

(CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY)

Experiments in the Colchicine Field. IV. The Stereochemistry of the Tricyclic Keto Esters Obtained from the Cyclization of β -Carbomethoxy- β -(2-phenylcyclohexane)-propionic Acid¹

BY C. DAVID GUTSCHE, MAX W. WENDT AND KURT L. SELIGMAN

RECEIVED JANUARY 30, 1958

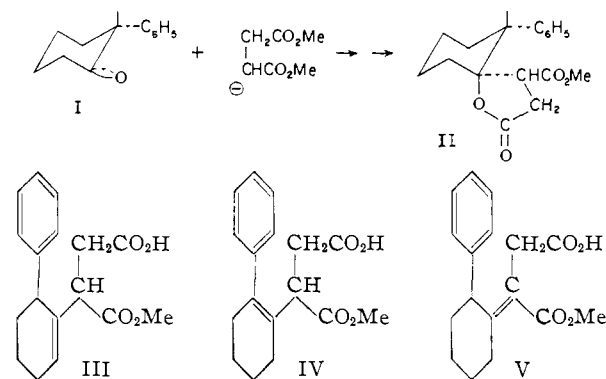
The α -isomer of β -carbomethoxy- β -(2-phenylcyclohexane)-propionic acid (VI) has been converted to the known *trans*-2-phenylcyclohexanepropionic acid thereby establishing the configuration on the cyclohexane ring of VI as *trans*. The half-esters α -VI and β -VI can be cyclized to six-membered B ring keto esters (α -X and β -X) or to seven-membered B ring keto esters (α -XII and β -XII). The keto esters of the α - and β -series are interconvertible as demonstrated by saponification and remethylation experiments. Thus the α - and β -series are epimeric at a carbon in ring B and identical in configuration (*trans*) at the B-C ring juncture. On the basis of conformational considerations it is assumed that the more stable epimer in the six-membered B ring series is the *trans-trans* isomer which leads to the conclusion that the more stable epimer in the seven-membered B ring series is the *trans-cis* isomer. A rationalization of this latter fact is based on a consideration of the balance between conformational interactions and resonance interactions.

Several years ago a method was published for the synthesis of hydrophenanthrene and hydrodibenzocycloheptatriene derivatives *via* cyclization by the hydrogenated Stobbe half-esters obtained from 2-phenylcyclohexanone and dimethyl succinate.² The present communication is concerned with the stereochemistry of the compounds discussed in that paper.³

When 2-phenylcyclohexanone (I) is condensed with dimethyl succinate in the presence of potassium *t*-butoxide a mixture of unsaturated half-esters is obtained from which it is possible to separate two pure isomers, designated as α -III and β -III. On the basis of ultraviolet spectral characteristics⁴ and oxidation experiments described earlier,² the double bond in both of these compounds has been assigned to an unconjugated position in the ring. The formation of III instead of IV and/or V is difficult to rationalize but is probably related to the ease of removal of a proton

from the paraconic ester (most probable structure is II⁵) which is presumed to be a reaction intermediate⁶ or to the relative stabilities of the possible olefins.⁷

Reduction of α -III proceeds in a highly stereoselective manner to give a 94% yield of a single isomer, α -VI. Reduction of β -III is less stereoselective and yields a mixture from which one pure isomer, β -VI, can be separated along with a lower melting compound which appears to be a eutectic containing β -VI.⁸ That the configuration of the groups on the cyclohexane ring is *trans* in α -VI and β -VI has been demonstrated by the following sequence of reactions: Conversion of α -VI to the reverse half-ester (VII) was carried out as previously described⁹; conversion of VII to the silver salt followed by pyrolysis in the presence of bromine gave the bromo ester VIII from which the bromine was removed with hydrogen and Raney nickel; the resulting ester gave the known *trans*-2-phenylcyclohexanepropionic acid (IX)¹⁰ upon hydrolysis. Since α -VI and β -VI differ only in configuration at C-7 (*cf.* following section for proof), this series of reactions establishes the configurations at C-1 and C-2 as *trans* in both of these isomers.¹¹



(1) This work was supported, in part, by grant-in-aid no. G-1886 from the National Science Foundation.

(2) C. D. Gutsche and K. L. Seligman, *THIS JOURNAL*, **75**, 2579 (1953).

(3) *Cf.* footnote 11 of ref. 2.

(4) The possibility that the styrene type absorption would not be manifested by a compound of structure IV due to restrictions to coplanarity of the phenyl ring and cyclohexene ring must be considered. However, two items suggest that compound IV should have a reasonably strong absorption near 250 $m\mu$: (a) R. B. Carlin and H. P. Landerl, *THIS JOURNAL*, **75**, 3969 (1953), found that substituents in 2-phenylcyclohexene at the *o*-position have a marked effect on the extinction coefficient of the band near 250 $m\mu$ but that substituents at the 1-position of the cyclohexene ring have a much less drastic effect on this absorption band. (b) 2-Phenylcycloheptene-1-acetic acid, a compound with some similarity to IV, has a rather strong band (ϵ 7800) at 243.5 $m\mu$ [C. D. Gutsche, *ibid.*, **73**, 786 (1951)].

(5) W. G. Dauben, G. J. Fonken and D. S. Noyce, *ibid.*, **78**, 2579 (1956), have shown, for instance, that the reduction of alkylcyclohexanones yields increasing amounts of axial alcohol as the bulk of the reducing agent increases. This is interpreted, in part, as resulting from the preferential approach by the nucleophilic agent at the less hindered face of the carbonyl group. Thus, the succinate anion would be expected to react with I in such a fashion as to give II.

(6) *Cf.* W. S. Johnson and G. H. Daub, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. VI, 1951, p. 1.

(7) H. C. Brown, *et al.*, *THIS JOURNAL*, **78**, 2190, 2193, 2197, 2199, 2203 (1956), have shown, for instance, that the direction of an E2 reaction is controlled by resonance stabilization (hyperconjugative factors in the cases studied) of the incipient olefin and by steric strains in the transition state including strains arising, *inter alia*, from the steric requirements of the groups attached to the incipient double bond.

(8) In the earlier communication² the α -isomer was designated as α_1 , the β -isomer as β_1 , and the eutectic as β_2 .

(9) Reported without experimental details by C. D. Gutsche and A. J. Lauck, *Chemistry & Industry*, 116 (1955).

(10) C. D. Gutsche, *THIS JOURNAL*, **70**, 4150 (1948).

(11) The formation of the *trans* isomer in the reduction of α -III and β -III provides further evidence in favor of the double bond position as represented by structure III. 2-Phenylcyclohexene-1-acetic acid (corresponding to structure IV) has been shown to give the *cis* isomer exclusively, and 2-phenylcyclohexylideneacetic acid (corresponding to structure V) a mixture of *cis* and *trans* isomers (*cis* predominating) on catalytic hydrogenation [R. P. Linstead, R. R. Whetstone and P. Levine, *ibid.*, **64**, 2014 (1942); J. W. Cook, C. L. Hewett and C. A. Lawrence, *J. Chem. Soc.*, 71 (1936)].

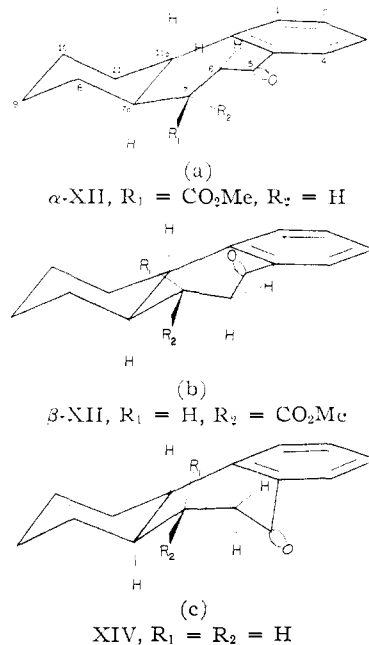
When VI is converted to the acid chloride and treated with a Lewis acid catalyst a cyclization with ester interchange to the six-membered B ring keto ester (X) or without ester interchange to the seven-membered B ring keto ester (XII) may be effected.² Cyclization of α -VI with ester interchange yields 85% of a neutral fraction consisting of α -X (m.p. 76°) and on one occasion 4% of an acidic fraction consisting of α -XI (m.p. 175°). Cyclization of β -VI with ester interchange yields 78% of a neutral oil, presumably β -X. Cyclization of α -VI without ester interchange yields 96% of a neutral fraction consisting of α -XII (m.p. 157°) and 2% of an acidic fraction consisting of α -XI (m.p. 175°). Cyclization of β -VI without ester interchange yields 91% of a neutral fraction consisting of β -XII (m.p. 97°) and 4% of an acidic fraction consisting of β -XI (m.p. 131°).

The interconvertibility of the α - and β -series is observed in the alkaline hydrolysis of the keto esters X and XII to the corresponding keto acids XI and XIII. In the six-membered B ring compounds both α -X (m.p. 76°) and β -X (oil) yield the same keto acid α -XI (m.p. 175°) upon saponification. That the inversion has occurred in the direction of β to α is shown by remethylation experiments; diazomethane treatment of the keto acid obtained by saponification of α -X or β -X yields a keto ester identical with α -X, while remethylation of the acid thought to be β -XI (obtained as a by-product in the cyclization of β -VI to β -XII as described above) yields an oil. Thus, α -XI and β -XI are epimeric at C-10 and identical in configuration at C-4a and C-10a; this configuration, as described in the previous section, has been shown to be *trans*. Numerous studies have indicated that in the cyclohexane series the larger of the groups attached to a ring carbon prefers to occupy an equatorial position.¹² Thus, the more stable isomer of X and XI is presumed to be the one in which the acetic acid side chain occupies an equatorial position and, accordingly, α -X is designated as the *trans-trans* isomer and β -X as the *trans-cis* isomer. In the seven-membered B ring compounds saponification of α -XII (m.p. 157°) yields a mixture containing about 85% of α -XIII and 15% of β -XIII, while β -XII (m.p. 97°) yields a mixture containing about 65% of α -XIII and 35% of β -XIII.¹³ That the inversion has occurred in the direction of β to α is shown by the reconversion of α -XIII to α -XII upon treatment with diazomethane. On the assumption that no inversion of configuration takes place during the cyclization of VI to XII, α -XII is the configurational relative of α -X and β -XII is the configurational relative of β -X. Consequently, α -XII is designated as the *trans-cis* isomer and β -XII as the *trans-trans* isomer.

(12) For review articles cf. (a) W. Klyne, "Progress in Stereochemistry," Academic Press, Inc., New York, N. Y., 1954, p. 36; (b) D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956); (c) W. G. Dauben and K. S. Pitzer in "Steric Effects in Organic Chemistry," ed. by M. S. Newman, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 3.

(13) Keto acid β -XIII was not isolated in pure form but as a eutectic containing approximately two parts of α -XIII and one part of β -XIII. The composition of the eutectic was determined by diazomethane methylation followed by separation of the resulting keto esters, α -XII and β -XII.

The greater stability of the *trans-cis* isomer (α -series) over the *trans-trans* isomer (β -series) in the seven-membered B ring compounds may be explained in the following manner. Due to the flexibility of the B ring a number of conformations can be constructed, three of which are represented by a, b and c. Disregarding non-bonded inter-

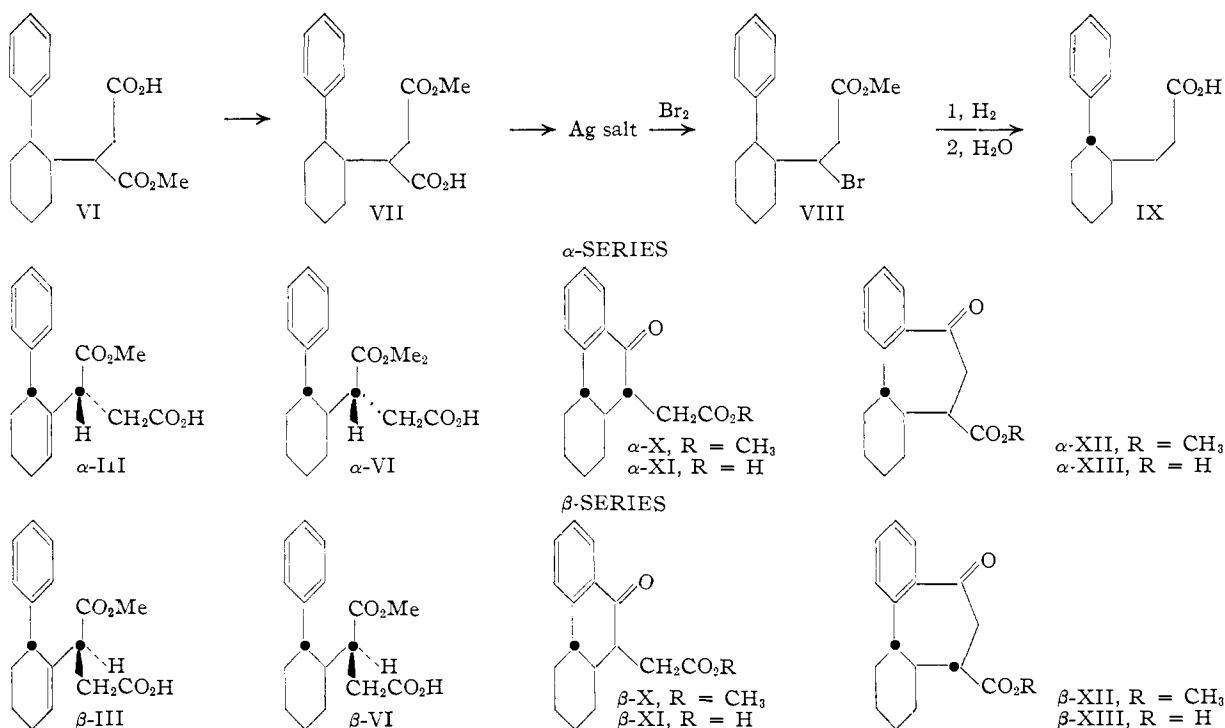


actions, conformation a should be the most stable for it places the carbonyl group co-planar with the phenyl group and thereby allows for maximum resonance stabilization.¹⁴ Conformations b and c, on the other hand, twist the carbonyl group about 70° out of the plane of the phenyl ring. Inspection of molecular models, however, reveals that in XIVa there is appreciable interference between the hydrogen atoms at C-6 and C-11a and an eclipsed conformation for hydrogen at C-7a:R₂, whereas no severe hindrances are present in XIVb and XIVc. Thus, it might be anticipated that a balance between non-bonded interactions and resonance interactions would exist in molecules of the XIV structure, and it would also be anticipated that various ring substituents might alter this balance. That such a balance does exist is indicated by the ultraviolet spectrum of XIV which has a maximum at 249 m μ and an extinction coefficient of 7700.¹⁵ Were the carbonyl and phenyl groups co-planar an extinction coefficient comparable with that of acetophenone (13,000) would be expected. Using these absorption data in the empirical formula of Braude¹⁶ the angle of twist in XIV can be calculated as 54°. If, now, the hydrogen at R₁ is replaced by the much larger carbomethoxy group (α -XII) non-bonded interactions between this group and various hydrogen atoms in the molecule exist in α -XIIb and α -XIIc (carbomethoxy group pseudo axial), but are relieved in α -XIIa (carbomethoxy group

(14) M. J. S. Dewar, *THIS JOURNAL*, **74**, 3345 (1952), states that the resonance energy varies with the \cos^2 of the angle of twist.

(15) C. D. Gutsche, *ibid.*, **73**, 786 (1951).

(16) E. A. Braude, F. Sondheimer and W. F. Forbes, *Nature*, **173**, 117 (1954).



pseudo equatorial). Thus, the non-bonded interactions involving the carbomethoxy group in the α -configuration work in conjunction with resonance interactions and would be expected to push the compound toward conformation α . The ultraviolet absorption of α -XII [λ 249 m μ (ϵ 8150)²] indicates that the angle of twist (51°) is, indeed, somewhat less than in the unsubstituted ketone XIV. On the other hand, if the hydrogen at R₂ is replaced by the much larger carbomethoxy group (β -XII) non-bonded interactions between this group and various hydrogen atoms in the molecule are greater in β -XIIa (carbomethoxy group pseudo axial) than in β -XIIb or β -XIIc (carbomethoxy group pseudo equatorial). In this case, further steric hindrance to co-planarity of carbonyl and phenyl groups would be expected, and this is indicated by the ultraviolet absorption of β -XII [λ 248 m μ (ϵ 7490)²] from which the angle of twist is calculated as 55°.

Experimental¹⁷

The α -isomer of β -carbomethoxy- β -(2-phenylcyclohexene-6)-propionic acid (α -III) of m.p. 143–144°, the β -isomer of β -carbomethoxy- β -(2-phenylcyclohexene-6)-propionic acid (β -III) of m.p. 90–91°, the α -isomer of β -carbomethoxy- β -(2-phenylcyclohexane)-propionic acid (α -VI) of m.p. 151–152°, and the β -isomer of β -carbomethoxy- β -(2-phenylcyclohexane)-propionic acid (β -VI) of m.p. 127–128° were obtained as previously described.²

α -Isomer of Methyl β -Carboxy- β -(2-phenylcyclohexane)-propionate (α -VII).—Saponification of α -VI yielded, as previously described,² the corresponding dibasic acid, m.p. 191–192°. Following the general procedure of Johnson and Goldman,¹⁸ a 15.0-g. sample of the dibasic acid was converted to the anhydride by refluxing for 2 hr. with acetyl chloride. After removal of the excess acetyl chloride, methanol was added and the reaction mixture was refluxed

an additional 2 hr. The methanol was removed under vacuum, and the residue was recrystallized 3 times from petroleum ether (b.p. 80–110°)–ethyl acetate (9:1 ratio) to give 10.8 g. (71%) of colorless prisms, m.p. 141–142°.

Anal. Calcd. for C₁₇H₂₂O₄: C, 70.32; H, 7.64. Found: C, 70.41; H, 7.47.

Conversion of α -Isomer of Methyl α -Carboxy- β -(2-phenylcyclohexane)-propionate (α -VII) to *trans*-2-Phenylcyclohexanepropionic Acid (IX).—A 0.76-g. sample of α -VII was converted to 0.93 g. (96%) of silver salt and treated with 0.72 g. of bromine in 5 ml. of carbon tetrachloride following the general directions for the Hunsdiecker degradation.¹⁹ After refluxing for 25 min. the bromine and carbon tetrachloride were removed under vacuum and the residue was taken up in ether. The neutral fraction contained 0.45 g. of material which was distilled to give 0.34 g. of a pale yellow, viscous oil. The acidic fraction consisted of 0.20 g. of starting material (α -VII). A 0.19-g. sample of the neutral fraction was dissolved in 25 ml. of absolute methanol containing 0.015 g. of dissolved sodium, treated with 0.50 g. of Raney nickel catalyst, and subjected to hydrogenation for 20 hr. at 1500 p.s.i. pressure at room temperature. The resulting product was distilled to give 0.11 g. of a colorless, mobile oil which was then saponified by refluxing for 1.5 hr. with aqueous ethanolic sodium hydroxide. The resulting acid was distilled and recrystallized from petroleum ether to give colorless blades, m.p. 80–82°, showing no depression in m.p. upon admixture with an authentic sample of *trans*-2-phenylcyclohexanepropionic acid,¹⁴ m.p. 83.5–84.5°. A sample of the acid was converted to the amide and obtained as a white powder, m.p. 135–136.5°, which showed no depression in m.p. upon admixture with an authentic sample of *trans*-2-phenylcyclohexanepropionamide,¹⁴ m.p. 134–135°.

α -Isomer of 6,7,7a,8,9,10,11,11a-Octahydro-7-carboxy-5-keto-5H-dibenzo[a,c]cycloheptatriene (α -XIII).—A solution of 4.65 g. of α -XII (m.p. 156–157°) in 100 ml. of ethanol was treated with 200 ml. of 5% aqueous sodium hydroxide, and the mixture was refluxed for 2 hr. The acidic fraction consisted of 4.40 g. (100%) of material, from which 2.86 g. (65%) of α -XIII was obtained as glistening needles after four recrystallizations from aqueous ethanol; m.p. 201–203°; $\lambda_{\text{max}}^{\text{EtOH}}$ (ϵ) 249 m μ (8100), 285 m μ (1490).

Anal. Calcd. for C₁₆H₁₆O₃: C, 74.39; H, 7.02. Found: C, 74.53; H, 6.75.

(17) All melting points are corrected; all boiling points are uncorrected.

(18) W. S. Johnson and A. Goldman, *THIS JOURNAL*, **66**, 1030 (1944).

(19) C. V. Wilson in "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. IX, 1957, p. 332.

The *p*-bromophenacyl derivative of α -XIII was obtained as flat, elongated, very small blades after 3 recrystallizations from aqueous ethanol; m.p. 157–158°.

Anal. Calcd. for $C_{24}H_{23}BrO_4$: C, 63.31; H, 5.09. Found: C, 63.28; H, 4.93.

Concentration of the filtrates from the purification of α -XIII gave 1.39 g. (32%) of a solid which after 3 recrystallizations from aqueous ethanol had m.p. 171–172°. This material proved to be a eutectic mixture of α -XIII and β -XIII (*cf.* below for further details) containing about 2 parts of α -isomer to 1 part of β -isomer. On this basis it can be estimated that the hydrolysis product contained about 8 parts of α -XIII to one part of β -XIII.

Treatment of 0.1 g. of α -XIII with ethereal diazomethane gave 0.08 g. (76%) of the starting ester, α -XII; m.p. 156–156.5°.

The β -isomer of 6,7,7a,8,9,10,11,11a-octahydro-7-carboxy-5-keto-5H-dibenzo[a,c]cycloheptatriene (β -XIII) could not be obtained in pure form. When a 0.60-g. sample of β -XII (m.p. 96–97°) was saponified under the conditions described above, 0.55 g. (97%) of an acidic product was obtained, m.p. 170–172°. After 4 recrystallizations from aqueous ethanol the m.p. was 171–172.5°. That this product was actually a mixture of α -XIII and β -XIII was indicated by remethylation experiments. When this material was treated with ethereal diazomethane the resulting product could be separated, by fractional crystallization, into 48–64% of α -XII (m.p. 156–157°) and 38–27% of β -XII (m.p. 96–97°). On this basis it can be estimated that the hydrolysis product contained about 2 parts of α -XIII to one part of β -XIII.

α -Isomer of 1,2,3,4,4a,9a,10,10a-Octahydro-9-ketophenanthryl-10-acetic Acid (α -XI). (a) By Saponification of α -X. — A 0.59-g. sample of α -X (m.p. 75–76°) was saponified under the conditions described above to yield, after one recrystallization from aqueous ethanol, 0.49 g. (88%) of α -XI, m.p. 173–175°. Further recrystallization gave colorless, very small needles, m.p. 175–176.5°; $\lambda_{\max}^{\text{EtOH}}$ (ϵ) 248 μ (11,600), 289 μ (1800).

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.42; H, 6.75.

The S-benzylthiouronium salt of α -XI was obtained as colorless, thick, square blades after several recrystallizations from ethanol; m.p. 157–157.5°.

Anal. Calcd. for $C_{24}H_{26}N_2O_3S$: C, 67.89; H, 6.65. Found: C, 67.91; H, 6.62.

Remethylation of α -XI with ethereal diazomethane gave a quantitative yield of α -X, m.p. 75–76°.

(b) By Saponification of β -X. — A 0.500-g. sample of β -VI (m.p. 127–128°) was treated with an excess of anhydrous hydrogen fluoride and the mixture allowed to stand at room temperature for 2 hr. The neutral product, isolated in the usual fashion, consisted of an oil which did not crystallize and which is presumed to be β -X (*cf.* below). Saponification of the neutral fraction yielded, after recrystallization of the product, 0.220 g. (50%) of colorless needles of m.p. 173–175° which showed no depression in m.p. when admixed with a sample of α -XI prepared as described above.

β -Isomer of 1,2,3,4,4a,9a,10,10a-Octahydro-9-ketophenanthryl-10-acetic Acid (β -XI). — When a 8.16-g. sample of β -VI was cyclized with aluminum bromide in carbon disulfide as described previously,² a 91% yield of β -XII was obtained. In addition, 4% of an acidic fraction was isolated and shown to be β -XI. It was purified by recrystallization from aqueous ethanol and obtained as a white powder, m.p. 129–131°; $\lambda_{\max}^{\text{EtOH}}$ (ϵ) 249 μ (12,100), 290 μ (1800).

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.12; H, 6.94.

The methyl ester of β -XI (β -X) was obtained by treatment of the acid described above with diazomethane. The product was obtained, after evaporative distillation at 80–90° (0.001 mm.), as an oil; $\lambda_{\max}^{\text{EtOH}}$ (ϵ) 249 μ (10,900), 290 (1800).

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.08; H, 7.66.

Ultraviolet Spectra. — The spectra of compounds α -X, β -X, α -XII, β -XII and XIV have been reported previously,^{2,15} the data having been obtained on a Beckman model DU spectrophotometer. The spectra of these compounds were redetermined for purposes of a closer comparison using, in the present instance, a Cary recording spectrophotometer. The data agreed very closely with those in the literature, and the differences in extinction coefficient between α -XII, β -XII and XIV appear to be real and reproducible. As a further check, the areas under the curves for the 250 μ bands were compared (oscillator strengths) and were found to fall in exactly the same order as the extinction coefficients.

ST. LOUIS, MO.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TENNESSEE]

The Properties of Some Phenylpyridylmethanols in Sulfuric Acid Solution

BY HILTON A. SMITH AND C. W. HOLLEY

RECEIVED FEBRUARY 27, 1958

The behavior of the following compounds in 100% sulfuric acid has been studied: phenyl-2-pyridylmethanol, phenyl-4-pyridylmethanol, diphenyl-2-pyridylmethanol and diphenyl-4-pyridylmethanol. The first two compounds show no evidence of carbonium ion formation, but appear to give polymers. The last two compounds form fairly stable carbonium ions. The properties of the solutions were investigated, utilizing *i*-factors, ultraviolet and near-visible spectra, titration studies and chemical reaction with methanol and water. The influence of the protonation of the pyridine nitrogen on carbonium ion stability of the phenylpyridylmethanols is discussed.

Introduction

The dissociation of diphenyl- and triphenylmethanols in 100% sulfuric acid to give relatively stable carbonium ions has been the subject of a number of investigations.^{1–9} The influence of

substituents on the stability of such ions has been studied by means of freezing point lowering, reaction with water and alcohols, ultraviolet absorption spectra and minimum sulfuric acid concentration necessary to produce a visible color. It has been demonstrated that the substitution of electron-releasing groups in the phenyl rings of diphenylmethanol increases the stability of the carbonium ion formed in sulfuric acid solution while electron-withdrawing groups decrease the thermodynamic stability and also promote the tendency for polymerization. Compounds such as tri-*p*-aminophenylmethanol and tri-*p*-dimethylaminophenylmethanol when dissolved in sulfuric acid form stable

- (1) H. A. Smith and R. J. Smith, *THIS JOURNAL*, **70**, 2400 (1948).
- (2) C. M. Welch and H. A. Smith, *ibid.*, **72**, 4748 (1950).
- (3) M. S. Newman and N. C. Deno, *ibid.*, **73**, 3644 (1951).
- (4) V. Gold and F. L. Tye, *J. Chem. Soc.*, 2172 (1952).
- (5) H. A. Smith and R. G. Thompson, *THIS JOURNAL*, **77**, 1778 (1955).
- (6) N. C. Deno and A. Schriesheim, *ibid.*, **77**, 3051 (1955).
- (7) R. G. Thompson and H. A. Smith, *ibid.*, **77**, 4432 (1955).
- (8) H. A. Smith and B. B. Stewart, *ibid.*, **79**, 3693 (1957).
- (9) B. B. Stewart and H. A. Smith, *ibid.*, **79**, 5457 (1957).