TABLE IV

AMINE HYDROCHLORIDES, C_6H_5—CH(R)—NHR'·HCl

R	R'	M. p., °C.	Chlorine, % Found	Calcd.
n-Pr	Me	150 (dec.)	18.0	17.8
i-Pr	Me	164–165 (dec.)	17.8	17.8
n-Pr	Et	180 (dec.)	16.7	16.6
n-Bu	Et	170 (dec.)	15.7	15.6
Benzyl	Et	235–236 (dec.)	14.2	13.6
Et	*n*-Pr	184 (dec.)	16.8	16.6
Phenyl	*n*-Pr	233–234 (dec.)	13.4	13.6
Et	*n*-Bu	198–199 (dec.)	16.1	15.6
Phenyl	*n*-Bu	195–197 (dec.)	11.2	10.9
Et	Benzyl	172–173	13.7	13.6

were discarded. Sometimes the amine hydrochloride precipitated at this point and could be removed by filtration; otherwise the bright green aqueous layer was made strongly basic with sodium hydroxide (the green color disappeared at this point) and extracted three times with ether. The extracts were dried over potassium hydroxide and distilled. When two moles of Grignard reagent were used per mole of aldimine the yields were excellent (60–90%), but when the reactions were carried out with equimolar amounts, the yields varied with the Grignard reagent, and especially with the alkyl group of the aldimine, as shown in Table I.

The amines were converted to the hydrochlorides in ether solution, and the salts were recrystallized from ethanol-ether mixtures. They were colorless, crystalline, nonhygroscopic solids. The data on the amines and their salts are summarized in Tables III and IV.

Reaction of Butylethynylmagnesium Bromide with Benzylidene Ethylamine.—Butylethynylmagnesium bromide was prepared by the addition of 82 g. (1 mole) of *n*-butylacetylene to a solution of 1 mole of ethylmagnesium bromide in 170 ml. of dry ether. A solution of 55 g. (0.41 mole) of benzylidene ethylamine in 50 ml. of dry ether was added dropwise and the mixture was refluxed for twenty-six hours. Hydrolysis was accomplished in the usual way. Distillation of the dried ether extract gave 32 g. of a viscous oil, b. p. 133–164° (0.5 mm.), which solidified. This product could be recrystallized from alcohol, high-boiling petroleum ether or acetone, and the purified material melted at 87–88°. It was fairly soluble in most organic solvents.

Anal. Calcd. for $C_{15}H_{21}N$: N, 6.5; mol. wt., 215. Calcd. for $C_{18}H_{24}N_2$: N, 10.4; mol. wt., 268. Found: N, 10.7, 10.5; mol. wt., 266. The substance formed a stable hydrochloride which melted at 246° with decomposition. *Anal.* Calcd. for $C_{15}N_{22}NCl$: Cl, 14.09. Calcd. for $C_{18}H_{26}N_2Cl_2$: Cl, 20.8. Found: Cl, 21.34.

Summary

1. Several new amines have been prepared by the action of Grignard reagents on Schiff bases.

2. The effect of structure of the aldimine and of the Grignard reagent on the yield of amine has been determined.

NOTRE DAME, INDIANA RECEIVED JULY 20, 1948

[CONTRIBUTION FROM HERCULES EXPERIMENT STATION, HERCULES POWDER COMPANY]

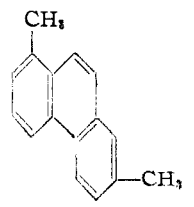
Resin Acids. VII. Isolation and Structure of Isodextropimarinal,[1] a Possible Resin Acid Precursor

BY GEORGE C. HARRIS AND THOMAS F. SANDERSON

Recently Sörensen and Bruun[2] reported the isolation of a tricyclic "diterpene-ketone" ("diterpene-camphor"), with melting point 50–52°, from Scots Fir (*Pinus sylvestris L.*) and termed it cryptopinone. Its purified semicarbazone melted at 223–224° and analyzed for $C_{21}H_{33}ON_3$ corresponding to a carbonyl compound with empirical formula $C_{20}H_{30}O$.

We have recently isolated what appears to be the same substance with melting point 50–52° from the neutral fraction of commercial wood and gum rosins whose source is the longleaf (*Pinus palustris*) and slash (*Pinus caribaea*) pines. Its semicarbazone melted at 223–225° in agreement with that obtained by Sörensen and Bruun from cryptopinone. Its 2,4-dinitrophenylhydrazone was also prepared, melted at 192–194°, and analyzed for a carbonyl compound with empirical formula $C_{20}H_{30}O$. A positive silver mirror test indicated the compound to be an aldehyde. The presence of two double bonds was shown by hydrogenation with palladium–carbon catalyst in methylcyclohexane and platinum oxide catalyst in acetic acid; one double bond was more resistant to hydrogenation.

The structure of the new aldehyde was determined as follows. It was shown to possess a hydrophenanthrene nucleus related to the pimaric-type acids since on dehydrogenation pimanthrene (I) was isolated in fairly good yield. As in the case of the pimaric-type acids[3] the trialkylated naphthalene hydrocarbon (II) was also isolated from the dehydrogenation mixture. The



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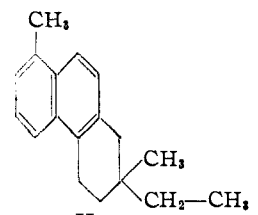


II

separation of the two hydrocarbons was readily accomplished by passing a hexane solution of the dehydrogenation mixture of hydrocarbons through a column of silica gel and separating two fractions,

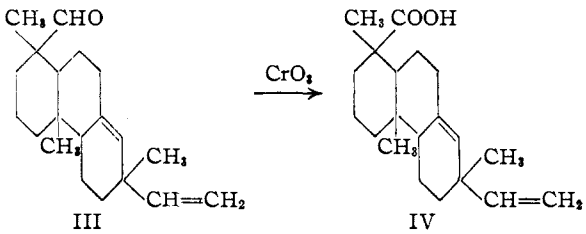
(1) The aldehyde of isodextropimaric acid has been termed isodextropimarinal. The acid was described by the authors in "Resin Acids. III," THIS JOURNAL, 70, 2079 (1948).

(2) N. A. Sörensen and T. Bruun, *Acta Chem. Scand.*, 1 [1], 112 (1947).

(3) G. C. Harris and T. F. Sanderson, "Resin Acids. IV," THIS JOURNAL, 70, 2081 (1948).

one (naphthalene derivative) that is transparent to ultraviolet irradiation and the other (pimanthrene) that demonstrates an intense violet coloration on irradiation with ultraviolet light. The carbonyl group was further shown to be in angular (or gem) configuration since the same hydrocarbons I and II were isolated from the dehydrogenation of the ethyl Grignard product of the carbonyl compound.

The aldehyde was ultimately shown to be a resin acid aldehyde and possess the structure represented by formula III after it was oxidized with chromic acid to obtain isodextropimaric acid (IV) in good yield.



III IV

Experimental

Isolation of Isodextropimarinal.—A 10-kg. sample of N wood or gum rosin was dissolved in 20 kg. of diethyl ether in a nitrogen atmosphere, and agitated vigorously with a "Lightnin" stirrer for thirty minutes with a solution of 1.2 kg. of sodium hydroxide in 38 kg. of distilled water previously sparged with nitrogen. The emulsion was allowed to separate, the aqueous layer siphoned and washed several times with fresh ether. The ether extracts were combined, concentrated, extracted further with 1% aqueous sodium hydroxide, washed with water, dried over sodium sulfate and the ether evaporated to obtain 960 g. of neutral material with acid number 3 to 5 from various runs.

The distillation of the neutral fraction was carried out at 1.0 mm. pressure to obtain a number of cuts between 133 to 188°. The aldehyde was found concentrated in the cuts that distilled between 148 and 152° and was separated from the mixture as its semicarbazone, m. p. 223–225°. The total amount present in the distillate was determined by the preparation of its very insoluble 2,4-dinitrophenylhydrazone, m. p. 192–194°, and found to be approximately 4.5% of the total neutral fraction.

Anal. Calcd. for $C_{26}H_{36}N_4O_4$: C, 66.78; H, 7.55; N, 12.00. Found: C, 66.90, 66.85; H, 7.59, 7.45; N, 12.10, 11.99.

The aldehyde was regenerated from its semicarbazone by refluxing the latter for twenty-four hours in 200 cc. of ethanol containing a solution of 50 cc. of concentrated sulfuric acid in 200 cc. of water. It was then distilled at 1.0-mm. pressure and a center cut crystallized from acetone and water, m. p. 50–52°.

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.89, 83.84; H, 10.52, 10.52.

A positive silver mirror test was obtained when a small sample of the crystalline compound was added to Tollens reagent prepared by the addition of a 2% solution of ammonia to 2 cc. of a 5% solution of silver nitrate containing 1 drop of 10% sodium hydroxide to the disappearance of the silver oxide.

Hydrogenation of Isodextropimarinal.—A 1.0-g. sample of the aldehyde was dissolved in 50 cc. of methylcyclohexane in an atmospheric pressure hydrogenation unit. A 1.0-g. sample of 5% palladium–carbon catalyst was added and the system filled with hydrogen. One mole of hydrogen was absorbed in approximately one hour according to the rate shown in Fig. 1, Curve 1. The presence of a more hindered double bond was shown by the hydrogenation of 1.0 g. of the pure aldehyde in 50 cc. of glacial acetic acid in the presence of 50 mg. of Adams catalyst. Two moles of hydrogen were absorbed at a rate shown in Fig. 1, Curve 2, at the end of six hours.

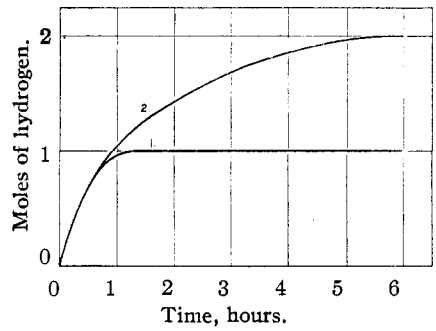


Fig. 1.—Hydrogenation of isodextropimarinal (1) in methylcyclohexane with palladium–carbon catalyst, and (2) in glacial acetic acid with Adams catalyst.

Dehydrogenation of Isodextropimarinal.—A 2.0-g. sample of the crystalline aldehyde was mixed intimately with 2.0 g. of 5% palladium–carbon catalyst and the mixture heated at 300–330° for four hours. The dehydrogenated product (1.3 g.) was filtered from the catalyst in ether solution and placed on a column of silica gel (commercial, average mesh 200, from the Davison Chemical Corporation) in hexane solution. The separation of the hydrocarbons is an easy one in that the first 500 cc. of hexane percolate containing the naphthalene derivative (0.7 g., 54% yield) was transparent to ultraviolet irradiation and subsequent hexane percolates, containing the pimanthrene (0.4 g., 30% yield) showed an intense violet coloration on irradiation with ultraviolet light. The trinitrobenzolates of each of the hydrocarbons was prepared by treating the latter with a saturated alcoholic solution of trinitrobenzene. That of pimanthrene (I) melted at 154–155° and that of the C_{18} hydrocarbon (II) at 122–124° as reported earlier.[3]

Dehydrogenation of the Grignard Product.—A 1.6-g. sample of the crystalline aldehyde in ether solution was added to an ether solution of an ethyl Grignard reagent prepared from 1.5 g. of magnesium and 6.6 g. of ethyl bromide. At the end of the addition, the clear solution was refluxed for one hour. The complex was decomposed with ammonium chloride and 1.7 g. of ethyl derivative isolated that could not be made to crystallize. It was then dehydrogenated at 300–330° for four hours with palladium–carbon catalyst and the same products obtained in the same yield as in the case of the dehydrogenation of the pure aldehyde.

Chromic Acid Oxidation of the Aldehyde.—To a solution of 2.8 g. of the pure aldehyde in 25 cc. of acetic acid was added a solution of 3.7 g. of chromic acid in 6 cc. of water and 12 cc. of acetic acid at 30–35°. The solution was stirred at this temperature for one hour after the addition. At the end of this time the solution was diluted with water and extracted thoroughly with diethyl ether. The ether solution was in turn washed well with water and separated into alkali-soluble and alkali-insoluble fraction by extraction with 1% aqueous sodium hydroxide.

The alkali-insoluble fraction (2.0 g.) was essentially unchanged starting material. The alkali-soluble material (1.1 g.) was treated with butanolamine in methyl acetate solution to precipitate the crystalline amine salt which was recrystallized once from methyl acetate. The pure resin acid was regenerated and crystallized by adding mineral acid to an alcohol solution of the salt and water to the resulting solution to incipient turbidity. The pure acid was obtained in 44% yield (0.35 g.) with melting point 158–161°. A mixed melting point with an authentic sample of isodextropimaric acid[1] showed no depression. An X-ray diffraction pattern of the oxidation product was identical

to that of isodextropimaric acid, thus confirming its identity.

Summary

The aldehyde of isodextropimaric acid, termed isodextropimarinal, has been isolated from the neutral fraction of both wood and gum rosins. Its identity was proved by oxidation with chromic acid to obtain the pure resin acid in good yield.

WILMINGTON, DELAWARE RECEIVED JULY 12, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Sterols. VI. 16-Methyltestosterone

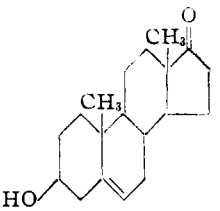
BY PERCY L. JULIAN, EDWIN W. MEYER AND HELEN C. PRINTY

The synthesis of homologs and analogs of the naturally-occurring steroidal hormones has elicited our interest not only with reference to the relation between physiological specificity of these regulators and chemical structure, but also with regard to the structural requirements necessary for the highest therapeutic efficiency. Thus while a naturally-occurring hormone might be much more active than a synthetic analog, when administered parenterally, the latter may conceivably show much greater therapeutic efficiency when administered orally, because of resistance to destruction or inactivation by metabolic processes. It therefore becomes important to define the structural limits within which physiological specificity might be correlated with therapeutic efficiency. As part of a broad program devoted to such considerations,[1] we have been particularly interested in the various possible methyl-testosterones. This paper reports the synthesis of a 16-methyltestosterone.

As one route to the various possible 16-methyltestosterones, we have chosen the Mannich reaction applied to dehydroisoandrosterone (I). Although the Mannich reaction has been employed extensively for the preparation of α-substituted cyclic ketones,[2] its application to steroidal ketones has not been recorded in the literature. This application offers many intriguing possibilities for the synthesis of a variety of new steroid-hormone types, especially in view of the fact that the majority of the steroid hormones are either ketonic in nature or may be readily derived from parent ketonic substances.

The condensation of dehydroisoandrosterone (I), dimethylamine hydrochloride and paraformaldehyde proceeded smoothly in isoamyl alcohol to yield the Mannich base, 16-dimethylaminomethyldehydroisoandrosterone (II). Similar condensations with piperidine hydrochloride and diethylamine hydrochloride gave the corresponding 16-aminomethyl derivatives of dehydroisoandrosterone (I). These steroidal amines formed hydrochlorides which were soluble in water to the extent of about 10 mg./ml.

In order to achieve our immediate goal, the



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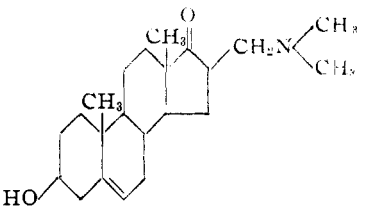

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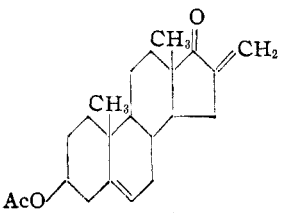
preparation of 16-methyltestosterone, it was necessary to eliminate dimethylamine from the amino-ketone (II). This elimination took place readily in acetic acid–acetic anhydride to yield 16-methylenedehydroisoandrosterone acetate (III). This method affords an interesting alternative to the known methods[2] for elimination of amines from β-alkylaminoketones.



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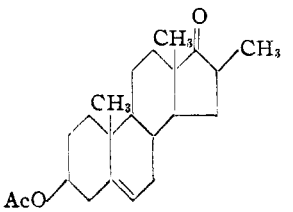

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Several 16-alkylidene-dehydroisoandrosterones have been described previous to the present investigation. Butenandt, Schmidt-Thomé and Weiss[3] prepared 16-alkylidene derivatives in poor yield by the condensation of dehydroisoandrosterone (I) with acetone and methyl ethyl ketone in the presence of sodium or sodamide. Ross[4] recorded an improved preparation of 16-isopropylidenedehydroisoandrosterone.

16-Methylenedehydroisoandrosterone acetate (III) possesses a light absorption maximum at 228 mμ (log ϵ = 3.9), a value in good agreement with that (225 ± 5 mμ) postulated by Woodward[5] for an α-substituted α,β-unsaturated ketone. The hydrogenation of this ketone in the presence of Raney nickel catalyst proceeded in a stepwise fashion; the first mole of gas was absorbed rapidly, while the second was taken up more slowly. By stopping the reaction after the rapid addition, there was isolated from the reaction mixture a

(1) Cole and Julian, THIS JOURNAL, 67, 1369 (1945).

(2) *Cf.* Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 303-341.

(3) Butenandt, Schmidt-Thomé and Weiss, *Ber.*, 72, 417 (1939).

(4) Ross, *J. Chem. Soc.*, 25 (1945).

(5) Woodward, THIS JOURNAL, 63, 1123 (1941); 64, 76 (1942).