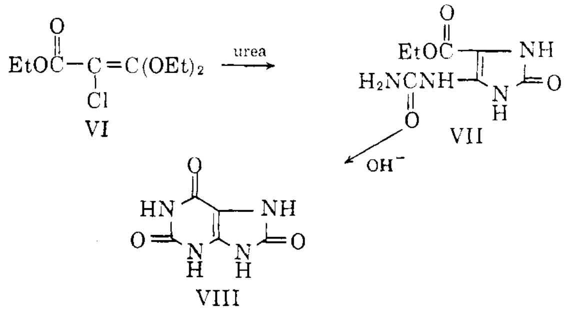
The bicyclic purine ring system is traditionally constructed from either a pyrimidine or imidazole precursor, with subsequent closure of the second ring (imidazole or pyrimidine, respectively), usually in the terminal step of the synthetic sequence.[2] The concept of employing a "skeletal backbone" intermediate which can serve as a building block for both rings is more recent. Examples of this approach to purine synthesis include the synthesis of hypoxanthine (III) in one step either from ethyl acetamidocyanoacetate (I), ammonia and ethyl orthoformate,[3] or from aminomalonamidamidine dihydrochloride (II) and ethyl orthoformate[4] (both reactions proceed *via* the intermediate formation of 4-aminoimidazole-5-carboxamide), and the synthesis of purine from phthalimidoacetonitrile and tris(formylamino)methane[5] (which proceeds *via* the intermediate formation of 4,5-diamino-pyrimidine).





In each of these examples, the 2 and 8 carbon atoms of the completed purine ring were supplied by a single one-carbon reagent.

A number of years ago Sweeting and co-workers[6] reported that the reaction of ethyl α-chloro-β,β-diethoxyacrylate (VI) with urea led first to the formation of 2-hydroxy-4-ureido-5-ethoxycarbonyl-imidazole (VII), which then underwent ring closure in alkali to give uric acid (VIII). This synthesis thus represented a further example of the utilization for purine synthesis of a "backbone" intermediate upon which both the pyrimidine and imidazole rings are constructed with a common second reagent. It appeared possible that the use of other polyfunctional three-carbon intermediates related to acrylic acid or acrylonitrile might extend the usefulness of this approach, and the present paper describes our investigations of this possibility.



By analogy with Sweeting's uric acid synthesis, the reaction of ethyl α-chloro-β,β-diethoxyacrylate with guanidine would be expected to give 2-amino-4-guanidino-5-ethoxycarbonylimidazole which, upon treatment with alkali, should cyclize to 2,8-diamino-6-hydroxypurine. To our surprise, the initial product formed from these two reagents was the conjugate addition compound IX, which cyclized quantitatively upon heating to give 2-amino-4-hydroxy-5-chloro-6-ethoxypyrimidine (X). Even prolonged, vigorous heating of this compound with excess guanidine failed to give a purine. This pyrimidine synthesis is thus analogous to the previously reported condensation of ethyl β,β-diethoxy-

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[2] For recent reviews of synthetic routes to purines, see (a) A. Bendich in "The Nucleic Acids, Chemistry and Biology," E. Chargaff and J. N. Davidson, ed., Academic Press, Inc., New York, N. Y., 1955, p. 81. (b) G. A. Howard in "Chemistry of Carbon Compounds," E. H. Rodd, ed., Vol. IVc, Elsevier Publishing Company, Amsterdam, 1960, p. 1635. (c) J. H. Lister, *Rev. Pure Appl. Chem.*, **11**, 178 (1961).

[3] E. C. Taylor and C. C. Cheng, *Tetrahedron Letters*, **12**, 9 (1959).

[4] E. Richter, J. E. Loeffler, and E. C. Taylor, *J. Am. Chem. Soc.*, **82**, 3144 (1960).

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[6] S. E. Gebura, C. W. Bills, J. D. Park, and O. J. Sweeting, 124th National Meeting of the American Chemical Society, Chicago, Ill., 1953, Abstracts, p. 44-O.