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On the Study of Various Reductions of 2-Benzoylcyclopentene-1-carboxylic Acid

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It was found that the Clemmensen reduction of 2-benzoylcyclopentene-1-carboxylic acid (**2a**) did not give rise to 2-benzylcyclopentene-1-carboxylic acid (**1**), but to a mixture of *cis*- and *trans*-2-benzylcyclopentane-1-carboxylic acid (**6a** and **7a**) contrary to the description in literature. Unsaturated acid (**1**) was obtained as a major product by the Wolff-Kishner-Huang-Minlon reduction of **2a** accompanied with 1-carboxy-6-phenylbicyclo[3.1.0]hexane (**8**). The reduction of **2a** with zinc dust in acetic acid and the reduction of the methyl ester (**2b**) by way of its thioketal were also investigated.

Organic chemists have long been interested in selective reduction of conjugated unsaturated carbonyl compounds. A large number of such selective procedures have been published.[1] Since the preparation of 2-benzylcyclopentene-1-carboxylic acid (**1**) was necessary during the course of the other investigations, various reduction procedures of 2-

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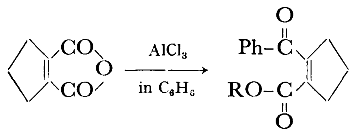
[1] a) E. L. Martin, "Organic Reactions," Vol. I, ed. by R. Adams, John Wiley & Sons, Inc., New York (1942), p. 155; b) G. R. Pettit and E. E. van Tamelen, *ibid.*, Vol. XII (1962), p. 356; c) D. Todd, *ibid.*, Vol. IV (1948), p. 378.

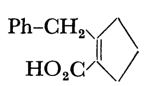
benzoylcyclopentene-1-carboxylic acid derivatives (**2a** and **2b**) were carried out. It may be interesting to study the reduction of this compound because a double bond is placed between a carbonyl group and a carboxyl group. The results will be described in this paper.

Results and Discussion

In 1950 Sengupta and Saha reported the synthesis of the unsaturated keto-acid (**2a**) by the Friedel-Crafts condensation of cyclopentene-1,2-dicarboxylic acid anhydride (**3**) with benzene.[2] They also reported that the Clemmensen reduction of **2a** gave an oil, bp 170—173°C/4 mmHg, which was assigned as the unsaturated acid (**1**). The assignment was based on further reaction sequence including dehydrogenation step into 2,3-trimethylenenaphthalene (**4**).

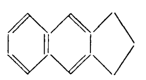


(**3**) (**2a**) R: H
(**2b**) CH$_3$

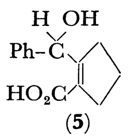


(**1**)

We repeated the synthesis of unsaturated keto-acid (**2a**) according to Saha's method. The IR and NMR spectra of the product support the above postulated formula. Its reduction with $NaBH_4$ gave a hydroxy-acid (**5**), mp 118—119°C, in high yield. It showed a sharp singlet characteristic for benzylic α-hydrogen at $\tau = 3.83$ along with other signals in its NMR spectrum. The results confirmed the presence of a tetrasubstituted double bond adjacent to the benzylic hydroxyl group.

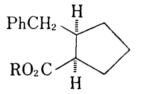


(**4**)

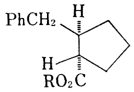


(**5**)

The Clemmensen reduction of **2a**[1a] was carried out with zinc amalgam in concentrated hydrochloric acid and toluene for 30 hr. IR and NMR spectra of the product oil, bp 153—154°C/2 mmHg, suggested that the product was not an α,β-unsaturated acid as reported by Sengupta and Saha but a mixture of saturated acids. Thus, the product was transformed to methyl esters with diazomethane. Vapor phase chromatography of the esters revealed that they consisted of two components, the ratio being about 1 : 2. The predominant component was purified by preparative VPC, followed by elemental analysis. It was shown that the analytical result was consistent not with the calculated value for the unsaturated ester, $C_{13}H_{16}O_2$, but for the saturated ester, $C_{13}H_{18}O_2$. From these data it may be evident that both a carbonyl group and a double bond in the unsaturated keto-acid (**2a**) were reduced in the Clemmensen reduction to give a mixture of *cis*- and *trans*-2-benzylcyclopentane carboxylic acids, **6a** and **7a** respectively.



(**6a**) R: H
(**6b**) CH$_3$



(**7a**) R: H
(**7b**) CH$_3$

Another selective reduction for α,β-unsaturated ketone is desulfurization of its thioketal with excess of Raney-Ni.[1b] Methyl ester (**2b**) of the unsaturated keto-acid was converted into the ethylene thioketal, followed by treatment with large excess of Raney-Ni. Without further purification the oil was subjected to careful VPC analysis. It was then found that the ester was also a mixture of two components identical with the products obtained by the Clemmensen reduction. In this case, however, the ratio of two geometric isomers was reversed, *viz.*, 2 : 1.

The Wolff-Kishner-Huang-Minlon reduction is also a useful procedure for selective reduction of a carbonyl group in an unsaturated ketone.[1c] A number of such examples have been reported.[3] Keto-acid (**2a**) was treated with hydrazine hydrate in concentrated alkaline solution mixed with triethylene glycol, followed by heating the reaction mixture to 220°C for 5 hr. The product thus obtained was a mixture of solids and an oil. The former was readily purified by recrystallization from a mixture of ether and light petroleum as colorless crystals, mp 121—122°C. By its IR spectrum it was suggested that the compound was an α,β-unsaturated acid. In its NMR spectrum, it showed a sharp singlet at $\tau = 2.78$ due to five aromatic protons and a characteristic singlet at $\tau = 7.53$ for two benzylic protons adjacent to a tetrasubstituted double bond, along with other signals. From these data and elemental analysis the crystalline product was identified as 2-benzyl-1-cyclopentene-1-carboxylic acid (**1**).

This unsaturated acid (**1**) was then hydrogenated in glacial acetic acid using the Adams catalyst to give a saturated acid. Its methyl ester was subjected to VPC analysis proving that the ester thus obtained consisted of mainly one isomer contaminated with a small quantity of the other. Since catalytic hydrogenation should preferentially give rise to *cis* isomer, the main product in this hydro-

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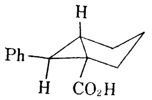
[2] S. C. Sengupta and N. N. Saha, *Current Sci.* (India), **19**, 381 (1950); S. C. S. Gupta and N. N. Saha, *J. Indian Chem. Soc.*, **29**, 331 (1952).

[3] A. Furst, R. C. Berlo and S. Hooton, *Chem. Rev.*, **65**, 51 (1965).

genation experiment could be characterized as *cis*-2-benzylcyclopentane-1-carboxylic acid (**6a**). From a comparison of the chromatogram of this methyl ester with that obtained by the above two other types of reductions, it may be evident that *trans* isomer (**7a**) predominated in the Clemmensen reduction product and that *cis* isomer (**6b**) predominated in desulfurization of thioketal.

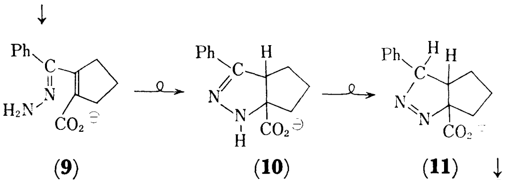
The latter oil produced by the Wolff-Kishner-Huang-Minlon reduction was converted into its methyl ester with diazomethane and was purified by preparative VPC. From both the elemental analysis and spectra data of this methyl ester it was suggested that the compound could be characterized as 1-carboxy-6-phenylbicyclo[3.1.0]hexane (**8**). It may be noted in its NMR spectrum that a doublet at $\tau = 7.10$ with $J = 9$ cps for one proton was assigned to benzylic cyclopropane ring proton and that a multiplet centered at $\tau = 9.85$ for one proton to the other cyclopropane ring proton attached to the bridge head.



(**8**)

In analogy to the other examples$^{4)}$ it seems that the intermediate hydrazone (**9**) might partially rearrange to pyrazoline derivatives (**10** and **11**), in which nitrogen molecule would be eliminated by heating the reaction mixture at higher temperature to form cyclopropane ring. Further experiments to establish the structure of **8** have not been performed.

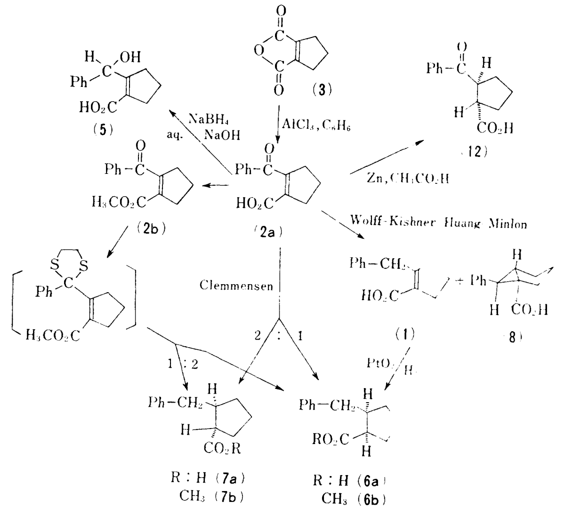
2a



(**9**) (**10**) (**11**) ↓ **8**

The unsaturated dione in which a double bond is inserted between two carbonyl groups has usually been reduced with zinc dust in glacial acetic acid to give a saturated dione$^{5)}$ A similar result was observed in the reduction procedure of an unsaturated keto-acid in which a double bond is placed between a carbonyl group and a carboxyl group.$^{6)}$ Unsaturated keto-acid (**2a**) was treated with zinc dust in glacial acetic acid under reflux for 2 hr. The reaction product, mp 80—82°C, was characterized as 2-benzoylcyclopentane-1-carboxylic acid (**12**) by spectral results and elemental analysis. Since this compound was recovered unchanged from its reaction with aqueous sodium hydroxide solution under reflux, stereochemically, the above product is assumed to be a thermodynamically more stable *trans* isomer.

All the results in the various reductions of substrates (**2a** and **2b**) are summarized in the following chart.



Experimental

2-Benzoylcyclopentene-1-carboxylic Acid (2a). A 200 m*l* three-necked round-bottomed flask was fitted with a mechanical stirrer, a 50 m*l* dropping funnel, a thermometer and a reflux condenser protected from the moisture in the air by means of a calcium chloride tube and also connected with a gas trap for disposing of evolved hydrogen chloride. In the flask was placed 28 g of anhydrous aluminum chloride and 40 m*l* of dry benzene. Ten and a half g of 1-cyclopentene-1,2-dicarboxylic acid anhydride (**3**)$^{2)}$ was added dropwise into the flask immersed in an ice-water bath at such a rate that addition was complete in about a half hour. The reaction mixture was stirred at 0—5°C for 3 hr, at room temperature for 10 hr and then at 40—50°C for 2 hr. Cooling the resulting reaction mixture to room temperature, the mixture was poured slowly into a mixture of 100 g of ice and 50 m*l* of 6N hydrochloric acid with stirring. The light brown precipitate was separated, collected on a Buchner funnel and washed with two portions each of 10 m*l* of benzene and of 20 m*l* of water. After drying the precipitate was dissolved in a 100 m*l* of 10% sodium carbonate solution at 50°C. The solution was filtered and the filtrate was acidified with 6N hydrochloric acid. The precipitate thus formed was filtered and then washed with two portions of 20 m*l* of warm water. The final product was recrystallized from a mixed solvent of methanol and benzene. Fourteen grams of 2-benzoylcyclopentene-1-carboxylic acid (**2a**),

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4) N. Kishner and A. Zavadovsky, *J. Russ. Phys. Chem. Soc.*, **43**, 1132 (1911); Y. R. Naves, *Helv. Chim. Acta*, **25**, 744 (1942); D. Davidson and J. Feldman, *J. Amer. Chem. Soc.*, **66**, 488 (1944).

5) L. F. Fieser and M. Fieser, "Reagents in Organic Synthesis," John Wiley & Sons, Inc., New York (1967), p. 1276.

6) E. Kyburz, M. V. Mijovic, W. Voser, H. Heusser, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **35**, 2073 (1952).

mp 184—185°C (lit,[2] 181—182°C), was obtained in 85% yield. IR (Nujol), 1680, 1660, 1650 and 720 cm^{-1}; NMR ($CDCl_3$), τ, 7.6—7.8 (m, 2H, $-CH_2-$), 7.21 (t, J=7 Hz, 4H, $-CH_2-C=C$), 2.0—2.6 (m, 5H, C_6H_5), 1.56 (s, 1H, CO_2H).

The Reduction of 2a with Sodium Borohydride. Into 20 m*l* of 5% aqueous sodium hydroxide solution which contained 5 g of **2a** was added 1.9 g of $NaBH_4$ dissolved in 20 m*l* of water, then the mixture was heated at 65°C for 30 min. Twenty m*l* of aqueous sodium hydroxide solution was added and the reaction solution was heated under reflux for 1 hr. After cooling the solution was acidified with dilute hydrochloric acid to pH 3. Crude 2-(α-hydroxybenzyl)-cyclopentene-1-carboxylic acid (**5**), mp 116—119°C, was obtained in 89% yield (4.5 g). Its recrystallization from benzene gave pure sample, mp 118—119°C. IR (Nujol), 3270, 1660, 730 and 690 cm^{-1}; NMR ($CDCl_3$), τ 7.9—8.5 (m, 2H, $-CH_2-$), 7.0—7.7 (d. t, J=7 Hz, 4H, $-CH_2-C=C$), 4.83 (s, 1H, CH-O-), 2.3—2.7 (m, 7H, C_6H_5, OH, CO_2H).

Found: C, 71.54; H, 6.47%. Calcd for $C_{13}H_{14}O_3$: C, 71.59; H, 6.66%.

Clemmensen Reduction of 2a. Amalgamated zinc was prepared by shaking a mixture consisting of 32.6 g of mossy zinc, 3.2 g of mercuric chloride, 50 m*l* of water and 1.5 m*l* of concentrated hydrochloric acid for 3 min. On decanting the mixture, the following reagents were added in turn into the flask: 10 m*l* of water, 50 m*l* of concentrated hydrochloric acid, 15 m*l* of toluene and 10.8 g of **2a**. The reaction mixture was boiled with vigorous stirring for 30 hr. Three 10 m*l* portions of concentrated hydrochloric acid were added at approximately 6 hr intervals during the reaction. After cooling, the aqueous layer was diluted with 200 m*l* of water and extracted with three 20 m*l* portions of ether. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed, then 7.6 g of oily product was obtained by distillation, bp 153—156°C/12 mmHg, in 75% yield. IR (neat), 1690, 750 and 710 cm^{-1}; NMR (CCl_4), τ 7.8—8.9 (m, 6H, $-CH_2-$), 7.0—7.8 (m, 4H, $-CH_2Ph$, -CH-), 2.90 (s, 5H, C_6H_5), -1.65 (s, 1H, CO_2H). Its methyl ester was prepared with diazomethane. It was found by VPC analysis that the ester consisted of two components: retention time, 9.2 and 10.0 min; column, SE 30, 1 m, oven temp, 155°C, carrier gas flow rate, N_2, 40 m*l*/min, area ratio, 2 : 1 respectively. The major product was purified by preparative VPC.

Found: C, 77.08; H, 8.23%. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31%.

Reduction of 2b by Way of Its Thioketal. 212 mg of crude methyl 2-benzoylcyclopentane-1-carboxylate (**2b**) prepared from **2a** and diazomethane, and, 310 mg of ethanedithiol were dissolved in 10 m*l* of chloroform, then dry hydrogen chloride was passed into the solution under cooling with ice water over a period of 9 hr. The resulting solution was washed with water, 5% aqueous sodium carbonate solution and water again. Organic layer was dried over anhydrous sodium sulfate. Removing the solvent under reduced pressure, 180 mg of thioketal was obtained. The substance was heated with 3 g of Raney-Ni in 4 m*l* absolute ethanol under reflux for 30 hr. After the reaction mixture was filtered and the solvent was removed under reduced pressure, 91 mg of the crude product was obtained. It was confirmed from VPC analysis that the product was a mixture of two components identical with the Clemmensen reduction product, but their ratio was reversed, namely 1 : 2. In the preparation of the above thioketal, anhydrous zinc chloride could be used instead of dry hydrogen chloride.

Wolff-Kishner-Huang-Minlon Reduction of 2a. A 100 m*l* three-necked round-bottomed flask was fitted with a thermometer and a take-off condenser equipped with a stopcock which might be opened to permit distillation. In the flask were placed 60 m*l* of triethylene glycol and 7.0 g of potassium hydroxide. The mixture was carefully heated with swirling under nitrogen in an oil bath until potassium hydroxide was dissolved. Then 10.8 g of powdered acid (**1a**) was dissolved into the solution under nitrogen atmosphere at 100°C. Further 7.6 m*l* of 80% hydrazine hydrate was added at 80°C and the mixture was heated at 100—120°C for 1 hr. After distilled water was removed from the take-off condenser, the flask was rapidly heated until reflux began. Boiling was continued for 5 hr. The reaction mixture was poured into 50 m*l* of water after cooling, then filtered off. The filtrate was washed with two portions of 20 m*l* of ligroin and acidified with 6N hydrochloric acid. The acidified mixture was extracted with three 30 m*l* of ligroin. The combined organic layer was washed with two portions of 20 m*l* of water and dried over anhydrous sodium sulfate. After most of the solvent was removed under reduced pressure, 5 m*l* of light petroleum was added to the residue. After it had been stood in a refrigerator, solids were precipitated. Collected colorless solids weighed 5.1 g and melted between 90 and 95°C. It was recrystallized repeatedly from the mixed solvent of ether and light petroleum to give a pure sample, mp 121—122°C, which was assigned as 2-benzylcyclopentene-1-carboxylic acid (**1**) from its spectral and analytical results. IR (Nujol), 1670, 740 and 700 cm^{-1}; NMR (CCl_4), τ 7.7—8.6 (m, 6H, $-CH_2-$), 7.53 (s, 2H, $-CH_2Ph$), 2.78 (s, 5H, C_6H_5), 0.05 (s, 1H, CO_2H).

Found: C, 77.36; H, 7.12%. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98%.

The crude oily product was treated with diazomethane to give a mixture of methyl esters, which was found by VPC analysis to consist of two components. The methyl ester other than the ester of **1** was purified by preparative VPC. IR (neat), 1720, 1270, 760 and 700 cm^{-1}; NMR (CCl_4), τ 9.58—10.15 (m, 1H, bridge head H), 7.55—9.00 (m, 6H, $-CH_2-$), 7.10 (d, J=8 Hz, 1H, CH-Ph), 6.38 (s, 3H, CH_3), 2.83 (s, 5H, C_6H_5).

Found: C, 77.64; H, 7.57%. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46%.

Catalytic Hydrogenation of 1. A mixture of 103 mg of 2-benzylcyclopentene-1-carboxylic acid (**1**) dissolved in 10 m*l* of glacial acetic acid and 26 mg of Adams catalyst was shaken under hydrogen atmosphere at 20°C. Eighteen m*l* of hydrogen was absorbed. After the catalyst was filtered, the solvent was removed under reduced pressure. The residue was treated with diazomethane in ether to give its methyl ester. The identity of this ester with that of minor product in the Clemmesen reduction was confirmed by VPC analysis described below.

Vapor Phase Chromatography of the Above Four Methyl Esters. The compounds, **6b**, **7b** and methylesters of **1** and **8**, were clearly separated by

VPC, using a 2 m column packed with Carbowax 20 M coated on Celite 545 in an oven heated at 225°C with a flow rate of carrier gas 40 m*l*/min. Under these conditions the retention times of **6b**, **7b**, **1**-Me and **8**-Me were 7.2, 6.5, 7.8 and 8.2 min respectively.

Reduction of 2a with Zinc Dust and Glacial Acetic Acid. Into a solution of 400 mg of 2-benzoylcyclopentene-1-carboxylic acid (**2a**) dissolved in 20 m*l* of glacial acetic acid was added 1.6 g of zinc dust. The mixture was heated under reflux with stirring for 2 hr. After cooling the miture was filtered and zinc dust washed with small portions of acetic acid. The solvent was removed under reduced pressure. 276 mg of crude product, mp 68—73°C, was obtained. The product was recrystallized from cyclohexane to give a pure sample, mp 80—83°C. IR (Nujol), 1690, 1675 and 719 cm^{-1}; NMR ($CDCl_3$), τ, 7.55—8.52 (m, 6H, $-CH_2-$), 6.20—6.75 (m, 1H, -CH-), 5.65—6.18 (m, 1H, -CH-), 1.92—2.70 (m, 5H, C_6H_5), 0.08 (s, 1H, CO_2H).

Found: C, 71.34; H, 6.54%. Calcd for $C_{13}H_{14}O_2$: C, 71.54; H, 6.47%.

Into a solution of 1 g of sodium hydroxide in 5 m*l* of water was dissolved 133 mg of the above crude product. The mixture was heated under reflux for 4 hr, then acidified with dilute hydrochloric acid and extracted with ether. Evaporation of the solvent gave 110 mg of recovered acid mp 67—70°C. Both the IR and NMR spectra of the recovered acid were essentially consistent with that of the pure sample (**12**).

The authors wish to express their hearty thanks to the late Professor S. Winstein, UCLA, for his encouragement throughout this work, and to Professor Kenji Fukui for his measurement of NMR spectra and to Mrs. Shinobu Imai for her earnest assistance.