Ketonic cleavage[15] of methyl α-isovalerylisovalerate gave a 63% yield of di-isobutyl ketone, b. p. 164–166°. The semicarbazone melted at 121.2–121.8°.[16] Acidic cleavage gave isovaleric acid, identified by its anilide, m. p. 109–111°.[18]

Summary

1. The carbethoxylation of di-isobutyl ketone with diethyl carbonate, which fails in the presence of sodium ethoxide, has been effected by means of sodium triphenylmethide to form ethyl α-isovalerylisovalerate. An attempt to carbethoxylate methyl ethyl ketone using this base in conjunction with ethyl 4-phenylphenyl carbonate has failed.

2. Four ketones, which are not carbethoxylated in the presence of sodium ethoxide, have been carbonated using sodium triphenylmethide and the resulting β-keto acids esterified with diazomethane to form the corresponding methyl β-keto esters.

3. The β-keto esters have been characterized by suitable reactions. The methyl group of methyl ethyl ketone was shown to undergo carbonation.

4. The relative amounts of carbonation and carbethoxylation of ketones that sodium triphenylmethide is capable of effecting is considered in connection with the mechanism of these reactions.

DURHAM, N. C. RECEIVED FEBRUARY 29, 1944

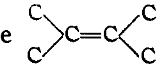
[CONTRIBUTION FROM THE HERCULES EXPERIMENT STATION, HERCULES POWDER COMPANY]

Resin Acids. The Structure of the Lactone of Hydroxytetrahydroabietic Acid[1]

BY RICHARD F. B. COX

The lactonization of dihydroabietic acids derived from abietic and levo-pimaric acids has always led to a single individual lactone melting at 131–132°. No stereoisomeric lactones have yet been produced from these dihydroabietic acids even though acids of rotations −30° to +108° have been investigated. This lactone appears, therefore, to be characteristic of the abietic family of dihydro acids.

Although the lactone has been known for many years[2a] there is very little known about its structure. Hasselstrom[2b] at one time suggested that on the basis of a γ-lactone structure the point of lactonization is probably C-10. Fleck and Palkin[3] then attempted to prove this structure by oxidizing the hydroxytetrahydroabietic acid obtained on saponification of the lactone. Under no conditions were they able to effect an oxidation to a keto acid which would be expected on the basis of Hasselstrom's formula. Moreover, they were unable to esterify the hydroxyl group of the free acid or its methyl ester. They concluded, therefore, that the hydroxyl group must be in a tertiary position which, to fit the molecular models, must be at C-4b.[2a]

It was expected that more concrete evidence in favor of formula I for the lactone might be given by an investigation of the reactions of the dihydroabietic acids produced by dehydration of the hydroxytetrahydroabietic acid. For example, only the Fleck and Palkin formula would be expected to lead to a dihydroabietic acid (4b, 8a) having the  $\genfrac{}{}{0pt}{}{C}{C}\!>\!C{=}C\!<\!\genfrac{}{}{0pt}{}{C}{C}$ type of double bond which will give a blue nitrosyl chloride derivative.

The stability of the lactone and the ease of lactonization of the hydroxytetrahydroabietic acid under dehydration conditions appeared at first to oppose this method of approach. It was then discovered in the course of our work on resin acids that the lactone underwent a reaction with methylmagnesium iodide which resembled a dehydration in that the product was a mixture of dihydroabietic acids.

The reaction appeared to be an abnormal Grignard reaction as a result of the highly hindered position of the carbonyl group of the lactone. One mechanism to explain the results is shown below.

According to this mechanism, the methylmagnesium iodide first forms a coördination complex (II) with the lactone, as a result of which the carbonyl carbon becomes deficient in electrons. The resulting increased attraction for the oxygen in the bridge then causes the formation of a carbonyl from this oxygen and a shift in the electron deficiency to C-4b. Simultaneously the methyl radical is freed to combine with the activated protons at positions 8a and 5 (III). The end-result of this rearrangement is thus the formation of the dihydroabietic acids as their magnesium salts (IV and V).

Since the gases produced in the reaction included hydrogen, it appears as though the protons at C-5 and C-8a have been displaced completely to combine either with another proton or the methyl radical. Thus the presence of hydrogen leads to the assumption that part of the

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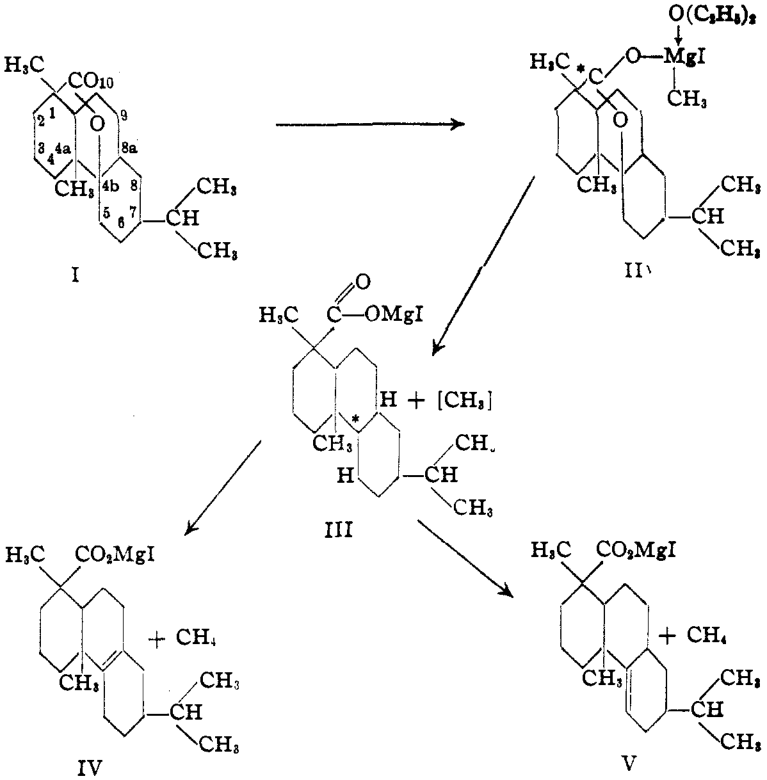
[1] Presented before the Division of Organic Chemistry at the 106th meeting of the American Chemical Society, Pittsburgh, Pennsylvania, September 7, 1943.

[2a] Ruzicka and Meyer, *Helv. Chim. Acta*, **5**, 333 (1922); Ruzicka, Waldmann, Meier and Hösli, *ibid.*, **16**, 178 (1933).

[2b] Hasselstrom and McPherson, THIS JOURNAL, **60**, 2340 (1938).

[3] Fleck and Palkin, THIS JOURNAL, **61**, 3197 (1939).



liberated methyl radicals combined to form ethane.

Further study of the reaction showed that the yield of the dihydroabietic acids is consistently about 69% of that expected even though a large excess of the methylmagnesium iodide is used. Likewise the ratio of the dextro to the levo acid remains constant at about 65:35 under varying conditions of reaction and ratios of reactants. Further study of the mechanism of this interesting reaction is not contemplated.

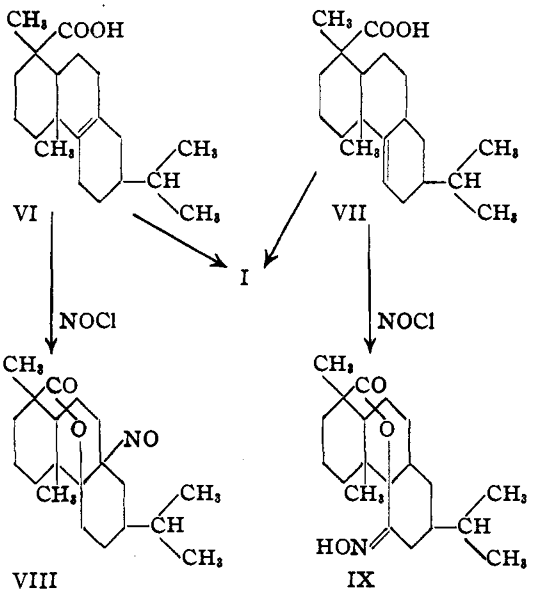
The dihydroabietic acids formed by the reaction of methylmagnesium iodide on the lactone differed sufficiently in crystal size when recrystallized from acetone that they were readily separated from each other by a combination of screening and crystallization. The acid of smaller crystal size melted at 185–186° and had a specific rotation −36°. The other dihydroabietic acid melted at 147–148° and had a specific rotation +68°. The properties of these acids are listed in Table I.

Both of these dihydroabietic acids produced from the lactone were stable in boiling acetic acid but lactonized readily in the presence of a little mineral acid. The lactone produced melted at 131–132° and was the same lactone which is produced from all other dihydroabietic acids. In 7.5% alcoholic hydrochloric acid the lactonization at 75°F. (24°C.) could be followed polarimetrically. The data showing the change in rotation during the course of such a lactonization are given in Table II. While the dextrorotatory acid appeared to lactonize the more readily, these data cannot be interpreted exactly without further knowledge of the products. When the lactonization products were isolated after 430 hours and titrated for unlactonized resin acid, the dextrorotatory acid was shown to have lactonized to the extent of 45% and the levorotatory acid to the extent of 35%. The rotations of the unlactonized acids after separation from the lactone showed that the dextrorotatory acid had undergone isomerization while the levorotatory acid was unchanged in rotation. The change in rotation of the dextrorotatory acid from +68° to acids of rotation +22° indicated the possibility that the isomerized acid mixture was 44% levorotatory acid and 56% dextrorotatory acid which is approximately the ratio of these acids as produced in the reaction between the Grignard reagent and the lactone. Apparently the levorotatory acid is more stable toward isomerization.

In regard to hydrogenation, the dextrorotatory dihydroabietic acid absorbed hydrogen the more readily. The rates of hydrogen absorption (Table III) show that after twenty-seven hours the dextrorotatory acid had absorbed 85% of the theoretical amount of hydrogen while the levorotatory acid had absorbed only 53% of the theoretical amount. Under the influence of reduced platinum oxide catalyst, as in hydrogenation conditions but in the absence of hydrogen, neither acid appeared to isomerize even after 60 hours treatment. In line with slower rates of hydrogenation and the higher melting points of related sterols having a double bond common to two rings, it was therefore expected that the levorotatory dihydroabietic acid might have the double bond in the 4b, 8a position and would give a blue nitroso derivative.

When the levorotatory dihydroabietic acid was treated with nitrosoyl chloride in acetic acid solution, it gave a blue solution from which a blue nitroso compound crystallized on the addition of water. This blue nitroso derivative contained no chlorine and was also formed by reaction with butyl nitrite and any mineral acid. Its neutral character and its analyses indicated that it probably was a nitrosolactone. It melted at 91.5–92° and had the unusually high specific rotation $[\alpha]_D$ −925° (2% in alcohol). Such high rotations are unknown in the resin acid field. The nitrosolactone underwent typical reactions such as hydrogenation to an aminolactone and it lost its nitroso group by hydrolysis in boiling hydrochloric acid with formation of the lactone of hydroxytetrahydroabietic acid, m. p. 131–132°. Based on these characteristics the nitrosolactone is assumed to have formula VIII.

Since the levorotatory dihydroabietic acid is the more stable toward isomerization, has the higher melting point, and gives a blue nitrosyl derivative, it is presumed to be Δ4b,8a-dihydroabietic acid (VI). Support for the Fleck and Palkin formula of the lactone of hydroxytetrahydroabietic acid is thus established.

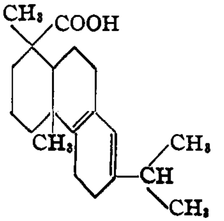


The dextrorotatory dihydroabietic acid when treated with nitrosyl chloride gave difficultly soluble white crystals in a light-blue mother liquor. These crystals melted at 185–186°, $[\alpha]_D$ −30° (1% in $CHCl_3$) and appeared to be an oximinolactone. Hydrolysis with mineral acids did not remove the oximino group but effected what may have been a Beckman rearrangement.[4] Formula IX has accordingly been assigned to the oximinolactone and Formula VII to the dihydroabietic acid from which it was formed.

Neither the dextro- nor the levo-dihydroabietic acid was found by the nitrosyl chloride reaction to be present in hydrogenated rosin or hydrogenated abietic acid. This is as might be expected in the case of abietic acid because of the position of the double bonds unless hydrogenation were accompanied by isomerization. The specificity of the nitrosyl chloride reaction toward certain dihydroabietic acids also indicates that the nitroso and oximino lactones are probably not the result of isomerization of the resin acids prior to addition of the nitrosyl chloride.

In the case of resin acids with one double bond in the 4b, 5 or 4b, 8a position and another in some other position, the more highly hindered 4b, 5 or 4b, 8a double bonds would be expected to be still present after partial hydrogenation. Thus, if rosin contained such resin acids, hydrogenated rosin would have been expected to give the oximinolactone or nitrosolactone.

Likewise, if abietic acid or levo-pimaric acid contained double bonds in the 4b, 5 or 4b, 8a positions, one of the dihydro acids produced from them would be expected to resemble the new dihydroabietic acids. Since there is no resemblance in physical properties between those dihydro acids reported in the literature and the new dihydroabietic acids, levo-pimaric acid probably does not have Formula X which was favored by Fieser and Campbell,[5] but has instead Formula XI which was favored by Ruzicka.[6]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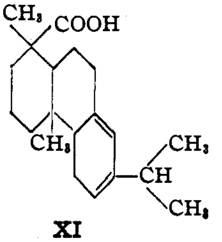
XI

TABLE I

PROPERTIES OF DIHYDROABIETIC ACIDS

		l-Dihydroabietic acid	*d*-Dihydroabietic acid
Formula assigned		VI	VII
Melting point, °C.		185–186	147–148
$[\alpha]_D$ (2% in alcohol)		−36°	+68°
Crystal system		Monoclinic	Monoclinic
Sign of double refraction		+	+
Optic axial angle (2*V*)		80° ± 5°	70° ± 5°
Nitrosyl derivative	Melting point, °C.	91.5–92	184–185
	$[\alpha]_D$ (2% solution)	−925° (alc.)	−30° (chloroform)

TABLE II

ISOMERIZATION OF DIHYDROABIETIC ACIDS

Time, min.	*d*-Dihydroabietic $[\alpha]_D$	*l*-Dihydroabietic $[\alpha]_D$
0	+68	−37
20	+59	−37
30	+57	−37
45	+54	−37
70	+41	−37
100	+40	−35
190	+33	−32
235	+29	−25
285	+19	−26
380	+ 8	−27
430	+ 9	−26

Experimental

Reaction of Lactone of Hydroxytetrahydroabietic Acid with CH_3MgI.—(a) One mole of methylmagnesium iodide was prepared from 24 g. of magnesium and 145 g. of methyl iodide in 750 ml. of ether. To the reagent was slowly added 304 g. of the lactone of hydroxytetrahydroabietic acid, melting point 131–132° in 1000 ml. of dry benzene. A small amount of heat was given off in the reaction. After standing for one hour, the mixture was warmed on

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[4] Investigation not yet completed.

[5] Fieser and Campbell, THIS JOURNAL, **60**, 159 (1938).

[6] Ruzicka and Kaufman, *Helv. Chim. Acta*, **23**, 1346–1356 (1940).

TABLE III

HYDROGENATION OF DIHYDROABIETIC ACIDS

Time, min.	Hydrogen absorbed by 0.450-g. samples Acid $[\alpha]_D$ −36°, ml.	Acid $[\alpha]_D$ +68°, ml.
0	0	0
72	8.1	16.6
96	8.8	19.2
160	10.8	22.2
205	12.1	23.5
253	12.6	23.4
301	13.2	24.0
349	13.7	24.1
1330	18.1	27.0
1655	17.9	27.2

the steam-bath under reflux for sixteen hours, during which time much of the ether was lost. At the end of this time all of the reagent had been used up. The mixture was washed with 5% ammonium chloride and then with water. Then the ether and benzene were distilled off to get a brownish residue. This was crystallized from acetone to get three fractions: (1) lactone, melting point 131–132°; (2) an acid, melting point 145–150°; (3) an acid, melting point 185–186°. The acid of melting point 145–150° weighed about twice as much as the higher melting acid. The acids were further purified by conversion to their sodium salts in alcohol followed by dilution with water to allow non-acidic materials to precipitate. After filtering, the acids were again isolated and recrystallized from ethyl acetate. The purified low melting acid melted at 147–148° and had a specific rotation (2% in alcohol) +68.00°. *Anal.* Calcd. for $C_{20}H_{32}O_2$: C, 79.0; H, 10.6; equiv. wt., 304. Found: C, 78.7, 78.9; H, 10.45, 10.47, neut. equiv., 305.5. It was unsaturated to $C(NO_2)_4$ and lactonized readily in sulfuric acid to the lactone melting point 131–132°.

The high melting acid was recrystallized from ethyl acetate to a constant rotation. Its melting point was then 185–186° and its specific rotation −36° (2% in alcohol). It was unsaturated as shown by testing with tetranitromethane and lactonized in sulfuric acid to the lactone, melting point 131–132°. Its neutral equivalent was 304, which is the theoretical for a dihydroabietic acid. *Anal.* Calcd. for $C_{20}H_{32}O_2$: C, 79.0; H, 10.6. Found: C, 78.9, 79.0; H, 10.49, 10.52.

In crystallizing these two acids it was found that the large stubby prisms of the lower melting acid could be separated by screening from the small needles of the higher melting acid. In using this method of separation, purification was achieved quite readily, only three cystallizations being necessary to reach the stage where the properties were constant.

(b) One-tenth mole of methylmagnesium iodide was prepared in the usual manner from 15 g. of methyl iodide and 2.3 g. of magnesium using ether as the solvent for the methyl iodide. To this Grignard solution at room temperature was added 30.4 g. of lactone, melting point 131–132°, in dry benzene. When addition was complete, the ether was distilled and the mixture was heated overnight on the steam-bath. The product was then poured into ice water containing 25 g. of ammonium chloride. The benzene layer was then extracted with 2% sodium hydroxide, extract acidified and the acids recovered, dried and weighed: 21.0 g. (69%), N. E., 295 (trace of HCl still remaining), $[\alpha]_D$ +29° (1% in alcohol), bromine no. 74.5; yield calculated from specific rotation, 62.5% $[\alpha]_D$ +68° acid, 37.5% $[\alpha]_D$ −36° acid.

This run was repeated using the same amount of magnesium and methyl iodide but only 15.2 g. of lactone. The same procedure was followed and the acids extracted, dried and weighed; wt. 8.0 (52%), N. E., 295; $[\alpha]_D$ +32° (1% in alcohol); yield calculated from specific rotation, 65% $[\alpha]_D$ +68° acid, 35% $[\alpha]_D$ −36° acid.

Reaction of the Lactone at Room Temperature with CH_3MgI.—The reaction of 0.1 mole of the lactone with 0.1 mole of Grignard reagent described above was repeated exactly except that the reaction mixture was allowed to stand at room temperature overnight instead of being heated overnight. The product, worked up in the usual manner, weighed 29.6 g. It yielded on extraction with alcoholic alkali, 3 g. of acid mixture. This yield of acids is only about one-quarter the yield obtained at the higher temperature.

Quantitative Study of Reaction between Lactone and Methylmagnesium Iodide.—A solution of methylmagnesium iodide was made by combining 2.5 g. of magnesium and 15.6 g. of methyl iodide in 80 ml. of phenetole. To this reagent in a nitrogen atmosphere in a closed vessel fitted with a gas evolution device was added 30.4 g. of lactone in 100 ml. of dry benzene. Some heat was given off and the temperature accidentally rose to 45°. The gas evolution was 305 ml. (760 mm., 0°). The reaction mixture was then heated by boiling water for one and one-half hours. During this time the total gas evolution was 2100 ml. (760 mm., 0°).

Analysis of gas	Sample 1, %
Methane and other saturated hydrocarbons	25.6
CO_2	0.0
Unsaturates	1.0
Oxygen	11.2
CO	0.0
H_2 by CuO	1.4
H_2 by slow combustion	11.1
Nitrogen	49.7

After the heating period the addition of ethyl alcohol caused no gas evolution showing that the reagent had all reacted. The product was worked up without heating and extracted with alkali to isolate 13.4 g. of acids of which about 9 g. melted at 147–148° and 5 g. melted at 185–186°. These results may be tabulated as

	Moles
Lactone	0.100
Methylmagnesium iodide	.109
Methane (saturated hydrocarbons)	.022
Hydrogen	.010
Dihydroabietic acids	.044

If we assume the formation of one mole of ethane for each mole of hydrogen produced, the gases contain 0.012 mole of methane (from 0.012 mole CH_3MgI). Thus 0.032 mole of CH_3MgI is accounted for in the gases formed and 0.044 mole of CH_3MgI in the dihydroabietic acids produced.

Reaction of the Dihydroabietic Acids with Nitrosyl Chloride.—(a) 0.3 g. of dihydroabietic acid, melting point 185–186° $[\alpha]_D$ −36°, was dissolved in 5 ml. of glacial acetic acid containing 0.2 ml. of butyl nitrite. Then 5 ml. of glacial acetic acid containing 0.2 g. of dry hydrogen chloride was added. After standing overnight at 25°, the solution was a dark greenish-blue. About 5 ml. of water was added dropwise to effect crystallization and the resulting light-blue crystals weighing 0.2 g. were filtered out. These crystals melted at 88–88.5° and were recrystallized from a minimum amount of methanol at −70° to raise the melting point to 91.5–92°. The specific rotation $[\alpha]_D$ was −920° (0.2% in alcohol); −925° (2% in alcohol). *Anal.* Calcd. for $C_{20}H_{31}O_3N$: N, 4.2. Found: N, 4.49; Cl, nil.

(b) 0.3 g. of dihydroabietic acid, melting point 147–148°, $[\alpha]_D$ +68°, was dissolved in 5 ml. of glacial acetic acid containing 0.2 ml. of butyl nitrite and 5 ml. of acetic acid containing 0.2 g. of dry hydrogen chloride was added. The mixture turned dark amber but within two hours was light-blue with white crystals in suspension. The crystals were removed by filtration and were washed with alcohol in which they are very insoluble. The yield was 0.1 g., melting point 169–170°. These crystals were recrystallized from a chloroform–methanol mixture to a constant melting point 184–185°; $[\alpha]_D$ −30° (2% in $CHCl_3$). *Anal.* Calcd. for $C_{20}H_{31}O_3N$: N, 4.2. Found: N, 4.33; Cl, nil.

(c) 42 g. of a mixture of dihydroabietic acids produced by the reaction of methylmagnesium iodide on the lactone of hydroxytetrahydroabietic acid was dissolved in 300 ml. of glacial acetic acid. To this solution was added 30 ml. of butyl nitrite and 450 ml. of glacial acetic acid containing 31 g. of hydrogen chloride. The mixture turned dark and then gradually greenish-blue and crystals separated. The crystals were removed by filtering and were washed once with methanol. They weighed 3 g. and were oximino lactone crystals, melting point 185–186°. The mother liquor was diluted cautiously with water to get 16.3 g. of blue crystals, melting point 91–92°, and 3 g. of white crystals of lactone, melting point 130–131°.

(d) To a solution of 0.3 g. of dihydroabietic acid, melting point 185–186°, $[\alpha]_D$ −36°, in 5 ml. of glacial acetic acid, was added 0.2 ml. of butyl nitrite and then 5 ml. of glacial acetic acid containing 0.2 ml. of concentrated nitric acid (d. 1.42). After two hours at room temperature, water was added to get crystals which were recrystallized from methanol at −70°, melting point 91.5–92°, $[\alpha]_D$ −905° (1% in alcohol).

Reduction of the Blue Nitrosolactone.—To a solution of 2 g. of lactone of hydroxynitrosotetrahydroabietic acid $[\alpha]_D$ −925° in 75 ml. of ethanol was added 2 g. of sodium sulfide (hydrated) in 14 ml. of 70% alcohol. The mixture was refluxed for one hour during which time the blue-green color disappeared. Water was added dropwise to produce crystals and to dissolve inorganic salts. The crystals were taken up in ether and converted to the amine hydrochloride by bubbling hydrogen chloride into the solution. Gradual addition of petroleum ether caused crystals to separate. The free amine was then liberated by neutralizing a methanol solution of the salt with dilute sodium hydroxide. The free amine was then crystallized by diluting the methanol solution with water and was further purified by crystallization from methanol until a melting point of 144–145°, $[\alpha]_D$ ±1° (1.76% in alcohol) was reached. *Anal.* Calcd. for $C_{20}H_{33}O_2N$: N, 4.37. Found: N, 4.27.

Hydrogenation of the Blue Nitrosolactone.—0.268 g. of nitrosolactone, m. p. 91.5–92.5°, $[\alpha]_D$ −925° (2% in ethanol), was dissolved in 10 g. of glacial acetic acid. To this solution was added 0.265 g. of $PtO_2 \cdot H_2O$ (Adams platinum oxide catalyst). The solution was shaken with hydrogen at atmospheric pressure in an apparatus for measuring the volume of hydrogen absorbed. A blank was run on the catalyst in acetic acid at the same time and applied as a correction for the hydrogen absorbed by the catalyst. The corrected volume of hydrogen absorbed was 33.9 ml.

After removal of the catalyst the product was precipitated by adding water. The crystalline aminolactone was then crystallized from methanol. It melted at 146–147° and was shown by mixed melting point to be the same amine which was obtained by reducing the blue nitrosolactone with sodium sulfide.

Hydrolysis of Nitrosolactone—A solution of 1 g. of nitrosolactone, m. p. 91.5–92.5°, in 25 ml. of acetic acid containing 10 ml. of concentrated hydrochloric acid was refluxed. The blue color disappeared in about three hours, but the refluxing was continued forty hours. The product was isolated by adding water and then crystallized from methanol. It amounted to 0.35 g., m. p. 130–131°. It was shown by mixed melting point and microscopic examination to be the lactone of hydroxytetrahydroabietic acid.

Acid Isomerization of Dihydroabietic Acids.—A solution of 0.1000 g. of dihydroabietic acid, melting point 147–148°, $[\alpha]_D$ +68° in 10 ml. of glacial acetic acid was refluxed for thirty minutes. The solvent was evaporated and replaced by 10 ml. of ethanol. The rotation was unchanged by this treatment. Similar treatment of dihydroabietic acid melting point 185–186°, $[\alpha]_D$ −36° did not change the rotation.

A solution of 0.1000 g. of dihydroabietic acid in 5 ml. of ethanol was diluted to 10 ml. with alcoholic hydrogen chloride (15 g. of HCl gas in 100 ml. of solution). The rotation was determined immediately and was followed at 75°F. (29°C.) for twenty days. The change in rotation for both the dextro- and the levo-dihydroabietic acids is given in Table II.

After 430 hours of isomerization, the product was recovered by evaporation and dried over sodium hydroxide pellets *in vacuo*. Titration of these residues indicated that 35% of the levorotatory acid had been converted to the lactone and 45% of the dextrorotatory acid had been converted to the lactone. The lactone was removed from the neutralized solutions by ether extraction and the acids were recovered from the salts. The acid mixture from isomerization of the dextrorotatory acid was +22° indicating the possibility of about 44% levorotatory acid in the mixture. The acid mixture from isomerization of the levorotatory acid was −37° indicating no isomerization to the dextrorotatory acid.

Hydrogenation of Dihydroabietic Acid.—Samples of dihydroabietic acid weighing 0.450 g. were placed in the flasks of a quantitative hydrogenation apparatus, containing 15 ml. of glacial acetic acid. After the resin acid was dissolved, the solution was cooled and 0.401 g. $PtO_2 \cdot H_2O$ catalyst was added. The sample was shaken under a slight pressure of hydrogen for twenty-seven hours. Both dihydroabietic acids $[\alpha]_D$ +68° and $[\alpha]_D$ −36° and a blank on the catalyst were run simultaneously. The data in Table III are corrected for the blank.

After twenty-seven hours, the dextrorotatory acid had absorbed 85% of the theoretical amount of hydrogen and the levorotatory acid had absorbed 53% of the theoretical amount of hydrogen. In both cases the acid mixtures isolated from solution had $[\alpha]_D$ −6°. By lactonizing the remaining dihydroabietic acid and removing the tetrahydroabietic acids, it was found that the tetrahydroabietic acid in each case had zero rotation. By correcting the crude acid mixtures −6° for the rotation of the tetrahydroabietic acid present the unhydrogenated acid from the dextrorotatory acid had $[\alpha]_D$ −40° and that from the levorotatory acid had $[\alpha]_D$ −12°. This is indicative that the hydrogen absorption of the dextrorotatory acid was decreased by isomerization of the original acid to a levorotatory acid.

In order to determine whether the catalyst caused either or both of the acids to isomerize, 0.45-g. samples of each were added to freshly reduced catalyst and acetic acid and were shaken for sixty hours. After this treatment the levorotatory acid had $[\alpha]_D$ −37° and the dextrorotatory acid had $[\alpha]_D$ +66°, which showed no change from the original acid.

Acknowledgment.—The author wishes to acknowledge the skillful assistance of Mr. Thomas F. Sanderson in carrying out the experimental work reported here.

Summary

The lactone of hydroxytetrahydroabietic acid melting at 131–132° has been converted by the reaction with methylmagnesium iodide into two dihydroabietic acids, m. p. 147–148°, $[\alpha]_D$ +68° and m. p. 185–186°, $[\alpha]_D$ −36°, respectively.

Both of these dihydroabietic acids lactonize readily to give only the original lactone, m. p. 131–132°.

The dextrorotatory dihydroabietic acid reacts with nitrosyl chloride to form an oximino lactone. The levorotatory dihydroabietic acid under the same conditions forms a blue nitroso lactone.

The levorotatory dihydroabietic acid absorbs hydrogen in the presence of a platinum catalyst more slowly than does the dextrorotatory acid. In the process of lactonization, the levorotatory acid lactonizes more slowly and does not isomerize while the dextrorotatory acid lactonizes more

rapidly and at the same time isomerizes to the levorotatory acid.

All of these data support the formula for the lactone of hydroxytetrahydroabietic acid in which the point of lactonization is at C-4b.

WILMINGTON, DEL. RECEIVED JANUARY 6, 1944

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

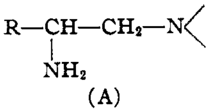
Amino Ketones. II. The Synthesis of α,β-Diamines from α-Amino Ketones*

BY NORMAN H. CROMWELL AND HERMAN HOEKSEMA

In a previous investigation[1] the synthesis of α,γ-diamines from β-amino ketones was reported. It seemed of interest to investigate similar synthesis of α,β-diamines from α-amino ketones to compare the relative yields in the two series.

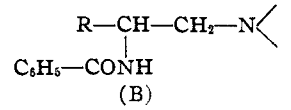
Several investigations[2] by other workers have been concerned with the conversion of α-amino ketones to α-amino alcohols in order that the two series of compounds could be studied for their relative values as pressor agents. A similar comparison of the α-amino ketones with their corresponding α,β-diamino compounds should also prove to be interesting. Furthermore, such α,β-diamino compounds might be converted to the benzamides. It has been shown previously that compounds containing the grouping $-\mathrm{CONH}\overset{|}{\underset{|}{\mathrm{C}}}-\overset{|}{\underset{|}{\mathrm{C}}}-\mathrm{N}\langle$ often possess local anesthetic activity.[3]

Thus a series of diamines (A) and the corresponding benzamides (B) might prove to be of considerable interest, pharmacologically.



$\mathrm{R-\underset{NH_2}{\underset{|}{CH}}-CH_2-N}\langle$

(A)



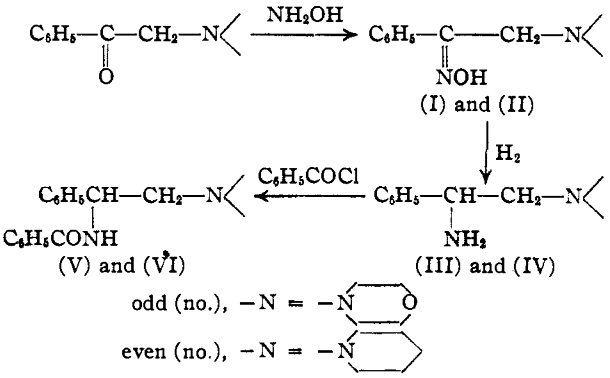
$\mathrm{R-\underset{C_6H_5-CONH}{\underset{|}{CH}}-CH_2-N}\langle$

(B)

Attempts were made to obtain in good yields the oximes of ω-N-methylbenzylaminoacetophenone,[4] ω-tetrahydroisoquinolinoacetophenone[5] and ω-tetrahydroquinolinoacetophenone,[6] without success.

The oximes of ω-morpholino-[2b] and ω-piperidinoacetophenone[7] were both obtained in good yields. An extensive investigation was made of the reduction of one of these, (I), to the corresponding α,β-diamine. Sodium and alcohol was found to be the most efficient of the reagents tried. It was interesting to find that α-amino ketoximes are reduced to give better yields of the α,β-diamines by catalytic hydrogen, than were the β-amino ketoximes to give α,γ-diamines.[1] In the latter case it was shown that β-amino ketoximes lost the β-amino group on such treatment, probably because of the tendency to form an α,β-unsaturated ketoxime. The absence of such a tendency with α-amino ketoximes accounts for their greater yields of diamines on catalytic reduction.

The general low yields of α,β-diamines experienced even with sodium and alcohol were caused by condensation of the diamine with itself, through loss of ammonia during distillation. This was shown by the detection of ammonia in the forerun of such distillations and by treating the crude diamine ether solution with benzoyl chloride, and determining the yield of benzamide obtained.



The benzamides (V) and (VI) were readily prepared in good yields from the corresponding α,β-diamines (III) and (IV).

These benzamides have been found to be strong local anesthetics. The various compounds reported in this paper are being fully investigated for various pharmacological activities by L. W. Rowe and others of the Parke, Davis and Company Laboratories. A detailed pharmacological report will be published by them in another journal.

Experimental[8]

ω-Morpholinoacetophenone Oxime (I).—A cooled solution of 200 g. (4.35 mole) of potassium hydroxide in one liter of methanol was mixed with a solution of 61 g. (0.88

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[1] Cromwell, Wiles and Schroeder, THIS JOURNAL, **64**, 2432 (1942).

[2] (a) Hartung, *Chem. Rev.*, **9**, 435–437 (1931); (b) Rubin and Day, *J. Org. Chem.*, **5**, 54 (1940).

[3] (a) Wenker, THIS JOURNAL, **60**, 158 (1938); (b) Eisleb, U. S. Patent 2,073,100; *C. A.*, **31**, 3211⁷ (1937).

[4] Cromwell and Witt, THIS JOURNAL, **65**, 311 (1943).

[5] Allewelt and Day, *J. Org. Chem.*, **6**, 384 (1940).

[6] Kunckell, *Ber.*, **30**, 576 (1897).

[7] Rabe and Schneider, *ibid.*, **41**, 874 (1908).

[8] Micro Dumas analyses for nitrogen and semi-micro analyses for carbon and hydrogen by the Analytical Laboratory, Department of Chemistry, University of Nebraska, under the supervision of H. Armin Pagel.