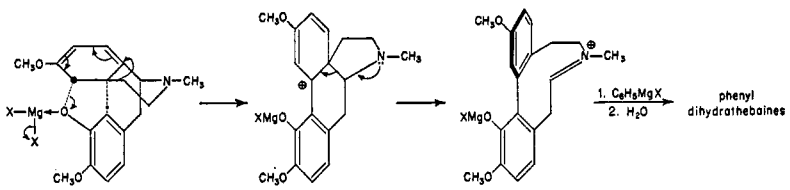
It seems, however, that the process thus described and illustrated is equivalent to the statement that as C_{15} becomes attached to C_{14}, the dihydroanisole ring becomes aromatic and the C_9–C_{14} bond is broken. The more detailed description of Schmid and Karrer has little heuristic value. Further, the detachment of the ethanamine chain as a *cation* is observed only in those morphine derivatives in which the C_9–N bond has previously been broken, thus allowing the stabilization of the incipient C_{15} cation by the spacially proximate basic nitrogen.[18] This situation cannot occur when the C_9–N bond is present and the loss of C_{15} as a cation becomes equivalent to the formation of an unstabilized primary carbonium ion. This applies even more strongly to Schmid and Karrer's representation where the presence of a positive charge on C_9 would make still more difficult the stabilization of a C_{15} cation by the nitrogen electrons.[19]

The change thebaine → phenyldihydrothebaine seems to be most simply represented as



The first step is a simple Wagner–Meerwein rearrangement which is here shown as a concerted process, although this is not an essential feature of the scheme, while the second step is merely the establishment of the aromatic ring with transfer of the positive charge to the nitrogen atom. The resulting asymmetric intermediate now reacts with a phenyl anion with the formation of optically active phenyldihydrothebaines.

(18) The rearrangements of the morphine alkaloids in which the side chain is *not* lost (*e.g.*, apomorphine, morphothebaine, metathebainone, etc.) although sometimes said to be the result of a "cationoid" tendency of the ethanamine chain, obviously never involve C_{15} as a detached cation, since in the migration from C_{13} to C_{14}, C_{15} is always bonded to one or both of these atoms.

(19) The separation of C_{15} as a "cation" is observed only in the special circumstance noted above, *e.g.*, in the change from α-methyl morphimethine to methylmorphol under the influence of HCl.

CAMBRIDGE, MASSACHUSETTS RECEIVED JULY 25, 1951

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

4-Arylcyclohexanones[1]

BY E. C. HORNING,[2] M. G. HORNING, M. S. FISH[3] AND M. W. RUTENBERG[4]

A new method of synthesis of 4-arylcyclohexanones from the corresponding arylacetonitriles is described.

An apparently general method for the synthesis of 4-arylcyclohexanones, from the corresponding arylacetonitriles, is outlined in Fig. 1. We have applied this new sequence of established reactions to the preparation of 4-(3′,4′-dimethoxyphenyl)-cyclohexanone, and have confirmed the validity of the method through the preparation of known 4-phenylcyclohexanone. The trinitrile II, obtained by the Bruson cyanoethylation of I, was converted to the dimethyl ester with hydrogen chloride in methanol. The ester was cyclized through the use of sodium–potassium alloy, without affecting the tertiary nitrile group, to the ester IV. Hydrolysis–decarboxylation of IV in hydrochloric–acetic acid gave V, which was converted to the ketal VI with ethylene glycol. This method of protection of the ketone function was employed by Schinz and Schäppi,[5] in connection with a sodium–alcohol reduction; we have used it here to protect the ketonic group during removal of the tertiary cyano group by the procedure of McElvain.[6] The McElvain method, using sodium and ethanol in toluene, gave excellent results in this application. Hydrolysis of the ketal VII by a method involving steam distillation to remove ethylene glycol proved satisfactory.

4-Phenylcyclohexanone may be obtained from 4-phenylphenol, by reduction to 4-phenylcyclohexanol, followed by oxidation. This method is not sufficiently general to permit its use for the preparation of certain methoxyphenylcyclohexanones, and the procedure described here was therefore developed for this purpose.

Experimental

All melting points are corrected.

γ-Cyano-γ-(3′,4′-dimethoxyphenyl)-pimelonitrile (IIA).—To a solution of 159 g. (0.9 mole) of 3,4-dimethoxyphenylacetonitrile in 300 ml. of *t*-butyl alcohol there was added with stirring 5 ml. of acrylonitrile (freshly distilled) and a solution of 5 g. of potassium hydroxide in 10 ml. of methanol. Acrylonitrile (95 g., 1.8 mole) was added at such a rate that the temperature remained at 30–40°. Stirring was continued for two hours after addition was complete. In order to recrystallize the product, 100 ml. of ethanol (95%) was added, and the mixture was heated until a solution resulted. While cooling and stirring, 200 ml. of water was added, the crystallized product was removed by filtration, washed with 50% ethanol and air-dried. There was obtained 222 g. (86%) of light tan crystals, m.p. 112–114°. Recrystallization from methanol gave a colorless sample, m.p. 112–113°.

Anal. Calcd. for $C_{16}H_{17}O_2N_3$: C, 67.82; H, 6.05. Found: C, 67.95; H, 5.89.

Dimethyl γ-Cyano-γ-(3′,4′-dimethoxyphenyl)-pimelate (IIIA).—A stirred solution of 215 g. of crude γ-cyano-γ-

(1) This paper is taken in part from a thesis submitted by M. W. Rutenberg to the Graduate School of the University of Pennsylvania in partial fulfilment of the requirements for the degree of Doctor of Philosophy. Aided by a Grant-in-Aid form the American Cancer Society recommended by the Committee on Growth of the National Research Council.

(2) National Heart Institute, Bethesda, Maryland.

(3) American Cancer Society Predoctoral Fellow, 1949, 1950.

(4) Bristol Laboratories Fellow, 1948–1949.

(5) Schinz and Schäppi, *Helv. Chim. Acta*, **30**, 1483 (1947).

(6) Walter and McElvain, THIS JOURNAL, **56**, 1614 (1934).

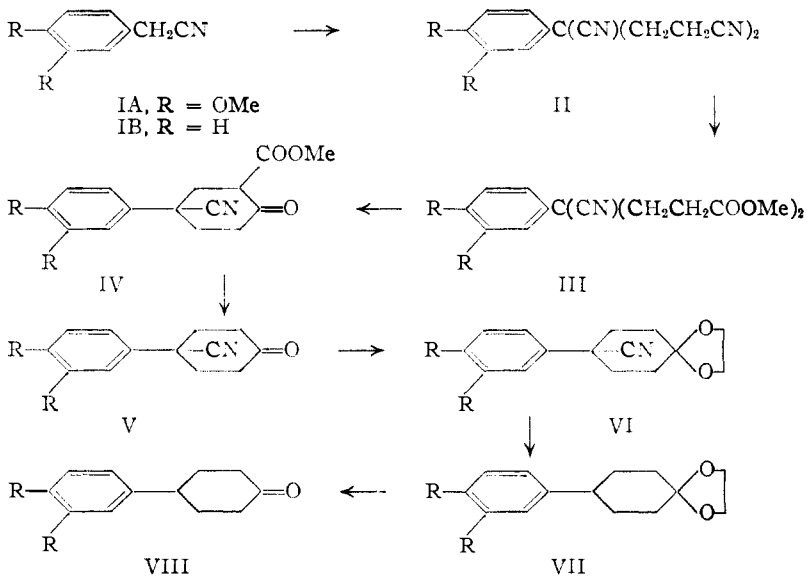


Fig. 1.

(3',4'-dimethoxyphenyl)-pimelonitrile in 975 ml. of methanol was saturated with hydrogen chloride over 30–40 minutes, and then heated under reflux for two hours. The alcohol was removed by distillation and 770 ml. of water was added. The product was extracted with three 300-ml. portions of ether; the extract was washed with 200 ml. of water, three 150-ml. portions of 5% sodium bicarbonate solution, with 200 ml. of water and dried over magnesium sulfate. After evaporation of the filtrate there was obtained 239 g. (90%) of product as a light yellow oil which solidified on standing (m.p. 69–75°). Acidification of the basic wash gave 41.5 g. of acidic material. Recrystallization from methanol provided a colorless sample, m.p. 75–77°.

Anal. Calcd. for $C_{18}H_{23}O_6N$: C, 61.87; H, 6.63. Found: C, 61.76; H, 6.54.

4-Cyano-4-(3',4'-dimethoxyphenyl)-cyclohexanone (VA).—The cyclization was carried out using a potassium–sodium sand prepared from 8.3 g. of sodium and 1.3 g. of potassium in 200 ml. of dry toluene. To the hot toluene suspension there was added with stirring 125.6 g. (0.36 mole) of the ester in 50 ml. of toluene at such a rate that gentle reflux was maintained without external heating. After an additional 50 ml. of toluene was added, the mixture was refluxed for 1.5 hours. Methanol (30 ml.) was added and most of the toluene was distilled from the flask; 50 ml. of acetic acid and 300 ml. of water were added and distillation continued. When the volume was reduced to 300 ml., there were added 100 ml. of concd. hydrochloric acid and 200 ml. of acetic acid, and the mixture was refluxed for three hours. After cooling, the mixture was neutralized with dilute sodium hydroxide and the product extracted with three 300-ml. portions of ether–ethyl acetate (1:1). The extract was washed with three 200-ml. portions of water, 200 ml. of 5% acetic acid, 200 ml. of 5% sodium bicarbonate solution, and with water. After drying and removal of the solvents, there was obtained 72.7 g. (78%) of pale yellow oil which crystallized on standing. Recrystallization from cyclohexane–ethyl acetate gave a colorless product, m.p. 114–116°.

Anal. Calcd. for $C_{16}H_{17}O_3N$: C, 69.48; H, 6.61. Found: C, 69.30; H, 6.42.

8-(3',4'-Dimethoxyphenyl)-8-cyano-1,4-dioxaspiro[4.5]decane (VIA).—In a flask equipped with a stirrer, reflux condenser and water separator were placed 51.8 g. (0.2 mole) of 4-cyano-4-(3',4'-dimethoxyphenyl)-cyclohexanone, 15 ml. of ethylene glycol, 100 ml. of toluene and 200 mg. of benzenesulfonic acid. The mixture was maintained under reflux for four hours during which period slightly more than the theoretical amount of water separated (3.6 ml.). At this point 100 ml. of 5% sodium bicarbonate solution was added and the toluene was removed by steam distillation. After cooling, the crystalline product was extracted with four 200-ml. portions of ether–ethyl acetate (1:1). The extract was washed with 200 ml. of 5% sodium bicarbonate solution, two 200-ml. portions of water and dried. After removal of the solvent, there was obtained 63.6 g. of pale yellow oil. Distillation gave 42.0 g. (69%) of product, b.p. 200–204° (0.5 mm.), m.p. 92–96°. Several recrystallizations from methanol raised the melting point to 98.5–100°.

Anal. Calcd. for $C_{17}H_{21}O_4N$: C, 67.31; H, 6.98. Found: C, 67.60; H, 6.46.

8-(3',4'-Dimethoxyphenyl)-1,4-dioxaspiro[4.5]decane (VIIA).—Sodium sand (18.0 g., 0.78 mole) was prepared in 100 ml. of dry toluene. To the refluxing solution was added 39.4 g. (0.13 mole) of the ketal of 4-cyano-4-(3',4'-dimethoxyphenyl) - cyclohexanone in 100 ml. of toluene and 19 g. of ethanol, at such a rate that refluxing continued without external heating. When the introduction of the ketal was complete, 19 g. of ethanol was added dropwise to decompose the remaining sodium. A final 30 ml. of 95% ethanol was added and the mixture poured into 600 ml. of water. The product was extracted with three 200-ml. portions of ether–ethyl acetate (1:1), and the extract was washed with water, with 5% hydrochloric acid, with 5% sodium bicarbonate solution, and with water, and dried. After removal of the solvent there remained 35.8 g. (99%) of colorless crystalline product, m.p. 77–81°. Recrystallization from methanol raised the melting point to 80–81.5°.

Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.87; H, 7.72.

4-(3',4'-Dimethoxyphenyl)-cyclohexanone (VIIIA).—A mixture of 88.6 g. (0.32 mole) of VIIA, 530 ml. of ethanol, 400 ml. of water and 27 ml. of concd. hydrochloric acid was refluxed for two hours. After the addition of 20 ml. of 1:1 sulfuric acid, the mixture was steam distilled, with a vigorous flow of steam, for one hour. The residual mixture was refluxed for an additional two hours after the addition of 500 ml. of ethanol; after cooling, a slightly discolored product was obtained by filtration. A total yield of 50.3 g. (77%) (m.p. 69–72°) was obtained (two crops). An analytical sample was obtained by chromatographic purification on alumina, followed by recrystallization from methanol, m.p. 76.5–78°.

For preparative purposes, the crude material was generally recrystallized once from methanol; m.p. 75–78°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.82; H, 7.70.

γ-Cyano-γ-phenylpimelonitrile.—By following the usual procedure there was obtained from 105 g. (0.9 mole) of phenylacetonitrile and 95 g. (1.8 mole) of acrylonitrile in 300 ml. of *t*-butyl alcohol, using 5 g. of potassium hydroxide in 10 ml. of methanol as a catalyst, 160–173 g. (80–86%) of colorless crystalline product, m.p. 68–70° (reported[7] m.p. 70°).

Dimethyl γ-Cyano-γ-phenylpimelate (IIIB).—From 89.2 g. (0.4 mole) of γ-cyano-γ-phenylpimelonitrile there was obtained 98–117 g. (84–100%) of product as a nearly colorless oil. This crude diester was cyclized directly.

4-Cyano-4-phenylcyclohexanone (VB).—A sodium–potassium sand was prepared from 8.3 g. (0.36 mole) of sodium and 1.3 g. (0.038 mole) of potassium in 200 ml. of dry toluene. To the hot solution (80–90°) 103.5 g. (0.36 mole) of crude dimethyl γ-cyano-γ-phenylpimelate in 100 ml. of dry toluene was added at such a rate that gentle reflux was maintained without external heating. After addition was complete, the solution was refluxed for 2.5 hours. After cooling, 30 ml. of methanol was added, and the toluene was removed in part by distillation; 50 ml. of glacial acetic acid and 300 ml. of water were added and the distillation continued until the final volume was about 300 ml.

(7) Bruson and Riener, THIS JOURNAL, 65, 23 (1943).

It was possible at this point to isolate **2-carbomethoxy-4-cyano-4-phenylcyclohexanone**. In a separate experiment (starting with 13.7 g. of 4-cyano-4-phenylpimelonitrile) the ester was isolated to yield 13.8 g. (90%) of an oil which solidified on standing, m.p. 89–92°. Purification by evaporative distillation at 100–135° (0.4 mm.) followed by recrystallization from methanol gave a colorless crystalline product, m.p. 95–96°.

Anal. Calcd. for $C_{15}H_{15}O_2N$: C, 70.02; H, 5.88. Found: C, 70.15; H, 5.73.

Hydrolysis and decarboxylation were effected as usual with hydrochloric–acetic acids. From the ether–ethyl acetate extract there was obtained 51–66 g. (73–92%) of light-brown crystalline product, m.p. 76–91°. Recrystallization from benzene–pentane gave colorless crystalline 4-cyano-4-phenylcyclohexanone, m.p. 114.5–115°.

Anal. Calcd. for $C_{13}H_{13}ON$: C, 78.36; H, 6.57. Found: C, 78.36; H, 6.49.

The oxime was recrystallized from dilute methanol, m. p. 150–151°.

Anal. Calcd. for $C_{13}H_{14}ON_2$: C, 72.89; H, 6.59. Found: C, 72.83; H, 6.37.

γ-Cyano-γ-phenylpimelic acid.—A solution of 1.5 g. of dimethyl γ-cyano-γ-phenylpimelate in 20 ml. of 10% sodium hydroxide and 10 ml. of methanol was refluxed for three hours. The solution was diluted with 100 ml. of water and extracted with two 50-ml. portions of ether. Acidification of the alkaline solution gave a colorless crystalline material which was extracted with three 50-ml. portions of ether. After the ether solution had been washed with water and dried, the solvent was removed to yield 1.0 g. of colorless crystalline product, m.p. 165–167°. Recrystallization from water gave a pure sample, m.p. 171–172.5°.

Anal. Calcd. for $C_{14}H_{15}O_4N$: C, 64.35; H, 5.78; neut. equiv., 130.6. Found: C, 64.47; H, 5.62; neut. equiv., 134.

This acid was also produced in 81% yield by the alkaline hydrolysis of 2-carbomethoxy-4-cyano-4-phenylcyclohexanone.

8-Phenyl-8-cyano-1,4-dioxaspiro[4.5]decane (VIB).—From 90.0 g. (0.45 mole) of 4-cyano-4-phenylcyclohexanone there was obtained, after one recrystallization from methanol, 82.4 g. (75%) of ketal, m.p. 123–125.5°. Recrystallization was effected from ether (Dry Ice); m. p. 124–125°.

Anal. Calcd. for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04. Found: C, 73.94; H, 6.91.

8-Phenyl-1,4-dioxaspiro[4.5]decane (VIIB).—Removal of the cyano group was carried out on a 0.35-mole scale to yield 90–95% of product, m.p. 49–50°. Recrystallization from aqueous ethanol gave an analytical sample, m.p. 54–56°.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.10; H, 8.68.

4-Phenylcyclohexanone (VIIIB).—Hydrolysis of the ketal gave 4-phenylcyclohexanone, m. p. 74–77°, in 69–77% yield. A recrystallized sample melted at 77–79° (reported[8] m.p. 76–77°).

(8) Fieser, Leffler, *et al.*, THIS JOURNAL, **70**, 3186 (1948).

PHILADELPHIA, PENNA. RECEIVED JUNE 29, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

Size and Shape of Bovine Fibrinogen[1]

BY COLIN S. HOCKING,[2] MICHAEL LASKOWSKI, JR., AND HAROLD A. SCHERAGA

Flow birefringence and viscosity measurements indicate that the bovine fibrinogen molecule may be approximated by a rigid prolate ellipsoidal model of length 670 Å. and axial ratio 18 to 1. From light scattering a molecular weight of 407,000 is obtained. A comparison of the molecular parameters of bovine and human fibrinogen indicates little difference in the size and shape of these two proteins. The dissymmetry method for determining lengths from light scattering data is not easily applicable to the present system because it is very sensitive to traces of large particle impurities.

Recent results for the length and molecular weight,[3] and for the intrinsic viscosity and sedimentation constant[4] of bovine fibrinogen raise the question of possible differences in the size and shape of bovine and human fibrinogen. Since much attention is being directed to the study of the reactions of these proteins, it was considered desirable to determine some of the molecular parameters of bovine fibrinogen using viscosity, flow birefringence and light scattering techniques, and to compare these parameters with those for human fibrinogen.[5]

Experimental Methods and Results

Materials.—Experimental work was carried out both with fibrinogen samples prepared from fresh steer blood and also from Armour bovine Fraction I. The results reported here were obtained by refractionation of the Armour material using Laki's procedure[6] which gave preparations which were 91–94% clottable with thrombin. All measurements were carried out on freshly fractionated material without drying the protein. The purified fibrinogen solutions were dialyzed against a solution made by mixing 85% by volume of 0.45 *M* NaCl with 15% of sodium citrate buffer of ionic strength 0.45. The final *p*H of the samples was 6.3.

Clottable protein was determined by the gravimetric method of Morrison[7] using Parke, Davis thrombin and the per cent. clottability by that of Laki.[8]

Viscosity.—Ostwald type viscometers having a flow time of two to three minutes with buffer at 25.00 ± 0.02° were used. From a plot of reduced specific viscosity, η_{sp}/c, against concentration of *fibrinogen* in g./100 ml. an intrinsic viscosity of 0.25 was obtained; this value corresponds to an axial ratio of 18 for an unhydrated prolate ellipsoid of revolution[9] if a partial specific volume of 0.725 is assumed.[9]

This value for the intrinsic viscosity confirms that obtained by Nanninga[10] (0.27 at *p*H 7) but is lower than the value 0.34 obtained by Shulman and Ferry[4] who have pointed out that their value may be too high because of a small contribution from non-clottable proteins.

Flow Birefringence.—The apparatus used for the flow birefringence studies has already been described.[11,12]

The orientation theory of Peterlin and Stuart[13] gives the extinction angle, χ, as a function of the parameter $\alpha =$

(1) This work was supported by contract N6-onr 26414 between Cornell University and the Office of Naval Research.

(2) Rotary Foundation Fellow, 1950–1951.

(3) R. F. Steiner and K. Laki, THIS JOURNAL, **73**, 882 (1951).

(4) S. Shulman and J. D. Ferry, *J. Phys. Colloid Chem.*, **55**, 135 (1951).

(5) J. T. Edsall, J. F. Foster and H. Scheinberg, THIS JOURNAL, **69**, 2731 (1947).

(6) We wish to thank Dr. Laki for sending us the details of his purification and assay procedures.

(7) P. R. Morrison, THIS JOURNAL, **69**, 2723 (1947).

(8) R. Simha, *J. Phys. Chem.*, **44**, 25 (1940).

(9) S. H. Armstrong, Jr., M. J. E. Budka, K. C. Morrison and M. Hasson, THIS JOURNAL, **69**, 1747 (1947).

(10) L. Nanninga, *Arch. Neerland. Physiol.*, **28**, 241 (1946).

(11) J. T. Edsall, C. G. Gordon, J. W. Mehl, H. Scheinberg and D. W. Mann, *Rev. Sci. Instruments*, **15**, 243 (1944).

(12) H. A. Scheraga and J. K. Backus, THIS JOURNAL, **73**, 5108 (1951).

(13) A. Peterlin and H. A. Stuart, *Hand. u. Jahrb. d. Chem. Physik, Bd. 8, Abt. IB* (1943).