Study of Stereospecificity in the α-Phenylethylation of the Dicarbanions of Certain β-Diketones in Liquid Ammonia[1]

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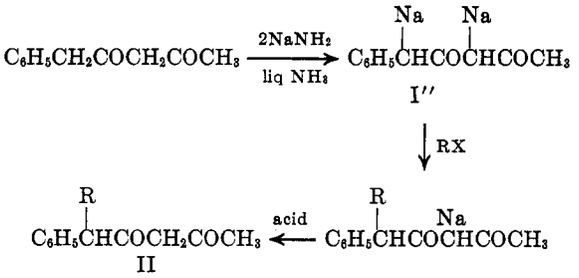
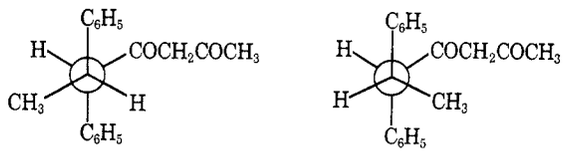
The α-phenylethylations of 1-phenyl-2,4-pentanedione and 1,4-diphenyl-2,4-butanedione were effected with α-phenylethyl chloride through their dicarbanions, which were prepared by means of 2 mol equiv of sodium amide in liquid ammonia. In both of these condensations, only one of the two possible diastereomeric products was isolated, and none of the other isomer could be detected. Each of these diastereomers was shown by independent, stereospecific synthesis to have the *erythro* configuration. Since the *threo* isomer of one of these products was not epimerized appreciably under conditions similar to those of the reaction, the alkylation is considered to follow a stereospecific course.

Recently,[3] alkylation at the benzyl site of β-diketone I was effected with certain alkyl halides to form II through disodio salt I″, which was prepared by means of 2 mol equiv of sodium amide in liquid ammonia (Scheme I). No alkylation at the methyl or α-methylene group was observed.[3]

SCHEME I



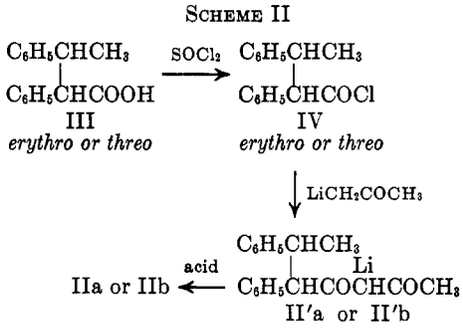
In the present investigation, the stereochemical course of this type of alkylation was studied. Thus, disodio salt I″ was alkylated with α-phenylethyl chloride to form *erythro* isomer IIa; none of *threo* isomer IIb was found.



The general structure of IIa was supported by analysis and absorption spectra (see Experimental Section) and its specific configuration was established by comparison with authentic samples of the two isomers (IIa–b) employing thin layer chromatography (tlc). The tlc method involved visualization of the β-diketones on the silica gel G coated plates by spraying the developed plate with an ethanolic solution of ferric chloride. The resulting colors, characteristic of β-diketones,[4] made an excellent and sensitive method of locating β-diketones on the tlc plate. By examining prepared mixtures of diastereomers IIa–b, it was shown that the tlc technique could detect the *threo* isomer in amounts greater than 5%.

The authentic samples of the two isomers, IIa and IIb, were prepared from *erythro*- and *threo*-2,3-diphenylbutyric acids (III)[5] by means of condensations involving the corresponding acid chlorides (IV) with lithioacetone (Scheme II).

SCHEME II



These acylations of the lithioacetone were evidently stereospecific, since the *erythro* acid chloride IV afforded exclusively the *erythro* β-diketone IIa, and the *threo* acid chloride IV only the *threo* β-diketone IIb. To minimize further acylations of the lithio products II′a–b, 2 mol equiv of the lithio ketone to one of the acid chloride were used.[6]

The α-phenylethylation of disodio salt I″ (see Scheme I) to form *erythro* IIa was realized in 44–48% yield. Although this yield is not high, none of the *threo* isomer IIb appeared to be formed. Thus, the dark oil remaining after isolation of crystalline *erythro* IIa was shown by tlc to contain more of the *erythro* isomer IIa and starting β-diketone I but not the *threo* isomer IIb.

This preferential formation of the *erythro* isomer IIa evidently involved a stereospecific α-phenylethylation of the disodio salt I″, not the possible production of both the *erythro* and *threo* isomers followed by epimerization of the latter isomer. Thus, *threo* IIb failed to be converted to *erythro* IIa in the presence of disodio salt I″ under the conditions employed for the alkylation.[7]

(1) Supported in part at Duke University by the National Science Foundation and at Texas A & M University by the Petroleum Research Fund, administered by the American Chemical Society, and by The Robert A. Welch Foundation.

(2) National Science Foundation Cooperative Fellow, 1965–1966.

(3) K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **31**, 663 (1966).

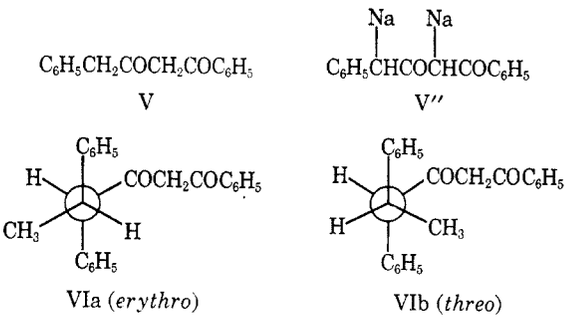
(4) See G. T. Morgan, H. D. K. Drew, and C. R. Porter, *Chem. Ber.*, **58**, 333 (1925).

(5) C. R. Hauser, D. Lednicer, and W. R. Brasen, *J. Amer. Chem. Soc.*, **80**, 4345 (1958).

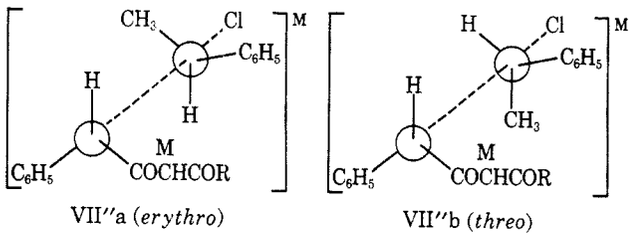
(6) See B. O. Linn and C. R. Hauser, *ibid.*, **78**, 6066 (1956).

(7) It should be mentioned that *threo* IIb was completely converted to *erythro* IIa on treatment with 2 mol equiv of sodium amide in liquid ammonia; apparently some ionization of the benzylic hydrogen occurred to permit this epimerization. However, this did not occur under the usual conditions of alkylation where essentially no excess alkali amide was present.

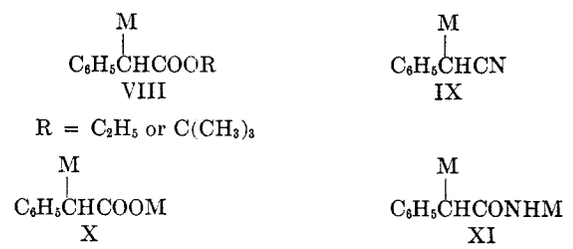
Similarly, β-diketone V was converted to its disodio salt V″ which was α-phenylethylated to form the *erythro* isomer VIa in 31% yield. None of the *threo* isomer VIb was detected (see Experimental Section).



These stereospecific alkylations, which are presumably SN2 type displacements, evidently occur because the nonbonded interactions in the transition states leading to the *erythro* isomer are less than those leading to the *threo* isomer, as indicated in VII″a and VII″b, respectively. The conformations of these transition states are assumed to resemble the conformations of the alkylation products.



The present results, which are of interest because of the wide usage of such alkylations in synthesis,[8] apparently furnish the first demonstrated stereospecific alkylation of a dicarbanion. Other α-phenylethylations of carbanions that have afforded largely or exclusively the *erythro* isomer of the alkylation product include those of the monocarbanions VIII[9] and IX,[10] and of the dianions X[5,11] and XI.[12] However, only VIII and X have been shown to involve stereospecific alkylations.



Experimental Section[13]

α-Phenylethylation of β-Diketone I.—To a stirred suspension of 0.10 mol of $NaNH_2$ in liquid ammonia (prepared from 0.1 g-atom of sodium in 400 ml of commercial, anhydrous liquid ammonia[14]) was added 8.8 g (0.05 mol) of 1-phenyl-2,4-pentanedione (I).[15] After the resulting green solution had stirred for 30 min, 7.0 g (0.05 mol) of α-phenylethyl chloride in 20 ml of anhydrous ethyl ether was added dropwise. The reaction mixture was stirred for 2 hr and then neutralized by the addition of 10 g of NH_4Cl. The ammonia was evaporated (water bath) as 200 ml of dry ether was added, and the resulting ethereal suspension was washed with several portions of 10% HCl. The ethereal solution was dried ($MgSO_4$) and concentrated (rotary evaporator) to a semisolid. The mixture was dissolved in hexane and allowed to crystallize. The precipitate was filtered to give 6.1 g (44%) of 2,3-diphenyl-4,6-heptanedione (IIa), mp 120–122°. Thin layer chromatography (tlc), as described below, indicated that the isolated β-diketone was at least 95% *erythro* IIa.

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.55; H, 7.20.

The reaction was repeated, except that the reaction mixture was allowed to stir for 11 hr before neutralization with NH_4Cl. This gave 6.7 g (48%) of IIa, mp 120–122°, a second crop of 2.3 g, mp 98–105°, and an oil (5 g). A sample of the second crop and the oil was analyzed on a silica gel G (Merck) tlc plate or silica gel (Eastman chromatogram sheet) using a 1:1 (v/v) mixture of CH_2Cl_2 and CCl_3 as a developing solvent. Visualization of the β-diketone, accomplished by spraying the developed plate with a 5% solution of $FeCl_3$ in ethanol, revealed red spots corresponding to starting β-diketone (R_f 0.29) and *erythro* IIa (R_f 0.23). None of the *threo* isomer IIb (R_f 0.20) was present.

Identification of the spots was accomplished by direct tlc comparison to samples of *erythro* and *threo* II prepared as described below. Various prepared mixtures of authentic *threo* IIb and *erythro* IIa were separated by tlc. It was observed that a mixture of 0.95 g of *erythro* IIa and 0.05 g of *threo* IIb could be separated adequately by tlc, but mixtures with smaller amounts of *threo* IIb were not consistently separated.

The infrared spectrum of a sample of the isolated *erythro* IIa, mp 120–122°, which was identical with that of authentic *erythro* IIa prepared as described below, showed peaks at 750 and 690 cm^{-1} (monosubstituted phenyl)[16] and a broad band centered at 1600 cm^{-1} (β-diketone).[16] The nuclear magnetic resonance (nmr) spectrum of *erythro* IIa in deuteriochloroform showed, in addition to the aromatic proton signals at 7.30 and 7.22 ppm (all chemical shifts are reported in δ downfield from an internal tetramethylsilane standard), a signal at 5.22 ppm, attributed to the vinyl proton of the enolic form; a complex multiplet centered at 3.57 ppm, assigned to the two benzylic protons on C-2 and C-3; a singlet at 3.19 ppm, assigned to the methylene protons at C-5 in the unenolized form; a pair of singlets at 1.68 and 1.60 ppm, assigned to the methyl protons at C-7 in the enol and keto forms, respectively; and a pair of doublets at 1.02 and 0.95 ppm, assigned to the C-1 methyl group.

Preparation of Authentic Samples of *erythro* IIa and *threo* IIb.—A sample of 8.4 g (0.035 mol) of *erythro*-2,3-diphenylbutyric acid (III)[5] was refluxed in 50 ml of thionyl chloride. After 3 hr, the excess thionyl chloride was removed by distillation and by evacuating the reaction flask to 1 mm for 30 min. The resulting *erythro*-2,3-diphenylbutyryl chloride (IV) remaining in the flask was condensed with lithioacetone as described below.

Tritylithium[17] was prepared by the addition of 44.0 ml (0.07 mol) of 1.6 *N* *n*-butyllithium in hexane[18] to 17.2 g (0.07 mol) of triphenylmethane in 100 ml of anhydrous ethyl ether. After stirring for 90 min, the dark red solution of tritylithium was cooled (ice bath), and 4.08 g (0.07 mol) of dry acetone was added. To the resulting solution of lithioacetone was added the acid

(8) See especially K. G. Hampton, R. J. Light, and C. R. Hauser, *J. Org. Chem.*, **30**, 1413 (1965); S. Boatman, T. M. Harris, and C. R. Hauser, *J. Amer. Chem. Soc.*, **87**, 82 (1965), and earlier references.

(9) W. G. Kenyon, R. B. Meyer, and C. R. Hauser, *J. Org. Chem.*, **28**, 3108 (1963).

(10) W. R. Brasen and C. R. Hauser, *J. Amer. Chem. Soc.*, **79**, 395 (1957); C. R. Hauser and W. R. Brasen, *ibid.*, **78**, 494 (1956).

(11) C. R. Hauser and W. J. Chambers, *ibid.*, **78**, 4942 (1956).

(12) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **26**, 3696 (1961).

(13) Melting points were taken on a Thomas–Hoover melting point apparatus in open tubes and are uncorrected. Analyses were performed by Janssen Pharmaceutica, Beerse, Belgium, and Triangle Chemical Laboratories, Chapel Hill, N. C. Infrared spectra were obtained with a Perkin-Elmer Model 137 or 237 spectrophotometer, using the potassium bromide pellet method. Nmr spectra were obtained on a Varian A-60 nuclear magnetic resonance spectrometer.

(14) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).

(15) K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **29**, 3511 (1964).

(16) See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Second Edition, John Wiley & Sons, New York, N. Y., 1958.

(17) H. Gilman and G. J. Gaj, *J. Org. Chem.*, **28**, 1725 (1963).

(18) Obtained from Foote Mineral Co., Exton, Pa.

chloride IV, prepared as described above, and the mixture was heated to reflux. After 6 hr, the suspension was cooled and neutralized with 10% HCl. The ethereal layer was dried ($MgSO_4$) and the solution concentrated (rotary evaporator); the triphenylmethane, which precipitated as the ether evaporated, was removed by filtration. Removal of all the ether left a solid residue which was shown by tlc to contain triphenylmethane and *erythro* IIa but no other β-diketone. Recrystallization of a portion of this residue from hexane yielded a sample of IIa whose infrared spectrum was superimposable upon that of IIa prepared from Ia.

Similarly, a sample of 1.6 g (0.067 mol) of *threo*-2,3-diphenylbutyric acid (III) was condensed through its acid chloride with 0.14 mol of lithioacetone to give exclusively *threo* IIb. Although IIb generated in this manner could not be completely separated from the triphenylmethane, its infrared spectrum was very similar to that of *erythro* IIa, with only minor differences in the 1350–1100-cm^{-1} region, and its nmr spectrum was similar to that of *erythro* IIa. Tlc indicated that none of the *erythro* IIa had been formed by the reaction.

α-Phenylethylation of β-Diketone V.—To a stirred suspension of 0.04 mol of $NaNH_2$ in liquid ammonia was added 5.0 g (0.021 mol) of 1,4-diphenyl-2,4-butanedione (V).[15] The resulting green–brown solution was stirred for 30 min, and 5.87 g (0.042 mol) of α-phenylethyl chloride in 50 ml of anhydrous ethyl ether was then added dropwise. After 8 hr, the mixture was neutralized with 10 g of NH_4Cl, the ammonia was replaced by ether, and the resulting suspension was washed with 10% HCl. The ether layer was dried ($MgSO_4$) and concentrated (rotary evaporator) to give, in several crops, 2.20 g (31%) of 1,4,5-triphenyl-1,3-hexanedione (VI), mp 172–174°. The oil obtained on removing all of the ether was distilled to give 3.62 g of α-phenylethyl chloride (1 equiv plus 24% of a second equiv) leaving 4.3 g of pot residue. Thin layer chromatography indicated that the isolated β-diketone was *erythro* VIa. A sample, recrystallized several times from hexane–ethanol, melted at 174–175°.

Anal. Calcd for $C_{24}H_{22}O_2$: C, 84.17; H, 6.47. Found: C, 83.98; H, 6.54.

A portion of the pot residue (see above) was analyzed on a silica gel G (Merck) coated tlc plate using a 4:1 (v/v) mixture of CCl_4 and CH_2Cl_2 as developing solvent. Visualization of the plate with an ethanolic solution of $FeCl_3$ indicated that the major component of the oil was *erythro* VIa (R_f 0.41). The only other β-diketone indicated to be present was the starting material V (R_f 0.30).

The infrared spectrum of a sample of the isolated *erythro* VIa, mp 174–175°, had a broad band centered at 1600 cm^{-1} (β-diketone)[16] and peaks at 750 and 690 cm^{-1} (monosubstituted phenyl).[16] The nmr spectrum of *erythro* VIa in deuteriochloroform solution showed aromatic proton signals centered at 7.28 ppm, a singlet at 5.90 ppm assigned to the vinylic proton at C-4, a complex multiplet centered at 3.30 ppm assigned to the benzylic protons at C-2 and C-3, and what appeared to be a pair of doublets at 1.04 and 0.95 ppm, similar to those found in the spectrum of *erythro* IIa, assigned to the methyl protons at C-1.

Preparation of an Authentic Sample of *erythro* VIa.—Similar to the preparation of authentic *erythro* IIa (see above), *erythro* VIa was prepared by condensing 0.017 mol of the acid chloride of *erythro* acid III with 0.034 mol of lithioacetophenone. The β-diketone product, identified by tlc using the $FeCl_3$ reagent, had the same R_f value as VIa prepared from the alkylation of V. Although the β-diketone could not be completely separated from triphenylmethane, that portion of its infrared spectrum not due to triphenylmethane was superimposable on that of VIa prepared from the α-phenylethylation of V.

Epimerization Studies of *threo* IIb.—To a solution of 0.10 mol of $NaNH_2$ in 400 ml of liquid ammonia was added 8.8 g (0.05 mol) of β-diketone I. After 30 min, the solution was considered to contain 0.05 mol of disodio salt I″. To this solution was added 2.0 g of *threo* IIb. *threo* IIb was contaminated with triphenylmethane (about 50%), and hence, only about 0.004 mol of IIb was present. The mixture was stirred for 2 hr and neutralized with 10 g of NH_4Cl. The ammonia was replaced by ether (water bath), and the resulting ethereal suspension was washed with 10% HCl. The ether solution was concentrated, and some of β-diketone I was removed *in vacuo*. The residue was shown by tlc to contain only *threo* IIb and β-diketone I. None of the *erythro* isomer IIa was indicated to be present. The fact that pure *threo* IIb was not used in this experiment does not affect the validity of the results, since more than enough I″ was present to compensate for impurities.

Similarly, a sample of *threo* IIb (0.37 g) was added to 0.002 mol of $NaNH_2$ in 50 ml of liquid ammonia. Since the sample of *threo* IIb was contaminated with triphenylmethane (see above), this represents *ca.* 2 equiv of sodium amide per equiv of β-diketone. After stirring for 1 hr, the mixture was neutralized with NH_4Cl. The ammonia was replaced by ether and the ether suspension was washed with 10% HCl. The ether layer was concentrated and subjected to tlc analysis, which indicated that *threo* IIb had been converted completely to *erythro* IIa.

Registry No.—Ammonia, 7664-41-7; IIa (*erythro*), 20406-81-9; VIa (*erythro*), 20462-26-4.