or 16-desoxy compounds resulted in the *trans* isomer exclusively for the examples reported.

A mechanism to account for the effect of alkali on the hydrogenation of α,β-unsaturated ketones is proposed.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

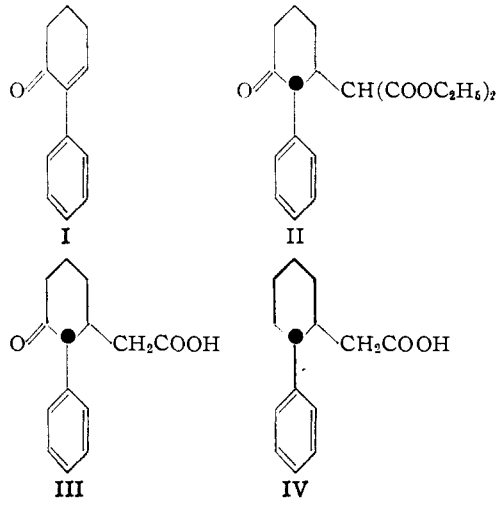
Reactions of 2-Arylcyclohexanones. IV. Michael Addition of Malonic Ester to 2-Phenyl-Δ^2-cyclohexenone

BY W. E. BACHMANN AND E. J. FORNEFELD[1]

Recently Bachmann and Wick[2] described the preparation of 2-phenyl-Δ^2-cyclohexenone (I) by dehydrobromination of the product formed by bromination of 2-phenylcyclohexanone. We have now carried out a Michael addition of diethyl malonate to the α,β-unsaturated ketone and obtained diethyl 3-oxo-2-phenylcyclohexanemalonate (II). As will be shown later, the reaction proceeded sterically in such a manner that the phenyl group and the malonic ester group became oriented in a *trans*-configuration. The reaction was unsuccessful when only small amounts of sodium ethoxide in ether or alcohol or when piperidine in boiling ethanol were used as the medium for the additions, but proceeded satisfactorily in the presence of an equivalent amount of sodium ethoxide and excess diethyl malonate. The successful addition of malonic ester to the unsaturated ketone is in contrast to the failure of diethyl malonate to add to ethyl α-phenylcinnamate, which also has the phenyl group next to the activating group.[3]

The substituted malonic ester II was converted into *trans*-3-oxo-2-phenylcyclohexaneacetic acid (III) by hydrolysis and decarboxylation in a boiling mixture of acetic acid and hydrochloric acid. Clemmensen reduction of the keto acid yielded *trans*-2-phenylcyclohexaneacetic acid (IV). The same acid was obtained when the substituted malonic ester II was subjected to Clemmensen conditions; hence *trans*-2-phenylcyclohexaneacetic acid IV can be obtained from 2-phenylcyclohexanone in a few steps. Confirmation of the structure and configuration of IV was obtained by cyclization of IV to the known *trans* 9-oxo-1,2,3,4-9,10,10a-octahydrophenanthrene. The reactions and intermediates offer promise in the construction of the morphine structure.

Linstead, Whetstone and Levene[4] condensed 2-phenylcyclohexanone with cyanoacetic ester at elevated temperatures and reduced the product to ethyl-2-phenylcyclohexanecyanoacetate. We obtained the last named compound from the ketone in one step at room temperature by carrying out the condensation in the presence of palladium and hydrogen according to the procedure employed by Alexander and Cope[5] on other ketones. Hydrolysis and decarboxylation of the product in a boiling mixture of acetic acid and hydrochloric acid gave *cis*-2-phenylcyclohexaneacetic acid in good yield.



I II III IV

Experimental

2-Phenyl-Δ^2-cyclohexenone (I).—It is essential to use pure 2-phenylcyclohexanone for good results. Following the procedure described,[2] a solution of 1.54 ml. of bromine (reagent grade) in 25 ml. of carbon tetrachloride (reagent grade) was added dropwise to a vigorously stirred, chilled (ice-bath) solution of 5 g. of 2-phenylcyclohexanone (m. p. 58–59°) in 30 ml. of carbon tetrachloride in a current of carbon dioxide. The crystalline bromoketone, which remained after the solution had been washed with water, dried and evaporated under reduced pressure below 30°, was heated with 50 ml. of 2,6-dimethylpyridine in a nitrogen atmosphere for twenty minutes, and the product was isolated as described.[2] After distillation at 0.1 mm. (bath temperature, 145–155°) and recrystallization from petroleum ether (60–75°) the 2-phenyl-Δ^2-cyclohexenone formed colorless needles; yield 3.5 g.; m. p. 93–94.5°.

In one run in which the bromoketone was recrystallized from acetone–petroleum ether, the 2-bromo-2-phenylcyclohexanone melted at 68.5–69° instead of the reported 103–104°. Apparently this represents another crystalline modification, for the melting point rose after several days and after recrystallization of the compound from methanol. It had the correct analysis and yielded the same unsaturated ketone as the higher-melting form.

Michael Addition of Malonic Ester.—To a solution of sodium ethoxide prepared from 0.66 g. of sodium in 50 ml. of absolute ethanol was added 23 g. of diethyl malonate

(1) From the Ph.D. dissertation of E. J. Fornefeld, 1950.

(2) Bachmann and Wick, THIS JOURNAL, **72**, 3388 (1950).

(3) Connor and McClellan, *J. Org. Chem.*, **3**, 576 (1939).

(4) Linstead, Whetstone and Levene, THIS JOURNAL, **64**, 2015 (1942).

(5) Alexander and Cope, *ibid.*, **66**, 886 (1944).

and 5 g. of 2-phenyl-Δ^2-cyclohexenone. The flask was stoppered and the mixture was swirled until it became homogeneous. After forty hours at room temperature the mixture was treated with 2 ml. of acetic acid and 25 ml. of water and the aqueous layer was extracted with ether. The product was separated from the excess malonic ester by fractional distillation; yield, 5.7–6.4 g.; b. p. 180–185° at 0.1 mm. The *trans*-diethyl 3-oxo-2-phenylcyclohexanemalonate (II) was analyzed in the form of its **semicarbazone**, which crystallized from methanol in small colorless rhombs; m. p. 154–155°.

Anal. Calcd. for $C_{20}H_{27}N_3O_5$: C, 61.7; H, 6.9. Found: C, 61.8; H, 6.7.

trans-**3-Oxo-2-phenylcyclohexaneacetic Acid** (III).—A mixture of 2 g. of II, 15 ml. of acetic acid and 25 ml. of concentrated hydrochloric acid was refluxed in a nitrogen atmosphere for fourteen hours. Removal of the solvents under reduced pressure left a liquid which crystallized when scratched under benzene. The keto acid crystallized from benzene in small colorless prisms; yield, 1 g. (71%); m. p. 121–123°, raised to 124–125° by further recrystallization.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.4; H, 6.9. Found: C, 71.6; H, 6.9.

The **methyl ester** of III, which was prepared by refluxing 0.49 g. of the acid with 10 ml. of methanol and 1 ml. of concentrated sulfuric acid for three hours, was recrystallized from petroleum ether (60–75°); yield, 0.35 g.; m. p. 68–70°, raised to 71–73.5° by further recrystallization.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.2; H, 7.3. Found: C, 73.4; H, 7.4.

The **2,4-dinitrophenylhydrazone** of the methyl ester crystallized from methanol in yellow needles; m. p. 126–127°.

Anal. Calcd. for $C_{21}H_{22}N_4O_6$: C, 59.2; H, 5.2; N, 13.1. Found: C, 59.1; H, 5.2; N, 13.0.

trans-**2-Phenylcyclohexaneacetic Acid** (IV).—A solution of 1 g. of diethyl-3-oxo-2-phenylcyclohexanemalonate in 25 ml. of toluene and a mixture of 20 g. of amalgamated zinc, 25 ml. of water and 35 ml. of concentrated hydrochloric acid were refluxed for thirty hours with frequent additions of hydrochloric acid. The reduced acid was extracted from the toluene layer with aqueous bicarbonate and precipitated from the aqueous solution by hydrochloric acid; weight, 0.38 g. (59%); m. p. 109–112°, raised to 112–112.5° by one recrystallization from aqueous methanol. Gutsche[6] has recently reported the literature on this compound.

(6) Gutsche, THIS JOURNAL, **70**, 4150 (1948).

Clemmensen reduction of 3-oxo-2-phenylcyclohexaneacetic acid by the same procedure gave a 61% yield of *trans*-2-phenylcyclohexaneacetic acid; m. p. 110.5–112°.

Treatment of 100 mg. of the acid with 3 ml. of concentrated sulfuric acid on a steam-bath for ten minutes[7] gave *trans*-9-oxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene, which crystallized from aqueous methanol in colorless needles; yield, 60 mg. (65%); m. p. 95.5–96.5°.

cis-**2-Phenylcyclohexaneacetic Acid**.—A mixture of 4.35 g. of 2-phenylcyclohexanone, 5.66 g. of ethyl cyanoacetate, 0.39 g. of ammonium acetate, 0.6 g. of acetic acid, 0.1 g. of palladium-charcoal catalyst and 10 ml. of absolute ethanol was shaken in an atmosphere of hydrogen at room temperature for twenty-four hours. The procedure differed from that of Alexander and Cope[5] for other ketones only in the use of double the amounts of the non-ketonic reagents. After the addition of benzene to the filtered solution, followed by washing with water, acid and aqueous bicarbonate, the product was fractionated under reduced pressure; the fore-run yielded unchanged ketone which crystallized. The ethyl *cis*-2-phenylcyclohexanecyanoacetate was collected at 149–151° and 0.1 mm.; weight, 4.3 g. (64%). When the reaction was carried out for only sixteen hours, the yield dropped to 47%. The product had the correct analysis for nitrogen, but was low in carbon.

A mixture of 1 g. of the cyanoester, 20 ml. of acetic acid, 10 ml. of concentrated hydrochloric acid and 5 ml. of water was refluxed for fifteen hours, an additional 10 ml. of hydrochloric acid was added and the refluxing was continued for three hours. Addition of water and cooling precipitated 0.69 g. (85%) of *cis*-2-phenylcyclohexaneacetic acid; m. p. 165–168.5°. One recrystallization from aqueous methanol gave 0.59 g. (73%) of the acid with m. p. 168–170°. Hydrolysis of the cyanoester by hydrochloric acid alone has been reported to be unsatisfactory.[4]

Summary

The Michael addition of malonic ester to 2-phenyl-Δ^2-cyclohexenone gave *trans*-3-oxo-2-phenylcyclohexanemalonic ester from which *trans*-3-oxo-2-phenylcyclohexaneacetic acid and *trans*-2-phenylcyclohexaneacetic acid were prepared.

The reductive condensation of 2-phenylcyclohexanone with cyanoacetic ester to give ethyl *cis*-2-phenylcyclohexanecyanoacetate is described.

(7) Blumenfeld, *Ber.*, **74**, 524 (1941).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, HARVARD UNIVERSITY]

Oxidation of Steroids. III. Selective Oxidations and Acylations in the Bile Acid Series[1]

BY LOUIS F. FIESER AND SRINIVASA RAJAGOPALAN[2]

In previous papers we reported high selectivity in the oxidation of the 7α-hydroxyl group of cholic acid[3] and the 6β-hydroxyl group of cholestane-3β,5α,6β-triol[4] by use of N-bromosuccinimide in bicarbonate solution or in aqueous acetone, dioxane or methanol–ether. Later experiments have shown that the specificity is associated with the solvent as well as the oxidizing agent and that our comparison of the behavior of N-bromosuccinimide in any of the above solvents with that of N-bromoacetamide in aqueous *t*-butanol[5] was misleading, since the bromoamides are much more powerful oxidizing agents in *t*-butanol than in the other solvents. Thus all three alcoholic functions of cholic acid are oxidized rapidly by either N-bromosuccinimide or N-bromoacetamide in aqueous *t*-butanol (experiments by Renato Ettore to be published

(1) This work was supported in part by grants from the U. S. Public Health Service, the Rockefeller Foundation and Research Corporation.

(2) Fellow of the National Cancer Institute.

(3) Fieser and Rajagopalan, THIS JOURNAL, **71**, 3935 (1949).

(4) Fieser and Rajagopalan, *ibid.*, **71**, 3938 (1949).

(5) Reich and Reichstein, *Helv. Chim. Acta*, **26**, 562 (1943).