[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

Substituted Cyclohexanones: 2-(2',3'-Dimethoxyphenyl)-2-ethylcyclohexanone[1]

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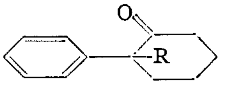
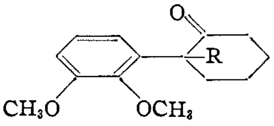
The synthesis of IIB is described; this ketone and its analog IIC were expected to be useful in projected syntheses of certain phenanthrene derivatives. The carbonyl function in IIB and IIC, in contrast to that in IB and IIA, was inert to ketonic reagents and Reformatsky conditions.

The successful synthesis of partially hydrogenated phenanthrenes from 2-arylcyclohexanones *via* the Reformatsky reaction has pointed the way to a number of valuable applications of this method. The ketone IIC was prepared[4] as a precursor for study in a proposed synthesis of tetrahydrodesoxycodeine; the preparation of IIB is described in this paper. Both of these ketones were expected to retain ketonic properties, since IB and IIA have been reported to react normally as far as the formation of derivatives and participation in the Reformatsky reaction are concerned.[5,6] The ketone IA shows no particular effect of steric hindrance, but it might be expected that IB, IIB and IIC would be approximately equivalent in this respect.



IA, R = H
IB, R = $C_2H_4OC_2H_5$



IIA, R = H
IIB, R = C_2H_5
IIC, R = $C_2H_4OC_2H_5$

The ketones IIB and IIC are apparently approximately equivalent in terms of steric hindrance of the carbonyl function, but they differ from IB in that they are virtually unrecognizable as ketones. No reaction was observed with the usual carbonyl reagents, and while a reaction apparently occurred during Reformatsky conditions, the ketones were recovered unchanged at the end of the usual sequence. The apparent reaction was probably due to enolization.[7]

In an attempt to use an active reagent of minimum size and shape which might lead to a useful product, the method of Heilbron,[8] employing ethoxyacetylene, was attempted without success.

These results are in accordance with somewhat similar results obtained with 2,6-dimethyl-2-(*p*-isopropylphenyl)-6-carbomethoxycyclohexanone,[9] except that in the cases described in this paper two substituents in the 2,2-position are sufficient to mask the carbonyl function.

Acknowledgment.—We are indebted to Mrs. Sarah M. Woods for the analyses.

Experimental

All melting points are corrected.

α-(2,3-Dimethoxyphenyl)-α-ethylpimelonitrile.—The alkylation of α-(2,3-dimethoxyphenyl)-pimelonitrile[4] with ethyl iodide was carried out in benzene solution with sodamide, following the general method developed previously for alkylations in this series. From 41.0 g. (0.16 mole) of the starting nitrile, there was obtained 36.1 g. (80%) of colorless viscous oil, b.p. 205–206° (0.6 mm.).

Anal. Calcd. for $C_{17}H_{22}O_2N_2$: C, 71.30; H, 7.74. Found: C, 71.21; H, 7.67.

2-(2',3'-Dimethoxyphenyl)-2-ethyl-6-cyanocyclohexanone Imine.—The cyclization of α-(2,3-dimethoxyphenyl)-α-ethylpimelonitrile was carried out with sodamide in boiling benzene, following the method described for the ethoxyethyl analog. From 24.5 g. (0.085 mole) of the starting nitrile, there was obtained 14.2 g. (58%) of viscous oil, b.p. 196–204° (0.1–0.2 mm.).

Anal. Calcd. for $C_{17}H_{22}O_2N$: C, 71.30; H, 7.74. Found: C, 71.11; H, 7.67.

2-(2',3'-Dimethoxyphenyl)-2-ethyl-6-cyanocyclohexanone.—A solution of 3.0 g. of the iminonitrile in 45 ml. of ethanol and 9 ml. of concd. hydrochloric acid was refluxed for one hour. Isolation of the product yielded 3.0 g. (100%) of crude colorless ketone. Recrystallization from ether–pentane provided an analytical sample, m.p. 106–107°.

Anal. Calcd. for $C_{17}H_{21}O_3N$: C, 71.05; H, 7.37. Found: C, 71.05; H, 7.28.

2-(2',3'-Dimethoxyphenyl)-2-ethyl-6-carbomethoxycyclohexanone.—A solution of 2.0 g. of the ketonitrile in 25 ml. of methanol was saturated with hydrogen chloride, and the mixture allowed to stand for 12 hours. Isolation of the product yielded 1.9 g. of crude keto-ester, which was purified by evaporative distillation (160–175° at 0.1–0.2 mm.) or recrystallization from hexane–ethyl acetate; m.p. 103–104°.

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.52. Found: C, 67.52; H, 7.70.

2-(2',3'-Dimethoxyphenyl)-2-ethylcyclohexanone.—Hydrolysis of the ketoester was effected in aqueous alcoholic potassium hydroxide and was followed by boiling the acidified solution for one hour. Isolation of the neutral product from 32.0 g. of ketoester gave a crude ketone which was evaporatively distilled (95–100° at 0.1–0.2 mm.) to yield 17.6 g. (67%) of colorless, viscous oil. After long standing the ketone solidified and was recrystallized from aqueous ethanol; m.p. 53–54°.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.09; H, 8.28.

2-(2',3'-Dimethoxyphenyl)-2-(β-ethoxyethyl)-cyclohexanone was prepared as described earlier.

Properties of IIA and IIB.—Masking of the ketone function of IIA and IIB, presumably by steric effects, was virtually complete. The usual reagents, including 2,4-dinitrophenylhydrazine, semicarbazide, hydroxylamine and hydrazine, did not react with the ketones. Although a reaction (possibly through the enol form) apparently occurred with zinc and ethyl α-bromoacetate, the ketones were recovered unchanged, and only traces of acidic materials were obtained from the usual Reformatsky procedure followed by dehydration and saponification conditions. The method of Heilbron,[8] using ethoxyacetylene, was also unsuccessful in this application.

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[4] E. C. Horning, M. G. Horning and E. J. Platt, THIS JOURNAL, **70**, 2072 (1948).

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